THE UNIVERSITY
of EDINBURGH

This thesis has been submitted in fulfilment of the requirements for a postgraduate degree (e.g. PhD, MPhil, DClinPsychol) at the University of Edinburgh. Please note the following terms and conditions of use:

This work is protected by copyright and other intellectual property rights, which are retained by the thesis author, unless otherwise stated.

A copy can be downloaded for personal non-commercial research or study, without prior permission or charge.

This thesis cannot be reproduced or quoted extensively from without first obtaining permission in writing from the author.

The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the author.

When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given.

Epidemiology of carbapenemase-producing organisms (CPO) in Scotland

Shengyuan Zhao

Doctor of Philosophy

The University of Edinburgh

2020

Declaration

I declare that this thesis has been composed by myself and the content of this thesis is my own work other than stated below. The work has not been submitted for any other degree or professional qualification.

Shengyuan Zhao

February 2020

Chapter 2:

Literature selection and data extraction were conducted independently by Melissa Taylor (a MSc student) and myself. Study quality assessment was performed independently by Ruby Tabor (an undergraduate student) and myself.

Chapter 3 and 4:

Data sources: Laboratory records of CPO isolates from the Electronic Communication of Surveillance in Scotland; medical records of individuals with CPO isolation from General Acute Inpatient and Day Case-Scottish Morbidity Record; mortality data from National Records of Scotland Deaths; midyear population estimates from National Records of Scotland Health Board Population estimates.

Identification of all CPO cases and controls, data extraction and linkage of datasets above and data anonymization were performed by Health Protection Scotland (HPS) and Information Services Division via electronic Data Research and Innovation Service.

Abstract

The emergence and spread of carbapenem-resistant organisms (CRO) is a global public health threat in healthcare settings, resulting in high mortality, prolonged healthcare and increased costs. In the last two decades, many papers aiming to identify individuals at high risk of acquiring CRO have been published. However, the results reported across these studies are inconsistent and there are no studies systematically summarising those findings. Carbapenem resistance is mediated by multiple mechanisms. Carbapenemase production is the most concerning as the encoding genes of carbapenemases are located on mobile genetic elements, facilitating horizontal genetic exchange and therefore promoting the acquisition and spread of resistance genes. Examination of the epidemiology of carbapenemase-producing organisms (CPO) will inform local infection prevention and control strategies.

This thesis has two main parts. The aim of the first part is to systematically summarise risk factors for CRO infection and colonisation in healthcare facilities worldwide and identify study characteristics contributing most to the heterogeneity across studies. In the second part I focused on CPO in Scotland to investigate the incidence, microbiological characteristics and outcomes of CPO and determine risk factors associated with CPO among hospitalised patients.

In the first part, I conducted a systematic review and meta-analysis to evaluate risk factors associated with infection and/or colonisation of CRO in healthcare facilities. In total, 227 papers published between 1986 and 2016 were identified. Using pooled odds ratio estimates and the likelihood of statistical significance as criteria, prior carriage of multidrug-resistant organisms, prior antibiotics usage (carbapenem or oxazolidinone), prior provision of medical devices (mechanical ventilation or nasogastric tube) and prior healthcare exposure (intensive care unit ICU stay, and longer hospital stay) were most consistently found to be leading risk factors for CRO infection and/or colonisation. Additionally, decubitus ulcer was a specific leading risk factor for

CRO infection, and prior antibiotics usage (polymyxin or cefepime) and steroid treatment were specific for hospital acquired CRO infection. However, prior provision of some medical devices (parenteral nutrition or gastrostomy or urinary catheter) were only leading risk factors for CRO colonisation. Study organism, case-control selection, study population, sample size, study setting and specialty (ICU or non-ICU) were the characteristics accounting for most heterogeneity across the published studies examined.

In the second part of this thesis, I focused on CPO in Scotland using data extracted from several national datasets. I performed a retrospective analysis on all CPO from clinical and screening cultures in 2003-2016 using generalised linear models and survival analyses, and then conducted a matched case-control study to determine risk factors for CPO infection and colonisation among hospitalised patients using conditional logistic regression models. In total, 243 CPO isolates were identified in 214 individuals from 13 of 14 NHS Boards. The overall incidence of CPO cases increased significantly (P<0.001), from 0.02 to 1.38 per 100,000 population. The case fatality rate was 5.6%. Enterobacteriaceae isolates predominated (84.8%) and increased significantly faster than non-fermenters. Community-associated CPO were more likely to be colonisations while healthcare-associated CPO were more likely to be infections. The ‘big 5’ carbapenemases (VIM, NDM, KPC, OXA-48 and IMP) predominated (96.7%). Awareness is required that older patients, with systemic infection or organ failure or presenting non-fermenters are at higher 30-day mortality risk from CPO. Patients with CPO infection had higher hospital mortality and longer hospital stay. A history of prolonged hospitalisation, prolonged ICU or high dependency unit (HDU) stay and being immunocompromised all independently increased the risk of CPO infection, while a history of HDU stay and ‘endocrine, nutritional and metabolic diseases’ were independent risk factors for CPO colonisation.

In conclusion, this thesis sheds light on patients at high risk of being infected or colonised by CRO including CPO in healthcare facilities. Pre-emptive management should be prioritised for these patients. The findings also

demonstrate the necessity of continuing the existing acute hospital admission screening programme for carbapenemase-producing Enterobacteriaceae in Scotland. Future efforts are required to understand underlying factors accounted for mortality, evolution and transmission of carbapenem resistance in Scotland.

Lay Summary

Since their discovery 90 years ago, antibiotics have saved countless lives from infections. Due to extensive usage, resistance to antibiotics emerged, including the last resort antibiotics-carbapenems. Increasing numbers of carbapenem-resistant organisms (CRO) have been found globally over the past decade. Studying CRO worldwide and locally will help healthcare professionals and policy makers to address key questions of infection prevention and control of CRO.

To determine who is likely to acquire CRO in healthcare facilities, I summarised the findings from published papers on this topic worldwide in the last 30 years. The results highlight the leading risk factors, such as prior treatment with specific antibiotics and medical devices. I identified some study-design characteristics that warrant more careful consideration in future studies.

Carbapenem resistance arises from multiple mechanisms, but carbapenemase-producing organisms (CPO) are the most concerning due to their easy transferability. I conducted a retrospective epidemiology study of CPO since its first report in 2003 until the end of 2016 using data in Scotland. My results show that the incidence of CPO is relatively low but increasing rapidly. CPO infections are more likely to be healthcare-associated while community-associated CPO is associated with colonisation. Mortality for individuals in Scotland with CPO is low but CPO infections result in prolonged hospital stay. A history of (prolonged) healthcare exposure and being immunocompromised were independently associated with CPO infections. Also, a subgroup of patients that are at a higher risk of death from CPO were identified.

These findings highlight the importance of CPO surveillance in both hospitals and the community. Knowledge of risk factors for acquiring CRO including CPO will help policy makers to develop more effective strategies for the prevention and control of carbapenem resistance, and encourage healthcare staff to notice, isolate and treat patients with CRO as quickly as possible.

Acknowledgements

Three and a half years ago, I started my PhD more than 5,500 miles away from home. I still clearly remember the first day I arrived in Edinburgh and the first time I walked into Ashworth Building, it is just like yesterday. This is a precious and bittersweet journey, and I have thoroughly enjoyed every moment of it. This journey would have never been possible without the support and encouragement of many people whom I shall endeavour to thank here.

First and foremost I would express my sincere appreciation to my supervisors Professor Mark Woolhouse and Dr Margo Chase-Topping. Thanks for providing a novice in statistics and epidemiology the opportunity to do a PhD in the group, and guiding me through every step. I am well supported by their invaluable expertise and experience. I am always inspired by their enthusiasm and highly professional dedication which I think will also stimulate me for my future career aspirations.

Many thanks to the members of my PhD Annual Review Panel, Professor Harish Nair and Dr Ian Laurenson for providing constructive feedback and suggestions for the project over the process of my PhD study.

My heartfelt gratitude goes to the staff at Health Protection Scotland and the Information Services Division in National Services Scotland for helping with and pushing the application process of data used in this work. In particular, I would like to thank Sharon Kennedy, Julie Wilson, Eleanor Anderson and Michael Lockhart for their expertise in public health and microbiology, and contribution to datasets extraction and linkage. Thanks to the electronic Data Research and Innovation Service Team for the use and maintenance of the secure analytical platform within the National Safe Haven. I would like to thank Melissa Taylor and Ruby Tabor for being the second independent reviewers of the systematic review. Thanks to Su Wang for providing papers published in Chinese databases.

I would like to thank China Scholarship Council and The University of Edinburgh for the financial support over the first three years, and Professor Mark Woolhouse for funding me afterward.

A huge thanks to all past and present members of Epigroup: Kath Tracey, Carlijn Bogaardt, Gail Robertson, Dishon Muloi, Bram van Bunnik, Bryan Wee, Jordan Ashworth, Stefan Rooke, Hannah Lepper and Alex Morgan. Thanks for being my lunch buddies, offering advice and discussion on my project and being friends. I would like to extend a particular thanks to Dr Meghan Perry for her clinical expertise, comments for drafts of this thesis, patience and humour. I am very lucky to do my PhD in a building with such a friendly and supportive atmosphere. Many thanks to the staff and students in Ashworth Laboratories for proving a clean and safe workplace, and light-hearted chats.

Special thanks go to Tahirah Yasmin, Feifei Zhang, Ning Zhao, Xiali Ding, Shuzhen Xiao, Lu Lu, Wei Huang and Mengyu Cao. I credit these friends for always lending an ear, providing a story to laugh at, offering nice food, travelling together and keeping me sane along the way, even though some of them are more than 5,000 miles away from me.

Thank you to my Master's supervisors, Dr Lizhong Han and Professor Yuxing Ni for their constant guidance and support to my PhD study. As an employee in Xiangya Hospital Central South University, I am extremely grateful to all my colleagues for their substantial support and encouragement which make me one of the team when I study abroad.

Finally, I feel immensely grateful to my beloved parents and grandparents for their endless love, support and belief in me. No matter the ups and downs, I know I could always rely on their hugs, jokes, smiles and homemade food. I am so proud of being their child. 我最亲爱的爸爸妈妈、外公外婆，谢谢你们，

我爱你们!

List of abbreviations

95%CI	95% confidence interval
AICc	corrected Akaike Information Criterion
antimicrobial agents	
AK	amikacin
AMC	amoxicillin-clavulanate
AMP	ampicillin
AMS	ampicillin-sulbactam
AMX	amoxicillin
ATM	aztreonam
CAZ	ceftazidime
CIP	ciprofloxacin
CTR	ceftriaxone
CTX	cefotaxime
ETP	ertapenem
FOX	cefoxitin
GM	gentamicin
IPM	imipenem
MEM	meropenem
SCF	cefoperazone-sulbactam
TMP	trimethoprim
TMP-SMX	trimethoprim-sulfamethoxazole
TZP	piperacillin-tazobactam
aOR	adjusted odds ratio
APACHE II	Acute Physiology And Chronic Health Evaluation II
CAI	community-acquired infection
carbapenemases	
AIM	Australia imipenemase
GES	Guiana extended spectrum
GIM	German imipenemase
IMI	imipenem-hydrolyzing β-lactamase
IMP	imipenemase
KHM	Kyorin University Hospital imipenemase
KPC	*Klebsiella pneumoniae* carbapenemase
NDM	New Delhi metallo-β-lactamase
NMC	non-metalloenzyme carbapenemase
OXA	oxacillinase
SIM	Seoul imipenemase
SME	*Serratia marcescens* enzyme
SPM	Sao Paulo metallo-β-lactamase
VIM	Verone integron-encoded metallo-β-lactamase
CCI	Charlson Comorbidity index
CLSI	Clinical and Laboratory Standards Institute
COPD	chronic obstructive pulmonary disease
CPE	carbapenemase-producing Enterobacteriaceae
CPO	carbapenemase-producing organisms
CRE	carbapenem-resistant Enterobacteriaceae

CRE-CRAB-CRPsA	carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*
CRO	carbapenem-resistant organisms
CSO	carbapenem-susceptible organisms
CVC	central venous catheter
E. coli	*Escherichia coli*
ESBL	extended-spectrum β-lactamases
EUCAST	European Committee on Antimicrobial Susceptibility Testing
HAI	hospital-acquired infection
HCAI	healthcare-associated infection
HDU	high dependency unit
HIV	human immunodeficiency virus
HPS	Health Protection Scotland
ICU	intensive care unit
IQR	interquartile range
LASSO	Lease Absolute Shrinkage and Selection Operator
MRSA	Methicillin-resistant *Staphylococcus Aureus*
NHS	National Health Service
NHS Boards	
AA	Ayrshire & Arran
BR	Borders
DG	Dumfries & Galloway
FF	Fife
FV	Forth Valley
GGC	Greater Glasgow & Clyde
GN	Grampian
HG	Highland
LN	Lanarkshire
LO	Lothian
OR	Orkney
SH	Shetland
TY	Tayside
WI	Western Isles
non-CPO	organisms not producing carbapenemase
OR	odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SD	standard deviation
SMD	standardised mean difference
SOFA	Sequential Organ Failure Assessment
UTI	urinary tract infection
VIF	variance inflation factor
VRE	vancomycin-resistant *Enterococci*
WHO	World Health Organization

Contents

List of Figures

List of Tables

List of Appendices

Chapter 1 Introduction

1.1 Emergence of carbapenem resistance

1.1.1 Development of carbapenems

Bacterial β-lactamases emerged and threatened the use of penicillin in the late 1960s (Cole, 1980; Rolinson, 1991). In 1976, scientists discovered the first β-lactamase inhibitors, olivanic acids, a natural product of *Streptomyces olivaceus*. However, they had poor chemical instability and penetration into the bacterial cell (Hood et al., 1979). Searches for other β-lactamase inhibitors identified two agents: clavulanic acid and thienamycin. Thienamycin was the first "carbapenem", naturally generated from *Streptomyces cattleya* (Birnbaum et al., 1985). It is not clinically useful due to instability in aqueous solution, sensitivity to mild base hydrolysis (above pH 8.0), and highly reactive to nucleophiles (Kahan et al., 1979), but it serves as the parent or model compound for all carbapenems. After that, clinically useful carbapenems were developed. Structurally, carbapenems are similar to penicillins but have some unique substitutions (Knapp and English, 2001), which confer enhanced Gram-negative coverage and activity as compared with other β-lactams as well as stability against extended-spectrum β-lactamases (ESBL) which are capable of hydrolysing almost all β-lactam antibiotics. Carbapenems have been proven to have low oral bioavailability and must be administered intravenously or intramuscularly because they cannot cross the gastrointestinal membranes readily (Papp-Wallace et al., 2011).

Carbapenems currently on the market are imipenem-cilastatin, meropenem, ertapenem, doripenem, biapenem and panipenem/betamipron (Codjoe and Donkor, 2018). Additionally, novel carbapenems such as razupenem, tebipenem, tomopenem and sanfetrinem are under development. Due to lack of the 1-β methyl group which confers resistance to renal hydrolysis by dehydropeptidase I (Knapp and English, 2001), imipenem must be administered with dehydropeptidase I inhibitor cilastatin. Panipenem is more

stable than imipenem against hydrolysis by dehydropeptidase I; however, it is still susceptible to hydrolysis by dehydropeptidase I, and is therefore administrated with a dehydropeptidase I inhibitor, betamipron. Carbapenems exhibit broad spectrum activity against Gram-negative bacilli and somewhat narrower activity against Gram-positive bacteria. In general, imipenem, panipenem and doripenem are effective against Gram-positive bacteria while meropenem, ertapenem, biapenem and doripenem are more potent against Gram-negative bacilli. In the UK, imipenem-cilastatin, meropenem and ertapenem are licensed in clinical practice.

- Imipenem was the first carbapenem developed in 1979 and was approved for clinical use in the United States in 1985 and in the United Kingdom (UK) in 2009 (Medicines and Healthcare products Regulatory Agency) (Figure 1-1). It is available in both intravenous and intramuscular formulations. Imipenem-cilastatin is particularly important for its activity against *Pseudomonas aeruginosa*, however, it is not active against Methicillin-resistant *Staphylococcus Aureus* (MRSA) (Papp-Wallace et al., 2011).

- Meropenem was approved for clinical use in the United States in 1996 and in the UK in 2010 (Medicines and Healthcare products Regulatory Agency) (Figure 1-1). It is just available in intravenous formulations. Meropenem is not as potent as imipenem or doripenem against *Acinetobacter baumannii* (Papp-Wallace et al., 2011).

- Ertapenem was launched in the United States in 2001 and in the UK in 2004 (Scottish Medicines Consortium) (Figure 1-1). It has longer elimination half-life than imipenem-cilastatin and meropenem, so is used as a long-acting carbapenem. It can be administered either intravenously or intramuscularly. Notably, ertapenem has limited activity against *Pseudomonas aeruginosa*, *Acinetobacter spp.*, MRSA and *Enterococci* (Di Modugno et al., 1994).

- Doripenem was launched in Japan in 2005 and approved for in the United States in 2007 (Figure 1-1). In the UK, doripenem was granted marketing authorisation in 2009, however, it was withdrew in 2014 due to lower cure rates and higher death rates compared with imipenem-cilastatin (Scottish Medicines Consortium, 2014; European Medicines Agency, 2014). It has similar activity as imipenem against Gram-positive bacteria and meropenem against Gram-negative bacilli, but it has lower minimum inhibitory concentration and higher blood concentration and longer half-life than imipenem and meropenem against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (Mandell, 2009; Bassetti et al., 2009). Additionally, doripenem is the carbapenem least susceptible to hydrolysis by carbapenemases (Queenan et al., 2010).

Due to the low activity of ertapenem against *Pseudomonas spp.*, the antipseudomonal carbapenems in clinical use worldwide comprise imipenem, meropenem and doripenem.

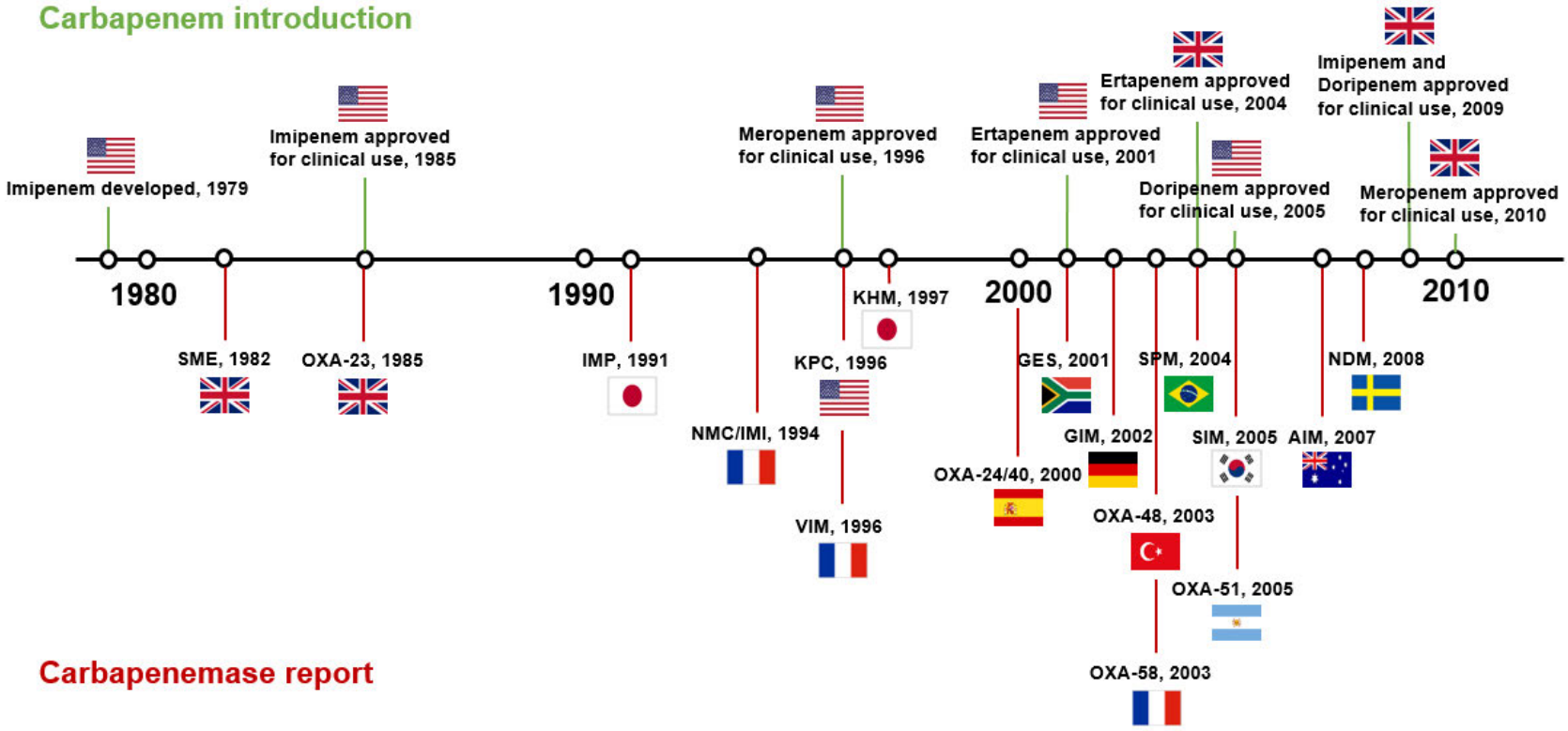


Figure 1-1. Timeline of introduction of carbapenems and first report of carbapenemases worldwide. The flags indicate the countries where carbapenems were first approved for clinical use worldwide, and the countries where carbapenemases were first reported from. The year in which each carbapenem was first licensed in the United Kingdom is also shown in this figure.

Source: (Medicines and Healthcare products Regulatory Agency; Scottish Medicines Consortium)

1.1.2 Mechanisms of carbapenem resistance

Due to their potent antibacterial activity, stability against β-lactamases, fewer adverse effects and concentration-independent killing effect, carbapenems are utilised as the last line agents for treating severe infections caused by multidrug-resistant organisms. In clinical practice, carbapenem resistance in Gram-negative bacilli comprising Enterobacteriaceae (e.g. *Escherichia coli*, *Klebsiella pneumonia*) and non-fermenters (non-glucose-fermenting Gram-negative bacilli, e.g. *Pseudomonas aeruginosa*, *Acinetobacter baumannii*) is of greatest concern. Of note, carbapenem resistance is intrinsic in some bacteria (*Stenotrophomonas spp.*, *Proteus spp.*, *Providencia spp.* and *Morganella spp.*) (Clinical and Laboratory Standards Institute, 2019). These bacteria are opportunistically pathogenic and not common among species of clinically importance. *Stenotrophomonas maltophilia* that possesses the endogenous metallo-beta-lactamases L1 is the only organism occasionally associated with hospital acquired infections (Sanchez, 2015). In addition, *Morganella morganii*, *Proteus spp.* and *Providencia spp.* have intrinsic imipenem resistance.

In general, resistance to carbapenems arises from two mechanisms: enzymatic or non-enzymatic. The enzymatic mechanism is production of carbapenemases. Non-enzymatic mechanisms include decreased outer membrane permeability or over-expression of efflux pumps with or without production of an ESBL and/or AmpC. Several studies have suggested that carbapenem resistance introduced by porin (components of outer membrane) defects is unstable. This could result from lower fitness and decreased growth ability of strains with an outer membrane permeability defect (Doumith et al., 2009). Additionally, carbapenem resistant strains that do not produce carbapenemases are usually less resistant to other antibiotics (Nordmann et al., 2012a) and their carbapenem resistance trait is not transferable. For this reason, carbapenem resistance arising from a non-enzymatic mechanism are considered of less clinical concern than carbapenemase production.

1.1.2.1 Carbapenemase mediated carbapenem resistance

Carbapenemases are able to inactivate carbapenems together with other β-lactam antibiotics, conferring high level resistance to most clinically used antibiotics. Carbapenemases are encoded by genes frequently carried on horizontally transferable mobile genetic elements such as plasmids and transposons that also carry genes encoding for other resistance determinants. Carbapenemase producers have largely been responsible for the rapid worldwide spread of carbapenem resistance (Nordmann, 2014).

According to Ambler's structural classification based on analogies of the peptide sequence (Ambler, 1980), β-lactamases are classified in 4 groups, A to D. Enzymes of groups A, C, and D are serine enzymes, while group B enzymes are metallo-beta-lactamases. Carbapenemases belong to group A, B, and D. Ambler class A carbapenemases consist of *Klebsiella pneumoniae* carbapenemase (KPC), *Serratia marcescens* enzyme (SME), non-metalloenzyme carbapenemase (NMC)/imipenem-hydrolyzing β-lactamase (IMI) and Guiana extended spectrum (GES). Ambler class B carbapenemases include imipenemase (IMP), Verone integron-encoded metallo-β-lactamase (VIM), New Delhi metallo-β-lactamase (NDM), German imipenemase (GIM), Sao Paulo metallo-β-lactamase (SPM), Seoul imipenemase (SIM), Australia imipenemase (AIM) and Kyorin University Hospital imipenemase (KHM). Ambler class D carbapenemases are the oxacillinase (OXA) β-lactamases, consisting of many variants. Although class C enzymes are not carbapenemases per se as their hydrolytic activity against carbapenems is very weak or non-existent, they can play a role in resistance to carbapenems in the context of permeability defects (Meletis, 2016). The principal characteristics and geographical epicentres of carbapenemases according to Ambler class are listed in Table 1-1.

Table 1-1. Characteristics and epicentres of carbapenemases

Ambler class	Enzymes	First Discovery	Location of encoding genes	Common Species	Geographical Epicentres¶
A	KPC	1996, USA (Yigit et al., 2001)	Plasmid	*Klebsiella pneumoniae*	USA, Greece, Italy, Israel, China (Yigit et al., 2001; Navon-Venezia et al., 2009; Nordmann et al., 2009; Borer et al., 2009; Patel et al., 2008; Schwaber et al., 2008; Logan and Weinstein, 2017)
	SME	1982, UK (Yang et al., 1990)	Chromosome	*Serratia marcescens*	USA (Troillet et al., 1999)
	NMC/IMI	1994, France (Naas et al., 1994)	Chromosome, plasmid	*Enterobacter spp.*	France, Argentina, USA, UK (Rasmussen et al., 1996; Naas et al., 1994; Radice et al., 2004)
	GES	2001, South Africa (Poirel et al., 2000a)	Plasmid	*Pseudomonas spp.* *Acinetobater spp.* Enterobacteriaceae	Africa, USA, Asia (Poirel et al., 2001; Poirel et al., 2002; Wachino et al., 2004; Pasteran et al., 2005; Duarte et al., 2003)
B	IMP	1991, Japan (Ito et al., 1995)	Plasmid	*Pseudomonas spp.* *Acinetobater spp.* Enterobacteriaceae	Taiwan, east of China, Japan, Greece (Hung et al., 2013; Koyano et al., 2013; Zhao and Hu, 2011b; Logan and Weinstein, 2017)
	VIM	1996, France (Poirel et al., 2000b)	Plasmid	*Pseudomonas spp.* Enterobacteriaceae	Southern Europe (Greece, Spain, Italy), Southeast Asia (South Korea, Taiwan) (Zhao and Hu, 2011a; Logan and Weinstein, 2017)
	NDM	2008, Sweden (Yong et al., 2009)	Plasmid	Enterobacteriaceae *Acinetobater spp.*	Indian subcontinent, Pakistan, Middle East (Yong et al., 2009; Kumarasamy et al., 2010; Nordmann et al., 2011; Livermore et al., 2011; Poirel et al., 2011; Logan and Weinstein, 2017)
	GIM	2002, Germany (Castanheira et al., 2004)	Non-transferable plasmids	*Pseudomonas spp.* Enterobacteriaceae	Germany (Rieber et al., 2012; Hamprecht et al., 2013)
	SPM	2004, Brazil (Poirel et al., 2004c)	Plasmid	*Pseudomonas spp.*	Brazil (Poirel et al., 2004c; Zavascki et al., 2005b)
	SIM	2005, South Korea (Lee et al., 2005)	Plasmid	*Acinetobater spp.*	South Korea (Lee et al., 2005)
	AIM	2007, Australia (Yong et al., 2007)	Plasmid	*Pseudomonas spp.*	Australia (Yong et al., 2007)
	KHM	1997, Japan (Sekiguchi et al., 2008)	Plasmid	*Citrobacter freundii*	Japan (Sekiguchi et al., 2008)
D	OXA-23-like (OXA-23/27/49)	1985, UK (Paton et al., 1993)	Chromosome, plasmid	*Acinetobater spp.*	China, South Korea, South America, Saudi Arabia, UK (Carvalho et al., 2009; Turton et al., 2005; Jeon et al., 2005; Lee et al., 2013b)
	OXA-24/40-like (OXA-24/40/25/26/72)	2000, Spain (Bou et al., 2000)	Chromosome, plasmid	*Acinetobater spp.*	Spain, Portugal, Belgium, USA (Da Silva et al., 2004; Bou et al., 2000; Zarrilli et al., 2009; Lolans et al., 2006)
	OXA-48-like (OXA-48/54/181)	2003, Turkey (Poirel et al., 2004b)	Plasmid	Enterobacteriaceae	Turkey, Germany, Middle East, South America, India, Italy (Carrer et al., 2010; Nordmann, 2014; Poirel et al., 2004b; Cuzon et al., 2010; Castanheira et al., 2011)
	OXA-51-like (OXA-51/69)	2005, Argentina (Brown et al., 2005)	Chromosome, plasmid	*Acinetobater spp.*	Taiwan (Chuang et al., 2014)
	OXA-58-like (OXA-58/96)	2003, France (Poirel et al., 2005)	Chromosome, plasmid	*Acinetobater spp.*	Europe, Argentina, Kuwait (Zarrilli et al., 2009; Coelho et al., 2006; Marque et al., 2005)

¶ Countries or regions either where bacteria producing such carbapenemases were mainly reported from or where the reported incidences of bacteria producing such carbapenemases were endemic, nationwide distribution, significant outbreaks or regional spread.

1.1.2.2 Non-carbapenemase mediated carbapenem resistance

In contrast to carbapenemase production, the non-enzymatic mechanism of carbapenem resistance is frequently associated with a loss in fitness to the organism and reduced transmissibility. These mechanisms include loss of expression of porin-encoding genes, mutations in chromosomally encoded porin genes, and overexpression of genes encoding efflux pumps. There are some differences of non-carbapenemase mediated carbapenem resistance between Enterobacteriaceae and non-fermenters.

For non-carbapenemase producing carbapenem resistant Enterobacteriaceae, the mechanisms include production of ESBL and/or AmpC in conjunction with outer membrane alterations. ESBL and AmpC could hydrolyse carbapenems at low levels, but in conjunction with decreased membrane permeability or efflux pump over-expression, these enzymes are more effective at preventing carbapenems from reaching their binding targets at sufficient concentrations to exert their antibacterial effect (Livermore and Woodford, 2006; Poirel et al., 2004a; Oteo et al., 2008). For non-carbapenemase producing carbapenem resistant non-fermenters, the mechanisms often work synergistically, consisting of efflux pumps, target modification and porin deficiency. The efflux pump associated with carbapenem resistance in *Acinetobacter spp.* is the chromosomally encoded AdeABC. Synergy between AdeABC and oxacillinases has been reported to result in higher levels of resistance to carbapenems (Heritier et al., 2005). MexAB-OprM is the most common pump system conferring intrinsic resistance in *P. aeruginosa*. It works together with other pump systems, like MexCD-OprJ, MexEF-OprN, MexJK-OprM and MexVW-OprM, to cause resistance to carbapenems (Poole, 2001).

Arranged by resistance mechanisms, the terms used to describe carbapenem resistance in Gram-negative bacilli are summarized in Table 1-2.

Table 1-2. Terms used to describe carbapenem resistance in Gram-negative bacilli

Term	Definition
Carbapenem-resistant organisms (CRO)	Enterobacteriaceae and non-fermenters that are resistant to carbapenems regardless of resistance mechanisms
Carbapenem-resistant Enterobacteriaceae (CRE)	Enterobacteriaceae that are resistant to carbapenems regardless of resistance mechanisms
Carbapenem-resistant non-fermenters	Non-fermenters that are resistant to carbapenems regardless of resistance mechanisms
Carbapenemase-producing organism (CPO)	Enterobacteriaceae and non-fermenters that are resistant to carbapenems due to carbapenemase production
Carbapenemase-producing Enterobacteriaceae (CPE)	Enterobacteriaceae that are resistant to carbapenems due to carbapenemase production
Carbapenemase-producing non-fermenters	Non-fermenters that are resistant to carbapenems due to carbapenemase production

1.2 Epidemiology of carbapenem resistance

An increased consumption of carbapenems has been reported worldwide in recent years (Klein et al., 2018; Rhodes et al., 2019; European centre for Disease Prevention and Control, 2018). As a result, there is an emerging global public health threat of CRO, leaving few effective therapeutic options available for multidrug-resistant organisms infections and ultimately causing high mortality and increased healthcare costs. In 2017, the World Health Organization (WHO) published a list of antibiotic-resistant bacteria that are of global priority which included carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacteriaceae (World Health Organization, 2017b). Therefore, some countries and/or regions have set up surveillance systems for CRO. Recent reviews of the epidemiology of CRO have found that the epidemiology varies geographically (Gniadek et al., 2016; van Duin and Doi, 2017), and there is still a scarcity of accurate and reliable data on CRO prevalence, outcomes, detection and infection prevention and control.

1.2.1 Prevalence and disease burden

Different methodologies used to detect carbapenem resistance and resistance mechanisms, and various antimicrobial administration and infection control and prevention measures and/or policies in both healthcare facilities and communities might account for the geographical diversity in epidemiology and disease burden of CRO. Despite these differences, it is widely reported that CRO are increasing globally and are associated with higher mortality rates, prolonged healthcare and increased healthcare costs (Falagas et al., 2014; Zilberberg et al., 2017). Moreover, in most regions carbapenem-resistant non-fermenters are the most problematic pathogens, carbapenem-resistant non-fermenters generally accounting for a higher proportion of CRO and higher resistance rates to carbapenems than CRE (Nordmann and Poirel, 2019).

1.2.1.1 North America

The 2019 report entitled 'Antibiotic Resistance Threats in the United States' listed CRE and carbapenem-resistant *Acinetobacter spp.* as urgent threats (Centers for Disease Control and Prevention, 2019). KPC is the most common carbapenemase while NDM, VIM and OXA-48 are also reported. The highest prevalence of carbapenem resistance among Gram-negative health care-associated infections in the United States, as reported by the National Healthcare Safety Network, was observed among *Acinetobacter baumannii* (62.6%) and *Pseudomonas aeruginosa* (26.1%). Among CRE, carbapenem resistance was highest among *Klebsiella pneumoniae*, at 12.8% (Sievert et al., 2013).

Compared with data in an earlier report (Centers for Disease Control and Prevention, 2013), the burden of CRE in the United States increased from 11,800 cases and 1,000 deaths in 2012 to 13,100 cases and 1,100 deaths in 2017. Infection with CRE was associated with a four-fold increased risk of receiving inappropriate empiric antimicrobial treatment, which in turn increased mortality (12%), the length of hospital stay (>5.2 days) and healthcare costs (extra $10,312) (Zilberberg et al., 2017). Furthermore, the cost associated with CRE is higher than the cost of many chronic and acute diseases, and costs rise proportionally with the incidence of CRE, increasing by 2.0 times, 3.4 times, and 5.1 times for incidence rates of 6, 10, and 15 per 100,000 persons respectively (Bartsch et al., 2017). Unlike CRE the burden of carbapenem-resistant *Acinetobacter spp.* decreased from 11,700 cases and 1,000 deaths in 2012 to 8,500 cases and 700 deaths in 2017. Despite the decline, the threat level for carbapenem-resistant *Acinetobacter spp.* was escalated to urgent because of the lack of antibiotics, both in clinical use and in development, available to treat these infections (Centers for Disease Control and Prevention, 2019).

Epidemiological data on CRO in Canada is quite limited. According to the report of the Canadian Nosocomial Infection Surveillance Program conducted between 2011-2015 in 64 acute-care hospitals (Government of Canada,

2016), the number and incidence rate of CPO infections were 16-27 and 0.033-0.041 per 10,000 patient-days while the number and incidence rate of CPO colonisations were 21-36 and 0.032-0.087 per 10,000 patient-days. All-cause 30-day mortality rate was 12.5-27.3 per 100 CPO cases. The most common carbapenemases were KPC (66.9% per year) and NDM-1 (17.3% per year), with a significant increase in OXA-48 between 2010 and 2014 (Mataseje et al., 2016).

1.2.1.2 Europe

Data from the European Antimicrobial Resistance Genes Surveillance Network and its predecessor the European Survey of Carbapenemase-Producing Enterobacteriaceae show that the situation for CPE worsened between 2010 and 2018 (Brolund et al., 2019). Increases in the epidemiological stage (stage 0-5: no case reported, sporadic occurrence, hospital outbreaks, regional spread, interregional spread and endemic) between 2015 and 2018 were observed in 11 out of the 37 participating countries, with 15 countries reporting interregional spread or an endemic situation (Brolund et al., 2019). KPC, NDM, OXA-48 and VIM were widely distributed carbapenemases. However, 29.3% (353/1203) of *Klebsiella pneumonia* and 60.3% (117/194) of *Escherichia coli* (*E. coli*) isolates were confirmed to have other resistance mechanisms as well (Grundmann et al., 2017). *E. coli* with resistance to carbapenems remained rare but showed a significantly increasing trend in Europe, ranging from 0% to 2.0% between countries. For *Klebsiella pneumoniae*, the national percentages of resistant isolates ranged from 0% to 63.9 % while for *Pseudomonas aeruginosa* and *Acinetobacter spp.* percentages of resistant isolates ranged from 0% to 55.1% and from 0% to 95.5% respectively in 2018 (European Centre for Disease Prevention and Control, 2019c). One survey conducted between May 2015 and June 2017 including 211 laboratories in 20 European countries and showed that 60 laboratories (36%) reported an outbreak of CRE during one of the two years preceding the completion of the survey. Rates of carbapenem resistant *Acinetobacter spp.* above 50% were reported by 74 laboratories (47%), particularly in the Western Balkan countries where the

rates were higher than 90% (Kostyanev et al., 2019). The highest percentages of carbapenem resistance were reported from southern and south-eastern European countries, a pattern that has also been reflected by point prevalence survey of healthcare-associated infection (HCAI) and antimicrobial use in European acute care hospitals (Plachourasi et al., 2018; Cassini et al., 2019).

According to the European Centre for Disease Prevention and Control study of the disease burden of antimicrobial resistance, CRO accounted for 16.0% (107,801 of 671,689) of infections caused by antibiotic-resistant bacteria, 26.5% (8,777 of 33,110) of attributable deaths and 31.5% (53.5 of 170) of the total disability-adjusted life-years per 100,000 population, respectively (Cassini et al., 2019). Of note, carbapenem-resistant *Klebsiella pneumoniae* had a high burden of disease because of its higher attributable mortality, and the burden increased the most (by 6 fold) in terms of number of infections and number of deaths between 2007 and 2015. In addition, the burden of infections with CRO was focused in the southern and eastern part of Europe: Italy, Greece, Croatia, Bulgaria and Hungary in particular. The proportion of disability-adjusted life-years due to all CRO increased from 18% (56,150 of 311,715) in 2007 to 28% (185,421 of 678,845) in 2015 (Cassini et al., 2019), indicating the emergence and rapid increase of CRO in Europe during this period. In terms of carbapenem usage in Europe, carbapenems ranked second among the most commonly antimicrobial prescriptions used for the treatment of HCAI (9.9%) (Plachourasi et al., 2018).

1.2.1.3 Asia-Pacific

In South and Southeast Asia, where the rates of carbapenem resistance are some of the highest in the world, estimated prevalence of carbapenem-resistant *Acinetobacter baumannii* ranged from 1% to >90% and that of carbapenem-resistant *Pseudomonas aeruginosa* ranged from 23.3% to 46.7% (Kiratisin et al., 2012; Sheng et al., 2013). Carbapenem resistance rates in Enterobacteriaceae have been lower (0.4%-25.0%) than those in carbapenem-resistant *Acinetobacter baumannii/Pseudomonas aeruginosa*, but longitudinal studies have shown dramatic increases in resistance rates

over time (Kiratisin et al., 2012; Sheng et al., 2013). Regional resistance surveillance programme results for 12 Asia-Pacific nations in 2011 indicated that carbapenem resistance rates for *Klebsiella spp.* ranged from 0% to 25% and carbapenem-resistant *Pseudomonas aeruginosa* from 0% to 50%, highest in Philippines (50%) (Mendes et al., 2013). Metallo-beta-lactamases (mainly NDM, IMP and VIM) and OXA-48 predominated in this region. In East Asia, the 2018 report from Japan Nosocomial Infections Surveillance which include 1,947 facilities reported that the non-susceptible rates to imipenem and meropenem were 0.2% and 0.1% for *E. coli*, 0.7% and 0.6% for *Klebsiella pneumonia*, 0.0-5.3% and 0.2-1.4% for other Enterobacteriaceae species, 19.8% and 15.9% for *Pseudomonas aeruginosa*, and 2.1% and 1.6% for *Acinetobacter baumannii*, respectively (Japan Nosocomial Infections Surveillance, 2018). The report from China CRE network covering 25 tertiary hospitals in 14 provinces found that the incidence of CRE infection in China was 4.0 per 10,000 discharges and the overall hospital mortality rate was 33.5% (Zhang et al., 2018). A five-year study from the same network showed that the overall in-hospital and 14-day mortality rates of bacteremia caused by CRE were 32.9% and 31.1%, respectively (Wang et al., 2019). KPC- and metallo-beta-lactamases-type carbapenemases were widespread in China.

Compared with the above regions, disease burden of CRO in New Zealand and Australia is relatively low currently. However, the rate of CPE colonisation and infection has increased sharply in recent years, and nearly all CPE have been imported from overseas (Australian Commission on Safety and Quality in Health Care, 2017; Blakiston et al., 2017). In New Zealand, the incidence of CPE has increased from three isolates in 2012 to 45 in 2016. The most common carbapenemases were NDM and OXA-48, accounting for 59% and 31% respectively of all carbapenemases identified in Enterobacteriaceae in New Zealand (Ministry of Health New Zealand Goverment, 2018). Carbapenemases commonly identified in clinical isolates in Australia include IMP, NDM, VIM, KPC and OXA48-like (Australian Commission on Safety and Quality in Health Care, 2017). The mortality rate associated with the first documented outbreak of CPE in Australia, involving 10 cases identified in the

seven months to December 2012, was 40% (Australian Commission on Safety and Quality in Health Care, 2017). Given this rapid growing public health threat, both governments issued relevant guides for screening and infection control and prevention management for CPE (Australian Commission on Safety and Quality in Health Care, 2017; Ministry of Health New Zealand Goverment, 2018).

1.2.1.4 Latin America

Recent surveillance in Latin America reveals that rates of carbapenem resistance range up to 66% for *Pseudomonas aeruginosa* and as high as 90% for *Acinetobacter baumannii* isolates across the different countries of Latin America, with the resistance rate among *Acinetobacter baumannii* isolates greater than 50% in many countries (Vincent et al., 2009; Gales et al., 2011). The percentages of *Pseudomonas aeruginosa* isolates non-susceptible to meropenem and imipenem were 43% and 48%, respectively, which compares unfavourably with *Pseudomonas aeruginosa* isolates collected in Europe (24% and 30%, respectively) and North America (11% and 15%, respectively) during the same period (Unal and Garcia-Rodriguez, 2005). In Latin America, the mortality rate among patients with nosocomial infections caused by metallo-beta-lactamases carrying *Pseudomonas aeruginosa* has been reported as greater than 50% (Zavascki et al., 2006b).

Even though information about the prevalence of carbapenemases in Latin America is scarce, a review of the literature on different classes and types of carbapenemases (Maya et al., 2013), including their current dissemination through the Latin American region concluded that carbapenemases belonging to all of the three classic classes (A, B and D) have been identified all over the Latin American region. New enzymes belonging to this group, as well as the ones that have been described in other regions around the world, are continuously being reported in Latin American countries (Maya et al., 2013).

1.2.1.5 Africa

Whilst the epidemiology of CRO has been widely described and reported in detail in the above regions since their emergence, sparse data are available and relatively little is known about the spread and distribution of CRO in Africa (World Health Organization, 2018). To inform the gaps, several studies have retrospectively reviewed the published work conducted in this region.

Most studies were conducted in North Africa (74%, 61/83), followed by Southern Africa (12%, 10/83). CPO were isolated from humans, the hospital environment and community environmental water samples. The prevalence of CPO in hospital settings ranged from 2.3% to 67.7% in North Africa and from 9% to 60% in sub-Saharan Africa. The carbapenemases detected comprised KPC, metallo-beta-lactamases, and OXA-48/58/163/181 (Manenzhe et al., 2015).

In East Africa, Tanzania exhibited the highest level of carbapenem resistance at 35% while Democratic Republic of Congo had the lowest level at 1%. Uganda was the only country with studies documenting carbapenem resistance obtained amongst hospital environment with incidence ranging from 21% in *Pseudomonas aeruginosa* to 55% in *Acinetobacter baumannii*. Carbapenem resistance was more common in *Acinetobacter baumannii* (23%), followed by *Pseudomonas aeruginosa* (17%), *Klebsiella pneumoniae* (15%), *Proteus mirabilis* (14%) and *E. coli* (12%) mainly isolated from respiratory tract, blood, urine and wound/pus. The regional carbapenemases detected were IMP, VIM-1, SPM-1, NDM-1, OXA-23/24/58 and KPC (Ssekatawa et al., 2018).

A review of carbapenem-resistant *E. coli*/*Klebsiella spp.* including data from 22 African countries highlighted data gaps in sub-Saharan Africa (Mitgang et al., 2018). Estimated crude median national carbapenem resistance proportions (>1%) for *E. coli*/*Klebsiella spp.* were reported from Uganda, Mauritania, Nigeria, Ethiopia, Madagascar, Kenya and Cameroon. The carbapenemases (or mechanism) accounted for carbapenem resistance included OXA, NDM,

VIM, IMP, KPC, DIM, GES and Porin-related mechanisms (Mitgang et al., 2018).

1.2.2 Detection

Antimicrobial susceptibility testing is the initial step for detection of carbapenem resistance, including disk diffusion, broth microdilution, E-test and automated systems. The results are interpreted according to the recommendations from Clinical and Laboratory Standards Institute (CLSI) (Clinical and Laboratory Standards Institute, 2019) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) (The European Committee on Antimicrobial Susceptibility Testing, 2019) guidelines (Table 1-3). Although the guidelines have lowered the breakpoints values to permit better detection of carbapenemases, using these breakpoints could still miss some carbapenemase producers like OXA-48/OXA-181 or KPC (Potron et al., 2011; Gagetti et al., 2016). There is no consensus on the cut-off breakpoint values of carbapenems that should be applied for carbapenemase activity. When a strain shows non-susceptibility (i.e., intermediate or resistant) to carbapenems in antimicrobial susceptibility testing, the mechanisms of resistance still remains unknown. Therefore, detection of carbapenemase production and/or presence of other resistance mechanisms are required. In practice, detection of carbapenemase comprise phenotypic and genotypic approaches.

Table 1-3. Breakpoints for carbapenems according to CLSI and EUCAST guidelines (as of December 2019)

Antimicrobial Agent	Zone Diameter Breakpoints (mm)						Minimum inhibitory concentration Breakpoints (µg/mL)					
	CLSI			EUCAST			CLSI			EUCAST		
	R	I	S	R	I	S	R	I	S	R	I	S
Enterobacteriaceae												
Doripenem	≤19	20-22	≥23	/	/	/	≥4	2	≤1	/	/	/
Ertapenem	≤18	19-21	≥22	<25	/	≥25	≥2	1	≤0.5	>0.5	/	≤0.5
Imipenem	≤19	20-22	≥23	<17	/	≥22	≥4	2	≤1	>4	/	≤2
Meropenem	≤19	20-22	≥23	<16	/	≥22	≥4	2	≤1	>8	/	≤2
Pseudomonas spp.												
Doripenem	≤15	16-18	≥19	/	/	/	≥8	4	≤2	/	/	/
Imipenem	≤15	16-18	≥19	<20	/	≥20	≥8	4	≤2	>4	/	≤4
Meropenem	≤15	16-18	≥19	<18	/	≥24	≥8	4	≤2	>8	/	≤2
Acinetobacter spp.												
Doripenem	≤14	15-17	≥18	/	/	/	≥8	4	≤2	/	/	/
Imipenem	≤18	19-21	≥22	<21	/	≥24	≥8	4	≤2	>4	/	≤2
Meropenem	≤14	15-17	≥18	<15	/	≥21	≥8	4	≤2	>8	/	≤2

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; R, resistant; I, intermediate; S, susceptible.

1.2.2.1 Phenotypic methods

A series of phenotypic tests has been developed for detection of carbapenemases, however, none of them has 100% sensitivity or 100% specificity. The advantages and disadvantages are summarised in Table 1-4.

The modified Hodge test is a phenotypic method recommended by CLSI which is based on whether the growth of indicator strain is affected by the test strain with an inactivation effect on carbapenems via carbapenemase production. The indicator strain is streaked to an agar plate first and then a 10 µg meropenem or ertapenem susceptibility disk is placed in the centre of the plate. The test strain is streaked from the edge of the disk to the edge of the plate in a straight line. After 16-24 hours of incubation, examine the plate for a clover leaf-type indentation at the intersection of the test strain and the indicator strain, within the zone of inhibition of the carbapenem susceptibility disk. This method usually works well for the detection of KPC and OXA-48 production but lacks sensitivity and specificity in detecting metallo-beta-lactamases. Moreover, this method is time-consuming as it requires at least 24-48 h. Additionally, carbapenemase-inhibition tests using molecules that inhibit the activity of carbapenemases is also an approach. Inhibition by ethylenediaminetetraacetic acid or dipicolinic acid are used for metallo-beta-lactamases detection while boronic acid is applied for KPC detection. However, these tests are not suitable for detection of carbapenemase producers among AmpC-positive species such as *Enterobacter spp.* or OXA-48/OXA-181 producers (Giske et al., 2011).

Another technique recommended by CLSI is the modified carbapenem inactivation method. This method detects the carbapenemase production of the test strain by measuring the growth of an indicator strain with a carbapenem which is inactivated by the test strain. Despite good sensitivity and specificity, this method is time-consuming as it requires at least 24-32 h (van der Zwaluw et al., 2015).

Colorimetric assay is a faster test with lower false-positive rate than modified Hodge test. The change of color corresponds to the change in pH of the reaction system caused by carbapenemase hydrolysis of carbapenems (Nordmann et al., 2012c). A variety of commercial colorimetric products are available like Carba NP test, Rapid Carb Blue Kit and Rosco Rapid Carb Screen. However, this technique is insufficiently sensitive for the detection of OXA-48 production (Tamma et al., 2017b).

Spectrophotometric assay is reported as an accurate method to detect carbapenemases which measure the hydrolysis of carbapenems at a specific wavelength (Takeuchi et al., 2018). This approach can differentiate carbapenemase-mediated carbapenem resistance and non-carbapenemase-mediated carbapenem resistance with high sensitivity and specificity. But it cannot discriminate different carbapenemase types and the extraction of carbapenemase is time-consuming, taking 12-18 h.

Matrix-assisted laser desorption ionization time-of-flight mass spectrometry is an increasing widely used method to detect carbapenemases by analysing the degradation spectrum of carbapenem hydrolysis (Burckhardt and Zimmermann, 2011). However, the technique requires expensive equipment.

1.2.2.2 Genotypic methods

Genotypic methods based on molecular techniques are reference or gold standards for detection of both enzymatic and non-enzymatic carbapenem resistance mechanisms and identification of specific carbapenemase types. Polymerase chain reaction is the most widely used traditional genotyping method, with more efficient methods, such as multiplex polymerase chain reaction and real-time polymerase chain reaction also available. Various commercial assays or systems based on polymerase chain reaction are available (Ledeboer et al., 2015; Cunningham et al., 2016), including GeneXpert platform, Check-Points system and Verigene. Whole genome sequencing is more widely used in recent years as it allows detection of both carbapenemase encoding genes and other associated resistance

mechanisms. However, these advanced approaches requires expertise, well-trained technicians and financial support. The advantages and disadvantages are summarised in Table 1-4.

Overall, using the genotypic methods as gold standards, sensitivity and specificity of these phenotypic methods ranged from 70% to >90% (Lutgring and Limbago, 2016; Cui et al., 2019; Nordmann and Poirel, 2019).

Table 1-4. Summary of advantages and disadvantages of different detection methods for carbapenemase production

Methods	Advantages	Disadvantages
Phenotypic methods		
Modified Hodge test	• KPC and OXA-48 production • Cost-effective • Good operability	• Insufficient for metallo-beta lactamases • Time-consuming • False-positive/negative
Carbapenemase-inhibition tests	• Cost-effective • Good operability	• Not suitable for AmpC-positive species • Not suitable for OXA-48/OXA-181 • Time-consuming
Modified carbapenem inactivation method	• All carbapenemases • Cost-effective • Good operability	• Time-consuming
Colorimetric assay	• KPC and metallo-beta lactamases • Cost-effective • Good operability	• Insufficient for OXA-48 • Time-consuming
Spectrophotometric assay	• High sensitivity and specificity • Differentiate resistance mechanisms • Time-saving	• Not suitable for discriminating carbapenemase types • Specific equipment • Variety of inflecting factors
Matrix-assisted laser desorption ionization time-of-flight mass spectrometry	• KPC and NDM • Time-saving • Good operability	• Insufficient for OXA-48 • Specific and expensive equipment • No acknowledged protocol and standard
Genotypic methods		
Polymerase chain reaction-based methods and whole genome sequencing	• Reference standard • All resistance mechanisms • Discriminating carbapenemase types	• Specific and expensive equipment • Expertise and well-trained technicians • Not suitable for novel mechanisms

Source: (Cui et al., 2019; Nordmann and Poirel, 2019)

1.2.3 Risk factors for acquiring carbapenem resistance

From both clinical and epidemiological perspectives, a comprehensive understanding of risk factors for acquiring CRO (i.e. infection or colonisation) is fundamental to designing infection prevention and control policies and helping healthcare staff make more effective judgements and select rational prophylactic/therapeutic options. Additionally, a thorough understanding of the risk factors will help to predict an individual's risk of CRO acquisition, through early identification of high risk populations and thus to prevent spread of CRO.

Many risk factors contribute to CRO acquisition and they can be generally classified into two groups: (1) patient-specific factors and (2) healthcare-associated factors. Patient-specific factors include demographic characteristics such as age, gender, ethnicity and comorbidities. Healthcare-associated factors comprise exposure to healthcare environment, invasive medical procedures undergone and previous antimicrobial treatments before CRO acquisition. Such factors include history of hospitalisation, length of intensive care unit (ICU) stay, history of surgical procedures, placement of an indwell catheter or colonization by other resistant bacteria. Nevertheless, risk factors for CRO acquisition have not been completely characterized and conflicting results have been reported in various studies conducted in different countries or healthcare facilities. The conflicting results usually result from great heterogeneity across these studies. Various factors might account for the huge heterogeneity, including study setting (such as acute healthcare facilities, long-term healthcare facilities and ICU), study design (retrospective or prospective study, case-control or cohort or cross-sectional study, active surveillance or screening), study population (such as neonates, children, adults and immunocompromised patients), definition of carbapenem resistance (such as CLSI guideline, EUCAST criteria and automatic systems), mechanism of carbapenem resistance (enzymatic and non-enzymatic), selection of cases and controls. Additionally, there are different definitions of CRO presence including acquisition (both infection and colonisation),

colonisation, infection, and the progression from colonisation to infection, amplifying the heterogeneity across studies.

To date, only one study has systematically reviewed the risk factors for CRE acquisition among hospitalized patients and quantified the effects of such risk factors by meta-analyses (van Loon et al., 2018). Moreover, the researchers also summarized the environmental sources/reservoirs and the most successful infection prevention strategies related to CRE. They found that the use of medical devices generated the highest pooled estimate for acquiring CRE (odds ratio, OR: 5.09; 95% confidence interval, 95%CI: 3.38-7.67), followed by carbapenem use (OR: 4.71; 95%CI: 3.54-6.26). To control hospital outbreaks, bundled interventions, including barrier/contact precautions used for patients colonised or infected with CRE, are needed (van Loon et al., 2018). Additionally, it is necessary to optimise the therapeutic approach, which is an important message to infectious disease specialists, who need to be actively involved in a timely manner in the treatment of patients with known CRE infections or suspected carriers of CRE (van Loon et al., 2018). Similarly, an earlier systematic review and meta-analyses investigating risk factors associated with carbapenem-resistant *Pseudomonas aeruginosa* and sources and reservoirs for the pathogen showed that carbapenem use (OR: 7.09; 95%CI: 5.43-9.25) and medical devices (OR: 5.11; 95%CI: 3.55-7.37) generated the highest pooled estimates (in 't Holt et al., 2014). Furthermore, cumulative meta-analyses indicated that the pooled estimate of carbapenem use was stable and the pooled estimate of medical devices increased with time. In multivariate analyses, use of carbapenem, use of fluoroquinolones, use of vancomycin, use of other antibiotics, having medical devices, ICU admission, having underlying diseases and length of hospital stay were significant risk factors (in 't Holt et al., 2014). Both studies highlighted the importance of prudent antibiotic stewardship and appropriate use of medical devices in curbing spread and outbreaks of CRO.

Despite the heterogeneity, a systematic review and meta-analysis based on all available evidences focusing on risk factors for different CRO acquisition

status (i.e. infection or colonisation) is still necessary to identify risk factors which are helpful for containment of CRO spread and clarifying current knowledge gaps warranting further study in the future.

1.2.4 Infection prevention and control measures

Infection prevention and control is universally acknowledged as a key component to combat the spread and outbreak of antimicrobial resistant microorganisms in healthcare systems. There is a global consensus that urgent infection prevention and control actions are needed and should be given to CRO which poses a significant public health threat worldwide (World Health Organization, 2017c). After highlighting carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (CRE-CRAB-CRPsA) as the top critical priority pathogens in the WHO publication in 2017 (World Health Organization, 2017b), WHO developed infection prevention and control guidelines for the prevention and control of CRE-CRAB-CRPsA in healthcare facilities accordingly later in the same year (World Health Organization, 2017c). The guidelines identified eight key recommendations listed below (Table 1-5) that could be applied to healthcare facility level, and these recommendations could also be used to improve the development of national policies on the infection prevention and control of CRE-CRAB-CRPsA transmission and infection within health sectors.

Table 1-5. WHO recommendations for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa (CRE-CRAB-CRPsA)

Number	Formal recommendation
1	Implementation of multimodal infection prevention and control strategies: multimodal infection prevention and control strategies should be implemented to prevent and control CRE-CRAB-CRPsA infection or colonisation and these should consist of at least the following: hand hygiene, surveillance (in particular, for CRE), contact precautions, patient isolation (single room isolation or cohorting), environmental cleaning.
2	Importance of hand hygiene compliance for the control of CRE-CRAB-CRPsA: hand hygiene best practices according to the WHO guidelines on hand hygiene should be implemented.
3	Surveillance of CRE-CRAB-CRPsA infection and surveillance cultures for asymptomatic CRE colonisation: surveillance of CRE-CRAB-CRPsA infection(s) should be performed; surveillance cultures for asymptomatic CRE colonisation should also be performed, guided by local epidemiology and risk assessment. Populations to be considered for such surveillance include patients with previous CRE colonisation, patient contacts of CRE colonised or infected patients and patients with a history recent hospitalisation in endemic CRE settings.
4	Contact precautions: contact precautions should be implemented when providing care for patients colonised or infected with CRE-CRAB-CRPsA.
5	Patient isolation: patients infected or colonised with CRE-CRAB-CRPsA should be physically separated from non-colonised or non-infected patients using single room isolation or by cohorting patients with the same resistant pathogens.
6	Environmental cleaning: compliance with environmental cleaning protocols of the immediate surrounding area (that is, the “patient zone”) of patients colonised or infected with CRE-CRAB-CRPsA should be ensured.
7	Surveillance cultures of the environment for CRE-CRAB-CRPsA colonisation/contamination: surveillance cultures of the environment for CRE-CRAB-CRPsA may be considered when epidemiologically indicated.
8	Monitoring, auditing and feedback: monitoring, auditing of the implementation of multimodal strategies and feedback pf results to health care workers and decision-makers.

Source: World Health Organization (World Health Organization, 2017c)

The European Centre for Disease Prevention and Control conducted a systematic review of the infection prevention and control of spread of CRE in 2014 (European Centre for Disease Prevention and Control, 2014). A group of experts attending meetings hosted by the European Centre for Disease Prevention and Control created a list of epidemiological risk factors placing patients “at-risk” of carriage (both colonisation and clinical infection) with CRE and constructed a list of core and supplemental infection prevention and control measures to be implemented for “at-risk” patients upon admission to healthcare settings (Magiorakos et al., 2017). According to the European Centre for Disease Prevention and Control guidance, individuals “at-risk” for carriage (both colonisation and clinical infection) of CRE included: (1) a history of an overnight stay in a healthcare setting in the last 12 months; (2) dialysis-dependent or cancer chemotherapy in the last 12 months; (3) known previous carriage (both colonisation and clinical infection) of CRE in the last 12 months; (4) epidemiological linkage to a known carrier of a CRE. Core infection prevention and control measures included antimicrobial stewardship, environmental cleaning, equipment reprocessing, faecal and medical waste management, guidelines and processes, hand hygiene, infrastructure and capacity for patient accommodation, microbiological capacity, staff education, staffing and surveillance (Magiorakos et al., 2017). Preliminary supplemental measures comprised pre-emptive isolation of patients on admission, active screening on admission and contact precautions (Magiorakos et al., 2017).

Both guidelines specified that they were putting forward recommendations and suggestions, and are in no way prescriptive for all countries and different healthcare settings. Therefore, such recommendations or suggestions could be adapted or tailored to local needs to establish local infection prevention and control measures and policies. Due to the alarming global increase in CRO and inspired by such guidelines, more and more countries have set up their own surveillance systems or programmes for antimicrobial resistance including CRO (European Centre for Disease Prevention and Control, 2019a; Ministry of Health New Zealand Goverment, 2018) or work together to build up regional

or global surveillance systems or programmes as described in the above Section 1.2.1.

1.3 Carbapenem resistance in the UK and Scotland

1.3.1 Disease burden

The disease burden of infections caused by carbapenem resistant *E.coli*, *Klebsiella pneumonia*, *Acinetobacter spp.* and *Pseudomonas aeruginosa* in disability-adjusted life-years in the UK in 2015 were lower than most countries of the European Union and European Economic Area (Cassini et al., 2019). The disability-adjusted life-years per 100,000 population, incidence per 100,000 population, mortality per 100,000 population caused by infections with these CRO were 0.10-2.43, 0.04-1.41 and 0.00-0.08, respectively (Cassini et al., 2019). A national study of CPE including 21 sentinel UK laboratories in 2013-2014 showed that 36% of CRE isolates produced carbapenemases, resulting in a national prevalence of CPE 0.02% (95%CI: 0.01%-0.03%) and incidence of CPE 0.007 per 1,000 patient-days (95%CI: 0.005-0.010) (Trepanier et al., 2017). The UK prevalence and incidence of clinically significant CPE is currently low, however, recommended infection prevention and control measures such as strict standard precautions and single en-suite room are not universally followed, notably screening high-risk patients on admission (applied by 86%), using a CPE 'flag' on patients' records (70%) and alerting neighbouring hospitals when transferring affected patients (only 30%) (Trepanier et al., 2017). Furthermore, the national percentages of carbapenem resistance increased significantly between 2015 and 2018 among *Klebsiella pneumonia* (from 0.4% to 0.7%) and *Pseudomonas aeruginosa* (from 2.4% to 6.0%) isolates (European Centre for Disease Prevention and Control, 2019c).

The reported incidence of CPE per 1,000 patient-days in Scotland (0.001) was lower than that in England (up to 0.033) and Northern Ireland (0.006) (Trepanier et al., 2017). In addition, the proportion of carbapenems among all antibacterials for systemic use was lower than that in England and Northern

Ireland according to a point prevalence survey conducted in 1,209 European acute care hospitals in 28 of 31 European Union and European Economic Area countries in 2016-2017 (Plachourasi et al., 2018). Nevertheless, the Scottish One Health Antimicrobial Use and Antimicrobial Resistance annual report showed that there has been a 39% year on year increase in the incidence of reported CPO isolates since 2013 while the secondary care use of carbapenems between 2014 and 2018 decreased by 3.9% (Health Protection Scotland, 2019b; Health Protection Scotland, 2018d). To date, up to 16 types of carbapenemases including both single carbapenemase type and carbapenemases combinations have been reported in Scotland (Health Protection Scotland, 2019b). Given the high incidence of carbapenem resistance in the surrounding countries, frequent and increasing travels between them and high transferability of carbapenemases between individuals and species, it is urgently recognised that further characterisation of CPO cases in Scotland is essential. This improved epidemic intelligence will inform interventions to reduce transmission of CPO including the further development of the national CPE admission screening policy (Health Protection Scotland, 2019b).

1.3.2 Healthcare system in Scotland

The National Health Service (NHS) Scotland consists of 14 regional NHS Boards which are responsible for the protection and the improvement of their population's health and the delivery of frontline healthcare services (Scotland's Health on the Web, 2019). The 14 regional NHS Boards are shown in Figure 1-2. The number of hospitals in each NHS Board and the midyear population estimates are listed in

Table 1-6. In addition, there are two national hospitals (Golden Jubilee National Hospital and The State Hospital). Golden Jubilee National Hospital provides quaternary cardiology, respiratory and orthopaedic services, and The State Hospital provides high security beds for detained patients, respectively. These two national hospitals are managed by a Special Health Board and provide services for the whole of Scotland.

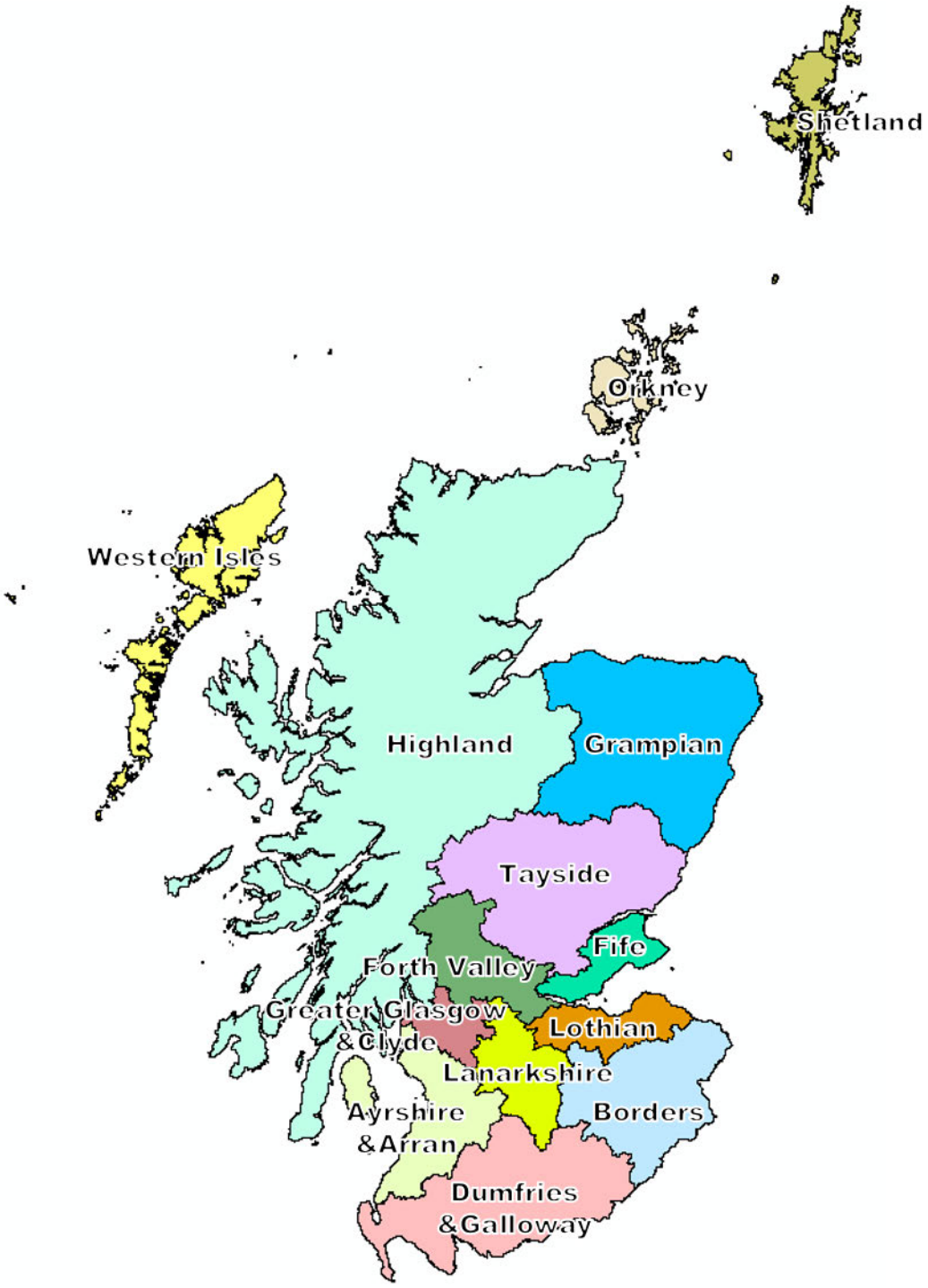


Figure 1-2. Map of National Health Service (NHS) Boards in Scotland (as of December 2019)

Table 1-6. Number of hospitals and midyear population estimates by National Health Service (NHS) Board in Scotland (as of December 2019)

NHS Board	Midyear population estimates	Number of hospitals
Ayrshire & Arran	369,670	16
Borders	115,270	15
Dumfries & Galloway	148,790	23
Fife	371,910	12
Forth Valley	306,070	8
Grampian	584,550	34
Greater Glasgow and Clyde	1,174,980	46
Highland	321,800	29
Lanarkshire	659,200	20
Lothian	897,770	36
Orkney	22,190	2
Shetland	22,990	1
Tayside	416,080	32
Western Isles	26,830	3

Source: National Records of Scotland (National Records of Scotland, 2019) and Information Services Division Scotland (Information Services Division Scotland, 2019)

1.3.3 Steps to identify CPO in Scotland

The steps to identify a CPO isolate (according to Health Protection Scotland staff Julie Wilson, personal communication by email, December 8, 2017) are illustrated in Figure 1-3. A specimen from clinical indications or surveillance programme is submitted to a diagnostic laboratory and cultured onto an agar plate. The strains that grow on the agar plate are identified by VITEK® microbial identification system. If VITEK reports the isolate as being non-susceptible to a carbapenem, the results including both the identifier and strain identification information are transmitted to the Electronic Communication of Surveillance in Scotland SQL server at Health Protection Scotland (HPS). The diagnostic laboratory then refers the carbapenem resistant isolate to the antimicrobial resistance and healthcare associated infections reference unit at Public Health England for detection of carbapenemase production. If the reference laboratory confirms the production of carbapenemase, it will email the result to HPS which is then manually entered into the Electronic Communication of Surveillance in Scotland database. Public Health England do not currently transfer any result electronically into Electronic Communication of Surveillance in Scotland. Antimicrobial susceptibility testing is only performed if the diagnostic laboratory has requested it.

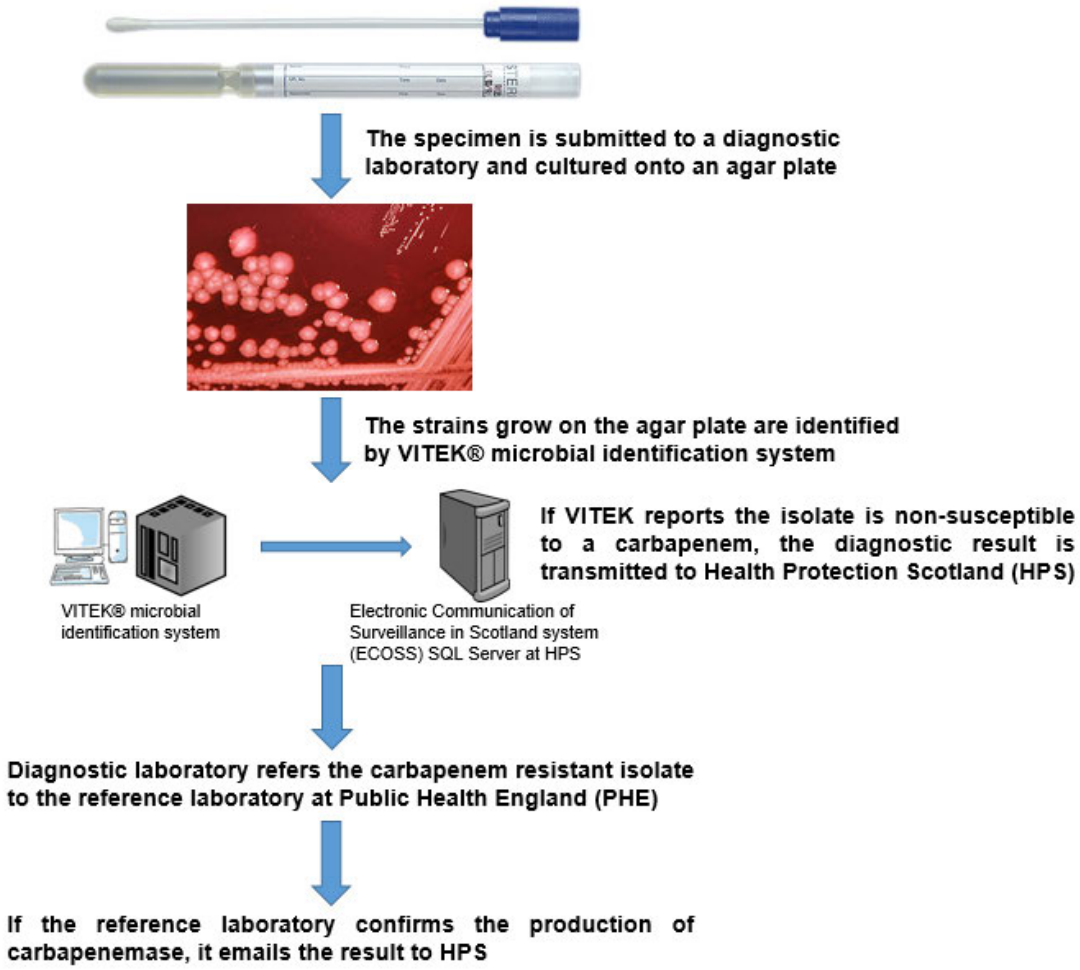


Figure 1-3. Steps to identify a carbapenemase-producing organism (CPO) isolate

Source: Health Protection Scotland staff Julie Wilson, personal communication by email, December 8, 2017

1.3.4 Policies and screening programme in the UK, including Scotland

In 2010, the Scottish Chief Medical Officer issued a letter on antimicrobial resistance to clinicians highlighting the need for awareness of carbapenemases and other emerging resistance (The Scottish Government, 2010). Emergence of CPE was flagged as a concern for the UK in the same year. The actions recommended were that clinicians should seek early advice from their local microbiologist if infection with a CPO is a possibility (The Scottish Government, 2010).

In 2013, a joint Chief Medical Officer/Chief Nursing Officer/Chief Pharmaceutical Officer letter described the emerging threat from CPE and the requirements for an acute hospital admission screening programme for CPE (The Scottish Government, 2013). Given that some European countries have moved to an endemic situation of CRO and that the number of CPE isolates in the UK and Scotland is rising, it is recommended that each Scottish NHS Board has a CPE action plan in place by December 2013. Additionally, hospitals should have systems in place to rapidly identify: (1) patients who have been transferred from a hospital abroad; (2) patients who have been hospitalised abroad within the last 12 months; (3) patients who have previously been positive for CPE at any body site. These patients should be immediately isolated and advice taken from the Infection Prevention and Control Team (The Scottish Government, 2013).

In 2015, the Scottish Government issued the mandatory healthcare associated infection and antimicrobial resistance policy requirements (The Scottish Government, 2015), stating that HPS were currently supporting NHS Boards to implement CPE screening. It is the expectation that NHS Boards will inform HPS of confirmed CPE cases as per the current guidance.

In May 2016, HPS published “Toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae in Scottish acute settings” which has been updated in May 2019 (Health Protection Scotland,

2016b). This toolkit has been adapted from Public Health England 'Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae' and takes account of published UK guidance multidrug-resistant organisms from the Healthcare Infection Society. It contains a set of recommendations based on scientific evidence and consensus of expert opinion to prevent cross transmission of CPE within acute healthcare settings in NHS Scotland. Shortly afterwards, Healthcare Improvement Scotland conducted a study and concluded that the current literature on identifying CPE in hospital screening samples is inadequate to inform selection of the most effective screening test and/or method to identify patients colonised by CPE (Healthcare Improvement Scotland, 2016). Also, the Scottish Microbiology and Virology Network Antimicrobial Susceptibility Testing Group endorsed use of the UK Standards for Microbiology Investigations (Public Health England, 2016) to test CPE.

Again, the Chief Nursing Officer letter issued in March 2017 reinforced the mandatory policy requirement for CPE screening in NHS Boards across Scotland (The Scottish Government, 2017).

In September 2017, HPS published "Toolkit for managing carbapenemase-producing Enterobacteriaceae (CPE) in Scottish non-acute care settings" (Health Protection Scotland, 2017). The guidance was adapted from Public Health England 'Carbapenemase-producing Enterobacteriaceae: non-acute and community toolkit' (Public Health England, 2015) and contains a set of recommendations and practical advice to reduce the spread of CPE in non-acute and community settings in Scotland, including management of individuals positive for CPE, communications within healthcare settings and household, and risk assessment on managing individuals positive for CPE. Also, CPE-related advice leaflets are also available, including 'Advice leaflet for individuals receiving care at home or in the community who have an infection with, or are colonised by carbapenemase-producing Enterobacteriaceae (CPE)', 'Advice leaflet for the family of a person who is a carrier of carbapenemase-producing Enterobacteriaceae (CPE)', 'Advice

leaflet for contacts of a carbapenemase-producing Enterobacteriaceae (CPE) carrier' (Health Protection Scotland, 2018b; Health Protection Scotland, 2018c; Health Protection Scotland, 2018a). These leaflets introduce knowledge regarding definition, clinical significance and spread of CPE and guidance on getting advices from healthcare providers to individuals with CPE and their families or contacts.

In summary, the Scottish government and HPS started to pay attention to CRO and set up a series of policies to screen for and control spread of CPE from 2010 onwards. By the end of 2017, guidance for the detection and management of CPE in both acute and non-acute care settings had been issued. Nevertheless, the level of compliance with these guidance remains unclear.

1.4 Aims of this thesis

I conducted a systematic review and meta-analysis on risk factors for CRO infection and colonisation in healthcare facilities worldwide, aiming to provide a critical appraisal of the existing evidence in the association between patient- and healthcare-associated factors and CRO acquisition (infection and colonisation) and to examine whether and to what extent certain study-design characteristics can account for heterogeneity across these published studies. Such an analysis will identify knowledge gaps and inform future work.

To date, unpublished sources suggest that the number of reported CPO in Scotland is increasing (Health Protection Scotland, 2019b). However, there has not been any rigorous temporal or spatial analysis of the data. Therefore, I conducted a retrospective epidemiology study of CPO in Scotland over the time period 2003 (when the first case was observed) to 2016. The aims are to calculate the incidence of CPO and examine the temporal trends and spatial distribution for the time frame of the study, to summarise the microbiological characteristics of CPO isolates, including species (e.g. *Escherichia coli*,

Pseudomonas aeruginosa), carbapenemases and antimicrobial susceptibility, and to determine mortality rate, survival and risk factors for all-cause 30-day mortality from CPO.

Finally, a subgroup of hospitalised patients infected with or colonised by CPO in Scortland were enrolled as cases in a matched case-control study, this study aims to determine risk factors for CPO infection and colonisation among hospitalised patients, to evaluate the impact of CPO on patient prognosis (mortality rates and survival), and to compare antimicrobial susceptibility between isolates from CPO cases and controls.

Chapter 2 Risk factors for the presence of carbapenem-resistant organisms (CRO) among patients in healthcare facilities: a systematic review and meta-analysis

2.1 Background

Carbapenems were introduced in 1985 to provide enhanced coverage as compared with other β-lactams and stability against extended-spectrum β-lactamases (ESBL) capable of hydrolysing almost all other β-lactam antibiotics (Pitout and Laupland, 2008). Accordingly, carbapenems are often used as last resort antibiotics for treatment of invasive multidrug-resistant infections. In the past two decades, there has been an increased usage of carbapenems because of the global spread of ESBL-producing isolates (European Centre for Disease Prevention and Control, 2017; World Health Organization, 2014; Centers for Disease Control and Prevention, 2013). As a result, there is an emerging global public health threat of carbapenem-resistance, leaving few effective therapeutic options available for multidrug-resistant infections and ultimately causing high mortality and increased care costs (Tischendorf et al., 2016; Daroukh et al., 2014). Carbapenem resistance occurs mainly in Gram-negative bacilli comprising Enterobacteriaceae such as *Escherichia coli* (*E. coli*) and *Klebsiella pneumonia* and non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. In 2017, the World Health Organization (WHO) published a list of antibiotic-resistant bacteria that are of global priority which included carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacteriaceae (World Health Organization, 2017b).

Effective and easily operationalized prevention and infection control strategies against carbapenem-resistant organisms (CRO) are imperative. From clinical and epidemiological perspectives, a comprehensive understanding of risk factors for the presence of CRO is fundamental to designing and tailoring such

infection prevention and control policies. Additionally, this will help to identify high risk individuals and populations. Though risk factors for CRO infections and colonisations are identified in published studies, the results are often inconsistent. This may reflect, at least in part, different study characteristics, such as study setting, design, population of interest, organisms, definition of resistance and selection of controls, generating great heterogeneity across studies. Conclusions obtained by combining studies without regard to this heterogeneity may be unreliable and potentially misleading (Choi and Lam, 2017). In addition, understanding the sources of heterogeneity could provide guide for better study design of risk factor studies. This chapter aims to provide an in-depth analysis of risk factors for CRO presence among patients in healthcare facilities worldwide and thus provide up-to-date information on this topic from both clinical and epidemiological perspective.

The specific aims of this chapter are:

1) to evaluate an estimation method of standard deviation from the sample size, median, range and/or interquartile range;
2) to investigate the risk factors for the presence, infection and colonisation of CRO in healthcare settings;
3) to compare risk factors for CRO infection and colonisation;
4) to investigate risk factors associated with hospital-acquired infection caused by CRO;
5) to explore study characteristics contributing most to the heterogeneity across studies.

2.2 Methods

2.2.1 Protocol

A protocol was developed according to the items in the checklist detailed in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Appendix 2-1) (Liberati et al., 2009) and registered on PROSPERO (International prospective register of systematic reviews)

(registration number: CRD42018081433). The review focuses on primary peer-reviewed papers of risk factor studies for the presence of CRO among patients in healthcare facilities worldwide published from Jan 1, 1986 to Dec 31, 2016.

2.2.2 Search strategy

Electronic literature searches using the pre-piloted search terms and subject headings and tailored search strategies with corresponding search terms were applied to four umbrella databases, Embase, MEDLINE, Global Health and Web of Science, as well as the top three Chinese databases, i.e., China National Knowledge Infrastructure (http://www.cnki.net/), Chongqing VIP databases (http://lib.cqvip.com/) and Wanfang Data (http://www.wanfangdata.com.cn/).

Literature searching was performed using Science Citation Index Expanded, Social Sciences Citation Index, Conference Proceedings Citation Index-Science, Conference Proceedings Citation Index-Social Science & Humanities, Book Citation Index-Science, Book Citation Index-Social Sciences & Humanities, Emerging Sources Citation Index, Current Chemical Reactions and Index Chemicus provided through Web of Science (https://apps.webofknowledge.com). Simultaneously, Embase, MEDLINE and Global Health were searched through OvidSP (http://ovidsp.tx.ovid.com), search strategy for Embase was appropriately tailored for searching the other databases. For Chinese databases, similar strategies and related search terms were used. The detailed search strategy with search terms for each database are listed in Appendix 2-2. The reference lists of review papers were hand searched for eligible papers included in the review.

2.2.3 Eligibility criteria

Any published primary peer-reviewed paper was included if it reported risk factors associated with the presence of CRO (infection, colonisation,

acquisition, i.e., infection, colonisation or both of them) in a defined population admitted to a healthcare facility (hospitals or long-term care facilities).

Inclusion criteria (studies fulfilled all of the following criteria):

- Primary peer-reviewed study published between 1st January 1986 and 31st December 2016 (1st January 1989-31st December 2016 for Chongqing VIP databases)
- Any language
- Study type: observational studies (case-control study, cohort study, or cross-sectional study)
- Study population: patients or residents in a healthcare facility, i.e., hospitals and long-term care facilities
- Any sample size
- Reporting risk factors associated with the presence (infection and/or colonisation) of CRO

Exclusion criteria (studies fulfilled any of the following criteria):

- Animal studies
- Environmental studies
- Reporting risk factors for multidrug resistance including carbapenem resistance
- Reporting risk factors for resistance to both carbapenem and other antibiotics
- Publication type: reviews, case reports, case series, comments, conference abstracts, conference posters, editorials, errata, weekly reports and letters to the editor
- No reply from or no means of contacting authors when further details were required on the candidate risk factors investigated and/or the numbers of cases and controls

2.2.4 Literature selection and data extraction

Titles, authors, journals, published year and abstracts from the databases were downloaded into an Endnote file. After deleting duplicate papers, titles were screened in conjunction with available abstracts against the inclusion and exclusion criteria to identify studies which merit further consideration, i.e. checking full text. Following perusal of the full text of these studies, a decision as to whether to include the study was made.

All the included studies were perused to extract variables of interest and were entered into a Microsoft Excel 2013 spread sheet for further analysis. Data was extracted under the following headings (defined in Appendix 2-3):

- Reference characteristics: author, year of publication, study period, study country and corresponding WHO region (World Health Organization, 2017a) and World Bank Income group (The World Bank, 2017).
- Study design characteristics: status, study type, study setting, healthcare type, specialty, study population, organism, resistance mechanism, definition of carbapenem resistance, definitions of cases and controls.
- Risk factor analysis characteristics: numbers of cases and controls, candidate risk factors, univariate or multivariate analysis and corresponding cut-off *p* value, numbers of cases and controls with exposure to candidate risk factors, odds ratio (OR), 95% confidence interval (95% CI) and corresponding *P* value of univariate/multivariate analysis.

After the literature search and excluding duplicate papers, I selected papers identified by literature search based on titles and abstracts, and then conducted the literature selection and data extraction by reading full text. Another investigator (Melissa Taylor, MSc student at Liverpool school of tropical medicine) performed literature selection based on titles and abstracts for 10% of the papers identified by literature search and found no new eligible

papers. Then we conducted the literature selection and data extraction independently by reading full text. Any uncertainties or discordance regarding literature selection and data extraction were arbitrated by my supervisor (Professor Mark Woolhouse).

2.2.5 Quality assessment

For all included studies, a quality assessment was performed by two investigators independently (Ruby Tabor, undergraduate student at Deanery of Biomedical Sciences and myself) using a modified system based on the Newcastle-Ottawa quality assessment scale for case-control and cohort studies (Appendix 2-4) (Wells et al., 2011). For case-control studies, the included studies were judged on three broad aspects: the selection of study groups, the comparability of the groups and assessment of exposure. Scores of 4, 2 and 2 were assigned for the three aspects, respectively. For cohort studies, the included studies were judged on three broad aspects: the selection of study groups, the comparability of the groups and assessment of outcome. Scores of 4, 2 and 1 were assigned for the three aspects, respectively. For cross-sectional studies, an eleven-item system based on Agency for Healthcare Research and Quality guidelines were used (Appendix 2-4) (Zeng et al., 2012). Because there has been controversy about how many stars should be used as a cut-off for a study to be of high quality, the percentage of each score that included studies achieved was listed instead of defining which studies were of high quality and which ones were not. Studies with the lowest scores in each scales for each study type (case-control, cohort and cross-sectional) were considered to have low quality. Study quality was not considered an exclusion criterion.

2.2.6 Definition of outcome and risk factors

The outcome of interest is the presence of CRO, including infection, colonisation and acquisition from any site of the body. CRO infection was defined as hospital-acquired if it fulfilled any of the following criteria: 1) the authors specified they investigated risk factors for hospital-acquired or

nosocomial infections caused by CRO; 2) Samples with CRO were collected at 48 hours or more after hospital admission (Cardoso et al., 2014; Horan et al., 1992).

The risk factors investigated were placed in one of five categories: group 1, demography including age and gender; group 2, prior healthcare exposure including prior hospitalisation, hospital transfer, intensive care unit (ICU) stay and presence of drug resistant organisms; group 3, comorbidities and severity of comorbidity index such as Charlson Comorbidity index scores (CCI), Acute Physiology And Chronic Health Evaluation II scores (APACHE II) and Sequential Organ Failure Assessment scores (SOFA); group 4, prior exposure to invasive medical procedure and/or devices; group 5, prior antibiotic exposure. Definitions of some risk factors varied substantially across the included papers which may resulted in different strengths of evidence for association between these risk factors and the outcome, so risk factors were defined as precisely as possible based on the original definitions in the included papers (Appendix 2-5).

2.2.7 Statistical analysis

All the reported risk factors including in these studies could be classified as either categorical or continuous.

For each categorical risk factor in each study, the OR and 95%CI were re-calculated using the raw data in the original study. A meta-analysis was performed accordingly to obtain pooled estimates of ORs using a random-effects model based on the method of DerSimonian-Laird (DerSimonian and Laird, 2015). This was done only if ≥5 studies reported the same risk factor. To summarise the evidence, four aggregate parameters were calculated for each risk factor: (i) frequency of being a candidate risk factor, defined as the number of studies that included the factor; (ii) frequency of being a statistically significant risk factor, from the re-analysis of the raw data; (iii) likelihood of statistical significance, defined as (ii)/(i); (iv) pooled OR estimates, from the re-analysis of the raw data. For each risk factor investigated in ≥5 studies, the

four parameters were calculated respectively for the three types of CRO status (presence, colonisation and infection including hospital-acquired infection as defined in Appendix 2-3) where appropriate. The I^2 statistic was used to quantify statistical heterogeneity (Higgins et al., 2003). For the risk factors investigated in more than ten studies with highest pooled OR estimates and/or most likely significant, potential sources of heterogeneity were explored with meta-regression and subgroup analyses if I^2 ≥75% (Choi and Lam, 2017). In addition, for risk factors investigated in no less than five studies after excluding studies of low quality, a sensitivity analysis was performed in comparison to pooled ORs calculated regardless of study quality to examine whether the results would differ substantially when the studies of low quality were excluded. Factors considered included World Bank Income group, study type, study setting, healthcare type, specialty, study population, organisms, resistance mechanism, CRO status, selection of cases and controls and sample size (Appendix 2-3). Publication bias was examined using Egger's test for factors investigated in more than ten studies (Egger et al., 1997).

For each continuous risk factor in each study, if the raw data were reported as median with range or interquartile range (IQR), mean was estimated from Wan's method [16]. Standard deviation (SD) were estimated from Wan's and Walter's methods separately (Wan et al., 2014; Walter and Yao, 2007), and standardised mean difference (SMD) and 95%CI were calculated accordingly. The results were compared. The summary statistics were defined as: m=the median, n=the sample size, a=the minimum value of the range, b=the maximum value of the range, q1=the first quartile, q3=the third quartile. The raw data was reported in three scenarios: C1=(m, n, a, b), C2=(m, n, q1, q3), C3=(n, a, b). Wan et al (Wan et al., 2014) provided formulas of mean and SD estimation for C1 and C2 while Walter et al (Walter and Yao, 2007) provided formulas of SD estimation for C3:

$$C1{:}\ mean \approx \frac{\mathrm{a} + 2\mathrm{m} + \mathrm{b}}{4}, \quad SD \approx \frac{b - a}{2\emptyset^{-1}\left(\frac{n - 0.375}{n + 0.25}\right)}$$

$$C2\colon\ mean \approx \frac{\mathrm{q1} + \mathrm{m} + \mathrm{q3}}{3}, \quad SD \approx \frac{q3 - q1}{2\emptyset^{-1}\left(\frac{0.75n - 0.125}{n + 0.25}\right)}$$

$$C3\colon\ SD \approx f \times (b - a)$$

For C1 and C2 formula, $\emptyset^{-1}(z)$ is the upper zth percentile of the standard normal distribution. For C3 formula, *f* is a tabulated conversion factor derived from linear interpolation according to corresponding tabulated values of sample sizes (Walter and Yao, 2007). If the raw data was reported as mean and SD, SMD and 95%CI were calculated with raw data in the original study. Publication bias was examined using Egger's test for factors investigated in more than ten studies (Egger et al., 1997).

All the analyses were performed using R version 3.3.3. Maps were drawn using ArcGIS (version 10.5.1). A *P* value less than 0.05 was considered statistically significant.

2.3 Results

2.3.1 Studies identified

The literature search identified 49,980 papers including 18,836 duplicates. Due to some short search terms involved in search strategies, many papers not relevant to the topic of interest were identified and they could be excluded by scanning the title and abstract. After applying inclusion and exclusion criteria at the title and abstract levels, 30326 papers not relevant to the topic and 21 non-primary peer-reviewed papers were excluded and the remaining 797 papers were retained for full text assessment (Figure 2-1). Finally, 227 papers were identified for data extraction and further review including 191 (84.1%) papers from English databases and 36 (15.9%) papers from Chinese databases (Figure 2-1). Because some papers reported more than one study due to different study characteristics, data from 254 distinct studies were

extracted from the 227 papers (Appendix 2-6). Twenty-three papers generated 2 studies and 2 papers generated 3 studies, details are listed in Appendix 2-6.

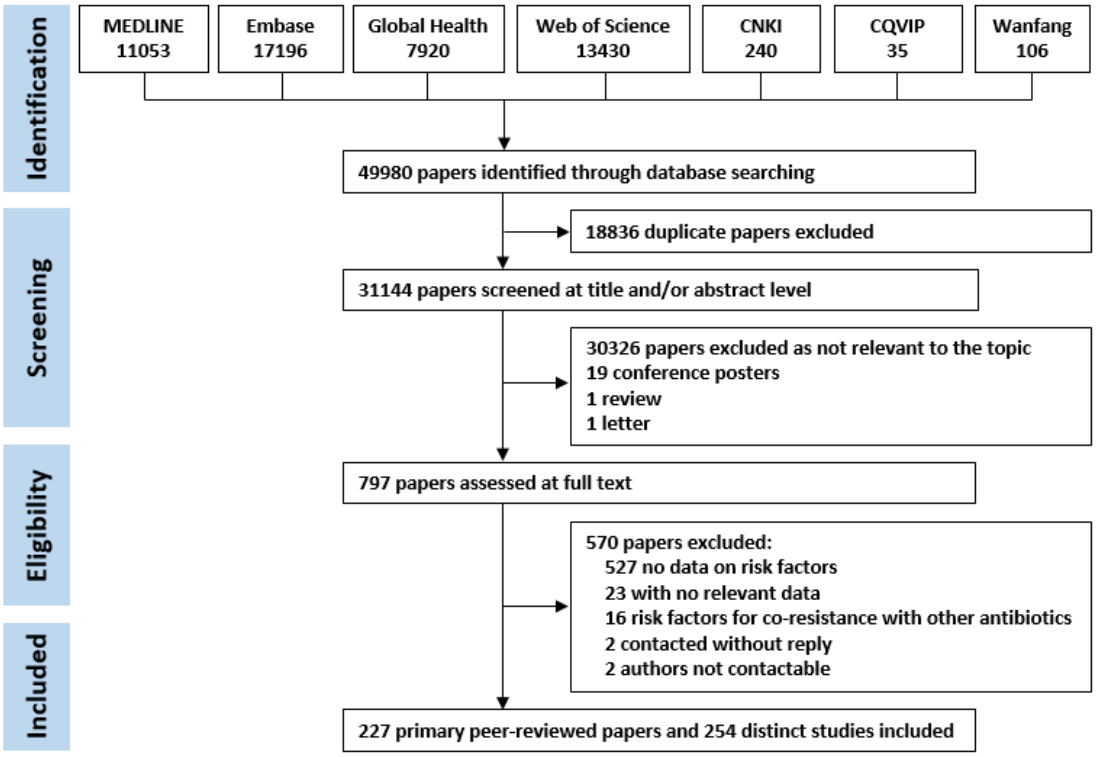


Figure 2-1. Flowchart of literature selection

2.3.2 Study characteristics

Understanding characteristics of included studies would provide a general idea of the variety of these studies regarding study design and research interest. Characteristics of studies included in the review are listed in Table 2-1. All the 227 papers included in the review performed univariate analysis and 202 of them performed multivariate analysis as well. Univariate *P* value of variables as cut-off for inclusion in multivariate analysis varied from $P \leq 0.05$ to $P \leq 0.5$ while all multivariate analyses set statistical significance at $P \leq 0.05$. The detailed information are shown below.

Table 2-1. Characteristics of included studies

Characteristics		Number of papers/studies
World Bank Income	High income	125/227 (55.1%)
	Upper-middle income	97/227 (42.7%)
	Lower-middle income	5/227 (2.2%)
Study setting	Single-centre	195/227 (85.9%)
	Multi-centre	32/227 (14.1%)
Healthcare type	Tertiary care hospital	190/227 (83.7%)
	Other	37/227 (16.3%)
Specialty	ICU	62/227 (27.3%)
	Non-ICU	165/227 (72.7%)
Study population	Adults	55/227 (24.2%)
	Paediatric	13/227 (5.7%)
	Adults and paediatric	159/227 (70.0%)
CRO status	Acquisition	64/254 (25.2%)
	Infection	149/254 (58.7%)
	Colonisation	41/254 (16.1%)
Study type	Case-control	171/254 (67.3%)
	Matched	37/254 (14.6%)
	Cohort	64/254 (25.2%)
	Cross-sectional	19/254 (7.5%)
Study organism	Enterobacteriaceae	125/254 (49.2%)
	Non-fermenters	117/254 (46.1%)
	Other	12/254 (4.7%)
Resistant mechanism	Carbapenemase production (genotypic resistance)	39/254 (15.4%)
	Carbapenem resistance (phenotypic resistance)	215/254 (84.6%)
Case-control selection	CRO versus CSO	144/254 (56.7%)
	CRO versus no CRO	78/254 (30.7%)
	CRO versus no pathogenic bacteria	29/254 (11.4%)
	CRO infection versus CRO colonisation	3/254 (1.2%)

ICU, intensive care unit; CRO, carbapenem-resistant organisms; CSO, carbapenem-susceptible organisms

2.3.2.1 Year of publication

The 227 papers included in this review were published between 1997 and 2016, showing an upward trend over time with a large rise in 2016 (Figure 2-2).

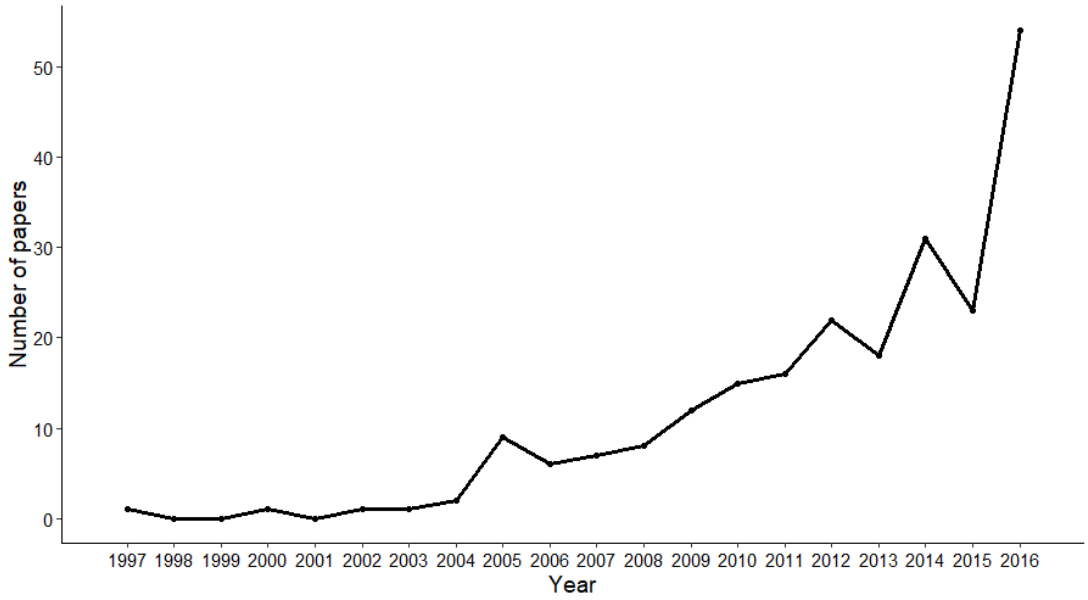


Figure 2-2. Number of papers published by year

2.3.2.2 Geographic distribution

According to the venue where the studies were conducted reported by the authors, the 227 papers involved in this review were from 37 countries/regions (Appendix 2-6), including 18 (48.6%) high income countries/regions, 16 (43.2%) upper-middle income countries/regions and 3 (8.1%) lower-middle income countries/regions by World Bank Income groups (Version 2017). None of these studies were conducted in low income countries. In terms of the number of papers, 125 (55.1%) were conducted in high income countries/regions, 97 (42.7%) in upper-middle income countries/regions and only 5 (2.2%) in lower-middle income countries/regions (Table 2-1). By WHO regions, most papers were from Europe (77/227, 33.9%), the Western Pacific (77/227, 33.9%) and the Americas (56/227, 24.7%). Over half of the studies were from China (60/227, 26.4%), America (33/227, 14.5%), Brazil (16/227, 7.0%) and Israel (16/227, 7.0%). Figure 2-3 shows the geographic distribution of papers regarding to administrative units, i.e., states and provinces where these studies were conducted.

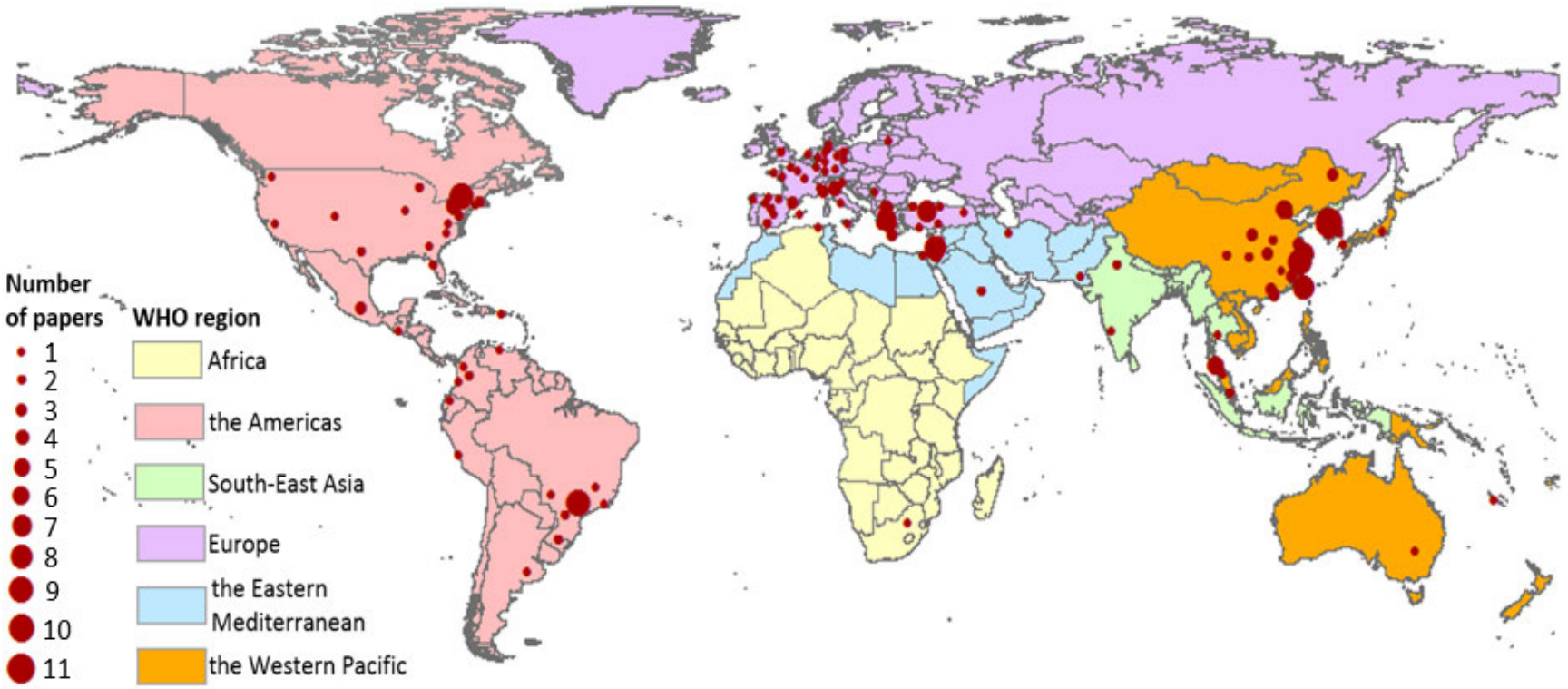


Figure 2-3. Geographic distribution of included papers

2.3.2.3 Study setting and study population

Thirty-two (14.1%) of all the 227 papers were multi-centre studies. Twenty-one of the 32 multi-centre studies were conducted in healthcare facilities located in the same city while 10 were conducted in different cities of the same country and 1 in seven Latin American countries.

Regarding type of healthcare facilities, the majority of these studies were conducted in tertiary care hospitals (190/227, 83.7%). Five studies were conducted in post-acute care settings, comprising 2 in post-acute care hospitals, 1 in long-term care facility, 1 in nursing homes and 1 in a rehabilitation hospital. Three were in secondary care hospitals while 2 studies were conducted in paediatric hospitals and 2 in long-term acute care hospitals. Additionally, the remaining 25 (11.0%) studies conducted in hospitals did not specify the type. It is noteworthy that 62 of 227 (27.3%) papers were conducted among inpatients in ICU.

In terms of study population, 55 (24.2%) papers focused on adults and the cut-off age for adult definition differed between studies though. Thirteen (5.7%) focused on paediatric patients, including 7 in neonates. Additionally, 9 papers were conducted specifically among solid organ or hematopoietic stem cell transplantation recipients while 3 were among burn inpatients.

2.3.2.4 Definition of carbapenem resistance

According to the updated definition of carbapenem resistance (Centers for Disease Control and Prevention, 2015), carbapenem resistance was defined following either of: 1) Phenotypic resistance. Resistant to any carbapenem antimicrobial including doripenem, meropenem, imipenem or ertapenem; 2) Genotypic resistance. Documented to produce carbapenemase. Definition of carbapenem resistance varied substantially across these studies. One hundred and one (44.5%) of the 227 papers interpreted carbapenem resistance according to Clinical and Laboratory Standards Institute (CLSI) guidelines issued in different years which differed from each other slightly.

However, most of these papers did not specify the method of antimicrobial susceptibility testing. On the contrary, 49 (21.6%) papers clarified the methods and corresponding standards they used, and they were various though. Additionally, 59 (26.0%) papers did not give explicit and/or useful information (Table 2-2).

Table 2-2. Definition of carbapenem resistance

Standard	Method		Total
	disk diffusion	minimum inhibitory concentration	
CLSI			101
CLSI-1999	/	/	1
CLSI-2000	2	/	4
CLSI-2001	/	/	2
CLSI-2002	/	/	1
CLSI-2003	/	/	1
CLSI-2004	/	1	2
CLSI-2005	2	/	2
CLSI-2001-2005	1	/	1
CLSI-2006	5	1	12
CLSI-2007	2	/	5
CLSI-2008	1	1	8
CLSI-2009	4	1	11
CLSI-2009/2010	/	/	1
CLSI-2010	5	1	13
CLSI-2011	1	/	5
CLSI-2012	/	3	9
CLSI-2012/2013	/	1	1
CLSI-2013	4	1	6
CLSI-2013/2014	/	/	1
CLSI-2014	2	1	5
CLSI-NS	/	1	10
Vitek 2	/	/	5
EUCAST	/	2	5
CRE toolkit	/	/	1
Others	6 IPM/MEM: ≤19 mm (1) IPM: ≤15 mm (1) <16 mm (1) <17mm (1) ETP/MEM: ≤22mm (1) ETP: <20mm (1)	50 carbapenem: ≥4 mg/l (1) IPM/ETP: ≥4 mg/l (1) ≥16 mg/l (1) IPM/MEM: ≥2 mg/l (1) ≥4 mg/l (1) ≥8 mg/l (11) ≥16 mg/l (8) ETP: ≥1 mg/l (2) ≥2 mg/l (2) IPM: ≥2 mg/l (1) ≥8 mg/l (8) ≥16 mg/l (5) MEM: ≥32 mg/l (1) Others: 7	56
No description			59

/, not applicable;
CLSI, Clinical and Laboratory Standards Institute; Vitek 2, automated antimicrobial susceptibility testing instrument (bioMérieux); EUCAST, European Committee on Antimicrobial Susceptibility Testing; CRE, carbapenem-resistant Enterobacteriaceae; IPM, imipenem; MEM, meropenem; ETP, ertapenem; CLSI-NS, the year of CLSI guidelines adopted were not specified.

2.3.2.5 Study design

In terms of study type, among 254 studies from the 227 papers, case-control studies predominated (171/254, 67.3%), including 37 matched case-control studies with matching ratios 1:1 (14), 1:2 (15), 1:3 (7) and 1:4 (1), respectively, followed by cohort studies (64/254, 25.2%) and cross-sectional studies (19/254, 7.5%), which included active surveillance studies. For the 64 cohort studies, 39 (60.9%) of them were retrospective while 25 (39.1%) were prospective.

According to the CRO status specified in the papers, 149 (58.7%) of all the 254 studies explored risk factors for infections (the authors of these studies clearly specified they investigated risk factors for CRO infections) caused by CRO while 64 (25.2%) explored risk factors for acquisition (the authors of these studies did not clearly specify whether they investigated risk factors for CRO infections or colonisation, i.e. no discrimination of infection and colonisation, it might be infections, colonisation or both) and 41 (16.1%) for colonisation (the authors of these studies clearly specified they investigated risk factors for CRO colonisation) (Table 2-3). Among 69 studies specifying types of infection, blood stream infection was the most common type (44, 63.8%). Thirty-one of 41 colonisation studies focused on intestinal colonisation while 1 on bacteriuria (Table 2-3).

Table 2-3. Number of included studies by carbapenem-resistant organisms (CRO) status

Status		Number of studies
Acquisition	Sub-total	64
Infection	Sub-total	149
	Not clarified	80
	Blood stream infection	44
	Respiratory tract infection	23
	Urinary tract infection (UTI)	1
	Pneumonia/UTI	1
Colonisation	Sub-total	41
	Not clarified	9

	Intestinal colonisation	31
	Bacteriuria	1

Nearly half of these studies (125/254, 49.2%) focused on Enterobacteriaceae while 117 of them (46.1%) focused on non-fermenters. *Klebsiella pneumoniae* predominated (78/254, 30.7%), with *Acinetobacter baumanmii* (64/254, 25.2%) and *Pseudomonas aeruginosa* (49/254, 19.3%) the other common species (Table 2-4). It is noteworthy that only one study focused on both carbapenem resistant Gram-positive and Gram-negative bacteria.

Table 2-4. Number of included studies by study organisms

Bacteria classification	Genus	Species	Number of studies
Enterobacteriaceae	*Klebsiella*	*Klebsiella pneumoniae*	78
		Klebsiella spp.	1
	Escherichia	*Escherichia coli*	3
		Escherichia coli+Klebsiella pneumoniae	2
	Enterobacter	*Enterobacter spp.*	1
		Enterobacter cloacae	1
		Enterobacter gergoviae	1
	Not specified	/	38
Non-fermenters	*Acinetobacter*	*Acinetobacter baumanmii*	64
		Acinetobacter spp.	3
		Acinetobacter nosocomialis	1
	Pseudomonas	*Pseudomonas aeruginosa*	49
Gram (-) bacteria	/	/	11
Organism: Gram (+/-)	/	/	1

/, not applicable. Gram (-), Gram-negative; Gram (+/-), both Gram-positive and Gram-negative

Regarding mechanisms of carbapenem resistance, 39 (15.4%) focused on carbapenemase production (genotypic resistance) specifically while 215 (84.6%) investigated risk factors for carbapenem resistance (phenotypic

resistance) and most of the 215 studies did not clarify which carbapenem the bacteria were resistant to (159/215, 74.0%). KPC production (14/39, 35.9%) was the most common carbapenemase of interest in the former mechanism while resistance to imipenem (46/56, 82.1%) predominated in the latter mechanism (Table 2-5).

Table 2-5. Number of included studies by mechanisms of carbapenem resistance

Type of resistance		Number of studies
Carbapenem resistance	Sub-total	215
	Imipenem	46
	Ertapenem	4
	Meropenem	4
	Meropenem-high level	2
	not specified	159
Carbapenemase production	Sub-total	39
	KPC	14
	VIM	4
	Metallo-beta-lactamases	4
	NDM	2
	OXA-232	2
	OXA-48	1
	OXA-23	1
	IMP	2
	SPM	1
	not specified	8

There is also a great variation in terms of definitions of cases and controls across these studies (Table 2-1). More than half (144, 56.7%) of the 254 studies chose CRO as cases and CSO as controls while nearly one third (78/254, 30.7%) compared patients with CRO with patients without CRO. Three studies performed a 'case-case' analysis (CRO infection versus CRO colonisation) to explore risk factors for CRO infection.

In general, there is a great diversity of study characteristics across included studies. Thus a random-effects model for meta-analyses is appropriate and it

is necessary to explore study characteristics contributing to the heterogeneity across studies most.

2.3.3 Study quality and publication bias

Quality assessments for included studies are listed in Table 2-6 and Appendix 2-4. Case-control studies scored between 3 and 6 stars on the modified Newcastle-Ottawa scale while cohort studies scored between 4 and 7 stars. The most common reasons for not awarding a star were (i) the use of hospital controls, (ii) no information about history of disease, (iii) the use of medical records only and (iv) insufficient comparability of study groups. Cross-sectional studies scored between 6 and 8 points on the Agency for Healthcare Research and Quality scale. The main reasons not to award points were no description of how confounding was assessed/controlled, response rates, follow-up and missing data.

Publication bias indicators were significant for few risk factors (9/88) (Appendix 2-7), none of which were among the leading risk factors in terms of likelihood to be significant and/or with the highest pooled ORs, so no restriction was included to limit publication bias.

Table 2-6. Number of included studies by study quality

Study type	Scale (total scores)	Scores (n, %)¶
case-control	Modified Newcastle-Ottawa scale (8)	3 (75/171, 43.9%)
		4 (40/171, 23.4%)
		5 (55/171, 32.2%)
		6 (1/171, 0.6%)
cohort	Modified Newcastle-Ottawa scale (7)	4 (22/64, 34.4%)
		5 (28/64, 43.8%)
		6 (10/64, 15.6%)
		7 (4/64, 6.3%)
cross-sectional	Agency for Healthcare Research and Quality scale (11)	6 (10/19, 52.6%)
		7 (7/19, 36.8%)
		8 (2/19, 10.5%)

¶ score (number of studies with the score/total number of studies of the study type, percentage);

2.3.4 Evaluation of two standard deviation estimation methods

Both Walter's and Wan's methods provided SD estimation from sample size and range. I performed both methods to estimate SD of 101 continuous variables which just provided sample size and range, and then calculated SMD using these SD values accordingly (Appendix 2-8). The 101 variables generated 202 SD values estimated for both cases and controls and accordingly 101 SMD values. One hundred and fifty-two of the 202 SD values differed from each other by 0.05 (75.2%), 29 (14.4%) by 0.05-0.10 and 21 (10.4%) by 0.10-0.98, respectively. Consequently, 90 (89.1%) of the 101 continuous variables showed identical results of SMD while 10 (9.9%) differed from each other by 0.01 and 1 (1.0%) by 0.05. However, all the differences did not affect the interpretation of the results (Appendix 2-8). Wan's method provides both SD and mean estimation from both range and IQR while Walter's method just provide SD estimation from range. For simplicity of calculation and scope of application, I chose Wan's method.

2.3.5 Risk factors associated with the presence of CRO

In total, 77 categorical and 11 continuous risk factors were included in the meta-analyses. The pooled OR estimates and SMD for each risk factor are listed in Appendix 2-7 The factors most likely to be significant and/or with the highest pooled ORs are labelled in Figure 2-4 A. Prior presence of CRO generated the highest OR estimate (pooled ORs 7.14, 95%CI 3.68-13.85, I^2=41%), followed by presence of vancomycin-resistant *Enterococci* (VRE) (pooled ORs 6.93, 95%CI 3.90-12.32, I^2=0%), prior imipenem usage (pooled ORs 6.60, 95%CI 4.67-9.33, I^2=74%) and prior any carbapenem usage (pooled ORs 4.79, 95%CI 4.17-5.51, I^2=76%). Prior combination therapy, oxazolidinone and vancomycin usage had high likelihoods of being statistically significant (72.73%, 64.71% and 63.04% respectively). Mechanical ventilation

(64.29%, pooled ORs 3.42, 95%CI 2.87-4.09, I^2=80%) and a nasogastric tube (61.11%, pooled ORs 3.33, 95%CI 2.50-4.44, I^2=86%) both had high likelihoods of being significant and a high pooled OR estimate. Although demography and comorbidities were commonly investigated, these factors generally had lower pooled OR estimates and likelihoods of being significant. An exception was decubitus ulcer (pooled ORs 3.08, 95%CI 1.90-4.99, I^2=63%) (Figure 2-4 A). In terms of continuous factors, increased length of ICU stay, hospital stay, mechanical ventilation, urinary catheter and carbapenem therapy were risk factors for CRO (Appendix 2-7). It is noteworthy that 75.0% of the 16 studies investigating whether duration of mechanical ventilation was a risk factor found that longer mechanical ventilation in days increased risk of CRO presence (SMD 0.70, 95%CI 0.47-0.93, I^2=76%). In addition, higher CCI and APACHE II scores were associated with CRO presence.

Sensitivity analyses were performed for 74 categorical risk factors (Appendix 2-9). Whether a risk factor is significant or not based on the pooled OR estimates and 95%CI was different for three factors when studies of low quality were included and excluded (Appendix 2-9), but none of them were leading risk factors.

2.3.6 Comparison of risk factors for CRO infection and colonisation

CRO infections usually result in higher mortality and require timely treatments while individuals with CRO colonisation tend to be asymptomatic but facilitates potential transmission of carbapenem resistance as the reservoir of CRO. Clinical staff and public health staff/policy makers might have different preferences for risk factors for infection and colonisation of CRO given that clinical staff would like to identify and treat infections as soon as possible while public health staff/policy makers would like to take infection prevention and control measures for people with CRO colonisation to prevent them from developing to infections. Different risk factors were expected, therefore it is important to look at them respectively. The pooled OR estimates and SMD for

each risk factor are listed in Appendix 2-7. The risk factors most likely to be significant and/or with the highest pooled ORs are labelled in Figure 2-4 B and C. Leading risk factors for both CRO infection and colonisation were prior carbapenem usage, prior oxazolidinone usage, ICU stay, and use of mechanical ventilation and nasogastric tube. For CRO infection, prior CRO carriage ranked first for both the likelihood of being significant (5/6, 83.3%) and pooled OR estimate (pooled ORs 5.82, 95%CI 3.03-11.20, I^2=31%) while no CRO colonisation study investigated this factor; decubitus ulcer ranked second for both likelihood of being significant (4/5, 80.0%) and pooled OR estimate (pooled ORs 5.08, 95%CI 1.98-13.05, I^2=82%). Prior combination therapy and amikacin usage had high likelihoods of being statistically significant (80.0%). Increased length of ICU stay, hospital stay, mechanical ventilation, CCI and APACHE II scores were associated with CRO infection (Appendix 2-7). In contrast, prior polymycin usage (pooled ORs 5.75, 95%CI 2.88-11.48, I^2=33%), insertion of a gastrostomy tube (pooled ORs 4.66, 95%CI 1.82-11.98, I^2=31%) and parenteral nutrition (pooled ORs 3.41, 95%CI 2.22-5.25, I^2=0%) were risk factors achieving higher pooled OR for CRO colonisation only. CRO infection and colonisation shared some same leading risk factors, however, there were different risk factors for infection and colonisation. CRO infections tend to be specifically associated with (severity of) comorbidities while colonisation with antibiotic and medical devices exposure.

Sensitivity analyses after removing studies of low quality for CRO infection and colonisation are summarized in Appendix 2-9. Whether a risk factor is significant or not based on the pooled OR estimates and 95%CI was different for two factors for CRO infection and three factors for CRO colonisation (Appendix 2-9) when studies of low quality were included and excluded, but none of them were leading risk factors.

2.3.7 Risk factors associated with hospital-acquired CRO infection

The pooled OR estimates and SMD for each risk factor are listed in Appendix 2-7. The risk factors most likely to be significant and/or with the highest pooled ORs are labelled in Figure 2-4 D. For hospital-acquired infection, prior carbapenem usage ranked first for both the likelihood of being significant (41/54, 75.9%) and pooled OR estimate (pooled ORs 4.28, 95%CI 3.27-5.59, I^2=80%). Similar to CRO infection, prior combination therapy, ICU stay and use of mechanical ventilation and nasogastric tube were also leading risk factors for hospital-acquired infection according to likelihood of being significant and/or pooled ORs (Figure 2-4 D). In particular, use of mechanical ventilator (likelihood of being significant 67.65%, pooled ORs 3.88, 95%CI 2.76-5.45, I^2=87%) and prolonged usage (likelihood of being significant 81.82%, SMD 0.80, 95%CI 0.49-1.11, I^2=77%) were significantly associated hospital-acquired infection. Additionally, prior polymyxin usage, prior cefepime usage and steroid treatment were risk factors achieving higher likelihoods of being significant and/or higher pooled OR estimates (Figure 2-4 D).

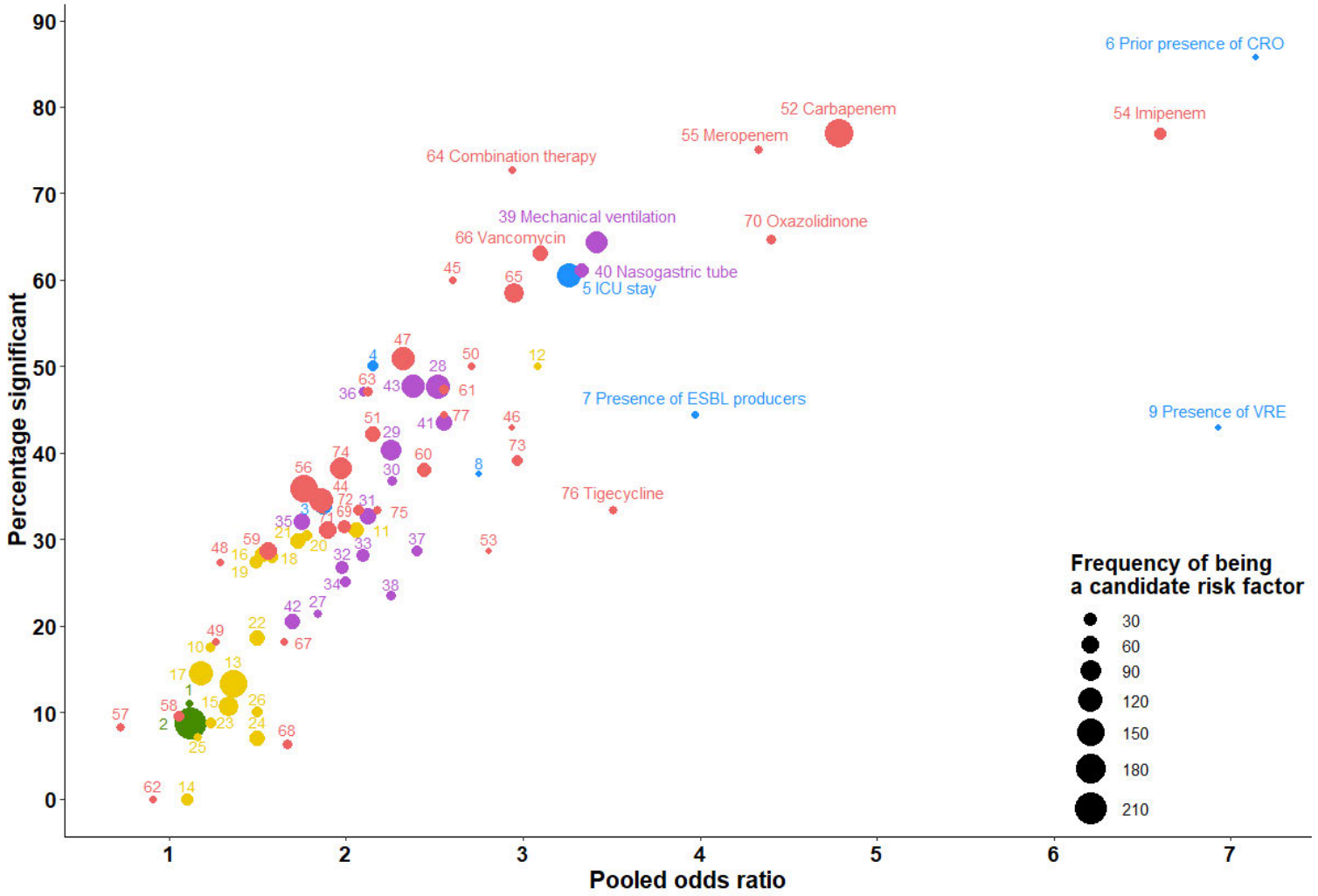


Figure 2-4. Panel (A) Risk factors for the presence of CRO

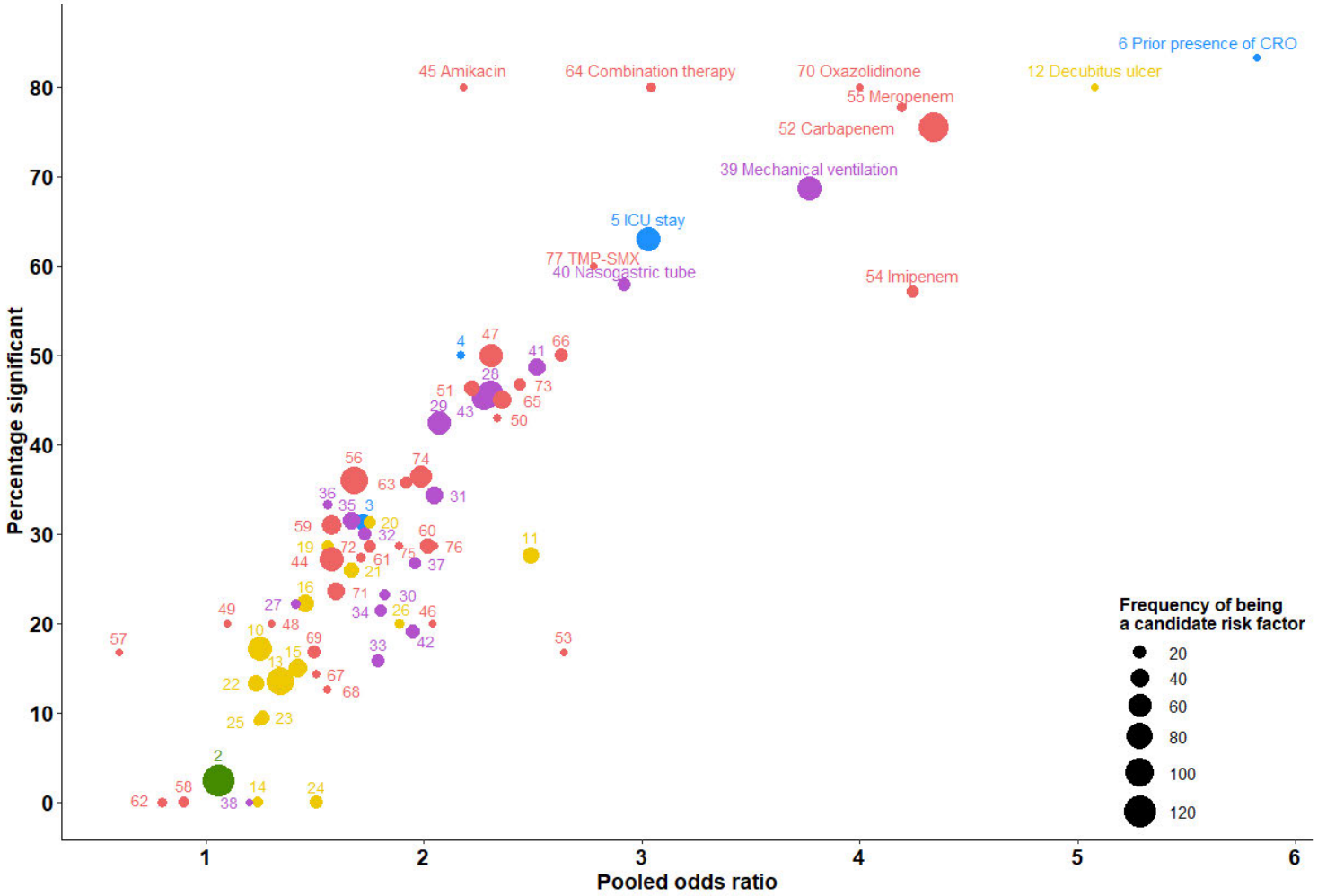


Figure 2-4. Panel (B) Risk factors for CRO infection

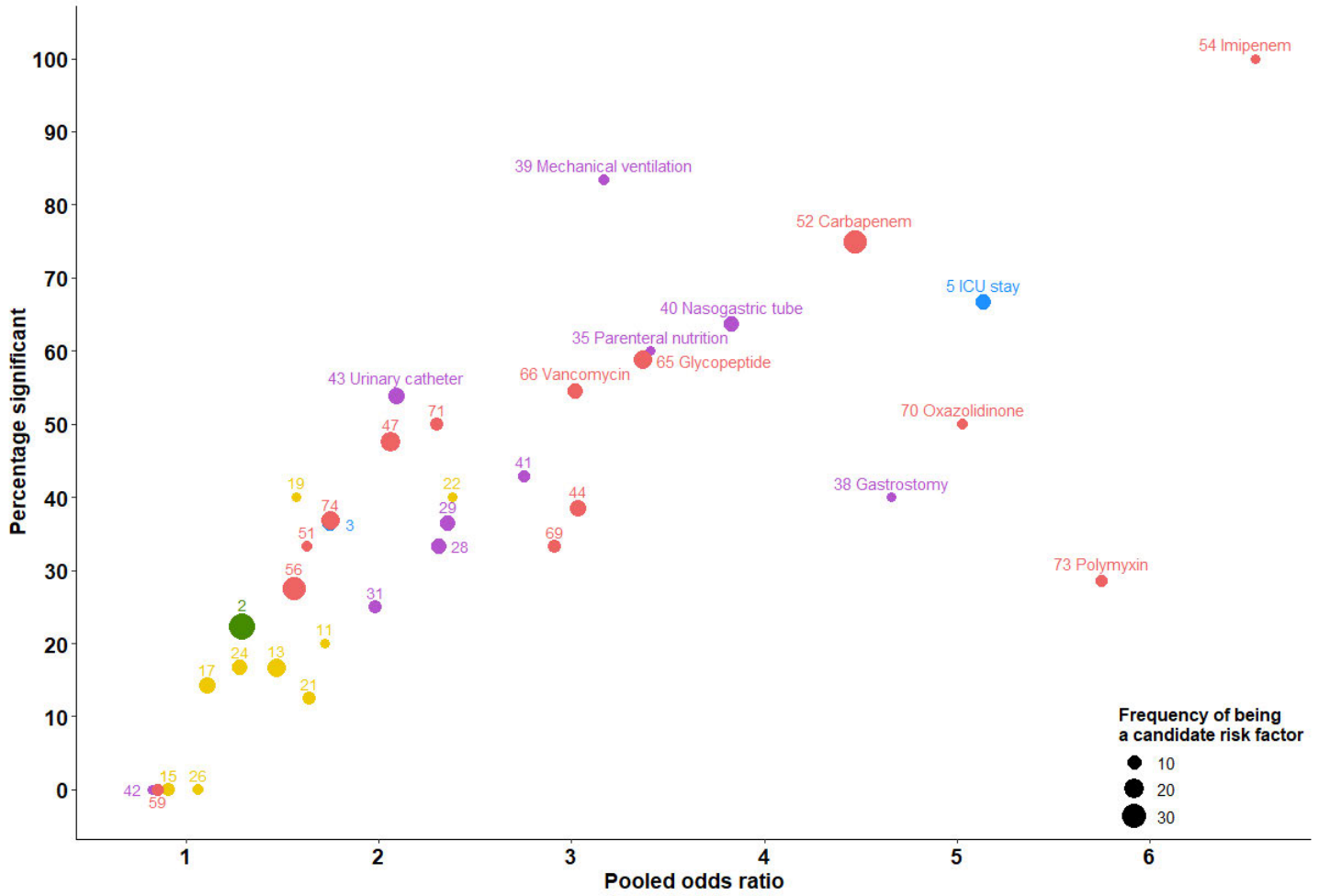


Figure 2-4. Panel (C) Risk factors for CRO colonisation

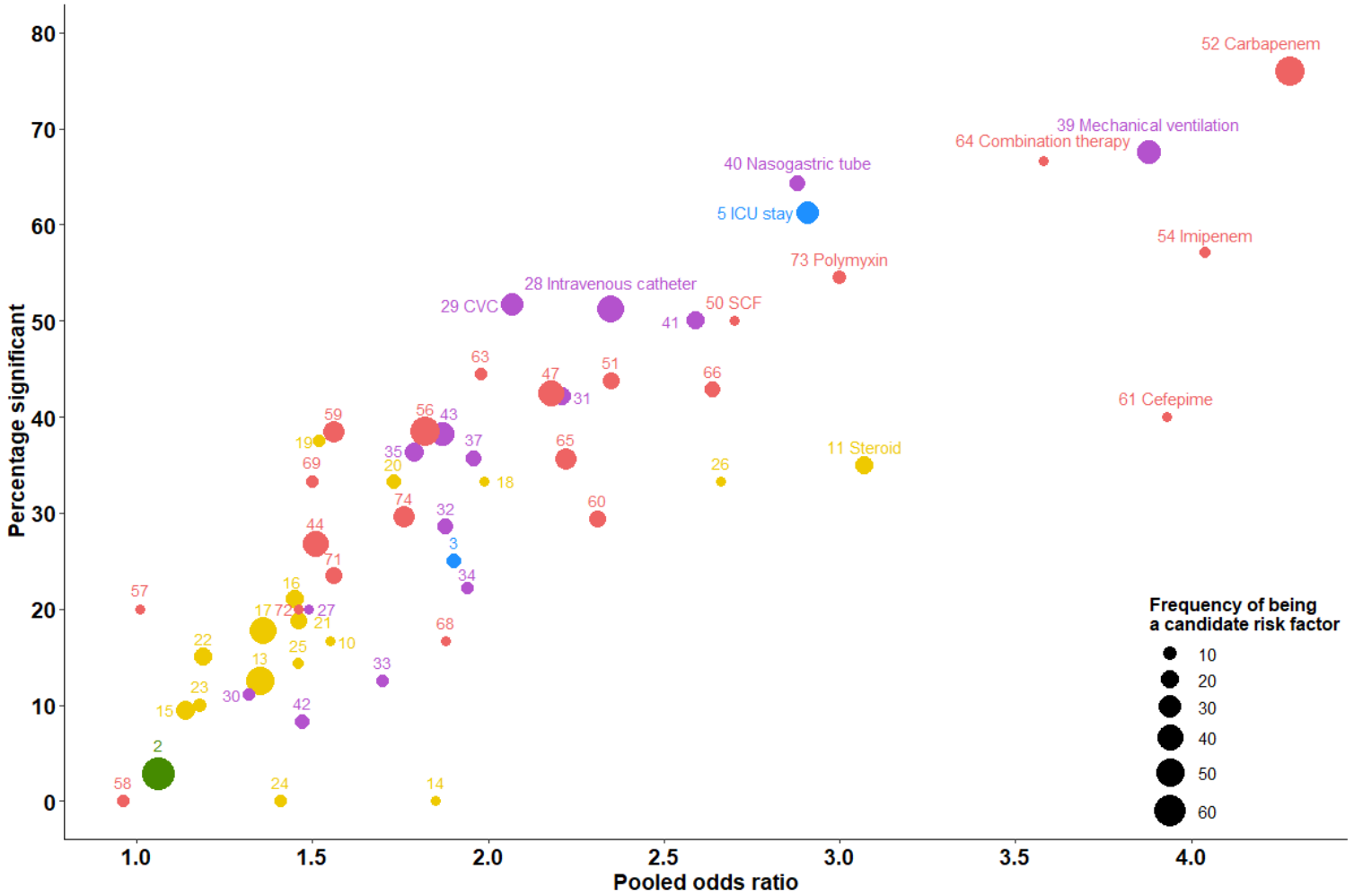


Figure 2-4. Panel (D) Risk factors for CRO hospital-acquired infection

Figure 2-4. Risk factors for carbapenem-resistant organisms (CRO) status showing pooled odds ratio (OR) against percentage of studies where risk factor was statistically significant for (A) Presence of CRO. (B) CRO infection. (C) CRO colonization. (D) CRO hospital-acquired infection. Size of dot denoting the number of risk studies in which the factor was included. Colour of point indicating one of five categories of risk factor: green, demography including age and gender; blue, healthcare-associated exposure; yellow, comorbidities; purple, exposure to invasive medical procedure and/or devices; red, prior antibiotic exposure. Risk factor Key: 1. Age (>65yrs); 2. Gender-male; 3. Prior hospitalisation; 4. Hospital transfer; 5. ICU stay; 6. Prior presence of CRO; 7. Presence of ESBL producers; 8. Presence of methicillin-resistant Staphylococcus aureus (MRSA); 9. Presence of vancomycin-resistant Enterococci (VRE); 10. Chemotherapy; 11. Steroid usage; 12. Decubitus ulcer; 13. Diabetes mellitus; 14. human immunodeficiency virus (HIV); 15. Liver diseases; 16. chronic obstructive pulmonary disease (COPD); 17. Malignancy; 18. Hematologic malignancy; 19. Neurological disease; 20. Neutropenia; 21. Renal failure; 22. Trauma; 23. Hypertension; 24. Heart failure; 25. Coronary artery disease; 26. Stroke; 27. Blood transfusion; 28. Intravenous catheter; 29. central venous catheter (CVC); 30. Arterial catheter; 31. Dialysis; 32. Hemodialysis; 33. Drainage; 34. Enteral nutrition; 35. Parenteral nutrition; 36. Endoscopy; 37. Endotracheal tube; 38. Gastrostomy; 39. Mechanical ventilation; 40. Nasogastric tube; 41. Tracheostomy; 42. Transplantation; 43. Urinary catheter; 44. Prior aminoglycoside use; 45. Prior amikacin use; 46. Prior antifungal use; 47. Prior β-lactam/β-lactamase inhibitor use; 48. Prior amoxicillin-clavulanate (AMC) use; 49. Prior ampicillin-sulbactam (AMS) use; 50. Prior cefoperazone-sulbactam (SCF) use; 51. Prior piperacillin-tazobactam (TZP) use; 52. Prior carbapenem use; 53. Prior ertapenem use; 54. Prior imipenem use; 55. Prior meropenem use; 56. Prior cephalosporin use; 57. Prior first generation cephalosporins use; 58. Prior second generation cephalosporins use; 59. Prior third generation cephalosporins use; 60. Prior fourth generation cephalosporins use; 61. Prior cefepime use; 62. Prior first/second generation cephalosporins use; 63. Prior third/fourth generation cephalosporins use; 64. Prior combination antimicrobial therapy; 65. Prior glycopeptide use; 66. Prior vancomycin use; 67. Prior clindamycin use; 68. Prior macrolide use; 69. Prior metronidazole use; 70. Prior oxazolidinone use; 71. Prior penicillin use; 72. Prior extended spectrum penicillin use; 73. Prior polymyxin use; 74. Prior fluoroquinolone use; 75. Prior ciprofloxacin use; 76. Prior tigecycline use; 77. Prior trimethoprim-sulfamethoxazole (TMP-SMX) use.

2.3.8 Study characteristics accounting for heterogeneity

Leading risk factors (from Figure 2-4) with high heterogeneity (I^2>75%) and consistent definitions were investigated for sources of heterogeneity. Study organism (5.5-44.1%), case-control selection (2.0-35.8%), study population (3.6-16.0%), sample size (6.6-15.2%), study setting (1.2-10.5%) and specialty (ICU or non-ICU) (3.1-10.2%) were the characteristics accounting for most heterogeneity (Appendix 2-10). However, generally the heterogeneity could not be reduced substantially through sub-group analyses based on these variables (noting that sample sizes were often small).

2.4 Discussion

From 2005 onward global carbapenem usage increased due to the appearance of multidrug-resistant organisms worldwide (Kwint et al., 2012; Liew et al., 2011; Meyer et al., 2010) and the number of studies on risk factors for CRO has shown an upward trend since then (Figure 2-2). The majority of these studies were conducted in European, the Americas and Western Pacific regions where CRO are endemic or epidemic. Also, the geographical distribution of published work mirrors the geographical distribution of Gross Domestic Product (The World Bank, 2017) with no studies from low income countries. The lack of financial support and a formal framework for collaboration among surveillance programmes across the regions providing accurate and reliable data may account for this gap. Some high income countries (e.g. Canada, New Zealand) have CRO surveillance programmes but have low incidence of CRO and have not published any risk factor studies.

2.4.1 Prior antibiotic exposure related risk factors

For both CRO presence and infection, prior CRO carriage had both the highest likelihood of being significant and the highest pooled OR estimate. Notably, most of these studies (6/7, 85.7%) showed that preoperative CRO colonisation increased the risk of postoperative CRO infection. The rate of postoperative

infection among colonised patients was consistently close to 40%, this whilst the patients were given targeted antibiotic prophylaxis (Freire et al., 2016c; Giannella et al., 2015; Salsano et al., 2016). Moreover, exposure to carbapenems and cumulative carbapenem exposure in days were widely reported as risk factors for CRO presence. It was reported that antimicrobial susceptible organisms in body flora of inpatients could be replaced with antimicrobial resistant strains over time (Ozkurt et al., 2005; Altoparlak et al., 2004; Erol et al., 2004) and for each additional day of antibiotic therapy, the risk of carbapenem resistant Enterobacteriaceae (CRE) isolation increased by 47% compared to general hospitalised controls (Lee et al., 2013a). This study found that combination therapy was among the leading risk factors for CRO infection including hospital-acquired infections. One reasonable explanation is that, empirical combination therapy consisting of cephalosporins or carbapenems combined with a glycopeptide or oxazolidinone for both Gram negative and positive coverage is initiated when an infection with multidrug-resistant organisms is suspected but before diagnostic test results (which may take 48 hours) are available (van Loon et al., 2018). Correspondingly, exposure to carbapenems or cephalosporins have been demonstrated as risk factors for VRE infections (Weinstein and Hayden, 2000; Morris et al., 1995; Beezhold et al., 1997; Tornieporth et al., 1996). Although some studies suggested that two or more antimicrobials could increase protection (Papadimitriou-Olivgeris et al., 2014; Tumbarello et al., 2012; Zarkotou et al., 2011; Tzouvelekis et al., 2012), a residual impairment of normal flora resulting from antimicrobial toxicity of combination therapy might increase the risk of acquiring CRO (Onguru et al., 2008; Salsano et al., 2016). It is generally accepted that selective pressure caused by antibiotic use could disrupt the commensal flora and thus predispose individuals to multidrug-resistant organisms colonisation and infection. A mouse model demonstrated that CRE intestinal colonisation was promoted by antibiotics that lacked significant activity against CRE but disrupted anaerobic flora (Perez et al., 2011).

In addition, prior polymyxin E (also known as colistin) usage was a leading risk factor for hospital-acquired CRO infection specifically. Some studies reported

that the commonly used antibiotics for nosocomial infections, such as antipseudomonal penicillins, carbapenems, glycopeptides, and colistin were determined as risk factors for the development of CRO infection due to selective pressure or cross-resistance (Akgul et al., 2016; Wu et al., 2011; Cardoso et al., 2012). Moreover, duration of colistin administration prior to carbapenem-resistant *Klebsiella pneumonia* isolation was independently associated with increased frequency of hospital-acquired carbapenem-resistant *Klebsiella pneumonia* infection (Mantzarlis et al., 2013). This may be explained by the fact that, patients with hospital-acquired CRO infection were extensively treated with colistin during ICU stay. This study found that prolonged ICU stay was a risk factor for hospital-acquired CRO infection. Papadimitriou-Olivgeris et al. demonstrated that patients in ICU were more likely to received colistin (31.6%) than patients in medical or surgical wards (0.8%) in addition to a longer length of ICU stay (Papadimitriou-Olivgeris et al., 2012). Similarly, patients with CRO nosocomial infection have more often received broad-spectrum antimicrobial therapy, such as cefepime which ranked third in terms of pooled OR estimate, and are associated with severe illness before infection onset (Zheng et al., 2013).

2.4.2 Prior healthcare exposure related risk factors

Among healthcare facility exposure, VRE carriage was a leading risk factor associated with CRO presence (as indicated by the magnitude of pooled OR estimates and the likelihood of being statistical significant). Interestingly, exposure to vancomycin and oxazolidinone (which is a recommended treatment of VRE infections) were also among the leading risk factors (Figure 2-4) (Bleumin et al., 2012; Dirajlal-Fargo et al., 2014; Ling et al., 2015; Tumbarello et al., 2014; Gomez Rueda and Zuleta Tobon, 2014; Sanchez-Romero et al., 2012; Daikos et al., 2010; Orsi et al., 2013; Papadimitriou-Olivgeris et al., 2012; Satlin et al., 2016; Swaminathan et al., 2013; Torres-Gonzalez et al., 2015). Again, these findings could be explained by the combination empirical or prophylactic therapy for both Gram negative and positive coverage.

2.4.3 Prior invasive medical procedure/devices exposure related risk factors

Invasive indwelling devices or procedures have been widely investigated as risk factors for multidrug-resistant organisms acquisition as bypass the innate host mechanical defences and provide a niche for microorganisms and/or facilitate the entry to the host (Papadimitriou-Olivgeris et al., 2014; Cunha et al., 2016; Borer et al., 2012). Mechanical ventilation and nasogastric tube were leading risk factors associated with different CRO status. More specifically, longer duration of mechanical ventilation was also a leading risk factor for CRO infection including hospital-acquired infection (Figure 2-4 C and D, Appendix 2-7). Mechanical ventilation is a treatment option that is often necessary in critical ill patients (ICU patients in particular) and it is related with the burden of the disease (Mantzarlis et al., 2013). Its duration might be considered as a marker of disease severity (Polito et al., 2011). Moreover, the application of mechanical ventilation usually requires sedation and thus favours the development of nosocomial infections (Nseir et al., 2010). Gastrostomy, parenteral nutrition and urinary catheter were leading risk factors for CRO colonisation specifically (Figure 2-4 C). However, it is usually difficult to confirm if these factors reflect the result of inter-patient/personnel cross transmission (Cunha et al., 2016; Hong et al., 2012; Anderton et al., 1993). Nevertheless, the exist of CRO in the natural or manmade environment is a prerequisite for the entry to occur, so implementation and good compliance of aseptic technique during invasive procedures and infection control measures during daily medical work.

All the above factors should be interpreted with caution as they may present surrogate markers of critical illness and extensive healthcare exposure rather than reflecting a direct association. The same risk factors are associated with multidrug-resistant organisms other than CRO (Lynch, 2001; Merrer et al., 2000; Nseir et al., 2011). Consistent with this interpretation, multiple other studies have reported that longer duration of ICU stay and of hospitalisation are known risk factors (Gregory et al., 2010; Routsi et al., 2013; Ben-David et al., 2014; Harris et al., 2011; Lautenbach et al., 2010). This study also identified

that ICU stay, longer ICU and hospital stay before CRO isolation were consistently leading risk factors for different CRO status (Figure 2-4, Appendix 2-7). Longer hospital stay could predispose to greater risk for colonization with CRO strains through patient-to-patient transmission (Kwak et al., 2005; Borer et al., 2012). Moreover, higher scores of the severity of comorbidity index CCI and APACHE II which is an ICU scoring system were risk factors for CRO presence and infection (Appendix 2-7).

2.4.4 Demography and comorbidities related risk factors

Demography and comorbidities were the most common candidate risk factors investigated by the majority of studies due to accessibility from medical records. Comparing with other groups of risk factors, demography and comorbidities are less likely modifiable in the respect of interventions to prevent emergence and transmission of CRO. However, almost all of them were risk factors with lower percentage of being a risk factor and pooled OR estimates for different CRO status with the exception of decubitus ulcers for CRO infection and steroid administration for CRO hospital-acquired infection (Figure 2-4). Patients with decubitus ulcer are more likely to have a history of hospitalisation and are more debilitated and prone to subsequent infections as decubitus ulcers are favourable sites for bacterial colonisation until they are closed (Ny et al., 2015; Patel et al., 2011). Steroid administration is well recognised as the marker of immunocompromised status (Coutinho and Chapman, 2011). They are usually to treat immunocompromised patients with malignancy or undergone transplantation who are vulnerable to infections (Barshes et al., 2004; Furtado et al., 2010).

2.4.5 Study characteristics contributing to the heterogeneity across studies

This study did not identify any protective factors in terms of pooled OR estimates/SMD and 95% confidence interval. Variation in a range of study characteristics potentially contributed to heterogeneity between studies. Although 44.5% of these studies defined carbapenem resistance according to CLSI guidelines (Table 2-2), the interpretation criteria of carbapenem

resistance issued in different years differed from each other slightly. Moreover, a previous study demonstrated that minimum inhibitory concentration testing revealed discordant results comparing with disk diffusion testing when the same guideline was adopted and susceptibility to one carbapenem did not necessarily correlate with susceptibility or resistance to the other carbapenems tested (Barron et al., 2016). The majority of these studies did not clarify the specific mechanisms of carbapenem resistance (215/254, 84.6%). However, the mechanisms of carbapenem resistance may be associated with different sets of risk factors, outcomes and transmission of resistance, given that carbapenemases are encoded by genes frequently carried on mobile genetic elements responsible for horizontal transmission among species and rapid worldwide spread of carbapenem resistance while the non-enzymatic mechanism is frequently associated with a loss in fitness to the organism and reduced transmissibility. In this respect, discrimination of mechanisms of carbapenem resistance is important for risk factor studies, especially detection of the presence of carbapenemases. This study showed that genotypic and phynotypic resistance could account for 1.2-7.8% of total heterogeneity (Appendix 2-10). van Loon et al. stated that all risk factors showed a decreased (or equal) pooled OR when only studies in which carbapenemase production was shown were included (van Loon et al., 2018). However, this study showed that higher pooled ORs but also greater heterogeneity were obtained when only studies investigating carbapenemase-producing organisms (CPO) were included. Some studies have found that healthcare associated exposure was more strictly related to non-CPO strains than CPO strains (Armand-Lefevre et al., 2013; Orsi et al., 2013) as carbapenemase production does not always confer high-level carbapenem resistance (Anderson et al., 2007).

It is not surprising that studies those focus on non-fermenters have less heterogeneity than those focus on Enterobacteriaceae as the former only involve *Pseudomonas spp.* and *Acinetobacter spp.* while the latter comprise multiple genera and species. Similarly, studies those focus on paediatric patients have less heterogeneity than those on adults and generated higher risk estimates due to better consistency of age definitions and immaturity of

immune system. Choices of controls accounted for substantial amount of heterogeneity (up to 35.8%). There has been considerable debate regarding the choice of controls in risk factor studies of antimicrobial resistance (Orsi et al., 2013; Satlin et al., 2016; Bleumin et al., 2012). More than half (144/254, 56.7%) of these studies chose CRO as cases and CSO as controls. Some studies argued that selecting patients harbouring CSO as controls might raise concerns as patients with CSO do not necessarily represent the source of studied population, thus overestimating the association between antimicrobial exposure and CRO cases (Ahn et al., 2014; Lee et al., 2013a). As discussed above, many risk factors may be surrogate markers of severe, prolonged illness that is not controlled for by selecting controls with similar severity of illness and length of stay. Choice of controls should reflect the question to be answered. Meta-regression analyses also indicated that risk factors showed more consistency and lower risk estimates when studies were conducted in ICU specifically, especially for risk factors associated with invasive indwelling devices (Appendix 2-10). This might be due to common use of such life support devices in ICU.

2.4.6 Estimation of standard deviation from sample size and range

For continuous factors, sample mean and SD are often used to perform meta-analysis. However, some studies only reported sample size, median, range and/or IQR. Thereby, sample mean and SD should be estimated from them. Two studies provided such estimation methods with different equations (Walter and Yao, 2007; Wan et al., 2014). The current study demonstrated the consistency of the two methods reached 89.1% with 101 factors being tested and all the different estimations generated from the two methods did not affect the interpretation of the risk factor. Considering that Walter and Yao's (Walter and Yao, 2007) method only provided equations estimating SD from sample size and range while Wan et al. (Wan et al., 2014) provided mean and SD estimation methods from both range and IQR, the latter estimation method was preferred and adopted. Of note, both methods are based on the assumption that data are normally distributed, the true underlying distribution is unlikely to

be known in practice and medians, ranges and IQRs are often reported when data do not follow a normal distribution. But it is difficult to get the raw data and if a distribution (more likely to be misspecified) is arbitrarily chosen, the estimates from the wrong model can be even worse than that from the normal distribution assumption (Wan et al., 2014). From such respects, the current method seems like a reasonable compromise.

2.4.7 Strengths and limitations

To the best of my knowledge, this is the first study to systematically review risk factors for the presence of CRO (including both Enterobacteriaceae and non-fermenters) in healthcare facilities worldwide, although there was a systematic review just focused on risk factors for CRE (van Loon et al., 2018). A strength of this study is that the overall risk estimates of multiple risk factors were evaluated by using raw data extracted from individual studies and summarised with four aggregate parameters. Some studies simply count up the number of significant and non-significant results in individual studies which is known as vote-counting (Gurevitch et al., 2018), neglecting the magnitude and statistical significance of effects. The metric of the likelihood of being a statistically significant risk factor measures the consistency of the risk factors while the frequency of being a candidate risk factor reflects what risk factors investigators are interested in and the accessibility of getting such information from medical records. However, for some risk factors, this metric should be interpreted with caution as only a small number of studies investigated them. Another strength is the exploration of potential study design-associated sources of heterogeneity for different CRO status which provide evidence and directions for future studies aiming to explore the risk factors for antimicrobial resistance. The sensitivity analysis showed that the pooled estimates were robust after removing studies of low quality.

There are also some limitations. First, only univariate analysis could be conducted without individual data from each study. In individual studies, some factors were significant in univariate analysis but were not independent risk factors in multivariate analysis adjusting for other factors. Therefore, I am not

able to evaluate to what extent one factor are confounded or biased by other factors. Second, although some possible causes of heterogeneity were explored, other methodological characteristics might accounting for heterogeneity such as study quality, time distribution of risk factors before CRO diagnosis and definition of carbapenem resistance were not considered. Hence, a random-effects model for meta-analyses were adopted.

2.5 Conclusion

The two estimation methods of standard deviation had good consistency. This study highlights that prior carriage of multidrug-resistant organisms, prior carbapenem or oxazolidinone use, presence of mechanical ventilation or nasogastric tube, ICU stay, longer ICU stay, longer hospital stay and longer duration of mechanical ventilation were most consistently found to be leading risk factors for CRO. Screening and pre-emptive managements should prioritise patients with these risk factors to limit the emergence and spread of CRO in healthcare settings. Given that most infections occur in early post procedure period and colonisation precedes infection, screening should be performed both before and after invasive procedures, mechanical ventilation and nasogastric tube in particular. Empirical combination therapy including carbapenem, oxazolidinone, vancomycin, colistin or cefepime should be initiated with caution. More efforts should be made to evaluate risk factors associated with CRO in low income countries and high income countries with low CRO incidence. In the future researchers should take study organism, case-control selection, study population, sample size and study setting into account when designing risk factor studies for carbapenem resistance.

Chapter 3 Clinical characteristics and outcomes of CPO

3.1 Background

In the past two decades, emergence of carbapenem-resistant organisms (CRO) has become a global public health crisis, leaving few effective therapeutic options available to treat multidrug-resistant infections (Kim et al., 2014c; Kim et al., 2012b). Resistance to carbapenems arises from two general mechanisms: carbapenemase production or non-enzymatic. CRO strains that do not produce carbapenemases (non-enzymatic) are usually less resistant to other antibiotics (Nordmann et al., 2012a) and their carbapenem resistance trait is not transferable. Carbapenemases, by contrast, are encoded by genes frequently carried on mobile genetic elements such as plasmids and transposons which could be transferred between different species and individuals. Therefore, carbapenemase-producing organisms (CPO) have largely been responsible for the rapid and extensive worldwide spread of CRO and considered of more clinical concern than non-enzymatic CRO.

In Scotland, an increasing number of CPO were reported since its first observation in 2003 (Palepou et al., 2005). Although the incidence of CPO isolates reported remains low, it shows an upward trend (Information Services Division Scotland, 2016). There has been an increase in carbapenems use in acute hospitals and incidence of CPO isolates over the past five years (Information Services Division Scotland, 2016; Health Protection Scotland, 2018d). The epidemiology of Scottish CPO isolates, however, remains unclear. Given that CPO are of more clinical concern as discussed in Section 1.1.2 and there are no comprehensive data of CRO in Scotland, this thesis specifically focuses on CPO reported in Scotland. The aim of this chapter is to conduct a detailed analysis of epidemiological characteristics of CPO in Scotland. Insights based on these findings will further the development of

effective and appropriate prevention and infection control strategies, thus curbing future emergence and spread of CPO in Scotland.

The specific aims of this chapter are:

1) to examine CPO incidence and temporal trend at national level;
2) to investigate the spatial distribution of CPO at National Health Service (NHS) Board level;
3) to investigate the microbiological characteristics of CPO isolates, including specimen (e.g. urine, blood and sputum), organism (e.g. *Escherichia coli*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa*), carbapenemase (e.g. KPC, VIM and NDM) and antimicrobial resistance profile;
4) to determine mortality rate of CPO cases and compare survival of CPO cases by gender, status (infection or colonisation), source (healthcare- or community-associated), organism and carbapenemase;
5) to determine risk factors for all-cause 30-day mortality among hospitalised patients with CPO.

3.2 Methods

3.2.1 Study design

This is a retrospective study of epidemiology of CPO isolated in Scotland between 2003 and 2016. This study was reviewed and approved by the Public Benefit and Privacy Panel for Health and Social Care (Reference number: 1617-0328) (Appendix 3-1). The study population were individuals from whom CPO isolates were isolated in Scotland.

3.2.2 Data

3.2.2.1 Data sources

All the data included in this study were extracted from the datasets listed below (Table 3-1). The additional data was acquired for 2017 including only the number of distinct individuals with CPO isolation.

Table 3-1. Datasets, variables and time frame included in the study

Datasets	Variables	Time frame
The Electronic Communication of Surveillance in Scotland	Laboratory records at individual level: • organism, carbapenemase type, specimen date, specimen site, NHS Board of treatment and residence • antimicrobial susceptibility testing results of CPO isolates	January 2003 to December 2017, only the number of distinct individuals with CPO isolation was available for 2017.
General Acute Inpatient and Day Case-Scottish Morbidity Record	Medical records at individual level: • demographic characteristics (sex and age) • comorbidity according to International Classification of Diseases-10th Revision codes • exposure to medical interventions and procedures according to the OPCS Classification of Interventions and Procedures version 4 in 90 days prior to CPO isolation • hospitalisation records in 90 days prior to CPO isolation	January 2003 to December 2016
National Records of Scotland Deaths	Mortality data at individual level: • date of death • causes of death (one primary cause and up to eight secondary causes) according to International Classification of Diseases-10th Revision codes	January 2003 to December 2017
National Records of Scotland Health Board Population estimates	Midyear population estimates by NHS Board and calendar year	January 2003 to December 2017

3.2.2.2 Data extraction, linkage, provision and storage

In Scotland, specimens with suspected CPO from clinical indications or surveillance programme were submitted to a Scottish diagnostic laboratory. Identification of isolates and antimicrobial susceptibility testing were performed by VITEK®2 (bioMérieux, Marcy-l'Étoile, France) (Trepanier et al., 2017). If the isolate was non-susceptible to ≥1 carbapenem, the diagnostic laboratory would refer the isolate to the antimicrobial resistance and healthcare associated infections reference unit at Public Health England for confirmation of carbapenemase production by in-house polymerase chain reaction (Trepanier et al., 2017).

Construction of the database required extraction and linkage of datasets held at Health Protection Scotland (HPS) and Information Services Division for all hospitalised patients testing positive for CPO. Linkages were performed by HPS and Information Services Division via electronic Data Research and Innovation Service. The Community Health Index number was replaced with an anonymised patient identifier in the file made available for analysis. The anonymised file was transferred to electronic Data Research and Innovation Service team which bases at the FARR Institute to enable preparation, provision and storage of data via the National Services Scotland National Safe Haven. The National Services Scotland National Safe Haven is a secure environment in which data are linked, accessed and analysed. This environment provides a high powered computing service, secure analytic platform, secure file transfer protocol for receipt of data, and provision of a range of analytic software (SPSS, STATA, SAS and R). Access is provided via a secure access point, a physically secure area containing a computer with no external devices e.g. disc, CD, USB drives or printer access, or remotely via an accredited organisation's personal computer or laptop. This allows trusted and authorised researchers to analyse linked individual level data while maintaining the utmost confidentiality. To remotely access the safe haven, there is a two factor authentication process, the first part of which will be receipt

of an access code via the researchers' mobile phone followed by entering the user name and periodically updated password.

3.2.2.3 Ethics

Patients have been informed of the use of their data via two main routes. The first involves the publication of generic leaflets explaining how National Services Scotland uses patient data and these are available in a wide range of healthcare premises. The second method is the National Services Scotland privacy notice which is published on the National Services Scotland website (https://nhsnss.org/how-nss-works/data-protection/). This notice provides information to persons on how National Services Scotland stores and uses NHS Scotland data. All data for analyses in this study were anonymised. Clinical Research Governance of College of Medicine & Veterinary Medicine of University of Edinburgh and NHS Lothian Research & Development team, West of Scotland Research Ethics Service and Usher Institute of University of Edinburgh were consulted for ethical approval. No Research & Development, NHS and formal departmental ethical review or approval were required. The study is covered by National Safe Haven generic ethics approval (Reference number: 1617-0328) (Appendix 3-1).

3.2.3 Definition

3.2.3.1 CPO and microbiological characteristics

CPO were defined as carbapenemase-producing Gram-negative bacilli isolated from both clinical and surveillance samples in Scotland confirmed by antimicrobial resistance and healthcare associated infections reference unit Public Health England. CPO were categorised as either carbapenemase-producing Enterobacteriaceae (CPE) or carbapenemase-producing non-fermenters and each CPO was described at family, genus and species levels (Table 3-2). All the samples where CPO were isolated in were aggregated into 7 specimen groups (Table 3-3). Carbapenemases included GES, KPC, IMI, IMP, NDM, VIM and OXA-48. According to Ambler's structural classification

based on analogies of the peptide sequence (Ambler, 1980), carbapenemases belong to class A (KPC, IMI and GES), B (IMP, VIM, NDM) and D (OXA-48). Amber class B enzymes are also known as metallo-beta-lactamases. AST were available from the VITEK® automated system. Antimicrobial agents tested were listed in Table 3-4. Intrinsic resistance means that the bacteria have the innate ability to resist the action of an antimicrobial agent as a consequence of the structural or functional characteristics of the bacteria.

Table 3-2. Carbapenemase-producing organisms (CPO) included in this study (Family, Genus and Species)

Family	Genus	Species
Enterobacteriaceae	*Citrobacter*	*Citrobacter freundii*
	Enterobacter	*Enterobacter cloacae*
		Enterobacter spp. (specific species unknown)
	Escherichia	*Escherichia coli*
	Klebsiella	*Klebsiella pneumonia*
		Klebsiella oxytoca
		Klebsiella spp. (specific species unknown)
	Proteus	*Proteus mirabilis*
	Providencia	*Providencia rettgeri*
		Providencia stuartii
Non-fermenters	*Acinetobacter*	*Acinetobacter baumannii*
		Acinetobacter indicus
	Pseudomonas	*Pseudomonas aeruginosa*
		Pseudomonas fluorescens
		Pseudomonas putida
		Pseudomonas stutzeri

Table 3-3. Specimens where carbapenemase-producing organisms (CPO) isolates were collected from

Aggregate specimen group	Specific specimen
Alimentary	faeces, rectal swab
Normally sterile site	ascetic fluid, aspirate, bile, blood, cerebrospinal fluid, knee tissue, peritoneal swab
Respiratory	broncho-alveolar lavage, endotracheal aspirate, sputum

Superficial	axilla swab, groin swab, penile swab, perianal swab, sacral swab, skin swab
Urine	catheter urine, mid-stream urine, urine
Wound	abscess/pus/ulcer, catheter/drain site swab, wound swab
Site unspecified	site unspecified

Table 3-4. Antimicrobial agents included in antimicrobial susceptibility testing

Antimicrobial class	Agents	Intrinsic resistance
Penicillin	Amoxicillin (AMX)	
	Ampicillin (AMP)	*Enterobacter cloacae* *Klebsiella pneumoniae* *Acinetobacter baumannii* *Pseudomonas aeruginosa*
β-Lactam/β-lactamase inhibitor combinations	Amoxicillin-clavulanate (AMC)	*Enterobacter cloacae* *Acinetobacter baumannii* *Pseudomonas aeruginosa*
	Piperacillin-tazobactam (TZP)	
Cephalosporin	Ceftriaxone (CTR)	*Acinetobacter baumannii* *Pseudomonas aeruginosa*
	Cefotaxime (CTX)	*Acinetobacter baumannii* *Pseudomonas aeruginosa*
	Ceftazidime (CAZ)	
Cephamycin	Cefoxitin (FOX)	*Enterobacter cloacae*
Monobactam	Aztreonam (ATM)	*Acinetobacter baumannii*
Carbapenem	Imipenem (IPM)	
	Meropenem (MEM)	
Aminoglycoside	Amikacin (AK)	
	Gentamicin (GM)	
Folate pathway inhibitors	Trimethoprim (TMP)	*Acinetobacter baumannii* *Pseudomonas aeruginosa*
Fluoroquinolone	Ciprofloxacin (CIP)	

3.2.3.2 Case, isolation and isolate

Each distinct individual with positive culture of CPO was defined as one CPO case. A hospitalised case is an individual that was hospitalised when CPO was diagnosed, i.e. date of CPO isolation was between date of admission to and date of discharge from a hospital. Index hospitalisation was the hospitalisation during which the specimen with positive culture of CPO was collected.

One CPO isolation was defined on the basis of organism (species level), carbapenemase, isolation date and specific specimen. Isolations different in any of these characteristics represented different isolations.

One CPO isolate was defined on the basis of organism at species level and carbapenemase. A difference in either organism or carbapenemase represented different isolates.

3.2.3.3 Source: healthcare-associated and community-associated

Regarding source, all cases were classified as either healthcare-associated or community-associated following the criteria: 1) healthcare-associated, specimen with a positive culture was collected at least 48 hours after hospital admission or specimen with a positive culture was collected within 48 hours of hospital admission in patients that had previous hospital admission within one year before the index hospitalisation admission or specimen with a positive culture was collected in community but the individual had previous hospital admission within one year before the index specimen collection; 2) community-associated, specimen with a positive culture was collected within 48 hours of hospital admission in patients that had no hospital admission within one year before the index hospitalisation admission or specimen with a positive culture was collected in community and the individual had no previous hospital admission within one year before the index specimen collection. If one case had more than one CPO isolations, the classification was based on the first isolation.

3.2.3.4 Status: infection and colonisation

As discussed in Section 2.3.6, infection and colonsiation have different implications for healthcare of antimicrobial resisatnce from clinical and public health perspectives, therefore the status of each CPO case was categorised as an infection, a colonisation or an unclassifiable subject. The definitions of status are listed in Table 3-5. CPO presence represented a positive test of CPO, regardless of the status.

For CPO infection cases, they were classified as hospital-acquired infection (HAI), healthcare-associated infection (HCAI) or community-acquired infection (CAI) following the definitions (Cardoso et al., 2014; Horan et al., 1992): 1) HAI, specimen with a positive culture was collected at least 48 hours after hospital admission; 2) HCAI, specimen with a positive culture was collected within 48 hours of hospital admission in patients that had previous hospital admission within one year before the index hospitalisation admission or specimen with a positive culture was collected in community but the individual had previous hospital admission within one year before the index specimen collection; 3) CAI, specimen with a positive culture was collected within 48 hours of hospital admission in patients that had no hospital admission within one year before the index hospitalisation admission or specimen with a positive culture was collected in community and the individual had no previous hospital admission within one year before the index specimen collection.

Table 3-5. Definition of status of carbapenemase-producing organisms (CPO)

Status	Definition
Infection	For cases with single isolation, fulfilled any of the following criteria: • For hospitalised patients, the specimen matched an infection diagnosis, e.g. the isolate was isolated from urine and with a diagnosis of urinary tract infection • For hospitalised patients, the primary diagnosis is sepsis with no source specified • For both hospitalised patients and non-hospitalised patients, the isolate was isolated from normally sterile sites For cases with multiple isolations: • If any isolation fulfilled the infection criteria above, the case would be classified as an infection case.
Colonisation	For cases with single isolation, fulfilled either of the following criteria: • For hospitalised patients, there was no infection diagnosis during hospitalisation; • For hospitalised patients, there was a clear infection diagnosis caused by a different organism(s) at a different site from CPO isolates; • For non-hospitalised patients, fulfilled either of the following criteria: 1. no hospitalisation within 1 year of CPO isolation; 2. no hospitalisation in the prior 1 year of CPO isolation and was admitted to a hospital within one year after CPO isolation but had no infection diagnosis For cases with multiple isolations: • If all the isolations of a case fulfilled the colonisation criteria above, the case would be classified as a colonisation case.
Unclassifiable	Those could not be definitely classified as either infection or colonisation, e.g. the isolate was isolated from urine but with a diagnosis of pneumonia without a specified causative organism.

3.2.3.5 Mortality

CPO attributed death fulfilled any of the following criteria: 1) infection was primary cause of death, no specimen restrictions and time lapse between CPO isolation and death ≤ 30 days; 2) chronic disease was primary cause of death, acute infection was secondary cause of death, specimen matched infection and time lapse between CPO isolation and death ≤ 30 days; 3) sepsis was secondary cause of death, no specimen restrictions and time lapse between CPO isolation and death ≤ 30 days; 4) specimen was from normally sterile sites, infection was either primary or secondary cause of death and time lapse between CPO isolation and death ≤ 30 days.

3.2.3.6 Rates

CPO incidence was calculated with midyear population estimates per year, using the formula:

$$\text{incidence} = \frac{\text{number of CPO cases per year}}{\text{midyear population estimates per year}} * 100{,}000$$

The percentage of infection, colonisation and unclassifiable cases per year was examined using the formula:

$$\text{Percentage of CPO cases of different status} = \frac{\text{number of CPO infection, colonisation or unclassifiable cases per year}}{\text{total number of CPO cases per year}} * 100$$

The percentage of healthcare- and community-associated cases per year was examined using the formula:

$$\text{Percentage of CPO cases of different sources} = \frac{\text{number of CPO healthcare} - \text{ or community} - \text{associated cases per year}}{\text{total number of CPO cases per year}} * 100$$

The percentage of each genus in each family and percentage of each carbapenemase per year was examined using the formula:

$$\text{Percentage of genus} = \frac{\text{number of CPO isolates of the genus per year}}{\text{total number of CPO isolates per year}} * 100$$

$$\text{Percentage of carbapenemase} = \frac{\text{number of CPO isolates producing the carbapenemase per year}}{\text{total number of CPO isolates per year}} * 100$$

Antimicrobial resistance rate was defined using the formula:

$$\text{Resistance rate} = \frac{\text{number of CPO isolates resistant or intermediate to the tested agent}}{\text{number of CPO isolates tested for this agent}} * 100$$

Case fatality rate was defined as the number of CPO attributed deaths per 100 CPO cases using the formula:

$$\text{case fatality rate} = \frac{\text{number of CPO attributed deaths}}{\text{number of CPO cases}} * 100$$

Hospital mortality rate was defined using the formula:

$$\text{Hospital mortality rate} = \frac{\text{number of CPO cases died in hospital}}{\text{total number of CPO cases}} * 100$$

All cause 30-day or 1-year mortality rate was defined using the formula:

$$\text{All cause } 30-\text{day or } 1-\text{year mortality rate} = \frac{\text{number of CPO cases died within 30 days or 1 year after CPO isolation}}{\text{total number of CPO cases}} * 100$$

3.2.4 Statistical analysis

All statistical analyses were carried out using R (version 3.5.1) on the secure analytical platform within the National Services Scotland National Safe Haven provided and supported by electronic Data Research and Innovation Service team. Maps were drawn using ArcGIS (version 10.5.1). A *P* value <0.05 was considered significant.

3.2.4.1 Temporal trends

The temporal trend of CPO incidence at national level was explored using an exponential model; temporal trends of Enterobacteriaceae and non-fermenters at national level (change in the number of cases with Enterobacteriaceae and non-fermenters over time offset by the corresponding midyear population estimates) were explored using a generalised linear model (Poisson regression or a quasi-Poisson regression for over-dispersed data, with a log link function). Differences in temporal incidence trends between Enterobacteriaceae and non-fermenters were examined by testing for an interaction between bacterial family and isolation year.

Temporal trends of CPO infection, colonisation and unclassifiable incidence at national level (change in the number of CPO infection, colonisation and unclassifiable cases over time offset by the corresponding number of CPO cases in each year) were explored using a generalised linear model (Poisson regression or a quasi-Poisson regression for over-dispersed data, with a log link function). Differences in temporal incidence trends between infection and colonisation were examined by testing for an interaction between status and isolation year.

Temporal trends of healthcare-associated and community-associated CPO incidence at national level (change in the number of healthcare-associated and community-associated cases over time offset by the corresponding number of CPO cases in each year) were explored using a generalised linear model (Poisson regression or a quasi-Poisson regression for over-dispersed data, with a log link function). Temporal trends of percentage by source (as defined in Section 3.2.3.6) among CPO cases (change in the number of CPO cases of each source over time offset by the corresponding number of CPO cases in each year) were explored using a generalised linear model (Poisson regression or a quasi-Poisson regression for over-dispersed data, with a log link function).

For HAI cases, NHS board of treatment was used; for the other cases, NHS board of residence was used. Given the possibility of patients being identifiable and personal information disclosure due to small numbers of CPO cases (less than 5 cases) and geographical proximity, NHS Highland/NHS Western Isles/NHS Orkney/NHS Shetland, and NHS Ayrshire & Arran/NHS Borders were respectively combined together. CPO incidence in each NHS Board was calculated following the formula defined in Section 3.2.3.6.

Temporal trends of percentage by genus and carbapenemase (as defined in Section 3.2.3.6) among CPO isolates (change in the number of CPO isolates of each genus/with each carbapenemase over time offset by the corresponding number of CPO isolates in each year) were explored using a generalised linear model (Poisson regression or a quasi-Poisson regression for over-dispersed data, with a log link function).

3.2.4.2 Microbiological characteristics

For one CPO case, if there were multiple isolations of the same isolate from the same specimen on different dates then only the first isolation was included in the study. This method was used in order to more uniformly assess diversity of carbapenemases and independent specimen sources for statistical analysis.

Antimicrobial resistance rates of each antimicrobial agent for Enterobacteriaceae and non-fermenters isolates were evaluated respectively. The resistance rates were compared between the two families and between infection and colonisation using Pearson’s Chi-squared test or Fisher’s exact test as appropriate.

3.2.4.3 Survival and mortality

The Kaplan-Meier method was used to plot 1-year survival curves. Differences between survival curves at 30-day and 1-year by gender, status (infection and colonisation), source (healthcare-associated and community-associated) and

bacterial family were evaluated by the log-rank test (Mantel, 1966; Peto and Peto, 1972).

For risk factors for 30-day mortality of hospitalised CPO cases, all the hospitalised CPO cases were divided into two groups: dead (non-survivor) or alive (survivor) within 30 days after CPO isolation. Independent variables included demographics, microbiological characteristics, comorbidities, healthcare exposure in the prior 90 days before CPO isolation (i.e. specimen date), invasive procedures in the prior 90 days before CPO isolation. The definition of each independent variable is listed in Appendix 3-2. A generalised linear mixed model with hospital where CPO was isolated as a random effect was used. Univariate analysis was performed first with each variable entered the model on its own and all variables with $P<0.10$ were carried forward for multivariate analysis. Correlations between variables with $P<0.10$ in univariate analysis were checked by calculating correlation coefficients (Spearman's rank correlation coefficient between continuous variables, Cramér's V between dichotomous variables or point-biserial correlation coefficient between continuous variables and dichotomous variables) and variance inflation factor (VIF). Also, possible interactions between variables were checked. For variables with high-level correlation (correlation coefficient≥0.70) and multicollinearity (VIF>4), variables with greater corrected Akaike Information Criterion (AICc) value were removed from the model, the remaining variables were considered to be included in the multivariate analysis. Models with all possible independent variable combinations were considered for the final multivariate model. These models were ranked based on AICc values (from low to high) and Akaike weights (from high to low). Candidate models were selected using $\Delta AICc<2$ and Akaike weights>0.05, with the best approximating candidate model having the highest Akaike weights (Anderson and Burnham, 2002). Model averaging was used to construct the final multivariate model using the Akaike weights of the candidate models (Anderson et al., 2000). For statistical purpose, variables with zero values in either group were removed from multivariate analyses, i.e. no patients in either group had exposure to the potential risk factor of interest. Odds ratio (OR) and 95% confidence interval

(95%CI) were calculated to determine the strengths of these associations. A *P* value <0.05 was considered significant.

3.3 Results

3.3.1 Overview

This section provides a comprehensive description of CPO including numbers of CPO cases/isolations/isolates, demographic and clinical characteristics of CPO cases, and status (infection/colonisation/unclassifiable) and source (healthcare-associated/community-associated) of CPO cases. A total of 290 persons were diagnosed with CPO isolation in Scotland between 2003 and 2017. Unfortunately, the metadata was not available for 2003 (n=1) and 2017 (n=75), so only 214 distinct CPO cases identified between 2004 and 2016 were included in subsequent analyses, other than incidence analysis at national level. Among the 214 CPO cases, 170 (79.4%) had a single isolation while 44 (20.6%) had multiple isolations, resulting in 285 CPO isolations. There was a total of 243 distinct CPO isolates obtained from the 214 CPO cases. One-hundred and seventy-three (71.2%) of the 243 isolates were isolated from hospitalised patients in 29 hospitals, including 12 tertiary care hospitals (107/173, 61.8%), 14 secondary care hospitals (63/173, 36.4%) and 3 community/rehabilitation hospitals (3/173, 1.7%), and the remaining 70 isolates were isolated in the community.

Metadata were not complete for 3 cases, all of which were female. Medical records were available for the remaining 211 cases and analysis of CPO status and source was performed on these. One hundred and fifty (71.1%) of the 211 cases were hospitalised patients. Clinical characteristics of CPO cases are listed in Table 3-6 and the definitions of these characteristics are listed in Appendix 3-2. Healthcare exposure characteristics of index hospitalisation were available only for 150 hospitalised CPO cases.

There were slightly more female cases (112/214, 52.3%) than male cases (102/214, 47.7%). The age of the 211 CPO cases ranged from 0 to 92 years (median age 63 years, interquartile range IQR 53-78 years). There was no difference in age between male cases (median age 64 years, IQR 53-75 years) and female cases (median age 63 years, IQR 52-78 years) (*P*=0.838, Wilcoxon rank-sum test). The percentage of female cases was generally higher than that of male cases other than 60-79 years age group (Figure 3-1).

Table 3-6. Clinical characteristics of carbapenemase-producing organisms (CPO) cases

Characteristics	Number (%)[¶]
Demographics	
Age, years, median (IQR, range)	63 (53-78, 0-92)[§], for 211 cases
Older (>60 years)	124/211 (58.8)
Gender, male	102/214 (47.7)
Comorbidities	
Certain infectious and parasitic diseases	70/211 (33.2)
Sepsis	18/211 (8.5)
Co-presence with other pathogens	24/211 (11.4)
Neoplasms and diseases of the blood and blood-forming organs	53/211 (25.1)
Malignancy	38/211 (18.0)
Solid	16/211 (7.6)
Hematologic	22/211 (10.4)
Anaemia	11/211 (5.2)
Endocrine, nutritional and metabolic diseases	37/211 (17.5)
Diabetes mellitus	21/211 (10.0)
With complications	8/211 (3.8)
Diseases of the circulatory system	51/211 (24.2)
Heart failure	3/211 (1.4)
Diseases of the respiratory system	53/211 (25.1)
Respiratory tract infection	33/211 (15.6)
Respiratory failure	5/211 (2.4)
Diseases of the digestive system	21/211 (10.0)
Diseases of the genitourinary system	58/211 (27.5)
Urinary tract infection	35/211 (16.6)
Renal failure	21/211 (10.0)
Diseases of the nervous system	21/211 (10.0)
Diseases of the skin and subcutaneous tissue	14/211 (6.6)

Characteristics	Number (%)¶
Diseases of the musculoskeletal system and connective tissue	19/211 (9.0)
External causes of morbidity	53/211 (25.1)
Injury, poisoning and certain other consequences of external causes	49/211 (23.2)
Immunocompromised status	44/211 (20.9)
Healthcare exposure	
HDU stay	58/211 (27.5)
Duration of HDU stay, days, median (IQR, range)	0 (0-1, 0-65)§, for 211 cases
ICU stay	45/211 (21.3)
Duration of ICU stay, days, median (IQR, range)	0 (0-0, 0-39)§, for 211 cases
Hospitalisation	87/211 (41.2)
Duration of hospitalisation, days, median (IQR, range)	8 (0-31.5, 0-91)§, for 211 cases
Hospital transfer	32/211 (15.2)
Ward transfer	97/211 (46.0)
Emergency admission	127/150 (84.7)
Admission from healthcare facilities	16/150 (10.7)
Surgical Specialty	69/150 (46.0)
Time at risk, days, median (IQR, range)	6.5 (1-25, 0-91)§, for 150 cases
Discharge type, death	32/150 (21.3)
Discharge to healthcare facilities	18/150 (12.0)
Invasive procedures	
Any	75/211 (35.5)
Centesis	10/211 (4.7)
Ectomy	20/211 (9.5)
Transplantation	4/211 (1.9)
Catheterisation	19/211 (9.0)
Urinary catheter	6/211 (2.8)
CVC	15/211 (7.1)
Dialysis or drainage	7/211 (3.3)
Endoscopic operation	17/211 (8.1)
Invasive ventilation	9/211 (4.3)
Other surgical procedures	26/211 (12.3)

¶, Number of cases with the characteristics/total number of cases investigated (percentage of cases with the characteristics), unless stated otherwise;
§, median (interquartile range IQR, range);
ICU, intensive care unit; HDU, high dependency unit; CVC, central venous catheter.

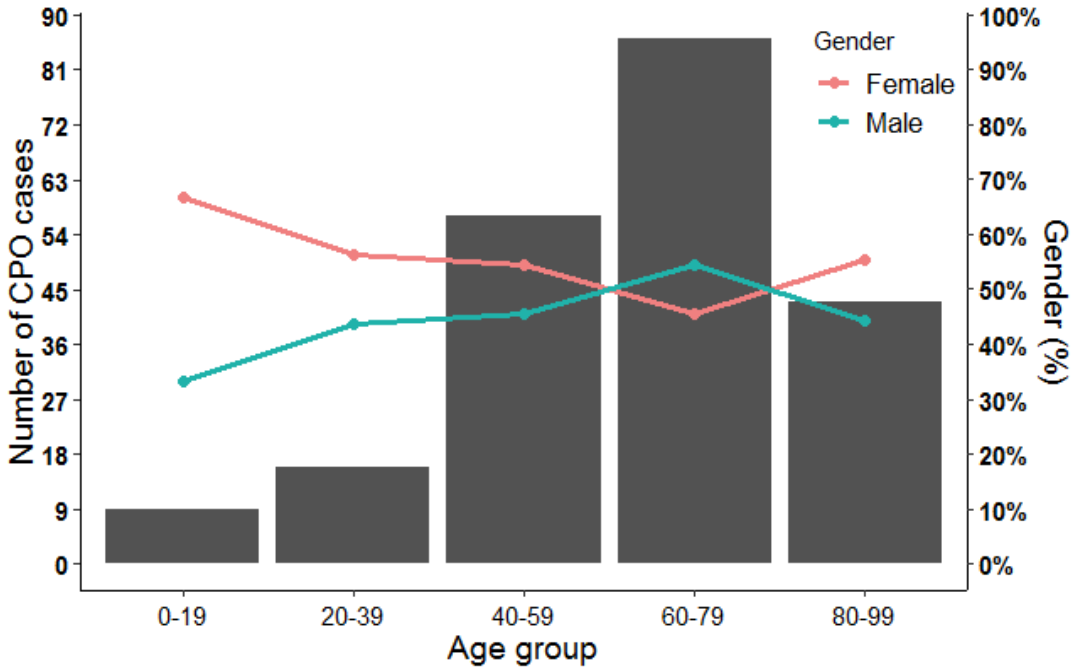
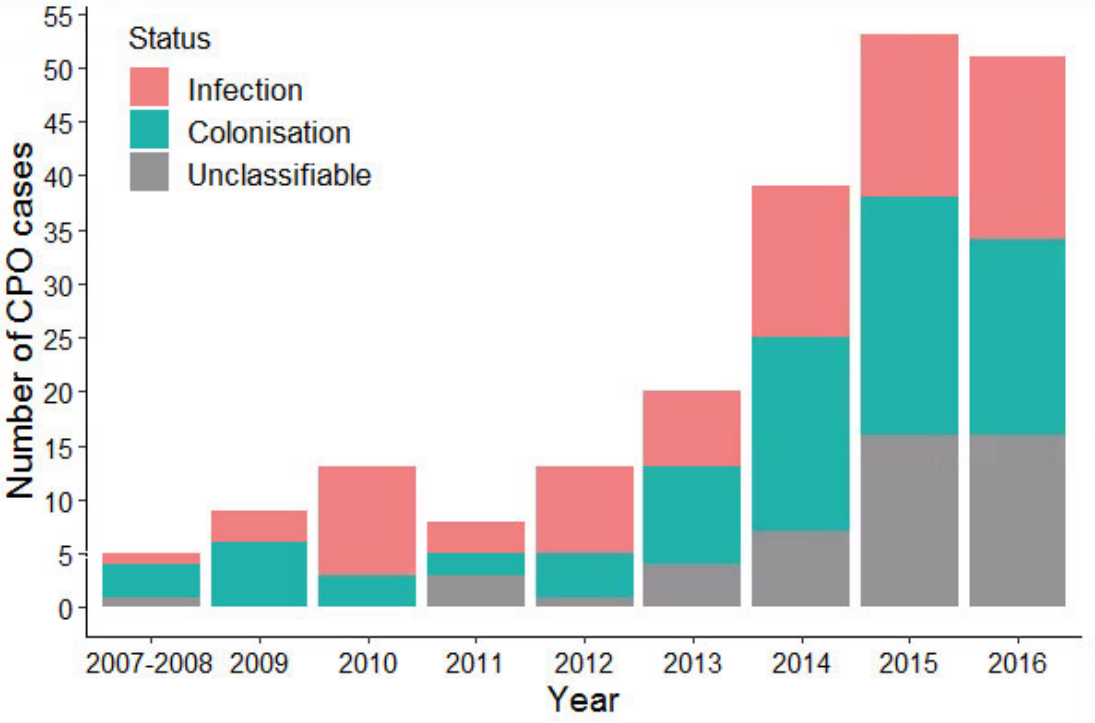


Figure 3-1. Gender distribution of 211 carbapenemase-producing organisms (CPO) cases within 20-year age groups. Bar chart shows number of cases per 20-year age group; scatter plot and line chart illustrate gender distribution of 211 CPO cases per 20-year age group.

The 211 cases comprised 78 (37.0%) infection cases, 85 (40.3%) colonisation cases and 48 (22.7%) unclassifiable cases. Due to the small numbers of cases in 2007-2008 (less than 5), they were combined together. The temporal distribution of CPO cases by status is shown in Figure 3-2. Among the 78 infection cases, there were 46 (59.0%) HAI cases, 18 (23.1%) HCAI cases and 14 (17.9%) CAI cases. Seventy-two of the 78 infection cases were hospitalised patients and nearly half (35/72, 48.6%) of them were hospitalised in surgical specialties while 25.0% (18/72) were in ICU/HDU. Urinary tract infection (UTI) (23/78, 29.5%) was the most common, followed by bloodstream infection (21/78, 26.9%), respiratory tract infection (12/78, 15.4%), wound infection (9/78, 11.5%), gastrointestinal infection (7/78, 9.0%), bacterial meningitis (3/78, 3.8%) and skin and soft tissue infection (3/78, 3.8%). Due to the small numbers of bacterial meningitis and skin and soft tissue infection cases (less than 5), they were combined together. Numbers of infection cases by infection

type and bacterial family and genus are shown in Figure 3-3. There were significant differences in the number of infection types associated with bacterial family (*P*<0.001, Fisher's exact test). All UTI and gastrointestinal infections were caused by Enterobacteriaceae isolates, majority of which were *Enterobacter spp.*, *Escherichia coli* (*E. coli*) and *Klebsiella spp.* isolates. Half (6/12, 50.0%) of respiratory tract infections were caused by *Pseudomonas spp.* isolates. For the other infection types, more infections were caused by Enterobacteriaceae isolates than non-fermenters.

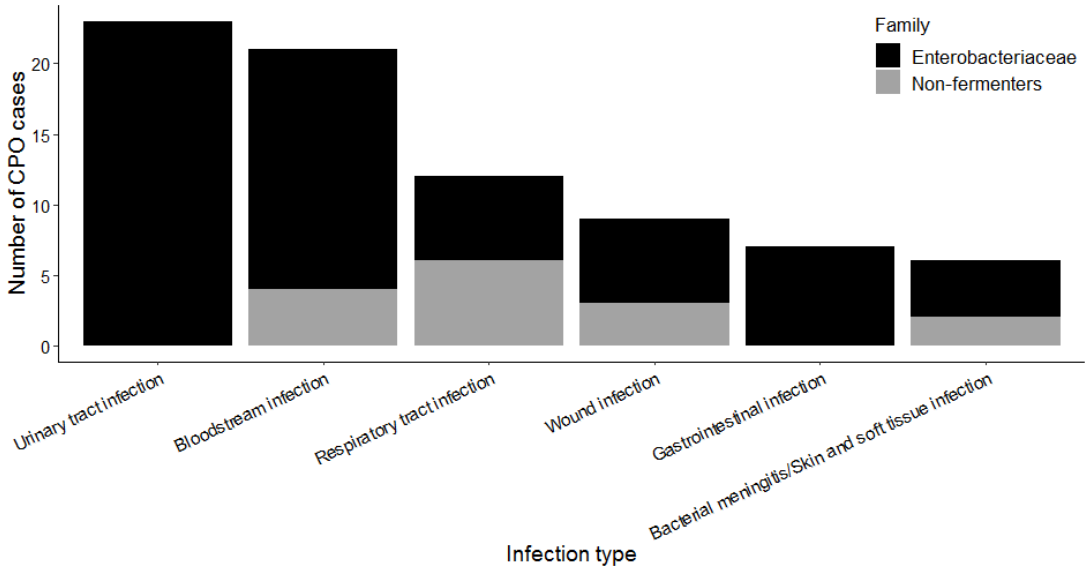
Incidence of infection increased significantly over time (*P*<0.001, based on a Poisson regression model) while proportion of infection cases tended to stay stably since 2013 (Figure 3-2). Among the 85 colonisation cases, more than half of the isolates were isolated from urine (47/85, 55.3%), followed by alimentary (9/85, 10.6%), wound (9/85, 10.6%), respiratory (4/85, 4.7%) and superficial (3/85, 3.5%) samples. Incidence of colonisation increased significantly over time (*P*<0.001, based on a Poisson regression model). There was no difference in temporal incidence trends between infection and colonisation (*P*=0.467, by testing the interaction between status and isolation year). Out of the 48 unclassifiable cases, 89.3% (43/48) were isolated between 2013 and 2016 while 33 (76.7%) of them were isolated from alimentary and urine samples. Incidence of unclassifiable cases increased significantly over time (*P*<0.001, based on a Poisson regression model).



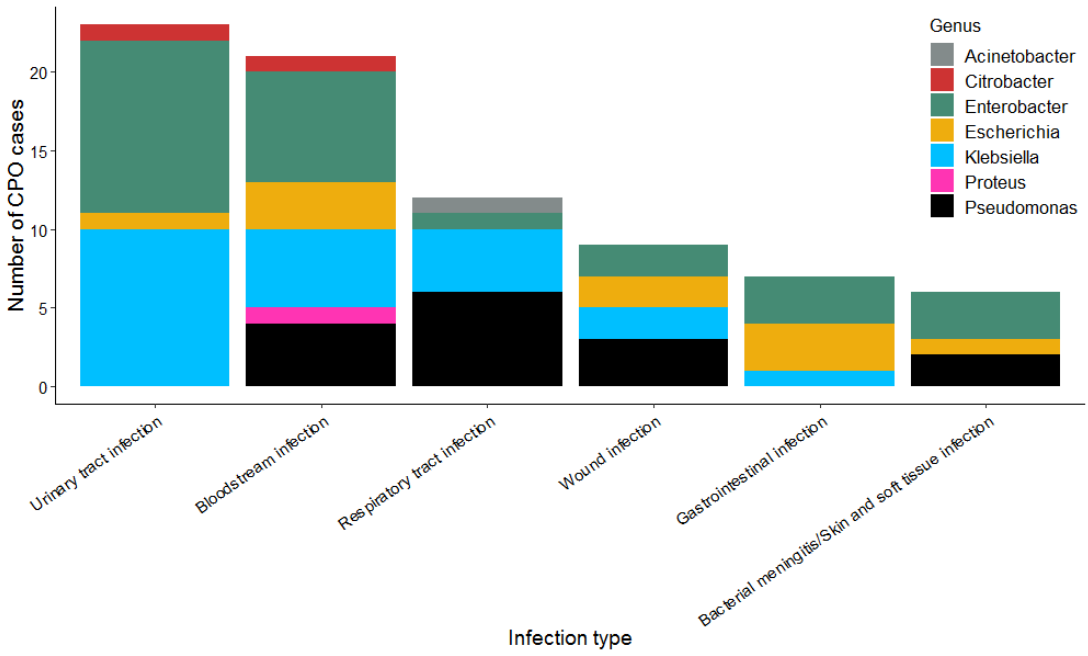
(A)

(B)

Figure 3-2. Temporal distribution of number and percentage of 211 carbapenemase-producing organisms (CPO) cases by status (infection, colonisation and unclassifiable). A, temporal distribution of number of 211 CPO cases by status. B, temporal distribution of percentage of 211 CPO cases by status.



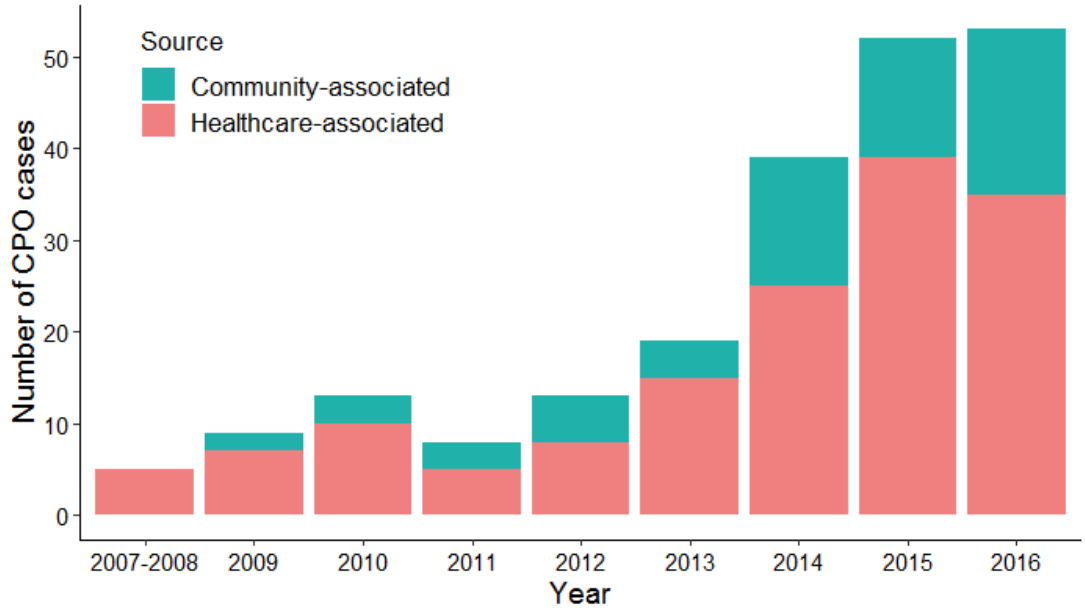
(A)



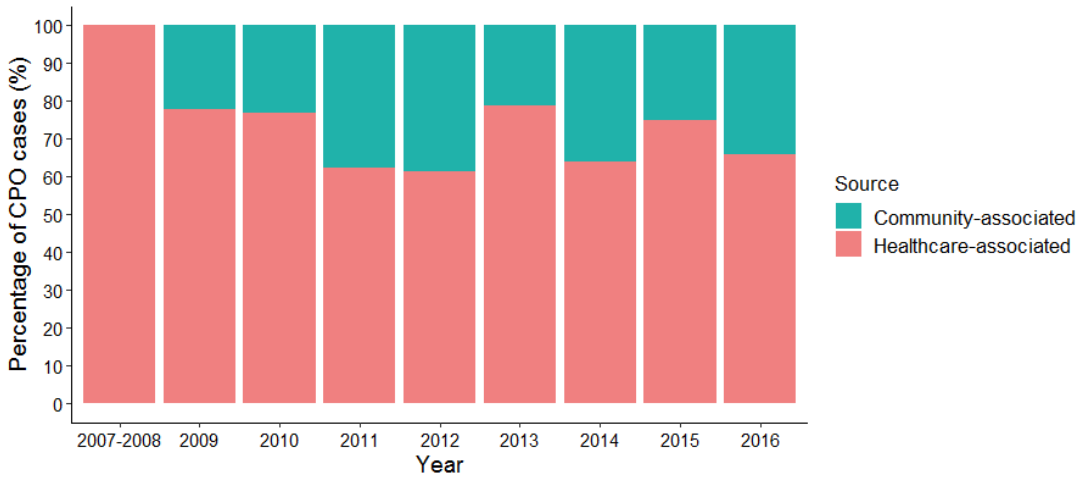
(B)

Figure 3-3. Infection types of carbapenemase-producing organisms (CPO) infection cases (n=78) by bacterial family (A) and genus (B).

Among the 211 cases, 149 (70.6%) were healthcare-associated cases. Due to the small numbers of cases in 2007-2008 (less than 5), they were combined together. The temporal distribution of CPO cases by source is shown in Figure 3-4. Incidences of both healthcare-associated and community-associated increased significantly over time (P<0.001, based on a Poisson regression model), but there was no difference in temporal incidence trends between them (P=0.310, by testing the interaction between source and isolation year). Community-associated cases were reported since 2009 and the number of community-associated cases increased dramatically after 2013 but the percentage of community-associated cases among all the cases reported in each year did not change significantly (P=0.374, based on a Poisson regression model). The source of CPO cases was differently distributed in different status (P<0.001, Pearson's Chi-squared test), i.e. community-associated cases were more likely to be colonisations (39/62, 62.9%) while healthcare-associated cases were more likely to be infections (64/149, 43.0%).



(A)



(B)

Figure 3-4. Temporal distribution of number and percentage of 211 carbapenemase-producing organisms (CPO) cases by source (healthcare-associated or community-associated). A, temporal distribution of number of 211 CPO cases by source. B, temporal distribution of percentage of 211 CPO cases by source.

Overall, there were slightly more colonisation cases than infection cases and most of CPO cases were healthcare-associated. Incidences of both CPO status（infection and colonisation) and source (healthcare-associated and

community-associated) increased significantly over time but there were no differences between different status and source.

3.3.2 Incidence and trends

Examination of CPO incidence and its temporal trends and spacial distribution would help to evaluate the resistance situation and current national acute hospital admission screening programme of CPE, thus enabling comparison of CPO incidences across NHS Boards, between Scotland and other nations/countries and informing local public health bodies to take further actions to combat CPO.

3.3.2.1 Incidence and temporal trends of incidence at national level

There were no CPO isolations in 2005 and 2006. Exponential models were used to fit the incidence data (Incidence~a*b^Year). The overall incidence of CPO cases increased between 2003 and 2017 (Incidence~0.025*1.332^Year, *P*<0.001), from 0.02 to 1.38 per 100,000 population (Figure 3-5). To evaluate the impact of active surveillance for CPE introduced in August 2013, an exponential model was used to fit the data before (2003-2013) its introduction. Before surveillance, the model was Incidence~0.021*1.330^Year (95%CI for b: 1.161-1.499). To compare incidences of the two bacterial families, Poisson regression models were used. Incidences of both Enterobacteriaceae and non-fermenters increased significantly over time (*P*<0.001), but incidence of Enterobacteriaceae (yearly increase of 42.5%) increased faster than that of non-fermenters (yearly increase of 21.5%) (*P*=0.001, by testing the interaction between bacterial family and isolation year) (Figure 3-6).

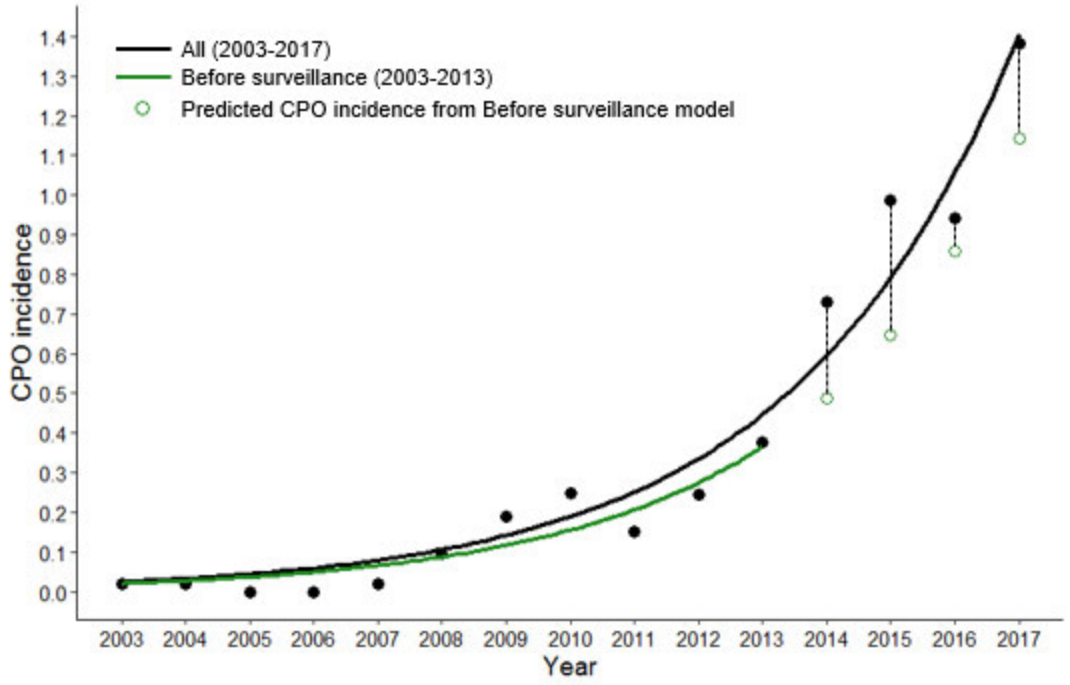


Figure 3-5. Carbapenemase-producing organisms (CPO) incidence in Scotland 2003-2017. Black circles show CPO incidence (number of CPO cases per 100,000 population) and black lines illustrate temporal trend of CPO incidence between 2003 and 2017, fitting based on exponential distribution. Green lines illustrate temporal trend of CPO incidence before conduction of Scottish CPE active surveillance (i.e. between 2003 and 2013) fitting based on exponential distribution and green open circles indicate the predicted CPO incidence between 2014 and 2017 from the before surveillance model (2003-2013). The black square dot dashes show the difference between the actual incidence and predicted incidence from before surveillance model between 2014 and 2017. For statistical purpose, 'Year' was replaced in the model by 0 (2003), 1 (2004), 2 (2005), etc.

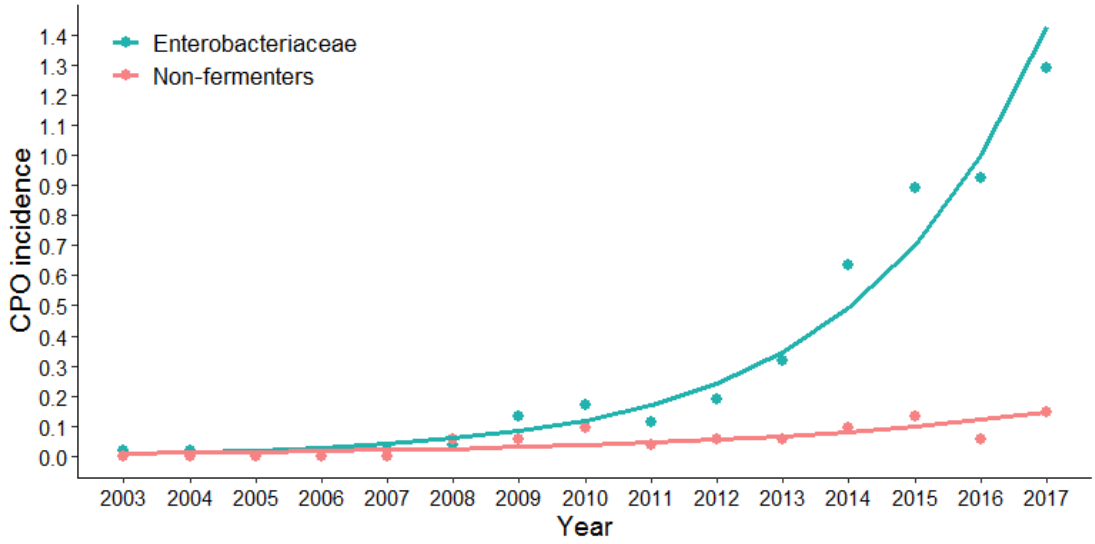


Figure 3-6. Carbapenemase-producing organisms (CPO) incidence in Scotland 2003-2017 by bacterial family (Enterobacteriaceae and non-fermenters). Circles show CPO incidence (number of CPO cases per 100,000 population) in each year for Enterobacteriaceae (green) and non-fermenters (red). Lines illustrate temporal trend of CPO incidence, fitting based on Poisson distribution.

3.3.2.2 Spatial distribution of incidence at NHS Board level

The 214 CPO cases were reported from 13 out of 14 NHS Boards in Scotland. NHS Dumfries & Galloway and NHS Forth Valley had the highest CPO incidence, followed by NHS Lothian and NHS Fife (Figure 3-7). Furthermore, the CPO cases from these four NHS Boards accounted for 71.5% (153/214) of all cases reported in Scotland between 2003 and 2016. The distribution of CPO cases by NHS Board over time is shown in Figure 3-8 A and more NHS boards had CPO cases reported over time (Figure 3-8 B). Source (healthcare-associated and community-associated) distribution of CPO cases varied among these NHS Boards (*P*=0.010, Fisher's exact test). Healthcare-associated cases were more than community-associated cases for all the NHS Boards except NHS Ayrshire & Arran/NHS Borders (Figure 3-9). Infection and colonisation distribution of CPO cases were similar among these NHS Boards (*P*=0.551, Fisher's exact test). Number of CPO infection cases were more than

that of CPO colonisation cases in NHS Lothian, NHS Greater Glasgow & Clyde and NHS Lanarkshire (Figure 3-10).

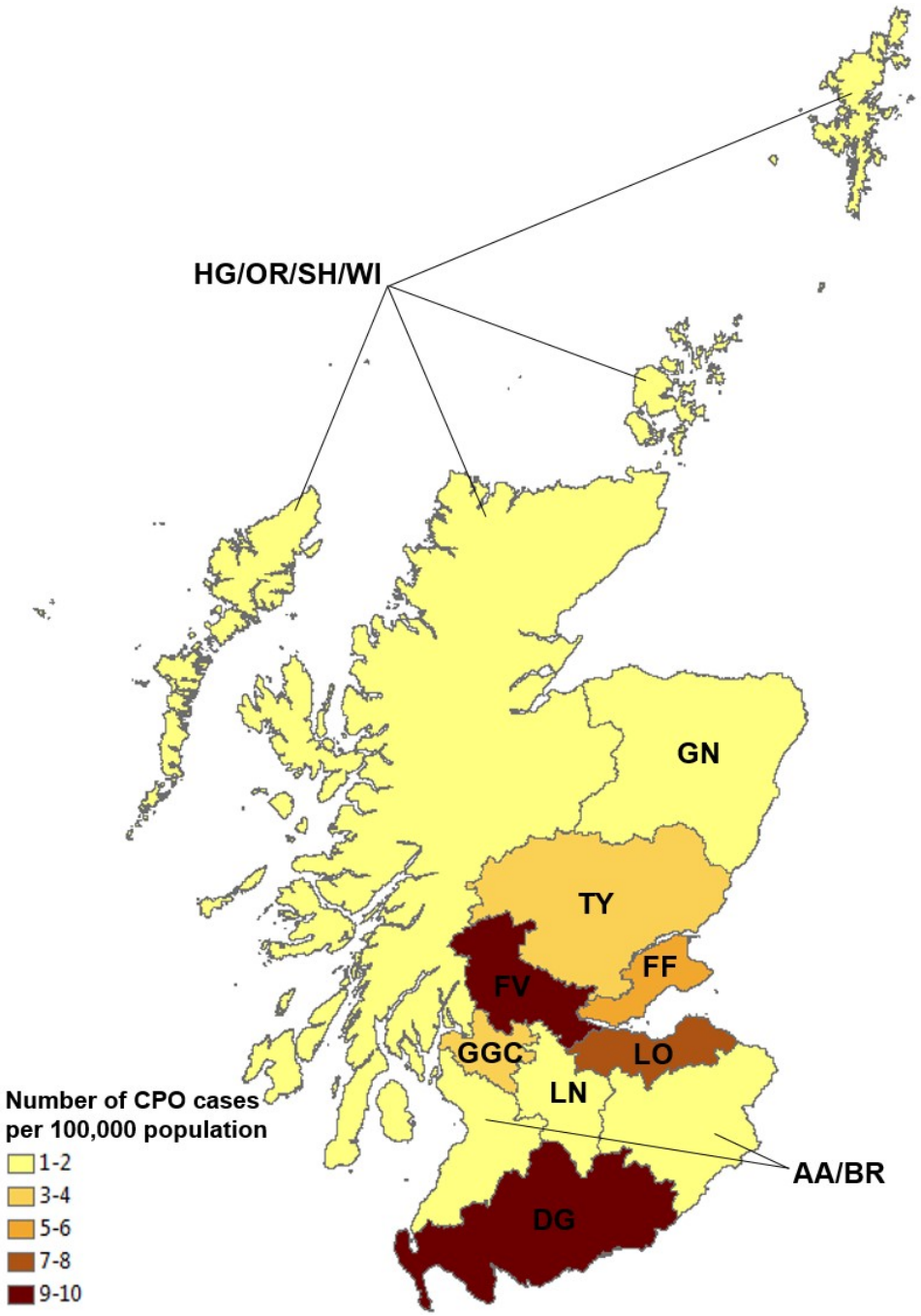
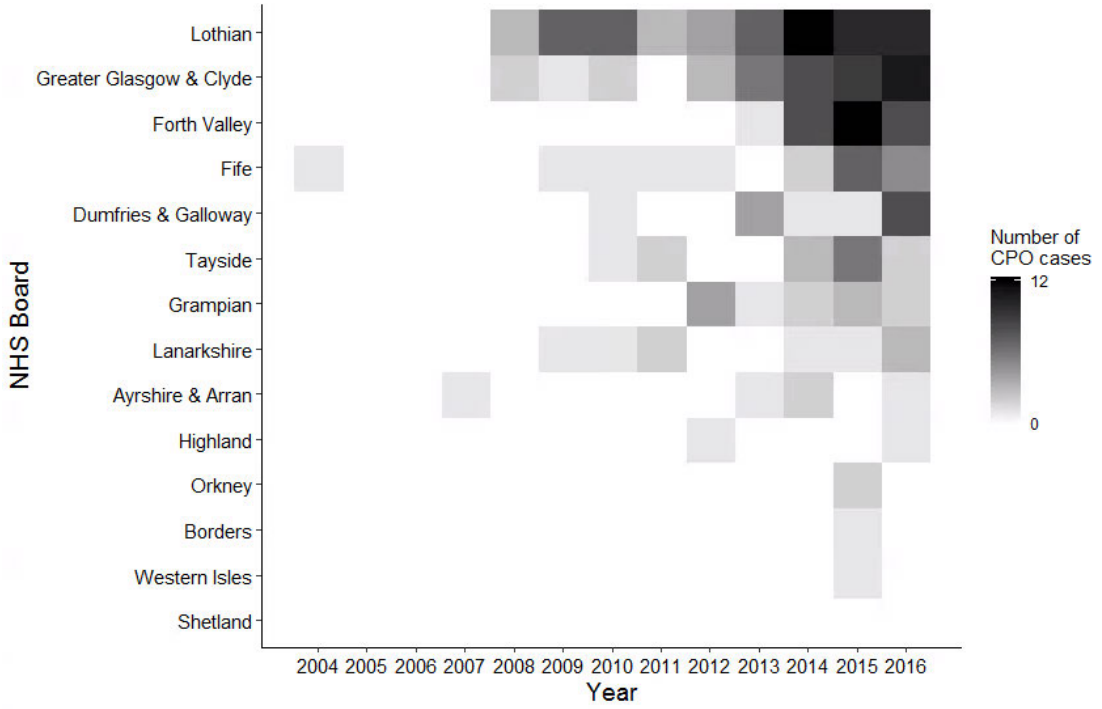
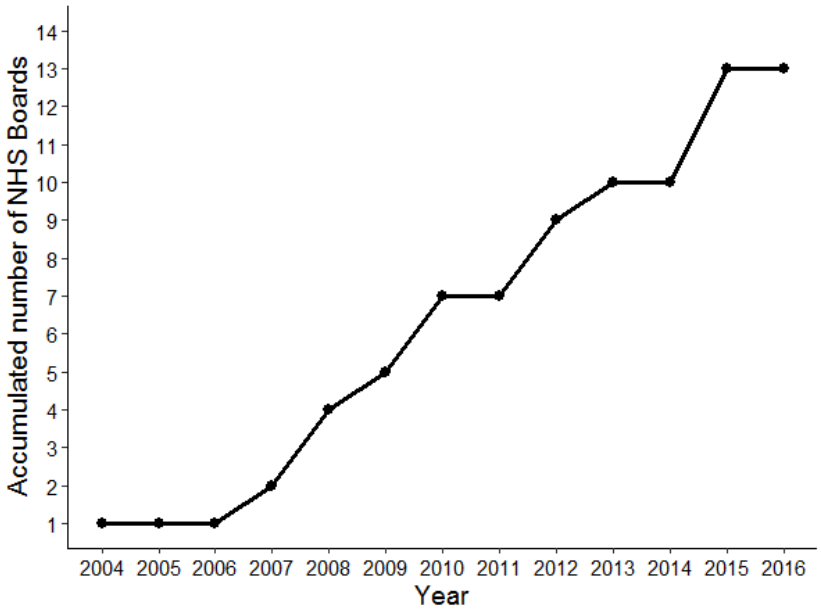


Figure 3-7. Spatial distribution of carbapenemase-producing organisms (CPO) incidence by National Health Service (NHS) Board. AA/BR, NHS Ayrshire & Arran/NHS Borders; DG, NHS Dumfries & Galloway; FF, NHS Fife; FV, NHS Forth Valley; GGC, NHS Greater Glasgow & Clyde; GN, NHS Grampian; LN, NHS Lanarkshire; LO, NHS Lothian; TY, NHS Tayside; HG/OR/SH/WI, NHS Highland/NHS Orkney/NHS Shetland/NHS Western Isles.

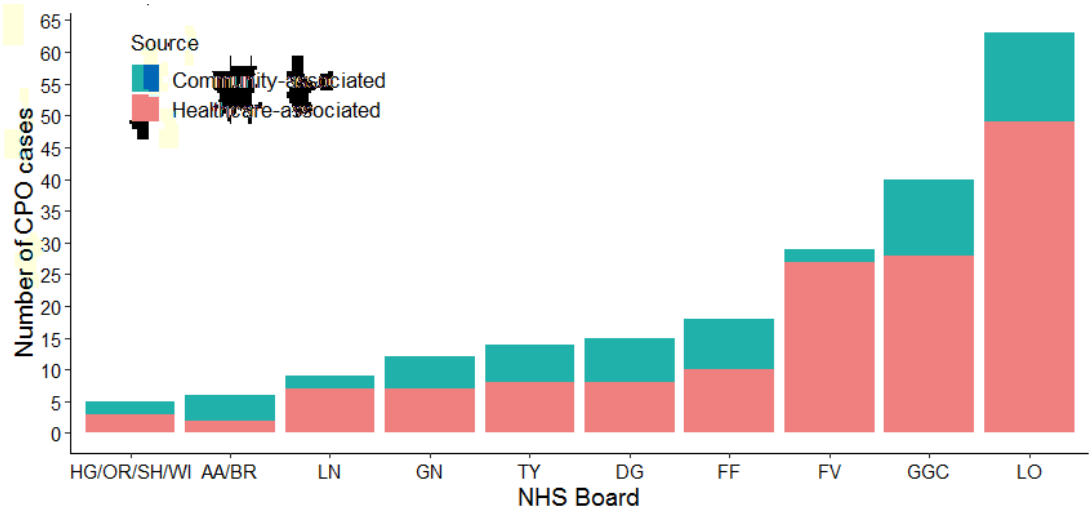


(A)

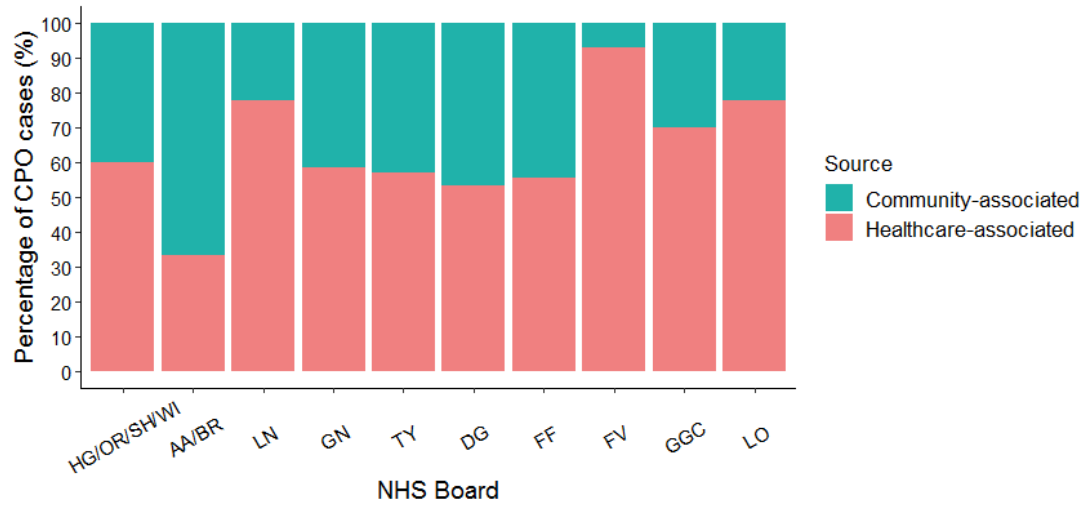


(B)

Figure 3-8. (A) Temporal distribution of 214 carbapenemase-producing organisms (CPO) cases by National Health Service (NHS) and (B) accumulated number of NHS Board with CPO cases reported over time.

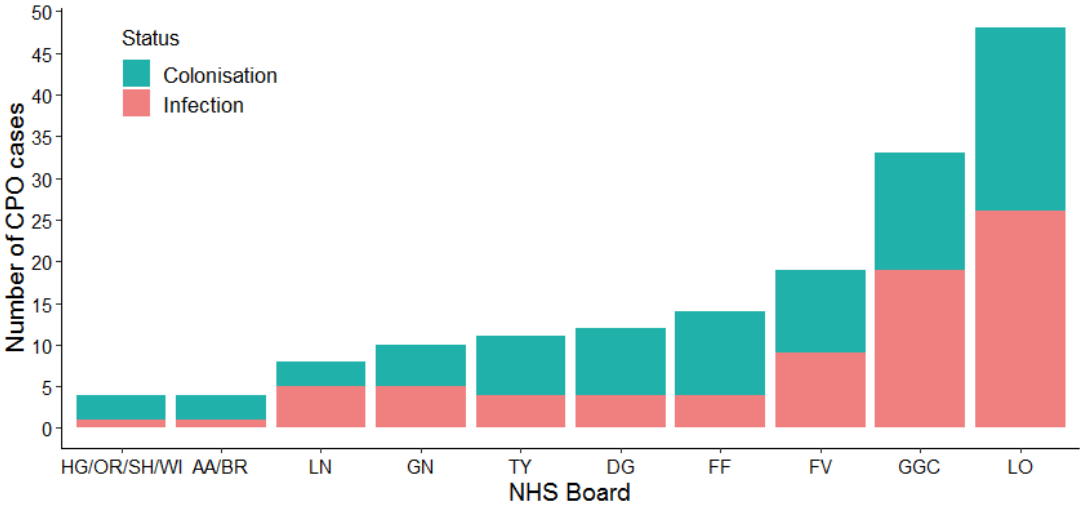


(A)

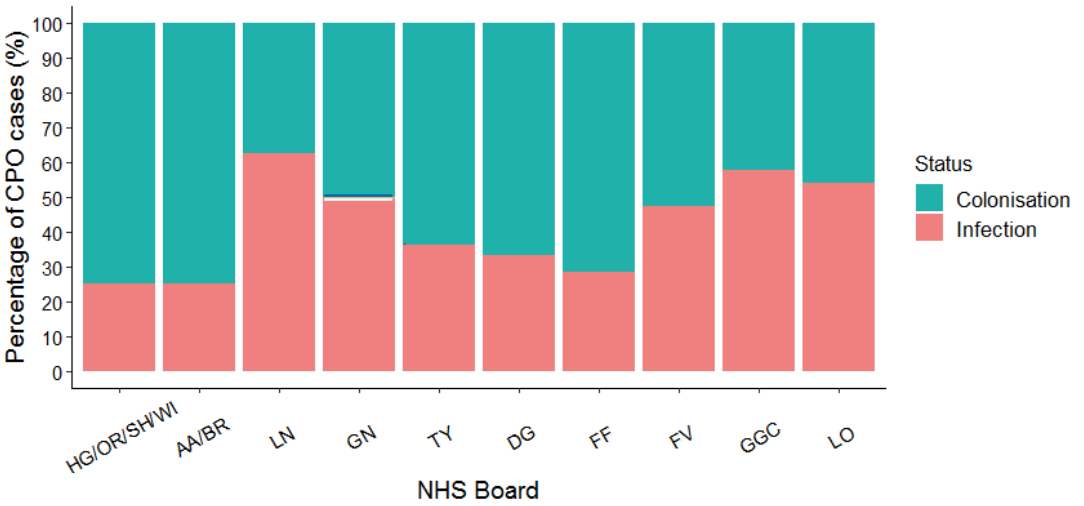


(B)

Figure 3-9. Spatial distribution of number and percentage of 211 carbapenemase-producing organisms (CPO) cases by National Health Service (NHS) Board and source (healthcare-associated and community-associated). (A) Number of 211 CPO cases by NHS Board and source (healthcare-associated and community-associated); (B) Percentage of 211 CPO cases by NHS Board and source. AA/BR, NHS Ayrshire & Arran/NHS Borders; DG, NHS Dumfries & Galloway; FF, NHS Fife; FV, NHS Forth Valley; GGC, NHS Greater Glasgow & Clyde; GN, NHS Grampian; LN, NHS Lanarkshire; LO, NHS Lothian; TY, NHS Tayside; HG/OR/SH/WI, NHS Highland/NHS Orkney/NHS Shetland/NHS Western Isles.



(A)



(B)

Figure 3-10. Spatial distribution of number and percentage of 211 carbapenemase-producing organisms (CPO) cases by National Health Service (NHS) Board and status (infection and colonisation). (A) Number of CPO cases (78 infection cases and 85 colonisation cases) by NHS Board and status; (B) Percentage of CPO cases (78 infection cases and 85 colonisation cases) by NHS Board and status. AA/BR, NHS Ayrshire & Arran/NHS Borders; DG, NHS Dumfries & Galloway; FF, NHS Fife; FV, NHS Forth Valley; GGC, NHS Greater Glasgow & Clyde; GN, NHS Grampian; LN, NHS Lanarkshire; LO, NHS Lothian; TY, NHS Tayside; HG/OR/SH/WI, NHS Highland/NHS Orkney/NHS Shetland/NHS Western Isles.

Overall, CPO incidence increased significantly and more NHS Boards reported CPO over time. The current national screening programme of CPE had an impact on the increasing incidence. CPO incidences and source (healthcare-associated/community-associated) varied across NHS Boards. More efforts should be made to explore factors accounting for these differences in the future.

3.3.3 Microbiological characteristics

3.3.3.1 Specimen type of CPO isolations

Specimen type of CPO isolations indicates where CPO isolates were isolated from and may provide reference for selection of samples used for active surveillance of CPO. There were 269 unique CPO isolations. Urine (103, 38.3%), alimentary (55, 20.4%) and wound (42, 16.0%) predominated at aggregate level with urine (99, 36.8%), rectal swab (45, 16.7%) and wound swab (32, 11.9%) being the most common specimens (Figure 3-11). In general, the number of CPO isolations from wound, urine and alimentary samples increased gradually. The majority of CPO isolations were from urine and alimentary samples from 2013 onward (Figure 3-12).

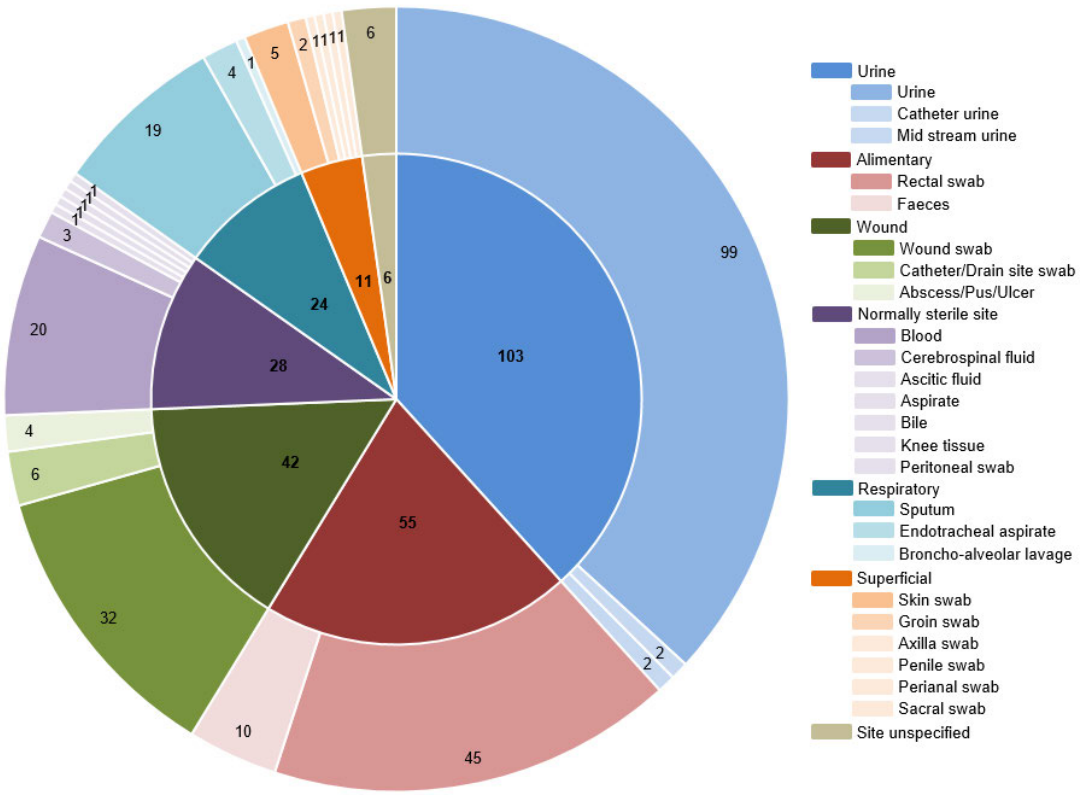


Figure 3-11. Specimen types of 269 carbapenemase-producing organisms (CPO) isolations according to aggregate specimen (inner circle) and specific specimen (outer circle)

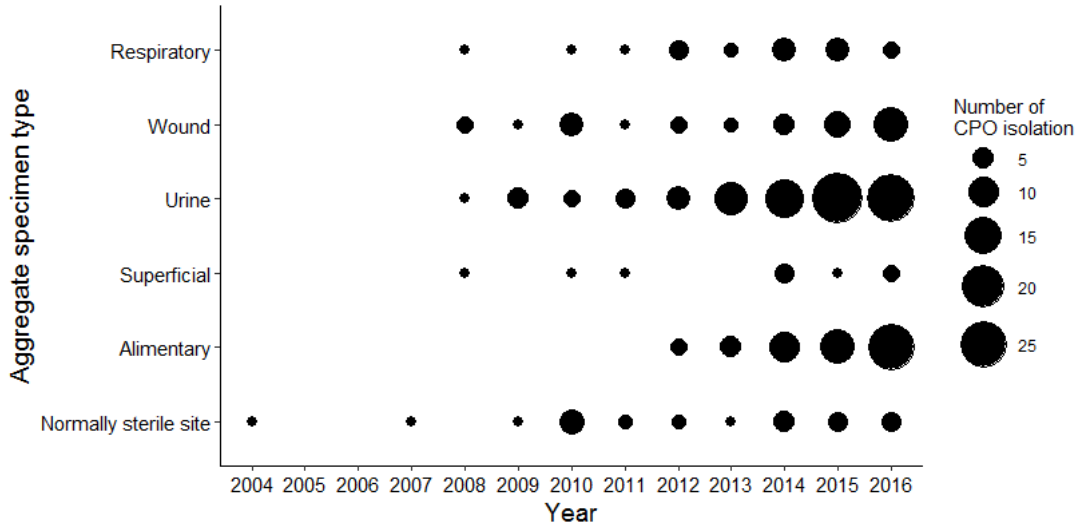


Figure 3-12. Temporal distribution of aggregate specimen types of 269 carbapenemase-producing organisms (CPO) isolations

3.3.3.2 Bacterial organisms and carbapenemases of CPO isolates

The 243 CPO isolates were represented by 8 genera and 14 species, the majority of them being in the bacterial family Enterobacteriaceae (206/243, 84.8%). *Klebsiella pneumoniae* (65/206, 31.6%), *Enterobacter cloacae* (52/206, 25.2%) and *E.coli* (50/206, 24.3%) were the most common species. *Pseudomonas aeruginosa* (29/37, 78.4%) predominated among non-fermenters (Figure 3-13).

VIM (75/243, 30.9%), NDM (56/243, 23.0%), KPC (43/243, 17.7%) and OXA-48 (43/243, 17.7%) were the most common carbapenemases (Figure 3-14). VIM-producing *Enterobacter spp.* (29/243, 11.9%), NDM-producing *E.coli* (25/243, 10.3%) and KPC-producing *Klebsiella spp.* (24/243, 9.9%) were the most common CPO isolates (Figure 3-15). Ambler class B enzymes (IMP, NDM and VIM) were commonly isolated from both Enterobacteriaceae and non-fermenters while class A and D enzymes were isolated from either Enterobacteriaceae or non-fermenters exclusively (Figure 3-15). The temporal distribution of these isolates producing Ambler class B enzymes in both

families showed that the percentage of Enterobacteriaceae producers increased over time while non-fermenters producers dropped (Figure 3-16). *Enterobacter spp.* and *Klebsiella spp.* were the species with the greatest enzyme variety. NDM was present in all genera. It is noteworthy that CPO isolates producing more than one carbapenemase emerged in 2015 and the two NDM/IMP-producing isolates were isolated from both Enterobacteriaceae and non-fermenters (Figure 3-15).

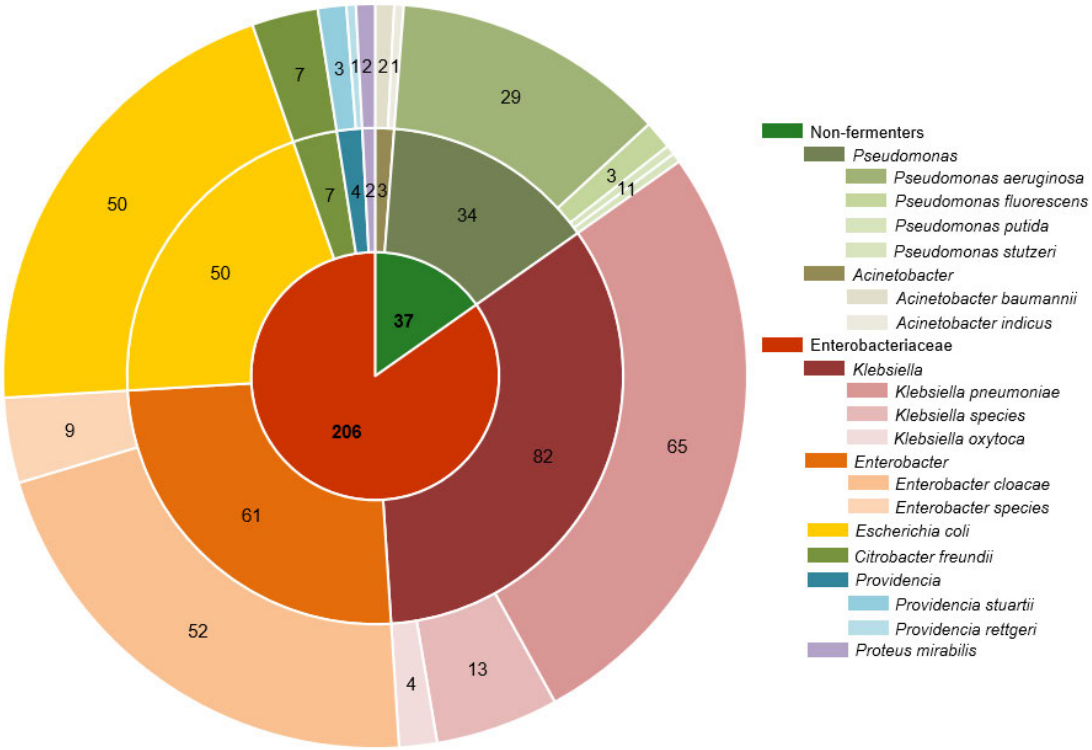


Figure 3-13. Family (inner circle), genera (middle circle) and species (outer circle) of 243 carbapenemase-producing organisms (CPO) isolates

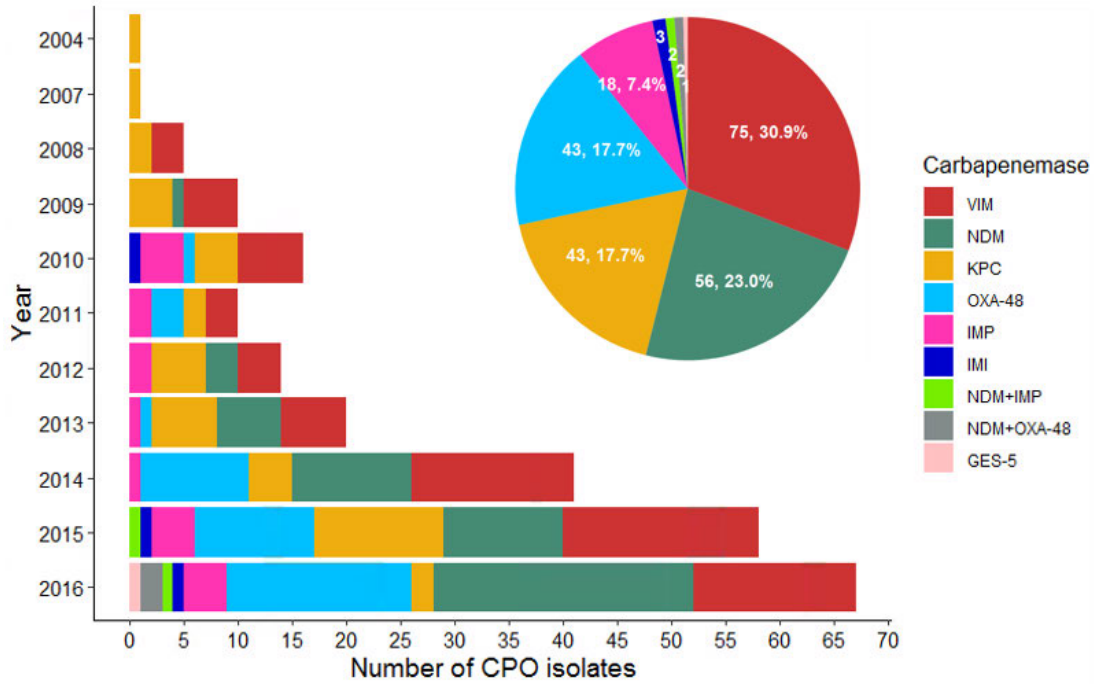


Figure 3-14. Carbapenemases of 243 carbapenemase-producing organisms (CPO) isolates. Stacked bar chart shows annual number of CPO isolates producing different carbapenemases between 2004 and 2016. Pie chart shows total number of CPO isolates producing different carbapenemases between 2004 and 2016.

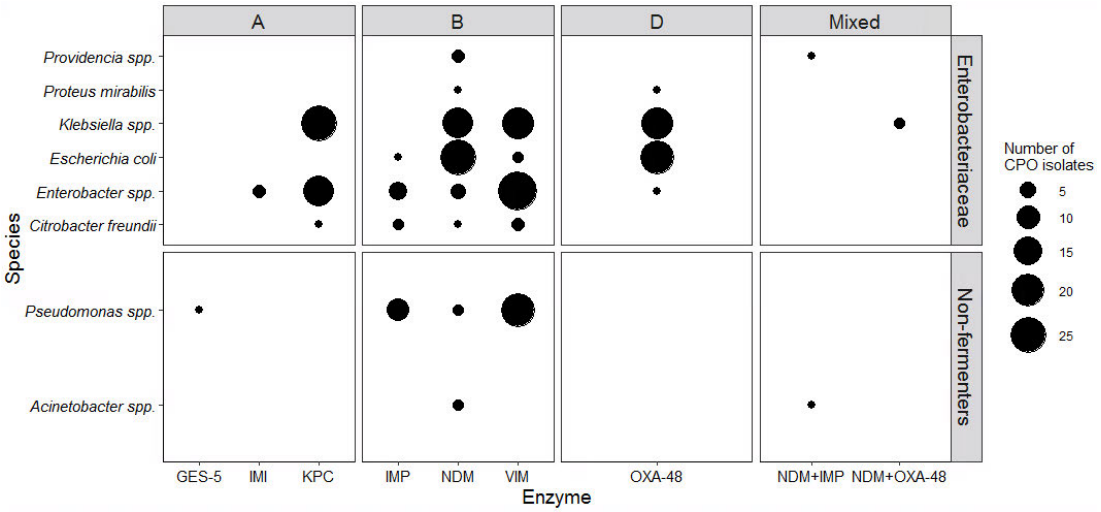


Figure 3-15. Distribution of species and carbapenemases of 243 carbapenemase-producing organisms (CPO) isolates. A, Ambler class A carbapenemases; B, Ambler class B carbapenemases; D, Ambler class D carbapenemases; Mixed, CPO isolates producing two carbapenemases simultaneously.

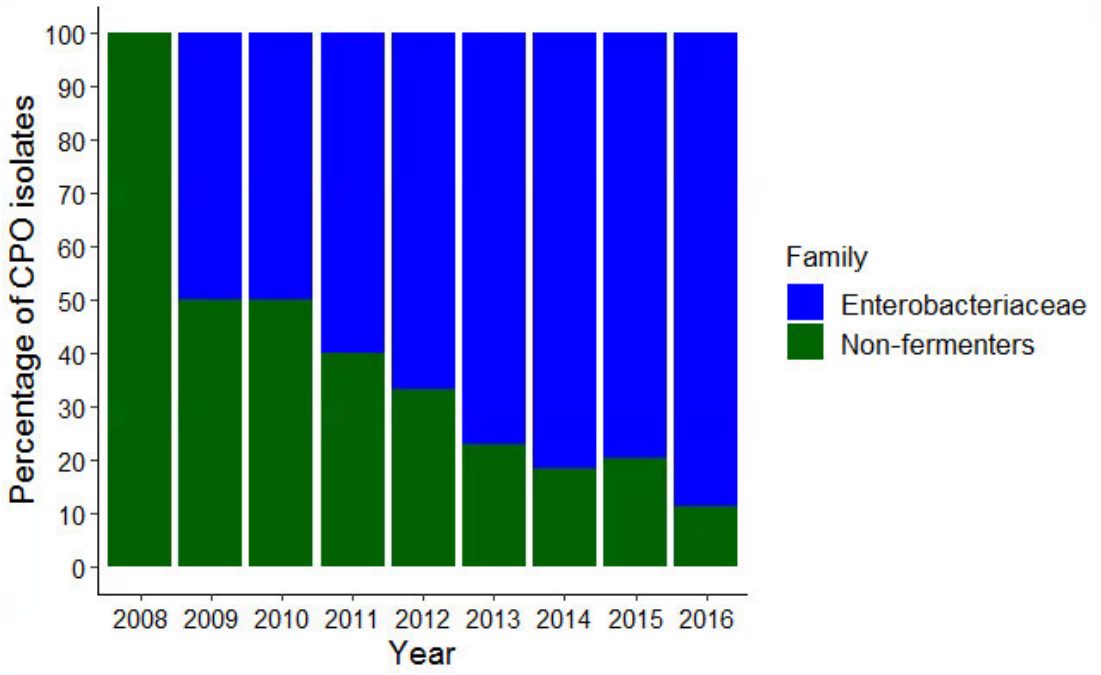


Figure 3-16. Temporal distribution of carbapenemase-producing organisms (CPO) isolates producing Ambler class B carbapenemases by bacterial family (Enterobacteriaceae and non-fermenters)

3.3.3.3 Carbapenemases of CPO cases by source and status

Examination of the association between carbapenemases and source/status will help to answer if the source or status has impact on survival of CPO cases with different carbapenemases. The percentages of healthcare-associated were higher than those of community-associated cases among four of the 'big 5' carbapenemases (VIM, NDM, KPC and IMP) (Figure 3-17). The percentages of source were different among either the 'big 5' carbapenemases or all carbapenemases (P<0.001, Fisher's exact test). More than half of CPO cases (21/36, 58.3%) producing OXA-48 were community-associated, followed by cases producing NDM (22/46, 47.8%). In contrast, all the cases with IMP were healthcare-associated. VIM and IMP producers were significantly associated with healthcare-associated source while NDM and OXA-48 producers were more likely to be community-associated (Table 3-7).

In terms of status (infection and colonisation), the percentages of status were different among either the 'big 5' carbapenemases (P=0.002, Pearson's Chi-squared test) or all carbapenemases (P=0.007, Fisher's exact test). Percentage of infection was higher than that of colonisation for cases with IMP (Figure 3-18, Table 3-8). VIM producers were more likely to cause infection (Figure 3-18, Table 3-8). In contrast, NDM and OXA-48 production were significantly associated with CPO colonisation (Figure 3-18, Table 3-8).

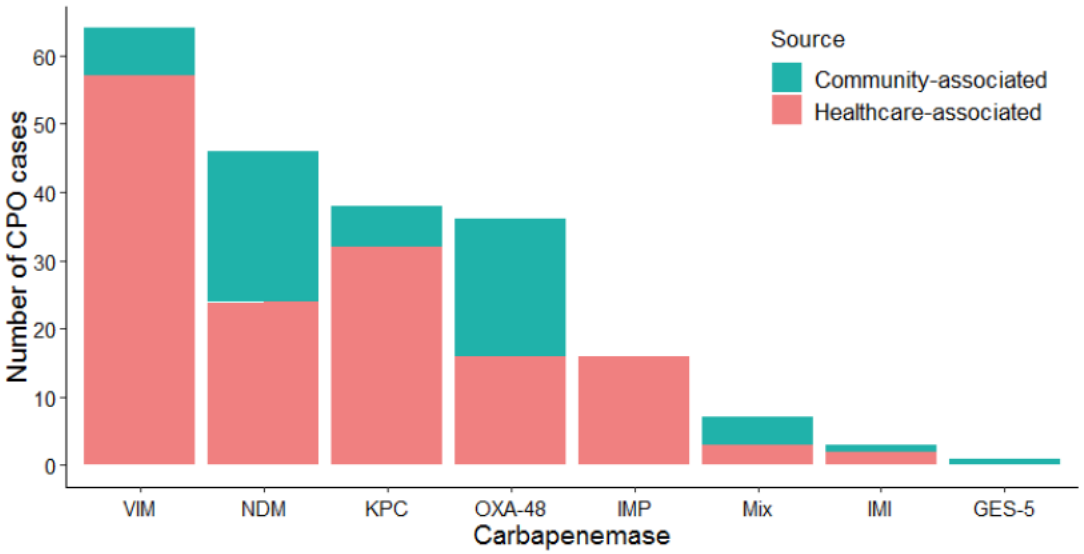


Figure 3-17. Distribution of source (healthcare-associated and community-associated) of carbapenemase-producing organisms (CPO) cases (n=211) with different carbapenemases. Mix means cases with CPO producing more than one carbapenemase.

Table 3-7. Comparison of source (healthcare-associated and community-associated) of carbapenemase-producing organisms (CPO) cases with different carbapenemases

Carbapenemase	Source		*P* value¶
	Healthcare-associated (%) (n=149)	Community-associated (%) (n=62)	
VIM	58 (38.9)	6 (9.7)	<0.001
NDM	24 (16.1)	22 (35.5)	0.003
KPC	31 (20.8)	7 (11.3)	0.149
OXA-48	15 (10.1)	21 (33.9)	<0.001
IMP	16 (10.7)	0 (0.0)	0.004‖

¶, Pearson's Chi-squared test, unless stated otherwise;
‖, Fisher's exact test;

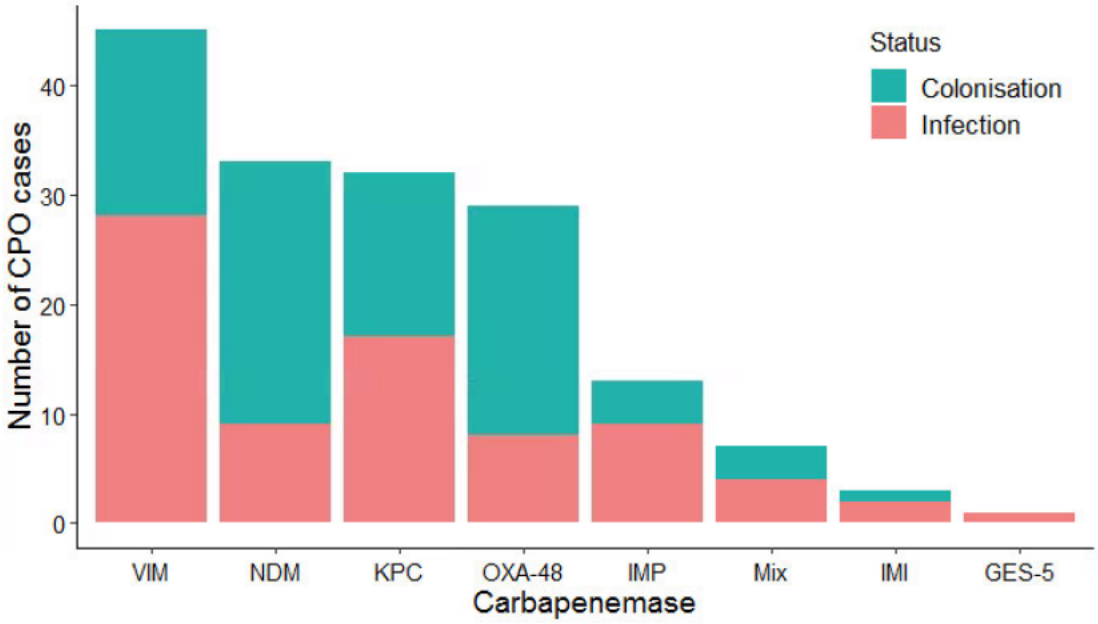


Figure 3-18. Distribution of status (infection and colonisation) of carbapenemase-producing organisms (CPO) cases (n=163) with different carbapenemases. Mix means cases with CPO producing more than one carbapenemase.

Table 3-8. Comparison of status (infection and colonisation) of carbapenemase-producing organisms (CPO) cases with different carbapenemases

Carbapenemase	Status		*P* value¶
	Infection (%) (n=78)	Colonisation (%) (n=85)	
VIM	28 (35.9)	17 (20.0)	0.036
NDM	9 (11.5)	24 (28.2)	0.014
KPC	17 (21.8)	15 (17.6)	0.639
OXA-48	8 (10.3)	21 (24.7)	0.027
IMP	9 (11.5)	4 (4.7)	0.187

¶, Pearson's Chi-squared test.

Carbapenemases differed by source and status. NDM and OXA-48 producers were more likely to be community-associated and colonisation while VIM producers were more likely to be healthcare-associated and cause infections.

3.3.3.4 Temporal trends of organisms and carbapenemases of CPO isolates

Understanding temporal trends of organisms and carbapenemases of CPO isolates will inform future efforts for surveillance and infection prevention and control measures for some specific CPO isolates with upward trends.

3.3.3.4.1 Temporal trend of organisms

In terms of both number and percentage of CPO isolates, *Klebsiella spp.*, *Enterobacter spp.*, *Escherichia spp.* and *Pseudomonas spp.* isolates predominated over time. Isolates reported in 2004 and 2007 were not included in the temporal trend analysis due to the quite small numbers (less than 5 isolates). The percentage of both *Enterobacter spp.* and *Pseudomonas spp.* isolates decreased significantly over time (Figure 3-19 A and B, Table 3-9). It is noteworthy that other species producing carbapenemases were reported since 2014, including *Providencia spp.*, *Acinetobacter spp.* and *Proteus spp.* (Figure 3-19 A and B). *Citrobacter spp.* isolates were first reported in 2009 and then in 2012, and persisted since 2014 (Figure 3-19 C). Among the 206 Enterobacteriaceae isolates, the percentage of *Enterobacter spp.* isolates decreased significantly over time (Figure 3-19 C and D, Table 3-9). The percentage of *Klebsiella spp.* and *Escherichia spp.* increased but they were not significant (Figure 3-19 C and D, Table 3-9). A temporal trend test of percentage of species among non-fermenters isolates was not performed due to small numbers of isolates (Figure 3-19 E).

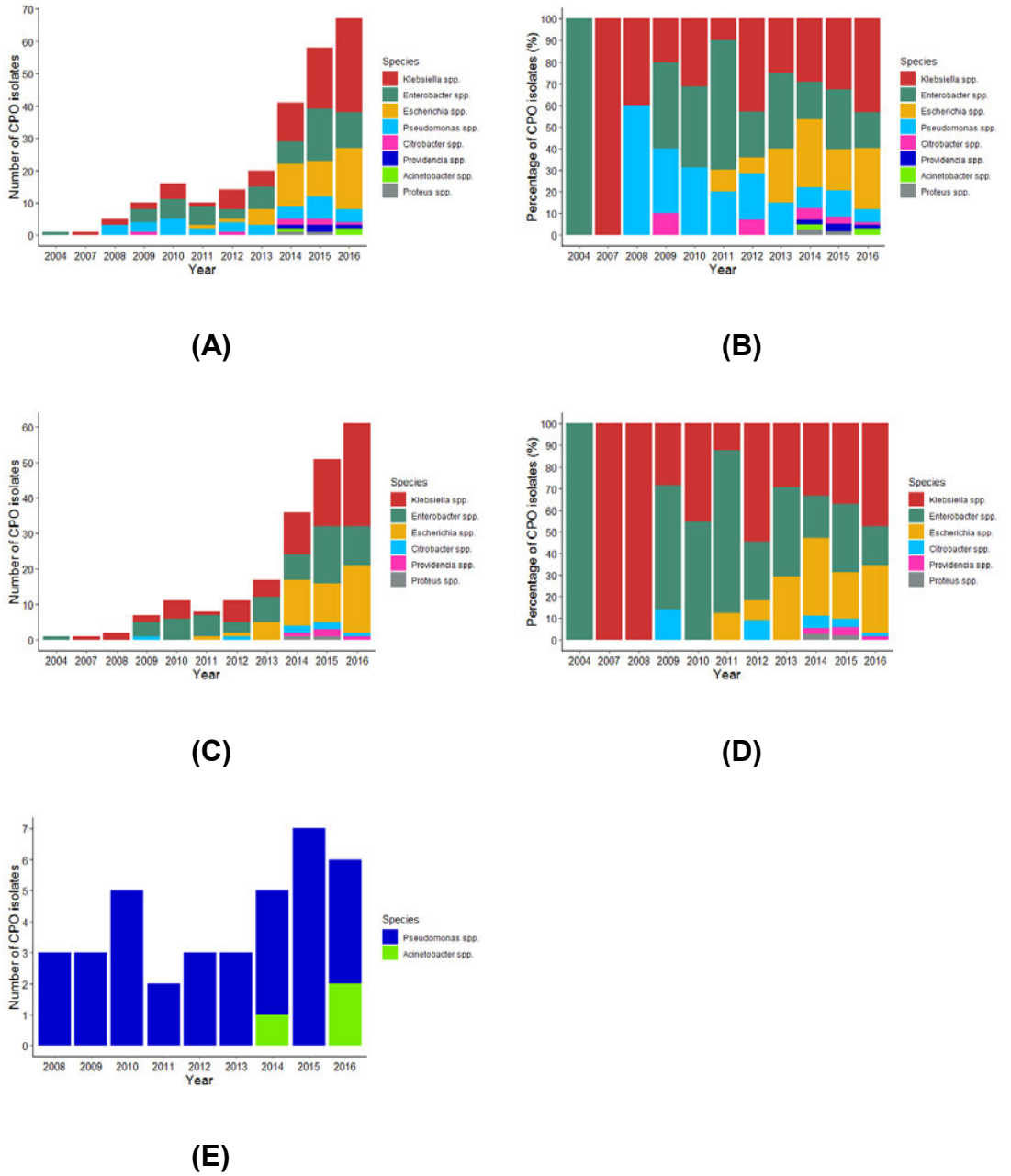


Figure 3-19. Temporal distribution of number and percentage of 243 carbapenemase-producing organisms (CPO) isolates by bacterial family and species. A, temporal distribution of number of 243 CPO isolates by bacterial species. B, temporal distribution of percentage of 243 CPO isolates by bacterial species. C, temporal distribution of number of CPO isolates by bacterial species among 206 Enterobacteriaceae isolates. D, temporal distribution of percentage of CPO isolates by bacterial species among 206 Enterobacteriaceae isolates. E, temporal distribution of number of CPO isolates by bacterial species among 37 non-fermenters isolates.

Table 3-9. Temporal trend of percentage of 243 carbapenemase-producing organisms (CPO) isolates by bacterial family and species tested by Poisson regression models

Bacterial family	Species	Year	Model	Estimate	Standard error	*P* value	Trend[§]
All							
	Klebsiella spp.	2008-2016	linear	0.069	0.055	0.208	↑
	Enterobacter spp.	2009-2016	linear	-0.129	0.056	0.022	↓↓
	Escherichia spp.	2011-2016	linear	0.126	0.108	0.243	↑
	Pseudomonas spp.	2008-2016	linear	-0.236	0.065	0.0003	↓↓
Enterobacteriaceae							
	Klebsiella spp.	2009-2016	linear	0.052	0.061	0.393	↑
	Enterobacter spp.	2009-2016	linear	-0.169	0.056	0.003	↓↓
	Escherichia spp.	2011-2016	linear	0.099	0.108	0.359	↑

[§], double symbols mean statistically significant while single symbol means not statistically significant;

3.3.3.4.2 Temporal trend of carbapenemases

KPC was the first reported carbapenemase and persisted throughout but the percentage among all the CPO isolates dropped significantly (Figure 3-20 A and B, Table 3-10). Likewise, IMP persisted through all the years since its first report in 2010, though the percentage decreased significantly in 2010-2016 and the number increased in 2015-2016 (Figure 3-20 A and B, Table 3-10). In contrast, the percentage of NDM producers increased significantly over time (Figure 3-20 A and B, Table 3-10). The percentage of VIM producers decreased while the percentage of OXA-48 producers rose, but both trends were not statistically significant (Figure 3-20 A and B, Table 3-10). Notably, IMI producers were first reported in 2010 and presented again since 2015, and all of them were *Enterobacter spp.* isolates. Multiple-carbapenemase and GES-5 producers were first reported in 2015 and the number of such isolates increased in 2016 (Figure 3-20 A).

Among the 206 Enterobacteriaceae isolates, temporal trends of different carbapenemases were similar to all CPO isolates except IMP (Figure 3-20 C and D, Table 3-10). The decrease in percentage of IMP producers was not significant (Figure 3-20 C and D, Table 3-10) as half (9/18) of IMP producers were *Pseudomonas spp.* isolates which dropped significantly over time (Table 3-9). A temporal trend test of percentage of carbapenemases among non-fermenters isolates was not performed due to few numbers of isolates (Figure 3-20 E and F).

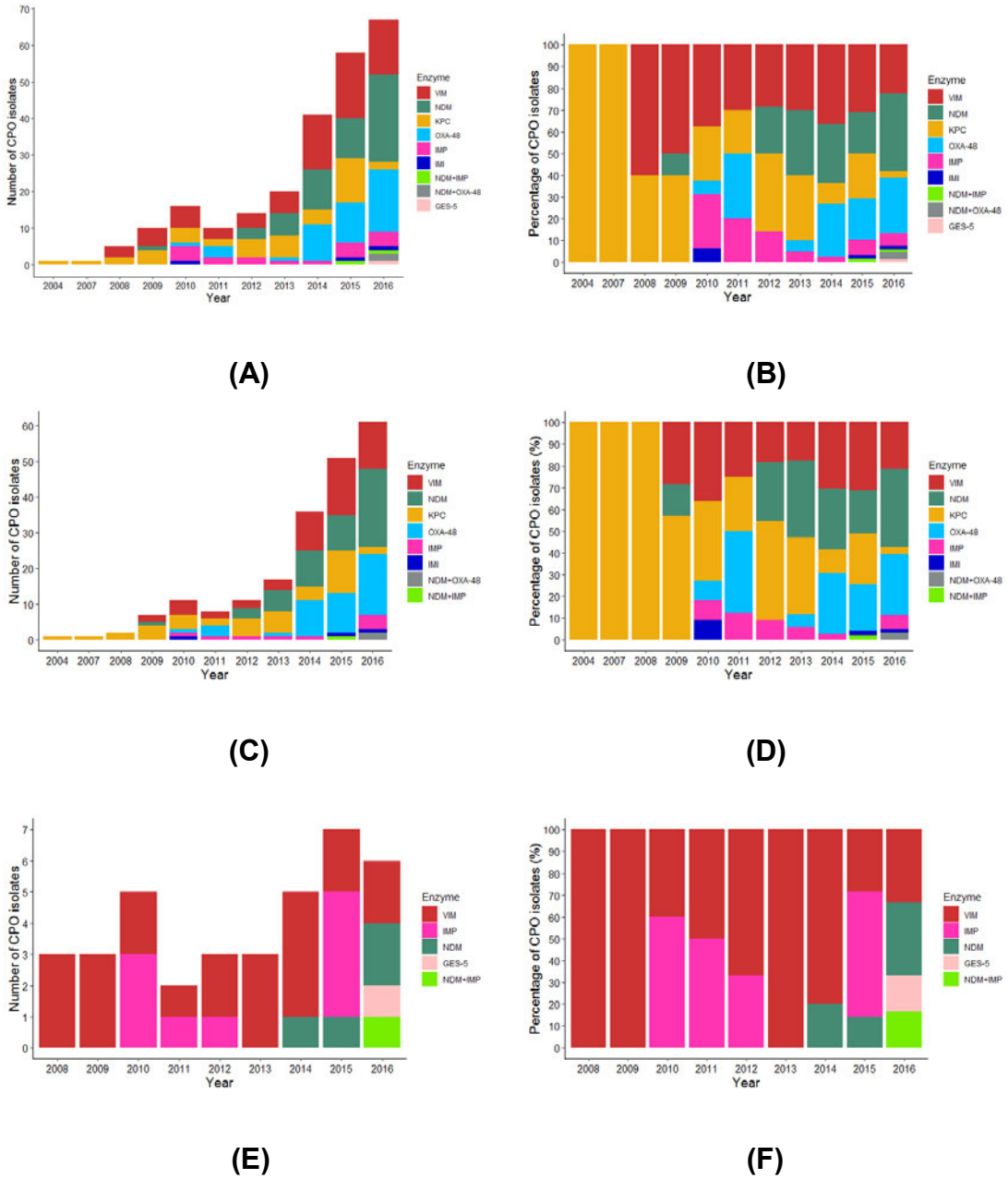


Figure 3-20. Temporal distribution of number and percentage of 243 carbapenemase-producing organisms (CPO) isolates by bacterial family and carbepenemase. A, temporal distribution of number of 243 CPO isolates by carbepenemase. B, temporal distribution of percentage of 243 CPO isolates by carbepenemase. C, temporal distribution of number of CPO isolates by carbepenemase among 206 Enterobacteriaceae isolates. D, temporal distribution of percentage of CPO isolates by carbepenemase among 206 Enterobacteriaceae isolates. E, temporal distribution of number of CPO isolates by carbepenemase among 37 non-fermenters isolates. F, temporal distribution of percentage of CPO isolates by carbepenemase among 37 non-fermenters isolates.

Table 3-10. Temporal trend of percentage of 243 carbapenemase-producing organisms (CPO) isolates by bacterial family and carbapenemase tested by Poisson regression models

Bacterial family	Carbapenemase	Year	Model	Estimate	Standard error	*P* value	Trend§
All							
	VIM	2008-2016	linear	-0.082	0.048	0.089	↓
	NDM	2009-2016	linear	0.229	0.086	0.008	↑↑
	KPC	2008-2016	linear	-0.201	0.060	0.0008	↓↓
	OXA-48	2010-2016	linear	0.182	0.101	0.073	↑
	IMP	2010-2016	linear	-0.266	0.111	0.017	↓↓
Enterobacteriaceae							
	VIM	2009-2016	linear	-0.025	0.068	0.719	↓
	NDM	2009-2016	linear	0.213	0.087	0.015	↑↑
	KPC	2009-2016	linear	-0.253	0.067	0.0002	↓↓
	OXA-48	2010-2016	linear	0.148	0.102	0.149	↑
	IMP	2010-2016	linear	-0.163	0.169	0.335	↓

§, double symbols mean statistically significant while single symbol means not statistically significant;

No significant increasing trend of organisms was found but percentage of NDM producers increased.

3.3.3.5 Spatial distribution of carbapenemases of CPO isolates

Understanding spatial distribution of carbapenemases by NHS Boards would indicate whether there was potential clonal spread of some carbapenemases within NHS Boards. Nearly half of CPO isolates were isolated in NHS Lothian (66/243, 27.2%) and NHS Greater Glasgow & Clyde (53/243, 21.8%) (Figure 3-21 A). NHS Greater Glasgow & Clyde had the greatest carbapenemase variety while NHS Forth Valley had the least only with VIM and OXA-48 (Figure 3-21 A).

Majority of VIM producers (65/75, 86.7%) were reported in NHS Forth Valley, NHS Lothian and NHS Greater Glasgow & Clyde (Figure 3-21 A). NDM producers were reported from most NHS Boards except NHS Forth Valley and the North West region (Figure 3-21 A). KPC producers were reported from most NHS Boards except NHS Forth Valley (Figure 3-21 A). OXA-48 producers were isolated from each NHS Board (Figure 3-21 A). The majority of IMP producers (13/18, 72.2%) were isolated in NHS Lothian and NHS Lanarkshire (Figure 3-21 A). IMI producers were only isolated in NHS Lothian and NHS Greater Glasgow & Clyde (Figure 3-21 A). Isolates producing NDM+IMP and GES-5 were only reported in NHS Greater Glasgow & Clyde (Figure 3-21 A).

In NHS Lothian, the percentage of VIM producers decreased significantly over time (P=0.015, based on a Poisson regression model) (Figure 3-21 C and D). All the 25 VIM-producing isolates were isolated from 23 cases and 22 (95.7%) of them were healthcare-associated cases. Eighteen of the 23 cases (78.3%) were hospitalised in Hospital A or had been hospitalised in the hospital in the prior 9 days before CPO isolation. Moreover, 16 of the 18 cases were from Haematology or Neurosurgery Specialties and 17 of them had been admitted to a HDU in the prior 90 days before CPO isolation. NDM-producing isolates were isolated from either urine or rectal swabs in 9 cases and 5 of them were community-associated cases. Thirteen OXA-48 cases were reported since 2013 and 7 (53.8%) of them were isolated in community or community-associated cases. In 2014, five of 6 cases carrying OXA-48 producers were

identified in surgical Specialties in the same hospital (Hospital B). IMP producers accounted half of the total IMP producers reported from Scotland (9/18, 50.0%). Interestingly, all of them were isolated in the Hospital A (healthcare-associated cases as well) and 8 of them were hospitalised in Haematology or Neurosurgery Specialties and 8 of them had been admitted to HDU in the prior 14 days before CPO isolation. In addition, IMP producers isolated between 2010 and 2012 were all *Pseudomonas spp.*, but all the all the isolates were Enterobacteriaceae afterwards.

In NHS Greater Glasgow & Clyde, the percentage of VIM producers decreased significantly over time (P=0.012, based on a Poisson regression model) (Figure 3-21 E and F). Ten (83.3%) of the 12 cases carrying VIM were healthcare-associated cases and 11 (91.7%) were *Pseudomonas spp.* carriers. The number of NDM producers increased continuously since the first report in 2013 which were isolated from 12 cases (Figure 3-21 E and F). Eight of the 12 were either community-associated cases or isolated from community. The number of OXA-48 producers rose continuously since the first report in 2014 which were isolated from 8 cases (Figure 3-21 E and F). Seven (63.6%) of the 11 isolates were from rectal swab/faeces/urine samples.

In NHS Forth Valley, the majority of CPO isolates were VIM producers (28/32, 87.5%) (Figure 3-21 A, B, G and H) and they were identified from 25 cases, of which all were healthcare-associated cases and 23 (92.0%) were isolated from urine/rectal swab samples. All of them were Enterobacteriaceae isolates. Notably, all of the 25 cases were hospitalised or had been hospitalised in prior two months in the same hospital (Hospital C), and 13 (52.0%) of the 25 cases were from Geriatric Medicine Specialty and 9 (36.0%) were from General Medicine Specialty.

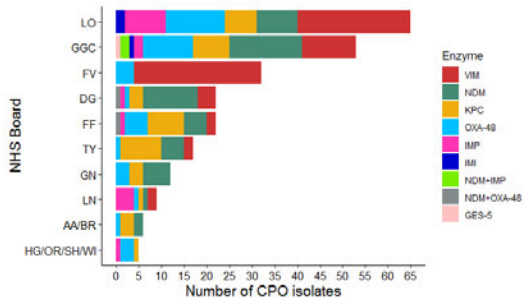
In NHS Dumfries & Galloway, there was a sudden increase of CPO isolates in 2016 and most (9/13, 69.2%) of the isolates were NDM-producers (Figure 3-21 I and J). All the 12 NDM-producing isolates (11 Enterobacteriaceae and 1 non-fermenters isolates) were isolated in urine and rectal swab samples from 9 cases and 7 of them were isolated in community or community-associated

cases. Seven of the 9 cases (77.8%) were reported in community or community-associated cases. The single OXA-48-producing case was a community-associated case and the isolates were from urine and rectal swab.

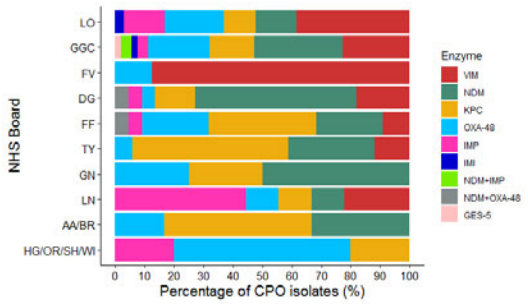
In NHS Fife, all the 8 cases with KPC were healthcare-associated cases. NDM- and OXA-48-producing isolates accounted for more than half of the isolates reported in 2015 and 2016 (8/12, 66.7%) (Figure 3-21 K and L). Six of the 8 isolates were isolated in community or from community-associated cases and 7 were isolated from urine/rectal swab samples.

For the other NHS Boards, due to small numbers of isolates (less than 20) they were not investigated in detail. However, NDM- and OXA-48-producing isolates in NHS Tayside and NHS Grampian had been reported since 2014. The two cases carrying IMP-producing isolates from NHS Lanarkshire in 2015-2016 and one case carrying IMP-producing isolate from NHS Dumfries & Galloway in 2015 had been hospitalised in the Cardiac Surgery Specialty in the same hospital (Hospital D).

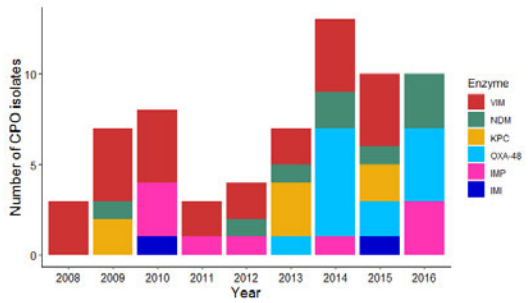
There might be clonal persistence and spread of some CPO isolates in some hospitals, however, more phylogeny analyses are required to confirm this.


NHS Board
LO
GGC
FV
DG
FF
TY
GN
LN
AA/BR
HG/OR/SH/WI
0 5 10 15 20 25 30 35 40 45 50 55 60 65
Number of CPO isolates
Enzyme
VIM
NDM
KPC
OXA-48
IMP
IMI
NDM+IMP
NDM+OXA-48
GES-5

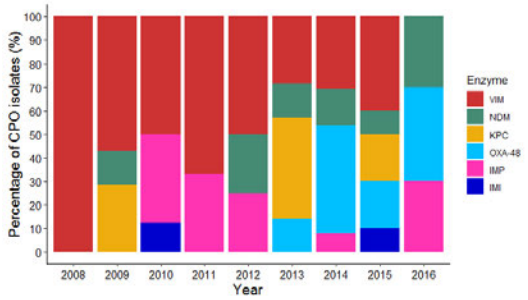
(A)


NHS Board
LO
GGC
FV
DG
FF
TY
GN
LN
AA/BR
HG/OR/SH/WI
0 10 20 30 40 50 60 70 80 90 100
Percentage of CPO isolates (%)
Enzyme
VIM
NDM
KPC
OXA-48
IMP
IMI
NDM+IMP
NDM+OXA-48
GES-5

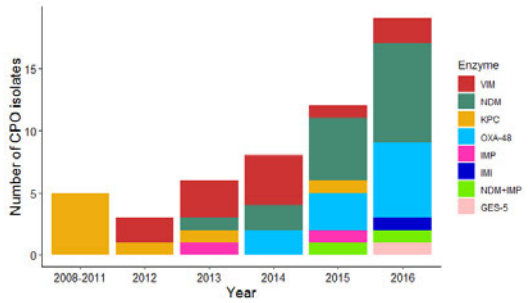
(B)


Number of CPO isolates
0
5
10
2008 2009 2010 2011 2012 2013 2014 2015 2016
Year
Enzyme
VIM
NDM
KPC
OXA-48
IMP
IMI

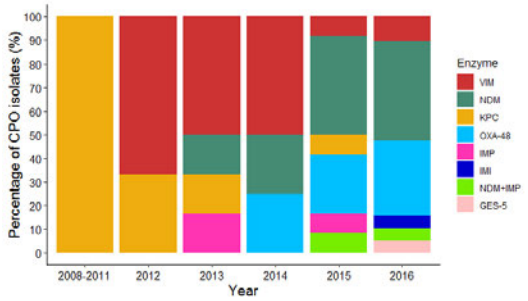
(C)


Percentage of CPO isolates (%)
0 10 20 30 40 50 60 70 80 90 100
2008 2009 2010 2011 2012 2013 2014 2015 2016
Year
Enzyme
VIM
NDM
KPC
OXA-48
IMP
IMI

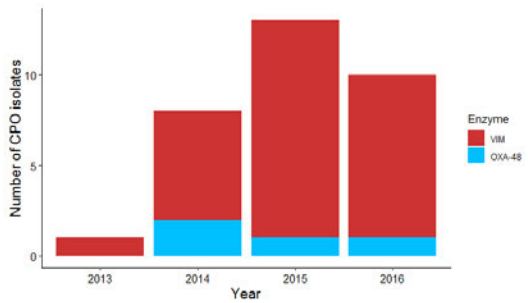
(D)


Number of CPO isolates
0
5
10
15
2008-2011 2012 2013 2014 2015 2016
Year
Enzyme
VIM
NDM
KPC
OXA-48
IMP
IMI
NDM+IMP
GES-5

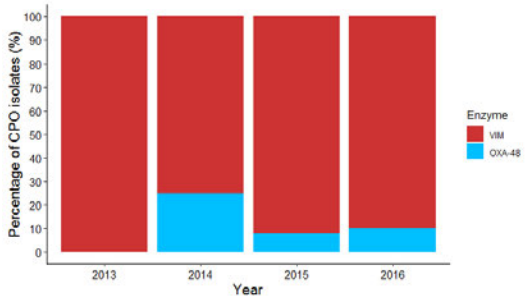
(E)


Percentage of CPO isolates (%)
0 10 20 30 40 50 60 70 80 90 100
2008-2011 2012 2013 2014 2015 2016
Year
Enzyme
VIM
NDM
KPC
OXA-48
IMP
IMI
NDM+IMP
GES-5

(F)


Number of CPO isolates
0
5
10
2013 2014 2015 2016
Year
Enzyme
VIM
OXA-48

(G)


Percentage of CPO isolates (%)
0 10 20 30 40 50 60 70 80 90 100
2013 2014 2015 2016
Year
Enzyme
VIM
OXA-48

(H)

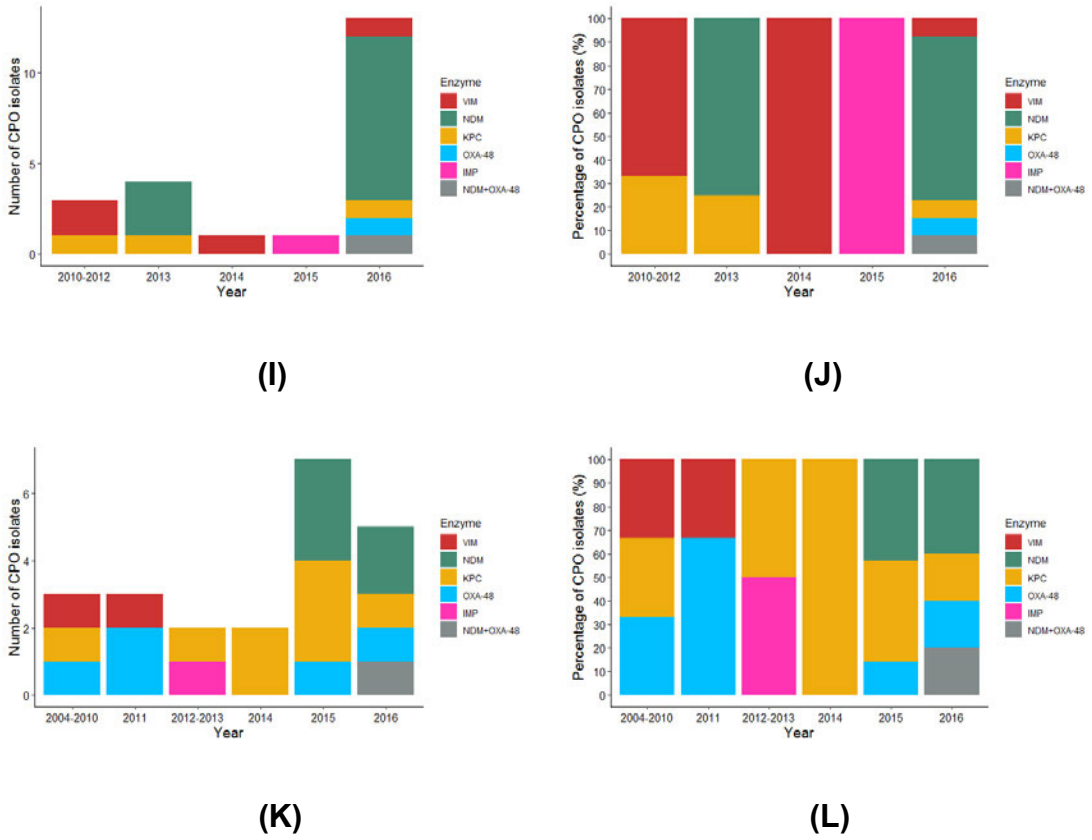


Figure 3-21. Number and percentage of 243 carbapenemase-producing organisms (CPO) isolates by carbapenemase and National Health Service (NHS) Board over time. A, number of CPO isolates by carbapenemase and NHS Board. B, percentage of CPO isolates by carbapenemase and NHS Board. Number (C) and percentage (D) of CPO isolates by carbapenemase in NHS Lothian. Number (E) and percentage (F) of CPO isolates by carbapenemase in NHS Greater Glasgow & Clyde. Number (G) and percentage (H) of CPO isolates by carbapenemase in NHS Forth Valley. Number (I) and percentage (J) of CPO isolates by carbapenemase in NHS Dumfries & Galloway. Number (K) and percentage (L) of CPO isolates by carbapenemase in NHS Fife. AA/BR, NHS Ayrshire & Arran/NHS Borders; DG, NHS Dumfries & Galloway; FF, NHS Fife; FV, NHS Forth Valley; GGC, NHS Greater Glasgow & Clyde; GN, NHS Grampian; LN, NHS Lanarkshire; LO, NHS Lothian; TY, NHS Tayside; HG/OR/SH/WI, NHS Highland/NHS Orkney/NHS Shetland/NHS Western Isles.

3.3.3.6 Antimicrobial resistance profiles of CPO isolates

Antimicrobial susceptibility analyses may provide alternative therapeutic options for CPO if they were susceptible to some antimicrobial agents. Antimicrobial susceptibility testing results of 54 CPO isolates from 47 CPO cases were available, including 42 Enterobacteriaceae isolates and 12 non-fermenters isolates. The 54 isolates involved in the analyses were from 14 hospitals located in 10 NHS Boards between 2008 and 2016. These isolates were highly resistant to majority of the antimicrobial agents except for aminoglycosides (Table 3-11, Figure 3-22). Enterobacteriaceae isolates were resistant to most of the antimicrobial agents, especially to the third generation penicillins (100%), imipenem (100%), β-Lactam/β-lactamase inhibitor combinations (94.4-96.7%) and the third generation cephalosporins (93.6-100%). By contrast, resistance rates were relatively low to aminoglycosides (26.2-28.0%) (Table 3-11, Figure 3-22). Also, non-fermenters isolates were highly resistant to most agents except for aztreonam (37.5%). It is notable that resistance rate to aztreonam of Enterobacteriaceae isolates was significantly higher than that of non-fermenters isolates while resistance rate to gentamicin of Enterobacteriaceae isolates was significantly lower than that of non-fermenters isolates (Table 3-11, Figure 3-22). For all the antimicrobial agents tested, there were no differences between isolates causing CPO infection and colonisation (Table 3-12). Aminoglycosides could be alternative therapeutic options for carbapenemase-producing Enterobacteriaceae and aztreonam for carbapenemase-producing non-fermenters.

Table 3-11. Antimicrobial resistance rates of carbapenemase-producing organisms (CPO) isolates and comparison between Enterobacteriaceae and non-fermenters isolates

Agents	All isolates§	Enterobacteriaceae§	non-fermenters§	*P* value¶
AMX	34/34 (100.0)	34/34 (100.0)	/	/
AMP	7/7 (100.0)	7/7 (100.0)	/	/
AMC	29/30 (96.7)	29/30 (96.7)	/	/
TZP	42/46 (91.3)	34/36 (94.4)	8/10 (80.0)	0.202
CTX	29/31 (93.6)	29/31 (93.6)	/	/
CAZ	44/45 (97.8)	34/35 (97.1)	10/10 (100.0)	1.000
CTR	15/15 (100.0)	15/15 (100.0)	/	/
FOX	18/25 (72.0)	18/25 (72.0)	/	/
ATM	27/35 (77.1)	24/27 (88.9)	3/8 (37.5)	0.007
IPM	10/11 (90.9)	4/4 (100.0)	6/7 (85.7)	1.000
MEM	28/51 (54.9)	19/39 (48.7)	9/12 (75.0)	0.205‖
AK	13/35 (37.1)	7/25 (28.0)	6/10 (60.0)	0.123
GM	23/54 (42.6)	11/42 (26.2)	12/12 (100.0)	<0.001‖
TMP	30/35 (85.7)	30/35 (85.7)	/	/
CIP	33/54 (61.1)	25/42 (59.5)	8/12 (66.7)	0.747

§, Number of resistant isolates/number of isolates tested (percentage of resistance);
¶, Fisher's exact test, unless stated otherwise;
‖, Pearson's Chi-squared test;
/, not applicable.
AMX, amoxicillin; AMP, ampicillin; AMC, amoxicillin-clavulanate; TZP, piperacillin-tazobactam; CTX, cefotaxime; CAZ, ceftazidime; CTR, ceftriaxone; FOX, cefoxitin; ATM, aztreonam; IPM, imipenem; MEM, meropenem; AK, amikacin; GM, gentamicin; TMP, trimethoprim; CIP, ciprofloxacin.

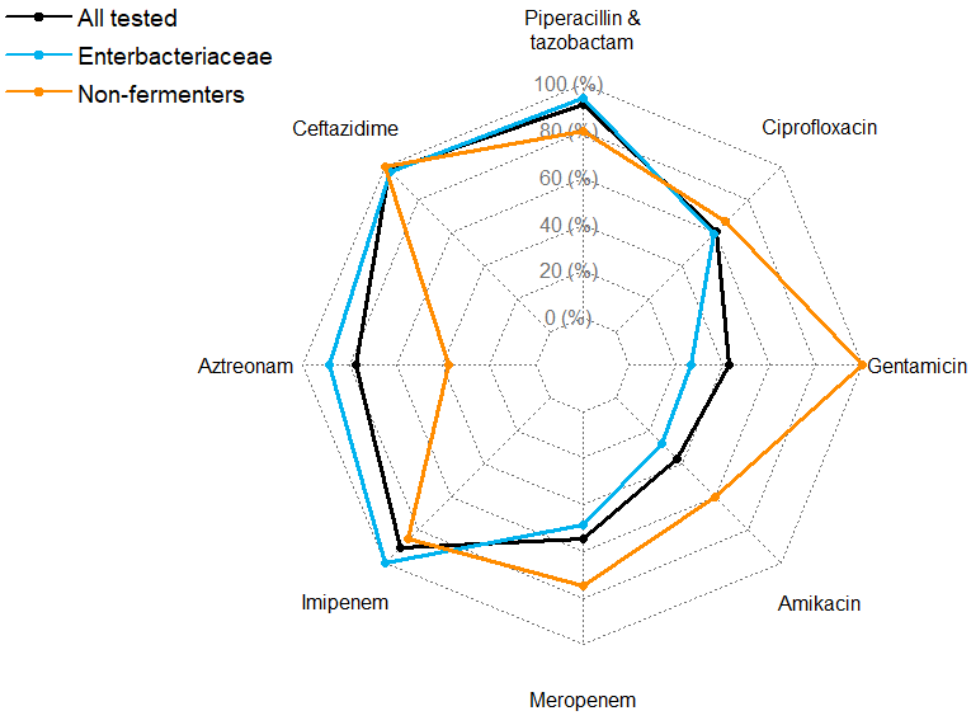


Figure 3-22. Radar plot of antimicrobial resistance rates of carbapenemase-producing organisms (CPO) isolates by bacterial family (Enterobacteriaceae and non-fermenters)

Table 3-12. Comparison of antimicrobial resistance rates of carbapenemase-producing organisms (CPO) isolates between infection and colonisation cases

Agents	Enterobacteriaceae-infection§	Enterobacteriaceae-colonisation§	*P* value¶	non-fermenters-infection§	non-fermenters-colonisation§	*P* value¶
AMX	15/15 (100.0)	13/13 (100.0)	1.000	/	/	/
AMP	2/2 (100.0)	4/4 (100.0)	1.000	/	/	/
AMC	17/17 (100.0)	16/17 (94.1)	1.000	/	/	/
TZP	14/15 (93.3)	12/13 (92.3)	1.000	5/5 (100.0)	3/5 (60.0)	0.444
CTX	11/12 (91.7)	12/13 (92.3)	1.000	/	/	/
CAZ	14/14 (100.0)	13/14 (92.9)	1.000	4/4 (100.0)	6/6 (100.0)	1.000
CTR	8/8 (100.0)	4/4 (100.0)	1.000	/	/	/
FOX	15/16 (93.8)	12/14 (85.7)	0.586	/	/	/
ATM	11/14 (78.6)	9/9 (100.0)	0.253	2/2 (100.0)	6/6 (100.0)	1.000
IPM	1/1 (100.0)	1/1 (100.0)	1.000	4/4 (100.0)	3/3 (100.0)	1.000
MEM	9/17 (52.9)	8/15 (53.3)	1.000‖	5/6 (83.3)	6/6 (100.0)	1.000
AK	6/15 (40.0)	4/7 (57.1)	0.652	3/4 (75.0)	3/3 (50.0)	1.000
GM	7/17 (41.2)	4/17 (23.5)	0.464‖	6/6 (100.0)	6/6 (100.0)	1.000
TMP	13/14 (92.9)	10/14 (71.4)	0.326	/	/	/
CIP	13/17 (76.5)	11/17 (64.7)	0.707‖	5/6 (83.3)	4/6 (66.7)	1.000

§, Number of resistant isolates/number of isolates tested (percentage of resistance).
¶, Fisher's exact test, unless stated otherwise.
‖, Pearson's Chi-squared test.
/, not applicable.
AMX, amoxicillin; AMP, ampicillin; AMC, amoxicillin-clavulanate; TZP, piperacillin-tazobactam; CTX, cefotaxime; CAZ, ceftazidime; CTR, ceftriaxone; FOX, cefoxitin; ATM, aztreonam; IPM, imipenem; MEM, meropenem; AK, amikacin; GM, gentamicin; TMP, trimethoprim; CIP, ciprofloxacin.

3.3.4 Outcomes of CPO cases

As metadata of CPO cases available were from 2003 to 2016 while the death data available were from 2003 to 2017, numbers of deaths within one year are accurate and complete. Three cases with incomplete medical records were excluded. All cause 30-day and one-year mortality rates were 11.8% (25/211) and 28.9% (61/211) respectively. Hospital mortality rate was 15.6% (33/211). Thirteen (52.0%) of the 25 cases that died within 30 days after CPO isolation were infection cases. Thirty-one (50.8%) of the 61 cases died within one year after CPO isolation were infection cases. The presence of CPO was a contributory cause of 12 deaths, therefore case fatality rate was 5.7% (12/211) and all of them were infection cases.

Among the 150 hospitalised cases, the median duration between CPO isolation and discharge from hospital was 17.5 days (IQR 8-39.25 days) with 16 (10.7%) patients discharged to healthcare facilities. For 72 hospitalised cases with CPO infection, the median duration between CPO isolation and discharge from hospital was 20 days (IQR 8.75-33.75 days) with 8 (11.1%) patients discharged to healthcare facilities. For 45 hospitalised cases with CPO colonisation, the median duration between CPO isolation and discharge from hospital was 17 days (IQR 6-45 days) and 6 (13.3%) patients were discharged to healthcare facilities. There were no differences of duration between CPO isolation and discharge from hospitals and the proportion of discharge to healthcare facilities between infection and colonisation (P=0.527 tested by Wilcoxon rank-sum test and P=0.946 tested by Pearson's Chi-squared test, respectively).

Comparison of survival of CPO cases by different factors in the subsections below could help to evaluate the impact of these factors on survival.

3.3.4.1 Survival by gender, status and source

There was no difference of 30-day or one-year survival between female and male cases (P=0.600/0.100, log-rank test) (Figure 3-23). There was no

difference of 30-day survival between infection and colonisation cases (*P*=0.100, log-rank test); however, one-year survival of infection cases was significantly lower than that of colonisation cases (*P*=0.003, log-rank test) (Figure 3-24). Among all the 211 cases, both 30-day and one-year survival of community-associated CPO cases were significantly higher than those of healthcare-associated CPO cases (*P*=0.010/0.001, log-rank test) (Figure 3-25). Regarding CPO infection, there was no difference of 30-day or one-year survival among different CPO source (*P*=0.700/0.400, log-rank test) (Figure 3-26).

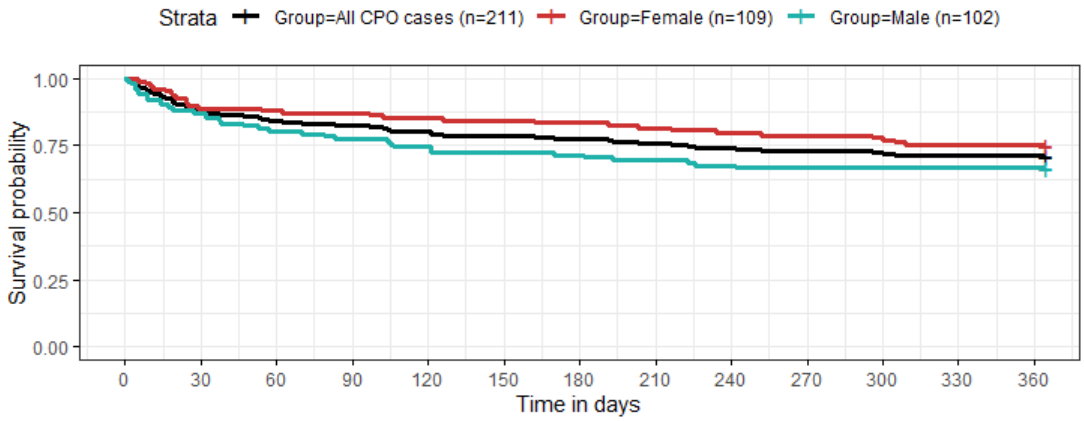


Figure 3-23. Survival (in days) of 211 carbapenemase-producing organisms (CPO) cases and comparison by gender

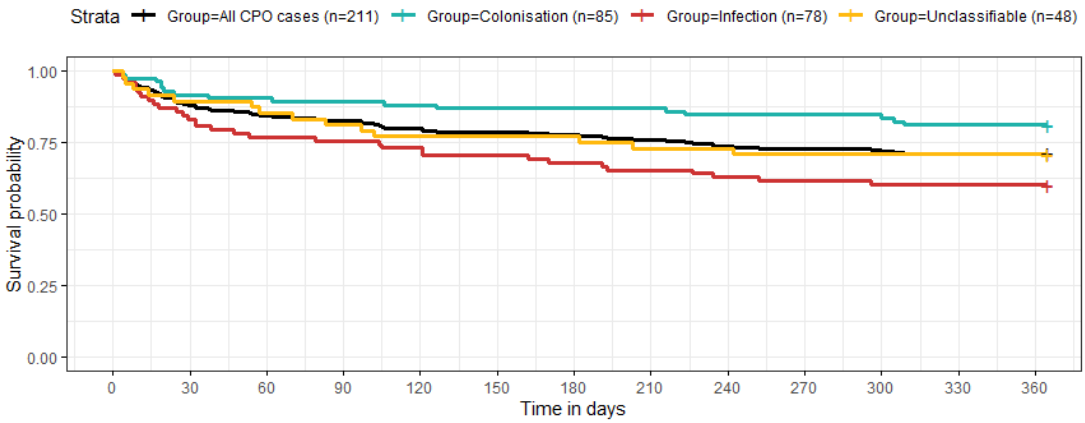


Figure 3-24. Survival (in days) of 211 carbapenemase-producing organisms (CPO) cases and comparison by status (infection, colonisation and unclassifiable)

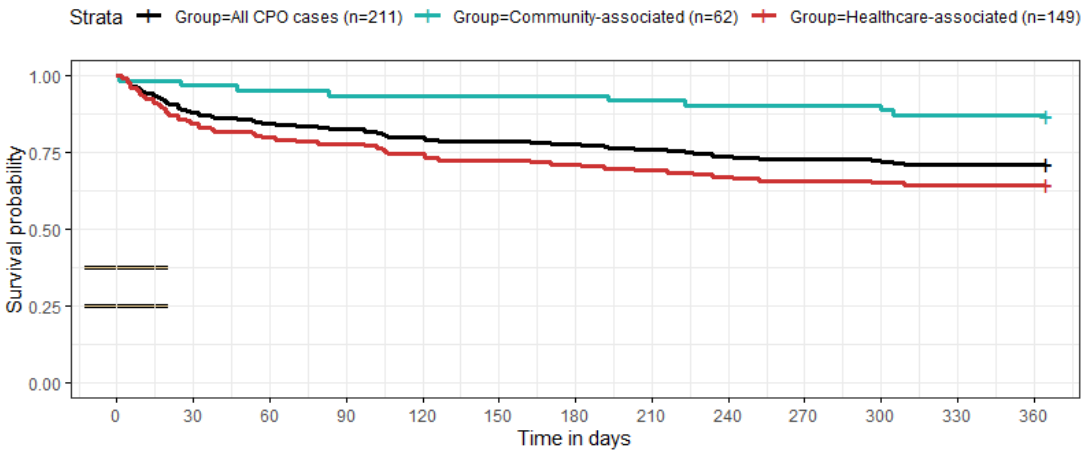


Figure 3-25. Survival (in days) of 211 carbapenemase-producing organisms (CPO) cases and comparison by source (healthcare-associated and community-associated)

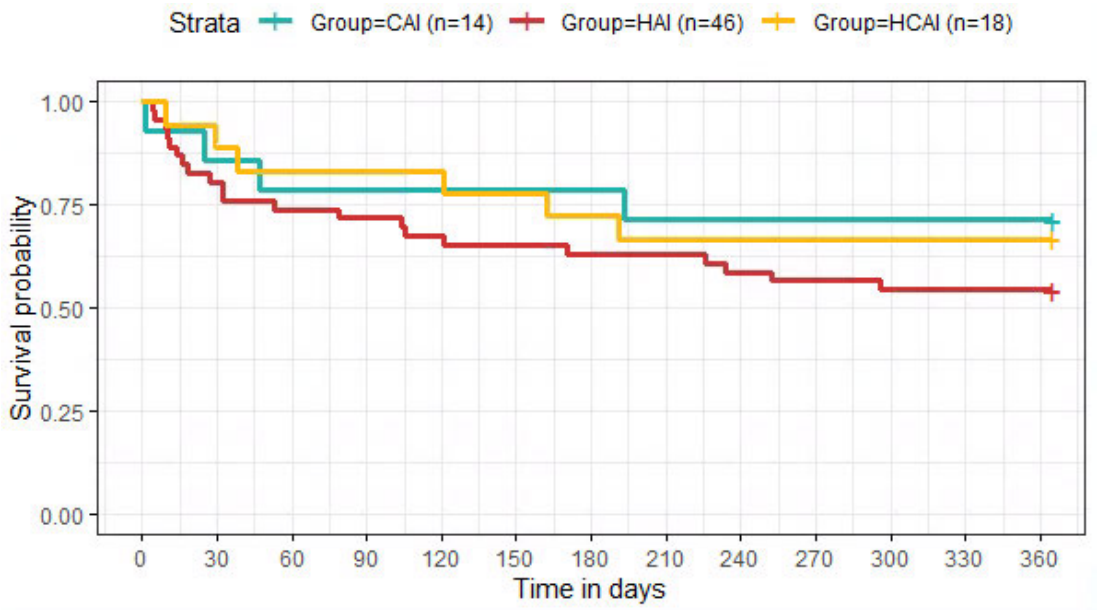


Figure 3-26. Survival (in days) of 78 carbapenemase-producing organisms (CPO) infection cases. CAI, community-acquired infection; HAI, healthcare-acquired infection; HCAI-healthcare-associated infection.

3.3.4.2 Survival by organism and carbapenemase

In terms of bacterial family, the 211 CPO cases comprise 177 (83.9%) cases only with Enterobacteriaceae, 29 (13.7%) cases only with non-fermenters and 5 (2.4%) cases with both Enterobacteriaceae and non-fermenters isolates. Four of the 5 cases with both Enterobacteriaceae and non-fermenters isolates were infection cases. Both 30-day and one-year survival of cases only with non-fermenters were significantly lower than those of cases only with Enterobacteriaceae (*P*<0.001/*P*=0.010, log-rank test) (Figure 3-27). Distribution of bacterial family (Enterobacteriaceae and non-fermenters) did not vary with CPO status (infection/colonisation/unclassifiable) (*P*=0.314, Pearson's Chi-squared test). Regarding carbapenemase, seven cases with CPO isolates produced more than one carbapenemases. IMI and GES-5 were combined together with KPC due to small numbers as all of them belong to Ambler class A. 30-day and one-year survival were significantly different among CPO cases with different carbapenemases (*P*<0.001/*P*<0.001, log-rank test) (Figure 3-28). It is noteworthy that OXA-48 producers had better survival as only two cases died within one year after CPO isolation (Figure 3-28). The distribution of carbapenemases varied among different CPO status (infection/colonisation/unclassifiable) (*P*=0.007, Fisher's exact test). Survival of cases with different carbapenemases were not compared further by status due to small numbers. Looking further by combining organism and carbapenemase, 17 cases with more than one carbapenemase-producing organism or produced more than one carbapenemase, and the groups with less than 5 cases were excluded from the analysis. There were significant differences among different groups of 30-day/one-year survival (*P*<0.001/*P*=0.003, log-rank test) (Figure 3-29). Cases with KPC producing *Enterobacter spp.* and cases with IMP producing *Pseudomonas spp.* had worse survival than cases with other CPO isolates (Figure 3-29). Survival of cases with different organisms and carbapenemases were not compared further by status due to small numbers.

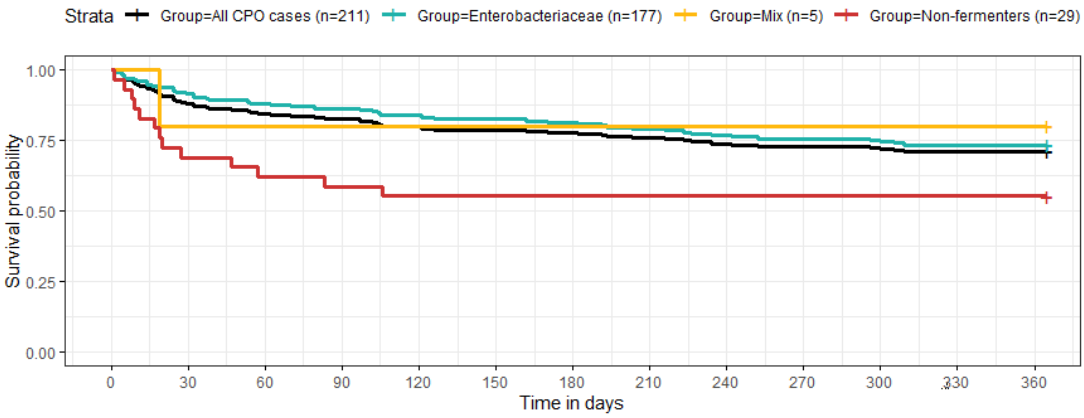


Figure 3-27. Survival (in days) of 211 carbapenemase-producing organisms (CPO) cases and comparison by bacterial family (Enterobacteriaceae and non-fermenters)

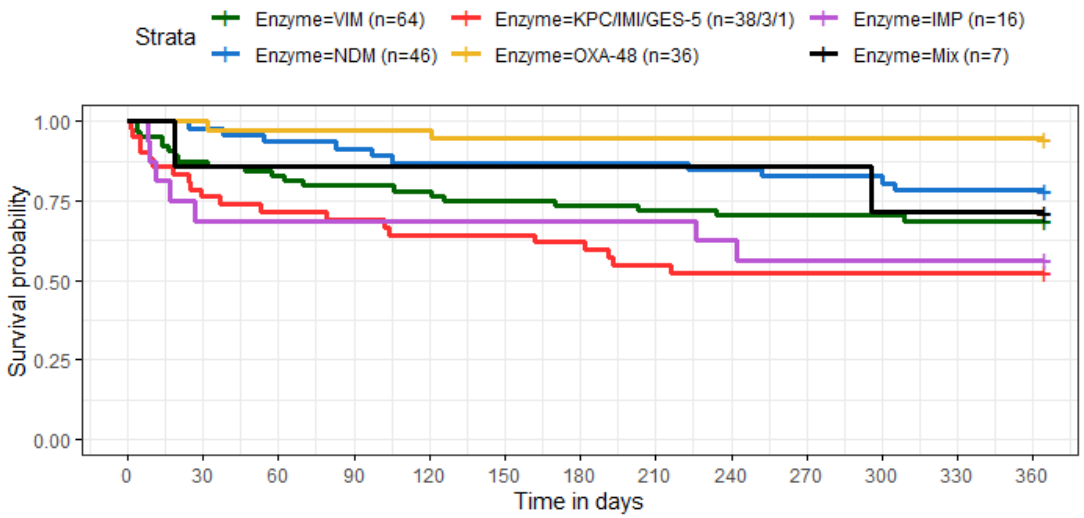


Figure 3-28. Survival (in days) of 211 carbapenemase-producing organisms (CPO) cases and comparison by carbapenemase

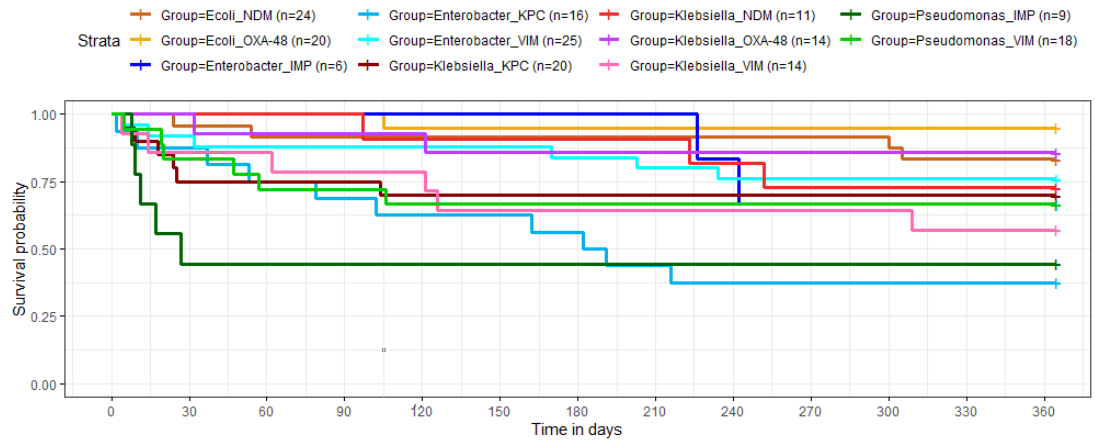


Figure 3-29. Survival (in days) of carbapenemase-producing organisms (CPO) cases and comparison by both organism and carbapenemase. Klebsiella_KPC, KPC producing *Klebsiella spp.*; Enterobacter_KPC, KPC producing *Enterobacter spp.*; Klebsiella_OXA48, OXA-48 producing *Klebsiella spp.*; Ecoli_OXA48, OXA-48 producing *E. coli*; Klebsiella_NDM, NDM producing *Klebsiella spp.*; Ecoli_NDM, NDM producing *E. coli*; Enterobacter_IMP, IMP producing *Enterobacter spp.*; Pseudomonas_IMP, IMP producing *Pseudomonas spp.*; Klebsiella_VIM, VIM producing *Klebsiella spp.*; Enterobacter_VIM, VIM producing *Enterobacter spp.*; Pseudomonas_VIM, VIM producing *Pseudomonas spp.*

Cases with non-fermenters, infections and being healthcare-associated had worse survival. Survival were significantly different among CPO cases with different carbapenemases.

3.3.4.3 Risk factors for 30-day all-cause mortality of hospitalised CPO cases

There were 150 hospitalised cases including cases infected or colonised by CPO and 23 of them (15.3%) died within 30 days after CPO isolation. Among all the potential risk factors with *P* value less than 0.1 in univariate analysis, respiratory tract infection was highly correlated with diseases of the respiratory system (correlation coefficient=0.74). Diseases of respiratory system had a higher AICc value and was accordingly removed from the multivariate model. Although sepsis was not highly correlated with systemic infection or organ

failure (correlation coefficient=0.60), given that sepsis is part of systemic infection or organ failure and had a higher AICc value, sepsis was removed from the multivariate model. Univariate analysis indicated that all-cause 30-day mortality was associated with advanced age, presence of carbapenemase producing non-fermenters, sepsis, malignancy, respiratory tract infection and systemic infection or organ failure (Appendix 3-3). Multivariate analysis showed that older than 60 years old (adjusted odds ratio, aOR 3.36, 95%CI 1.06-10.63, *P*=0.033), carbapenemase producing non-fermenters presence (aOR 4.88, 95%CI 1.64-14.47, *P*=0.005) and diseases of systemic infection or organ failure (aOR 4.21, 95%CI 1.38-12.81, *P*=0.032) were independent risk factors for 30-day mortality (Appendix 3-3). More aggressive healthcare should be considered for these patients to improve prognosis,

3.4 Discussion

The incidence of CPO in the UK was relatively low compared to other countries (Weiner et al., 2016; European Centre for Disease Prevention and Control, 2019b) and detection of CPO in Scotland (incidence rate 0.1 per 100,000 patient-days) was lower than that in England and Northern Ireland (incidence rate 0.85 per 100,000 patient-days) in healthcare settings (Grundmann et al., 2017). However, the number of CPO isolates isolated in Scotland has been increasing over recent years (Figure 3-14). Moreover, CPO had been reported from 13 of 14 NHS Boards and in more NHS Boards over time (Figure 3-7 and Figure 3-8). According to guidance from European Centre for Disease Prevention and Control, understanding and monitoring the local epidemiological situation is necessary to implement and refine CRO prevention and control strategies timely (Magiorakos et al., 2017). To date, no comprehensive epidemiology study of CPO at both national and individual level has been conducted in Scotland. To my knowledge, this is the first epidemiological study of CPO in Scotland.

There is currently no acknowledged episode definition and de-duplication criterion for a patient for CPO, and the work is underway to provide an appropriate definition at a UK level (Health Protection Scotland, 2016a). The longest interval between isolations with the same organism and carbapenemase from the same individual was 740 days in this study, indicating possible long-term persistence of CPO. As a result, no definition of episodes was attempted here and analysis was based on patients, i.e., CPO cases, using the first isolation for patients with multiple CPO isolations, unless stated otherwise.

3.4.1 CPO incidence: temporal trend and geographical distribution

In 2013, Scotland launched an acute hospital admission screening programme for CPE (Scottish Government, 2013). Therefore, the increase of CPO cases reported afterwards, CPE in particular, may reflect increased awareness and testing due to the introduction of CPE screening programme noting that 1) the true incidence was higher than the extrapolations from the model in 2003-2013 (Figure 3-5); 2) incidence of Enterobacteriaceae increased significantly faster than that of non-fermenters (Figure 3-6); 3) most of the isolates were from alimentary and urine samples which were usually used for screening and the number of isolates from these specimens increased since 2013 (Figure 3-11 and Figure 3-12). However, a real increase in CPO may also contribute to the observed increase as incidence of both CPO infection and colonisation cases also increased. Actually, CPO incidence might be underestimated as approximately only three quarters of patients audited had undergone CPE screening in line with national policy (76.1%) (Health Protection Scotland, 2019a).

More than half of CPO cases (58.8%) were older than 60 years old. The gender distribution of CPO cases by age groups was not the same as that of Scotland's population, but female cases were more frequent than male cases among cases older than 80 years old (Figure 3-1) which is similar to Scottish gender distribution (The Scottish Public Health Observatory, 2017). In addition,

survival of male cases was lower than that of female cases within one year after CPO isolation (Figure 3-23). Longer life expectancy/health life expectancy of Scottish females might account for these findings (Cristina et al., 2018).

In terms of geographical distribution, NHS Forth Valley and NHS Dumfries & Galloway had higher incidence than other NHS Boards. Some factors might contribute to the differences of CPO incidence across NHS Boards. First, the population size. CPO incidence was calculated based on population estimates (defined in Section 3.2.3.6) and the incidence might be high due to small population size even though the absolute number of CPO cases was small, rural areas in particular, say NHS Dumfries & Galloway. Second, healthcare capacity and compliance with the national screening programme. Large NHS Boards (such as NHS Lothian and NHS Great Glasgow & Clyde) have better healthcare capacity and uaually provide healthcare support for NHS Boards which are small and in rural areas. Third, environment and animal associated factors. Antimicrobial resistance is a threat involving humans, environment and animals. Whether antimicrobial resistance in the environment and animals contributes to carbapenem resisatnce in humans remains unknown in Scotland. Fourth, frequent travel and medical exchange between England and Scotland probably has an effect. The higher incidence in NHS Dumfries & Galloway which is the southernmost NHS Board might be an example.To better understand these potential underlying factors, the “One Health” approach (Thakur and Gray, 2019) and phylogeny analyses using both metadata and molecular data and collaboration across nations and NHS Boards are required. Also, the compliance with the national acute hospital admission screening programme of CPE in different NHS Boards should be evaluated to check if this contributed to the different geographical distribution of CPO.

In NHS Lothian, VIM and IMP which were associated with healthcare-associated and infection and had adverse impacts on survival accounted for more than half (34/65, 52.3%) of isolates reported from this Board. More

importantly, 84.4% (27/32) of all the cases with VIM/IMP had been hospitalised in the same hospital and 25 (78.1%) had been stayed in Haematology/Neurosurgery Specialties or HDU in the prior 90 days before CPO isolation. In NHS Forth Valley, all the cases with VIM had been admitted to the same hospital and more than half of them (13/25, 52.0%) had stayed in the General Medicine Specialty in the prior 90 days before CPO isolation. All the cases with IMP isolated in NHS Lanarkshire and Dumfries & Galloway in 2015-2016 had been admitted to Cardiac Surgery Specialty in the same hospital. These epidemiological data shows the possibility of clonal persistence and spread in some Specialties of some hospitals, however, the evidence was restricted by no access to whole genome sequence data of these isolates. NDM and OXA-48 producers were reported from most NHS Boards and they persisted in these Boards in recent years (2013-2016). Additionally, many of these isolates were isolated in the community or from community-associated cases from urine or alimentary samples, indicating the influence of active surveillance programme and the threat of CPO in the community.

3.4.2 Microbiological characteristics of CPO isolates

Similar to English data (Public Health England, 2018), the ‘big 5’ carbapenemases (VIM, NDM, KPC, OXA-48 and IMP) accounted for 96.7% of all the 243 CPO isolates. In contrast to a London study that reported 34% carbapenem resistant non-fermenters (Freeman et al., 2015), only 15.2% of all the CPO isolates in Scotland were non-fermenters. Carbapenemases were more diverse since 2015 as CPO isolates with combination enzymes NDM/IMP and NDM/OXA-48, and GES-5 emerged. All the 3 IMI-producing isolates were *Enterobacter cloacae* as has been described previously (Queenan and Bush, 2007) and all OXA-48-producing isolates were Enterobacteriaceae, mostly among *E. coli* and *Klebsiella spp.* which is consistent with the global distribution (Poirel et al., 2012). However, *Pseudomonas spp.* harbouring OXA-48 like families have been identified in England (Meunier et al., 2016). Metallo-carbapenemase enzymes, including VIM, NDM and IMP, are widely distributed in both Enterobacteriaceae and

non-fermenters. Indeed, such enzymes have historically been most common in *Pseudomonas aeruginosa* and *Acinetobacter spp.*, although they have recently moved to Enterobacteriaceae (Walsh, 2010; Daikos et al., 2009). This study also demonstrated the same overall trend (Figure 3-16). It is noteworthy that VIM producers have been reported from all species and they were more common in Enterobacteriaceae than in non-fermenters in Scotland, but has been found more common in non-fermenters than in Enterobacteriaceae in other countries (Cornaglia et al., 2011; Luzzaro et al., 2004).

The percentage of NDM and OXA-48 producers increased significantly over time while that of KPC and IMP producers dropped significantly over time. However, cases with NDM and OXA-48 producers had better survival than those with KPC and IMP producers (Figure 3-28). This study highlights another urgent public health threat, the presence and transmission of CPO in the community. The overall community-associated rate was 29.4% (62/211) and the number of community-associated cases increased after 2013 (Figure 3-4). A scoping review found that the percentage of either community-associated or community-onset Carbapenemase-resistant Enterobacteriaceae (CRE) ranged from 0.04% to 29.5% (Kelly et al., 2017) while a study reported the rate of community-onset infections caused by CPE as 22.9% (Pano-Pardo et al., 2016). Moreover, 69.4% (43) of the 62 community-associated cases in this study were NDM/OXA-48 producers and NDM/OXA-48 were associated with community-associated source and colonisation status (Figure 3-17 and Figure 3-18, Table 3-7 and Table 3-8). In contrast, KPC, VIM and IMP were more likely to be healthcare-associated (81.6%, 90.6% and 100.0%, respectively) and VIM/IMP were significantly associated with healthcare-associated source (Figure 3-17, Table 3-7). The occurrence of OXA-48 producers in the community is often a consequence of importations from endemic countries (Poirel et al., 2012). Also, it is well known that Indian subcontinent is the progenitor and epicentre of NDM and many of the UK NDM-1 positive patients had travelled to India or Pakistan within the past year, or had links with these countries (Kumarasamy et al., 2010). Unfortunately, travel information is not available in this study. Although enhanced data in the Electronic Reporting

System (ERS) submitted to the antimicrobial resistance and healthcare associated infections reference unit include foreign travel, such information is filled in retrospectively on a voluntary basis following confirmation of carbapenemase production and only 26% of records included foreign travel information (Public Health England, 2018). As travel is known to be associated with an increased risk for CPO it is therefore essential that travel history information, foreign travel to endemic countries in particular, should be collected routinely in the community and on admission to healthcare facilities. Given the increase in both the number and proportion of NDM/OXA-48 producers (Figure 3-20, Table 3-10), this could help to ensure that effective infection control measures are implemented promptly to curb CPO spread.

It is well known that carbapenemase-encoding plasmids frequently bear resistance determinants for aminoglycosides (aminoglycoside-modifying enzymes or 16S rRNA methylases) (Nordmann et al., 2012a). However, our study showed that Enterobacteriaceae isolates retained susceptibility to aminoglycosides which was consistent with the findings of a study conducted in two tertiary care hospitals in Scotland (Toner et al., 2019). In contrast to other studies (Buehrle et al., 2017; Tam et al., 2007), non-fermenters isolates showed high resistance to aminoglycosides, fluoroquinolones and piperacillin-tazobactam other than aztreonam. Discrepancies between studies may reflect different antimicrobial mechanisms and antimicrobial prescribing practices, highlighting the importance of understanding local antibiograms against CPO to preserve antibiotic utility and rational treatment. One-year survival of infection cases was significantly lower than that of colonisation cases, so precautions to improve survival for CPO infection individuals are still needed. Some studies suggested that higher antimicrobial resistance might contribute to unfavourable outcomes (Kohler et al., 2017; Daikos et al., 2009). Comparison of antimicrobial resistance between isolates from infection and colonisation cases in this study, however, argues against this hypothesis (Table 3-12).

3.4.3 Outcomes of CPO cases

3.4.3.1 Survival of CPO cases

The status (infection and colonisation) had significantly different impact on the survival (Figure 3-24), demonstrating the necessity of differentiating them. The survival advantage of cases with NDM and OXA-48 producers (Figure 3-29) might contribute to the predominance of NDM/OXA-48 producers in community due to prolonged urogenital or gastrointestinal colonisation. One study found that all OXA-48 producing *K. pneumoniae* isolates harboured genes which favour host colonisation and none of them were highly virulent genotypes (Beyrouthy et al., 2014). Other studies showed *E.coli* and *K. pneumoniae* as predominant species producing OXA-48; these are commensal bacteria that could be a reservoir of the *bla*$_{\text{OXA-48}}$ genes, contributing to the wide dissemination and transmission among different ecological sources (Potron et al., 2014; Mairi et al., 2019). In addition, all the 8 OXA-48 producers that underwent antimicrobial susceptibility testing remained susceptible to meropenem, indicating effective treatment options for these cases. Moreover, a lower proportion of infection among community-associated cases (14/62, 22.6%) than that among healthcare-associated cases (64/149, 43.0%) might contribute to the survival advantage of community-associated cases. The analysis did not reveal a significant difference in survival between CAI, HAI and HCAI cases (Figure 3-26).

In contrast, patients with Amber class A (mainly KPC) and IMP producing isolates had worse survival, KPC producing *Enterobacter spp.* and IMP producing *Pseudomonas spp.* in particular (Figure 3-28 and Figure 3-29). Some studies reported KPC-producing strains resulted in increased mortality due to resistance to immunological responses (Chiang et al., 2016), limited number of antimicrobial agents available to treat (Mouloudi et al., 2010; Papadimitriou-Olivgeris et al., 2017) and virulence conferring *K. pneumoniae* and *Enterobacter cloacae* complex which are predominant species producing KPC the ability to colonise mucous surface and evade the phagocytosis of immune cells (Paauw et al., 2009; Xu et al., 2018). To date, there is no study reporting an association between IMP production and increased risk of

mortality. But Cho *et al*. found that the coexistence of *pslA* which plays an important role in biofilm formation by *P. aeruginosa* and *bla*$_{IMP}$ contributed to the increase in antimicrobial resistance (Cho et al., 2018). Given that non-fermenters presence was an independent risk factor for 30-day mortality and *Pseudomonas spp.* are predominant species producing IMP, biofilm producing *Pseudomonas spp.* might be associated with worse survival rather than IMP production itself. The association between IMP production and mortality warrants more research. In contrast to studies reporting that metallo-beta-lactamases producers had no impact on increased risk of mortality partly due to an apparent susceptibility to various beta-lactams including carbapenems (Falcone et al., 2009; Kohler et al., 2017; Mouloudi et al., 2010), this study showed that only 10.3% (3/29) of metallo-beta-lactamases-producing isolates were susceptible to carbapenems and none to extended-spectrum cephalosporins. Another interesting finding is that VIM was more likely to be healthcare-associated and cause CPO infection (Figure 3-17 and Figure 3-18, Table 3-7 and Table 3-8) and patients with VIM producing *Klebsiella spp.* generally had worse one-year survival than patients with other isolates (Figure 3-29). VIM producing *Klebsiella spp.* have been reported mainly in southern Europe (Nordmann and Poirel, 2002) and several investigators have suggested that patients infected with VIM producing *Klebsiella pneumoniae* had four times increased risk to receive inappropriate empirical treatment which presumably led to worse outcome (Daikos et al., 2009; Kollef, 2000). Another factor that might have impact on the outcome could be an enhanced virulence of the resistant organisms (Kohler et al., 2017).

3.4.3.2 Risk factors for all-cause 30-day mortality

Both host- and pathogen-related factors were reported as drivers of an adverse outcome. This study found that advanced age, carbapenemase producing non-fermenters presence, malignancy, respiratory tract infection and systemic infection or organ failure were associated with overall 30-day mortality. Advanced age has been observed as a risk factor for mortality by many researchers as they represent a vulnerable population for drug resistant pathogen colonisation and infection (Mouloudi et al., 2010; Daikos et al., 2009;

Akgul et al., 2016). Patients with malignancies usually have more frequent exposure to healthcare such as immunocompromised therapy (radiotherapy and chemotherapy), invasive procedures (biopsies, bone marrow and spinal puncture) and longer hospitalisation and antimicrobial treatment. Respiratory infection has been described as a risk factor for 30-day mortality by other studies (Jiao et al., 2015; Li and Ye, 2017). The mucosal barrier injury of respiratory tract and altered lung tissue would decrease the capacity for bacterial clearance and increase probabilities of bacterial colonisation and/or infection. Moreover, bacteraemia which was an important driver of a fatal outcome generally begins with respiratory tract infection (Nabarro et al., 2017; Ng et al., 1996; Xiao et al., 2018), although this study showed that only 4 of the 21 bacteraemia cases stemmed from respiratory tract infection. Multivariate analysis revealed that both carrying non-fermenters and systemic infection or organ failure were independently associated with 30-day mortality, reinforced by the significant lower survival of carrying non-fermenters than that of Enterobacteriaceae. As far as I know, just one study investigated the association between organisms and mortality and did not find any particular organism to be linked to mortality (Kalam et al., 2014). Both virulence status and antimicrobial resistance may account for this. First, some studies have demonstrated that virulence determinants of *Pseudomonas* species such as the secretion of toxins and elastase activity could enhance pathogenicity against host defence mechanisms, thus having an unfavourable impact on the outcome. In addition, biofilm formation on the lumen of the respiratory tract could result in a higher risk of mortality by posing greater resistance against antibiotics (Jeong et al., 2014; Kipnis et al., 2006; Sadikot et al., 2005; Rossi Goncalves et al., 2017). Second, carbapenem resistance in non-fermenters usually stems from a combination of beta-lactamases, porin mutations and efflux pump overexpression, conferring reduced susceptibility to antibiotics and implying less treatment options and more treatment failure (Buehrle et al., 2017). However, no significant difference of antimicrobial susceptibility between Enterobacteria*ceae* and non-fermenters suggested that non-fermenters were simply more virulent. Systemic infection or organ failure is a

surrogate marker of critical illness. This host-related factor has been widely reported as a predictor of poorer outcome (Daikos et al., 2009; Jeong et al., 2014; Mouloudi et al., 2010; Bar-Yoseph et al., 2019; Xu et al., 2018). Aggressive therapy and infection prevention and control measures should be initiated timely in this population.

3.4.4 Limitations

There are some limitations of the study. First, not each case could be classified as either an infection or a colonisation case due to lack of clinical symptoms and laboratory testing data. But the definitions of status were assessed by consultant microbiologists and judgement were made accordingly. Second, antimicrobial susceptibility testing results were not available for each isolate and not all the isolates were tested for the same agents. Third, data on antimicrobial treatment in hospital at individual level were not available and such information has been reported as risk factors for unfavourable outcomes (Punpanich et al., 2012; Kim et al., 2012b). Fourth, no genomic data were available to identify possible clonal spread and virulence. Further molecular study is warranted to better understand of the phylogeny and pathogenicity of local CPO isolates.

3.5 Conclusion

This is the first epidemiological study of CPO in Scotland since the first report in 2003. Incidence and mortality rate of CPO in Scotland are relatively low but the incidence is increasing rapidly and CPO had been reported in 13 NHS Boards. Source and microbiological characteristics varied among NHS Boards. Enterobacteriaceae isolates predominated and increased faster than non-fermenters. Community-associated CPO were more likely to be colonisation while healthcare-associated CPO were more likely to be infection. The ‘big 5’ carbapenemases (VIM, NDM, KPC, OXA-48 and IMP) predominated. Cases with NDM/OXA-48 producers and Enterobacteriaceae had a survival advantage over other cases. Enterobacteriaceae isolates

retained susceptibility to aminoglycosides. Awareness is required that inpatients older than 60 years, with systemic infection or organ failure or presenting non-fermenters are at higher 30-day mortality risk from CPO. The findings of this study will inform screening programmes in both healthcare and community settings to help control the spread of CPO. Further molecular study is warranted for better understand of possible clonal spread and virulence of CPO isolates.

Chapter 4 Risk factors associated with CPO among hospitalised patients: a matched case-control-control study

4.1 Background

Carbapenem resistant organisms (CRO) have been gradually increasing worldwide since their first identification more than 30 years ago, thus posing a major global public health threat (European Centre for Disease Prevention and Control, 2019b; Logan and Weinstein, 2017). Infections caused by CRO are associated with significant morbidity and mortality as very few effective therapeutic options are available to treatment (Righi et al., 2017). Besides this, CRO are likely to result in a financial burden for healthcare systems due to prolonged hospital stays, restricted activities in the affected units, additional healthcare staff working hours and the screening of samples (Daroukh et al., 2014; Tischendorf et al., 2016). Resistance to carbapenems arises from carbapenemases production or non-enzymatic mechanisms. The latter include decreased outer membrane permeability or over-expression of efflux pumps with or without production of an ESBL and/or AmpC cephalosporinase (Bedenic et al., 2014). CRO strains that do not produce carbapenemases are usually less resistant to other antibiotics (Nordmann et al., 2012a) and their carbapenem resistance trait is not transferable. For this reason, CRO arising from non-enzymatic mechanisms are considered of less clinical concern than carbapenemase-producing organisms (CPO).

Many risk factors contribute to CPO acquisition and they could be generally classified into two groups: host-related and healthcare-related factors. Host-related factors include demographic characteristics such as advanced age, gender and comorbidities (Giuffre et al., 2013; Poole et al., 2016; Papadimitriou-Olivgeris et al., 2012; Tuon et al., 2012b). Healthcare-related factors include exposure to healthcare facilities, medical procedures and antibiotics (van Loon et al., 2018). Nevertheless, conflicting results are

reported in various studies conducted in different centres, most likely owing to the great heterogeneity between these studies, such as different study settings, study designs, population of interest, definition of resistance and selection of controls.

Incidence of CPO in Scotland is relatively low but increasing (Health Protection Scotland, 2019a). To date, most risk factor studies have been conducted in regions of high CRO endemicity (Balvinder et al., 2017; Jia et al., 2018; Khadem et al., 2017) and no risk factor studies have been conducted in a low incidence setting. Understanding local risk factors for CPO acquisition could help to make more targeted and effective surveillance programmes and infection prevention and control measures. In 2003, Scotland initiated an acute hospital admission screening programme for carbapenemase-producing Enterobacteriaceae (CPE), however, the focus was on high-risk individuals who has been previously confirmed CPE positive at any time, hospitalised or received dialysis outside of Scotland or a close contact of a person who has been colonised/infected with CPE in the last 12 months (Scottish Government, 2013; Health Protection Scotland, 2016b). The programme provided guidance on recommendations and practical advice to reduce the spread of CPE in non-acute and community settings in 2017 (Health Protection Scotland, 2017). This retrospective matched case-control study aims to provide more in-depth understanding of underlying factors associated with CPO among hospitalised patients in Scotland.

The aims of this chapter are:

1) to compare outcomes between CPO cases and controls;
2) to compare antimicrobial resistance rates to routine clinical tested antimicrobials between CPO cases and controls;
3) to investigate risk factors for CPO infection and colonisation among hospitalised patients.

4.2 Methods

4.2.1 Study design

This is a retrospective matched case-control study with two control groups (culture positive controls and demographic controls) among hospitalised patients in Scotland between 2010 and 2016. For risk factors associated with CPO, I attempted to answer two specific questions. First, what are the risk factors for acquiring CPO infection or colonisation among hospitalised patients? Namely what are the risk factors for being infected or colonised by the resistant organism CPO? Comparison between CPO cases and demographic controls will help to answer this question. Second, what are the risk factors for carbapenemase production among hospitalised patients with known pathogens? Namely what are the risk factors for the resistance (carbapenemase production) for one patient infected or colonised by a known bacterial pathogen. Comparison between CPO cases and culture positive controls will help to answer this question. Definitions of cases and controls are given in Table 4-1.

The outcomes of interest were CPO infection and CPO colonisation identified in surveillance or clinical cultures. Definitions of infection and colonisation for cases and culture positive controls are given in Table 4-2. To explore risk factors for CPO infection, each infection case was matched to up to 3 infection culture positive controls and 3 demographic controls respectively. To explore risk factors for CPO colonisation, each colonisation case was matched to up to 3 colonisation culture positive controls and 3 demographic controls respectively. Where more than 3 controls matched to one case within the defined criteria, the controls with closest admission dates to the CPO specimen date were chosen. Unless stated otherwise, controls mentioned below include both culture positive controls and demographic controls. The index hospitalisation was defined as the hospital stay during which the specimen with positive culture was collected for cases and culture positive controls and the equivalent hospital stay for demographic controls.

This study was reviewed and approved by the Public Benefit and Privacy Panel for Health and Social Care (Reference number: 1617-0328) (Appendix 3-1).

Table 4-1. Definition of cases and controls

Term	Definition
Case (CPO)	Patients hospitalised in Scottish hospitals testing positive for CPO isolated from any site identified in surveillance or clinical cultures between January 2010 and December 2016. CPO were categorised as either carbapenemase-producing Enterobacteriaceae (CPE) or carbapenemase-producing non-fermenters. The isolates from cases were non-susceptible to at least one carbapenem. Infection cases were differentiated from colonisation cases (Table 4-2).
Culture positive control (non-CPO)	A random selection of patients hospitalised in Scottish hospitals with positive surveillance or clinical cultures but not producing carbapenemase (non-CPO) during their hospital stay between January 2010 and December 2016. These controls were matched to cases by: • participating hospital • admission date (± 6 months) • specimen site (alimentary, normally sterile site, respiratory, superficial, urine, wound) • organism classification (Enterobacteriaceae or non-fermenters) Therefore, these non-CPO isolates include Enterobacteriaceae without carbapenemase production and non-fermenters without carbapenemase production. These non-CPO isolates might be resistant or susceptible to carbapenems but did not produce carbapenemase. Infection culture positive controls were differentiated from colonisation culture positive controls (Table 4-2).
Demographic control	A random selection of patients hospitalised in Scottish hospitals who did not have CPO isolation during their hospital stay between January 2010 and December 2016. These controls were matched to cases (infection or colonisation) by: • participating hospital • admission date (± 6 months) Therefore, demographic controls were not suspected to have any infection but whether they were colonised by pathogens remained unknown.

Table 4-2. Definition of infection and colonisation of cases and culture positive controls

Status	Definition
Infection	For cases and culture positive controls with single isolation, fulfilled any of the following criteria: • The isolate was isolated from normally sterile sites • The specimen matched an infection diagnosis, e.g. the isolate was isolated from urine and with a diagnosis of urinary tract infection • The primary diagnosis is sepsis with no source specified For cases with multiple isolations: • If any isolation fulfilled the infection criteria above, the case would be classified as an infection case.
Colonisation	For cases and culture positive controls with single isolation, fulfilled either of the following criteria: • There was no infection diagnosis • There was an infection diagnosis but caused by a different organism(s) at a different site from CPO isolates For cases with multiple isolations: • If all the isolations of a case fulfilled the colonisation criteria above, the case would be classified as a colonisation case.

4.2.2 Data

All the data included in this study were extracted from the datasets listed in Table 3-1 in Chapter 3. Data extraction and linkage of datasets for all cases and controls were performed via HPS/Public Health Intelligence's HPS Statistics Support Team as described in Chapter 3. All the data were anonymised and transferred to Public Health Intelligence's electronic Data Research and Innovation Service team which is based at the FARR Institute to enable preparation, provision and storage of data via the National Services Scotland National Safe Haven as described in Chapter 3. All analyses afterwards were performed within the National Services Scotland National Safe Haven. The ethics was reviewed and approved as described in Chapter 3.

4.2.3 Definition

Antimicrobial susceptibility testing were performed as described in Chapter 3 and the antimicrobial agents included are listed in Table 3-4 in Chapter 3. Antimicrobial resistance rates are defined as per the formula:

$$\text{Resistance rate} = \frac{\text{number of isolates resistant/intermediate to the tested agent}}{\text{number of isolates being tested for this agent}} * 100$$

Hospital mortality rates were defined as per the formula:

$$\text{Hospital mortality rate} = \frac{\text{number of cases/controls died during the index hospitalisation}}{\text{number of cases/controls}} * 100$$

All cause 30-day or 1-year mortality rate was defined as per the formula:

For CPO cases and culture positive controls,

$$\text{All cause } 30-\text{day or } 1-\text{year mortality rate} = \frac{\text{number of CPOcases/controls died within 30 days or 1 year after pathogen isolation}}{\text{total number of CPO cases/controls}} * 100$$

For demographic controls,

$$\text{All cause } 30-\text{day or } 1-\text{year mortality rate} = \frac{\text{number of controls died within 30 days or 1 year after admission date of index hospitalisation}}{\text{total number of controls}} * 100$$

The potential risk factors of interest associated with CPO infection and colonisation were placed in one of four categories: 1) Demographics, including age and gender; 2) Comorbidities; 3) Healthcare exposure, healthcare information in the prior 90 days before specimen date for cases and culture positive controls and admission date of index hospitalisation for demographic controls; 4) Invasive procedures, exposure to invasive medical procedure or devices in the prior 90 days before specimen date for cases and culture positive controls and admission date of index hospitalisation for demographic controls. The definitions of each potential risk factor of interest are listed in Appendix 4-1.

4.2.4 Statistical analysis

All statistical analyses were carried out using R (version 3.5.1) on the secure analytical platform within the National Services Scotland National Safe Haven provided and supported by Public Health Intelligence's electronic Data Research and Innovation Service team.

4.2.4.1 Control selection

Controls were randomly selected from hospitalised patients meeting the definitions listed in Table 4-1 by using the rv.uniform command in SPSS (according to HPS Statistics Support Team staff Sharon Kennedy, personal communication by email, October 3, 2019), which randomly allocated a value between 0 and 1 (based on continuous distribution) to each potential control where each value had the same chance of occurring. These were then stratified at the required level (an id variable is created for this purpose) and ranked by the id to allow selection of up to 3 controls. For cases with less than 3 potential controls, all available matched controls were used to maximise matches. Patients allocated to the culture positive controls were removed from the demographic controls before sampling for demographic control selection.

4.2.4.2 Survival analysis

The Kaplan-Meier method was used to plot 1-year survival curves. Differences of survival curves between cases and controls at 30-day and 1-year were evaluated by the log-rank test.

For comparison of outcomes between cases and controls, Pearson's Chi-squared test or Fisher's exact test as appropriate were used to compare mortality rates (all-cause 30-day, all-cause 1-year and hospital mortality rates) and rates of discharge to healthcare facilities/private residence. Univariate conditional logistic regression analyses were performed to compare length between bacteria isolation (cases and positive controls)/admission date (demographic controls) and hospital discharge.

4.2.4.3 Antimicrobial susceptibility comparison

Antimicrobial resistance rates to each antimicrobial agent for cases and culture positive controls with Enterobacteriaceae and non-fermenters isolates were evaluated respectively and the resistance rates were compared between cases and culture positive controls using Pearson's Chi-squared test or Fisher's exact test as appropriate.

4.2.4.4 Risk factor analysis for CPO infection and colonisation

To investigate risk factors for CPO infection, variables of interest listed in Appendix 4-1 were compared 1) between infection cases and infection culture positive controls, and 2) between infection cases and demographic controls. To investigate risk factors for CPO colonisation, variables of interest listed in Appendix 4-1 were compared 1) between colonisation cases and colonisation culture positive controls, and 2) between colonisation cases and demographic controls.

Conditional logistic regression modelling using LASSO (Least Absolute Shrinkage and Selection Operator) penalty as the variable selection method was performed (Tibshirani, 1996; Reid and Tibshirani, 2014). LASSO is a

powerful method that performs two main tasks: regularization and feature selection. It puts a constraint on the sum of the absolute values of the model parameters, the sum has to be less than a fixed value (upper bound). In order to do so the method applies a shrinking (regularization) process where it penalizes the coefficients of the regression variables by shrinking some of them to zero. During the features selection process the variables that still have a non-zero coefficient after the shrinking process are selected to be part of the model. The goal of this process is to minimize the prediction error. The regularization parameter lambda is chosen by cross validation. Univariate analysis was performed first to determine the unadjusted association between each potential risk factor of interest and CPO infection or colonisation. Correlation between variables with $P<0.10$ in univariate analysis were checked by calculating correlation coefficients (Spearman's rank correlation coefficient between continuous variables, Cramér's V between dichotomous variables or point-biserial correlation coefficient between continuous variables and dichotomous variables) and variance inflation factor (VIF). Also, interactions between potential risk factors were checked. For variables with high-level correlation (correlation coefficient≥0.70 or VIF>4), variables with greater corrected Akaike Information Criterion (AICc) value were removed from the model. After removing variables with high-level correlation, the remaining variables were considered to be included in the multivariate model and selected using LASSO (lambda used to choose variables=lambda.1se, the lambda that minimises cross validation error plus one standard error) (Friedman et al., 2010). The selected variables were included in the final multivariate analysis to determine the independent associations. For statistical purpose, variables with zero values in either group were removed from multivariate analyses, i.e. no patients in either group had exposure to the potential risk factor of interest. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to determine the strengths of these associations. A *P* value <0.05 was considered significant. To test the stability of the final multivariate model, variables in the model were removed in turn and the significance of the remaining variables were checked.

4.3 Results

4.3.1 Overview

Seventy hospitalised patients infected by CPO and 34 hospitalised patients colonised by CPO were identified. All infection and colonisation cases were matched with 3 demographic controls. Fifty-six (80.0%) of the 70 infection cases could be matched with at least one infection culture positive control while 32 (94.1%) of the 34 colonisation cases could be matched with at least one colonisation culture positive control (Figure 4-1). All these cases and controls were from 24 hospitals in 13 National Health Service (NHS) Boards.

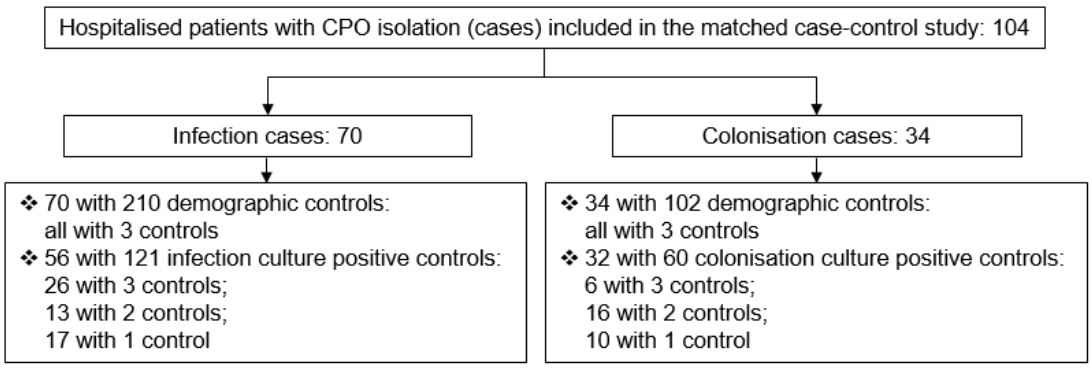


Figure 4-1. Flowchart of case and control selection

4.3.2 Outcome comparison between cases and controls

Comparison of outcomes (survival, mortality rate, length of post-isolation hospital stay and discharge information) between cases and controls would help to evaluate (1) whether CPO had an unfavourable impact on outcomes by comparing cases and demographic controls; (2) whether carbapenemase production of bacterial pathogens had an unfavourable impact on outcomes by comparing cases and culture positive controls. Comparisons of all-cause 30-day and 1-year survival between cases and controls by status (infection

and colonisation) and bacterial families (Enterobacteriaceae and non-fermenters) are shown in Figure 4-2, Figure 4-3 and Figure 4-4.

For infection, the 30-day and 1-year survival were significantly lower (P<0.001, log-rank test) (Figure 4-2) and all the mortality rates (all-cause 30-day and 1-year and hospital mortality) were significantly higher for CPO cases than for demographic controls (P<0.001) (Table 4-3). However, there were no significant differences regarding 30-day/1-year survival (P=0.600/0.100, log-rank test) (Figure 4-2) and all-cause 30-day/1-year mortality rates (P=0.667/0.153) (Table 4-3) between patients with CPO infection (i.e. cases) and non-CPO infection (i.e. culture positive controls). Notably, hospital mortality rate and length of post-isolation hospital stay of patients with CPO infection were significantly higher and longer than those of patients with non-CPO infection (Table 4-3). For in-hospital deaths, the duration between pathogen isolation and death for cases (range: 4-53 days, median: 18 days, interquartile range: 9.5-32 days) were significantly longer than for culture positive controls (range: 0-27 days, median: 4 days, interquartile range: 1.75-13.5 days) (P=0.010, Wilcoxon rank-sum test). In terms of bacterial families, there was no difference of 30-day/1-year survival between CPO patients and non-CPO patients (P=0.200/0.500, log-rank test) (Figure 4-3).

For colonisation, there was no difference of 30-day survival between cases and demographic controls (P=0.200, log-rank test), but the 1-year survival of cases was significantly lower than that of demographic controls (P=0.040, log-rank test) (Figure 4-4). No differences of mortality rates were found between cases and demographic controls (Table 4-3). Patients with CPO colonisation were more likely to discharge to healthcare facilities (P=0.023) while demographic controls to private residence (P=0.007) (Table 4-3). Interestingly, no differences were noted between patients with CPO colonisation and patients with non-CPO colonisation regarding 30-day/1-year survival (P=0.900/0.600, log-rank test) (Figure 4-4), mortality rates and length of post-isolation hospital stay (Table 4-3). Comparisons of survival between cases and

culture positive controls were not performed due to small numbers (less than 5).

In general, CPO infection resulted in worse survival and longer hospital stay among general hospitalised patients. If a patient was infected by a bacterial pathogen, carbapenemase production of the pathogen had no significant impact on survival but resulted in higher hospital mortality and longer hospital stay. CPO colonisation had no significant impact on survival but resulted in longer hospital stay among general hospitalised patients. If a patient was colonised by a bacterial pathogen, carbapenemase production of the pathogen had no significant impact on outcomes.

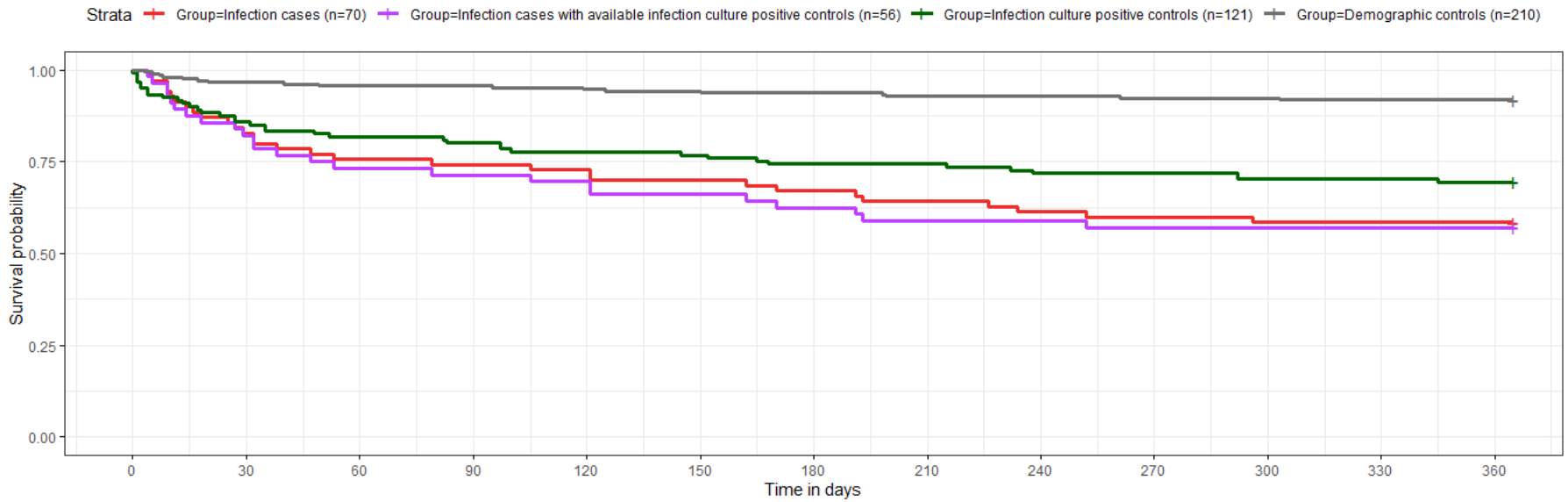


Figure 4-2. Survival (in days) of infection cases and controls

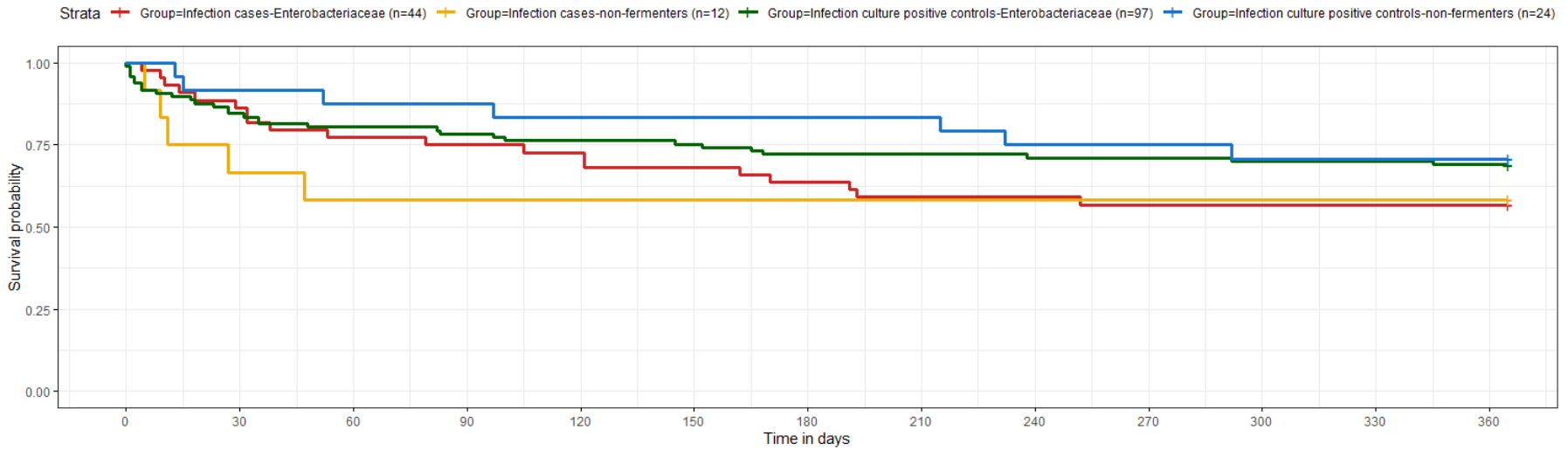


Figure 4-3. Survival (in days) of infection cases and infection culture positive controls by bacterial family (Enterobacteriaceae and non-fermenters)

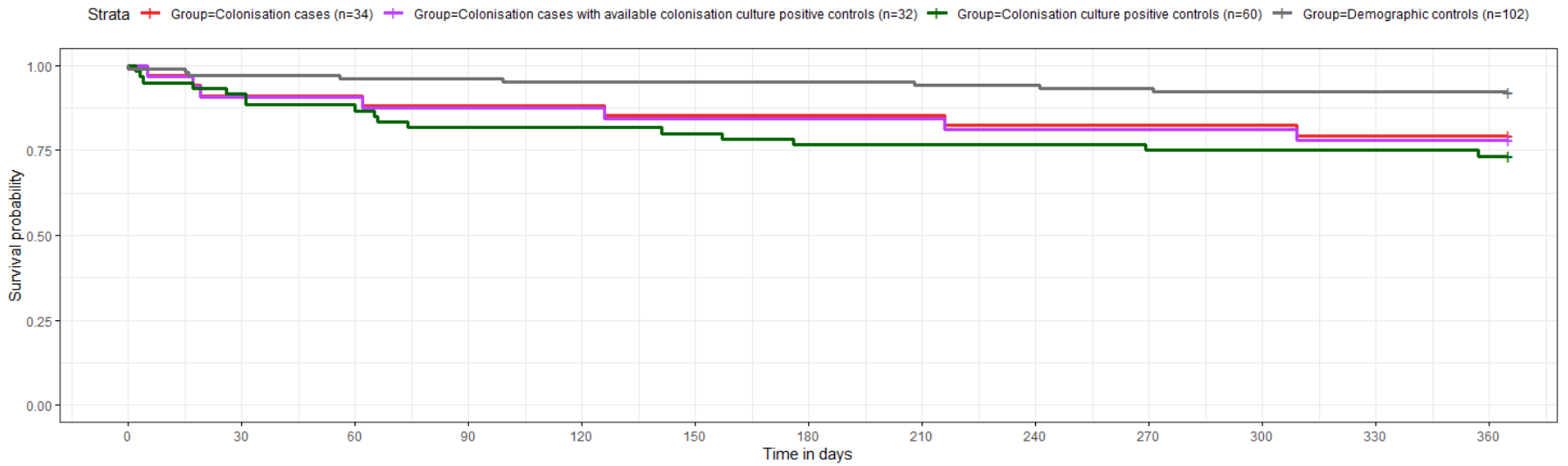


Figure 4-4. Survival (in days) of colonisation cases and controls

Table 4-3. Outcome characteristics and statistical comparisons of cases and controls

Characteristics	CPO infection						CPO colonisation					
	Cases vs. Demographic controls			Cases vs. Culture positive controls			Cases vs. Demographic controls			Cases vs. Culture positive controls		
	Inf-case[‖] N=70	DC[‖] N=210	*P*	Inf-case[‖] N=56	Inf-CPC[‖] N=121	*P*	Col-case[‖] N=34	DC[‖] N=102	*P*	Col-case[‖] N=32	Col-CPC[‖] N=60	*P*
All-cause 30-day mortality	12 (17.14%)	7 (3.33%)	<0.001[¶]	10 (17.86%)	17 (14.05%)	0.667[§]	3 (8.82%)	3 (2.94%)	0.165[¶]	3 (9.38%)	5 (8.33%)	1.000[¶]
All cause 1-year mortality	29 (41.43%)	17 (8.10%)	<0.001[§]	24 (42.86%)	37 (30.58%)	0.153[§]	7 (20.59%)	8 (7.84%)	0.056[¶]	7 (21.88%)	16 (26.67%)	0.801[§]
Hospital mortality	17 (24.29%)	8 (3.81%)	<0.001[§]	15 (26.79%)	12 (9.92%)	0.007[§]	3 (8.82%)	3 (2.94%)	0.165[¶]	3 (9.38%)	7 (11.67%)	1.000[¶]
Isolation to discharge, days, median (IQR, range)	17.5 (6.25-32.75, 0-551)[Φ]	1 (0-3, 0-69)[Φ]	<0.001*	17.5 (8.75-34, 2-551)[Φ]	8 (2-15, 0-155)[Φ]	0.041*	10 (2.25-32.75, 0-236)[Φ]	0 (0-1, 0-1)[Φ]	0.008*	12.5 (4.5-28.25, 0-236)[Φ]	4.5 (1-18.25, 0-219)[Φ]	0.266*
Discharge to healthcare facilities	6 (8.57%)	8 (3.81%)	0.122[¶]	3 (5.36%)	18 (14.88%)	0.116[§]	5 (14.71%)	3 (2.94%)	0.023[¶]	5 (15.63%)	6 (10.00%)	0.506[¶]
Discharge to private residence	47 (67.14%)	194 (92.38%)	<0.001[§]	38 (67.86%)	91 (75.21%)	0.400[§]	26 (76.47%)	96 (94.12%)	0.007[¶]	24 (75.00%)	47 (78.33%)	0.919[§]

[‖], number of cases/controls with the characteristic (percentage of cases/controls with the characteristic among the cases/controls investigated), unless stated otherwise;
[Φ], median (interquartile range, range);
[¶], Fisher's exact test;
[§], Pearson's Chi-squared test;
*, univariate conditional logistic regression;
Inf-case, infection cases; DC, demographic controls; Inf-CPC, infection culture positive controls; Col-case, colonisation cases; Col-CPC, colonisation culture positive controls; IQR, interquartile range.

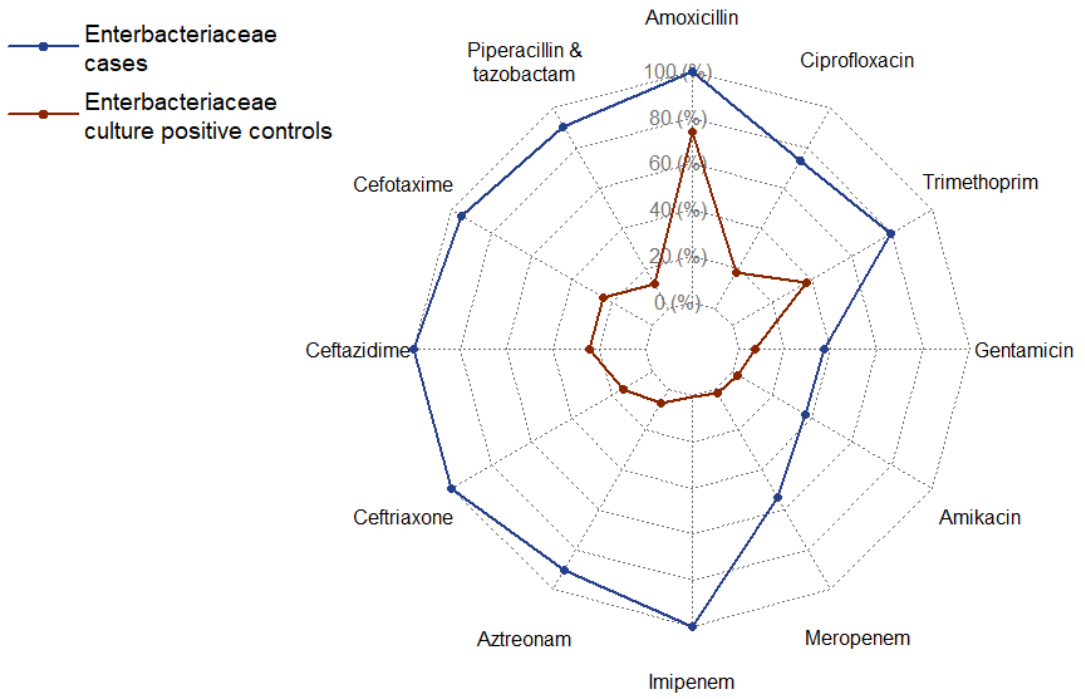
4.3.3 Antimicrobial susceptibility comparison between cases and culture positive controls

Thirty-three CPO isolates (27 Enterobacteriaceae isolates and 6 non-fermenter isolates) from 31 CPO cases and 87 non-CPO isolates (70 Enterobacteriaceae isolates and 17 non-fermenter isolates) from 87 culture positive controls were included in the analyses. These isolates were from 13 hospitals located in 8 NHS Boards between 2010 and 2016. The antimicrobial resistance pattern of cases and culture positive controls are illustrated in Table 4-4 and Figure 4-5. *In vitro* resistance to all tested antibiotics was higher in CPO isolates than their matched controls, i.e. non-CPO. In terms of Enterobacteriaceae, resistance rates to all the test agents of cases were significantly higher than those of controls (Table 4-4, Figure 4-5 A). Although resistance rates to all the test agents of cases with non-fermenters were higher than those of controls with non-fermenters, significant difference in resistance was observed for meropenem and gentamicin (Table 4-4, Figure 4-5 B). Carbapenemase production contributed to higher resistance rates to tested agents.

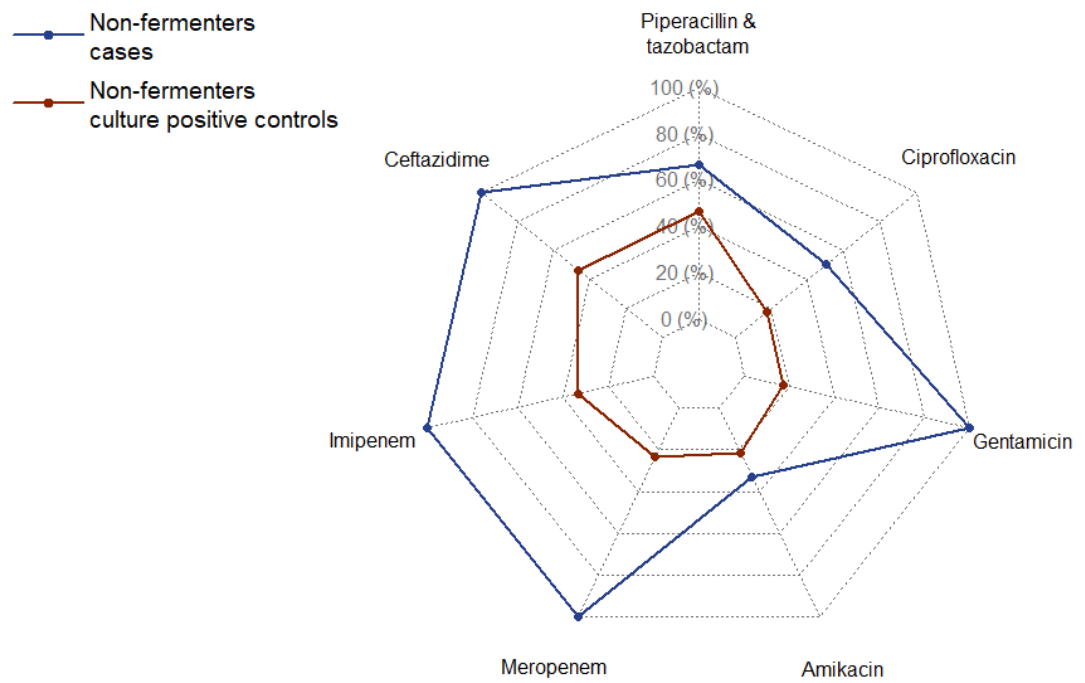
Table 4-4. Antimicrobial resistance rates of isolates from cases and culture positive controls

Agents	Cases-Enterobacteriacae§	Culture positive controls-Enterobacteriacae§	*P*‖	Cases-non-fermenters§	Culture positive controls-non-fermenters§	*P*‖
AMX	24/24 (100.0%)	45/61 (73.8%)	0.004	/	/	/
TZP	20/22 (90.9%)	8/63 (12.7%)	<0.001	4/6 (66.7%)	7/15 (46.7%)	0.635¶
CTX	19/20 (95.0%)	13/53 (24.5%)	<0.001	/	/	/
CAZ	20/20 (100.0%)	12/49 (24.5%)	<0.001	5/5 (100.0%)	6/13 (46.2%)	0.101¶
CTR	10/10 (100.0%)	3/21 (14.3%)	<0.001¶	/	/	/
ATM	18/20 (90.0%)	3/44 (6.8%)	<0.001	/	/	/
IPM	2/2 (100.0%)	/	/	4/4 (100.0%)	3/9 (33.3%)	0.070¶
MEM	13/24 (54.2%)	1/57 (1.8%)	<0.001¶	6/6 (100.0%)	4/17 (23.5%)	0.002¶
AK	7/19 (36.8%)	1/41 (2.4%)	0.001¶	2/6 (33.3%)	3/14 (21.4%)	0.613¶
GM	10/27 (37.0%)	5/70 (7.1%)	0.001¶	6/6 (100.0%)	3/17 (17.6%)	0.001¶
TMP	19/24 (79.2%)	24/64 (37.5%)	0.001	/	/	/
CIP	20/27 (74.1%)	12/66 (18.2%)	<0.001	3/6 (50.0%)	3/17 (17.6%)	0.279¶

§, Number of resistant isolates/number of isolates tested (percentage of resistance);
‖, Chi-squared test, unless stated otherwise;
¶, Fisher's exact test;
/, not applicable.
AMX, amoxicillin; TZP, piperacillin-tazobactam; CTX, cefotaxime; CAZ, ceftazidime; CTR, ceftriaxone; ATM, aztreonam; IPM, imipenem; MEM, meropenem; AK, amikacin; GM, gentamicin; TMP, trimethoprim; CIP, ciprofloxacin.



(A)



(B)

Figure 4-5. (A) Antimicrobial resistance rates of cases and culture positive controls for Enterobacteriaceae; (B) Antimicrobial resistance rates of cases and culture positive controls for non-fermenters.

4.3.4 Risk factors associated with CPO infection

When CPO infection cases were compared with demographic controls, the univariate analysis showed that a range of variables were associated with CPO infections, including all demographic variables, the majority of healthcare exposure variables and some comorbidities and invasive procedures (Table 4-5, Appendix 4-2). After removing highly correlated variables (Figure 4-6), the multivariate analysis indicated that hospitalisation, length of hospitalisation, length of ICU stay in the prior 90 days and being immunocompromised were independently associated with CPO infection (Table 4-7).

When CPO infection cases were compared with non-CPO infection controls, at univariate level, fewer variables were associated with CPO infections than for demographic controls, including gender, some healthcare exposure variables, hematologic malignancy, 'injury, poisoning and certain other consequences of external causes' and ectomy procedures (Table 4-5, Appendix 4-2). After removing highly correlated variables (Figure 4-7), the multivariate analysis showed that length of hospitalisation, length of HDU stay in the prior 90 days were independently associated with CPO infection (Table 4-7).

CPO infection were associated with extensive healthcare exposure (a history of prolonged hospital/ICU/HDU stay in particular) and immunodeficiency, more infection prevention and control measures should target patients with these risk factors.

4.3.5 Risk factors associated with CPO colonisation

The univariate analysis comparing CPO colonisation and demographic controls indicated that CPO colonisation were associated with age, 'endocrine, nutritional and metabolic diseases' including diabetes mellitus, endoscopic operation and majority of healthcare exposure variables (Table 4-6, Appendix 4-3). After removing highly correlated variables (Figure 4-8), the multivariate analysis showed that HDU stay in the prior 90 days and 'endocrine, nutritional

and metabolic diseases' were independent risk factors for CPO colonisation (Table 4-7). Compared with non-CPO colonisation controls, CPO cases were more likely to have 'endocrine, nutritional and metabolic diseases' (Table 4-6). However, no independent risk factors were found (Table 4-7). Among general hospitalised patients screening efforts warrant more consideration for those admitted to HDU in the preceding 90 days or with endocrine, nutritional and metabolic diseases.

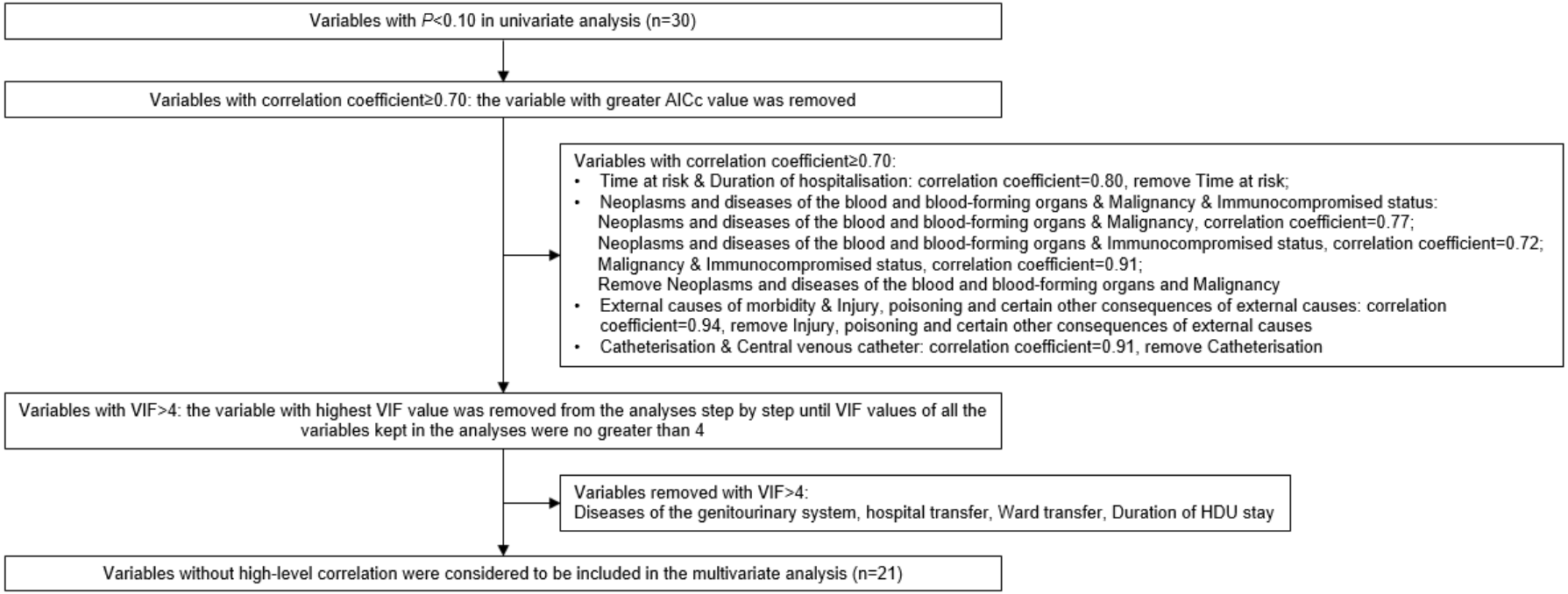


Figure 4-6. Selection of variables included in the multivariate analysis (Infection cases vs. Demographic controls). AICc, corrected Akaike Information Criterion; VIF, variance inflation factor.

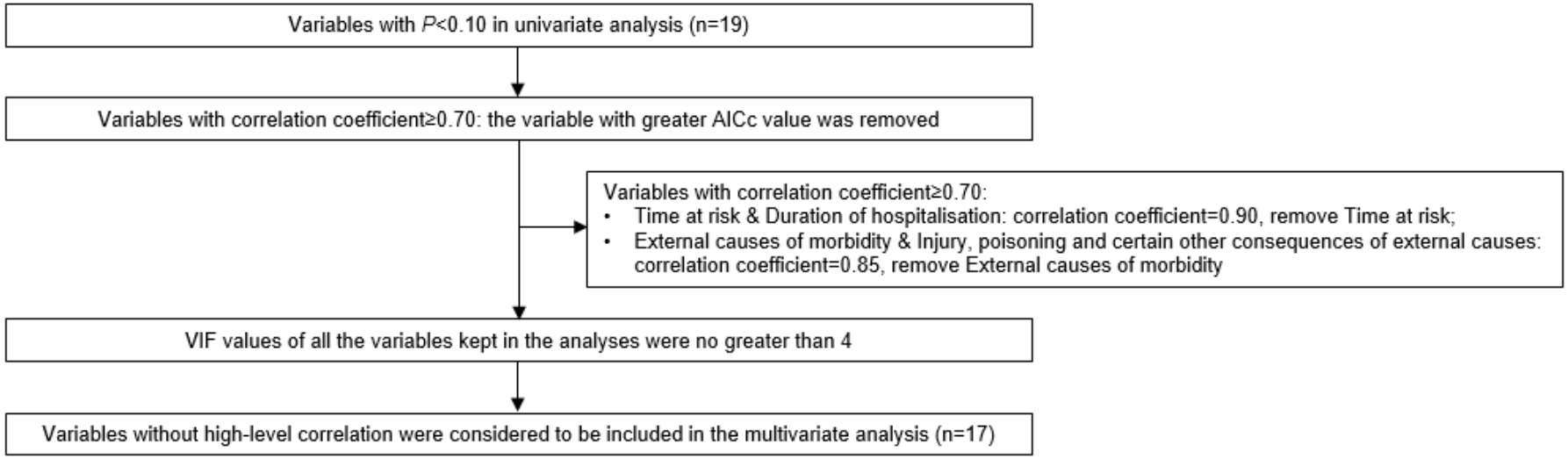


Figure 4-7. Selection of variables included in the multivariate analysis (Infection cases vs. Infection culture positive controls). AICc, corrected Akaike Information Criterion; VIF, variance inflation factor.

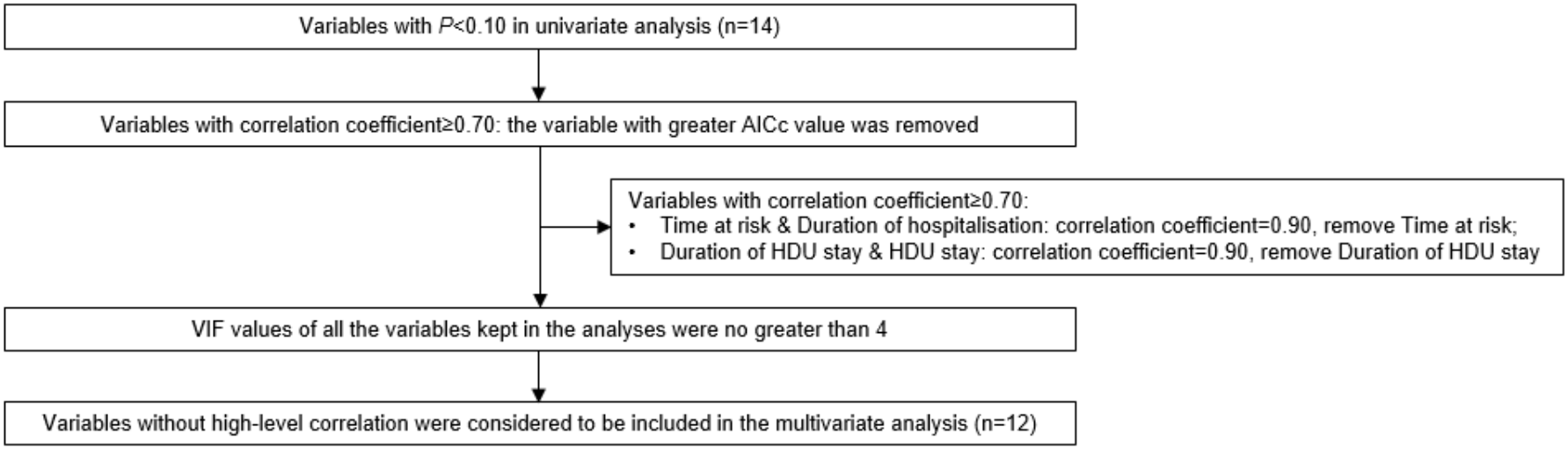


Figure 4-8. Selection of variables included in the multivariate analysis (Colonisation cases vs. Demographic controls). AICc, corrected Akaike Information Criterion; VIF, variance inflation factor.

Table 4-5. Univariate analysis of risk factors associated with carbapenemase-producing organisms (CPO) infection

Variables	Cases vs. Demographic controls		Cases vs. Culture positive controls		Cases vs. Demographic controls		Cases vs. Culture positive controls	
	Cases (%)§ N=70	Controls (%)§ N=210	Cases (%)§ N=56	Controls (%)§ N=121	OR (95%CI)	*P*	OR (95%CI)	*P*
Demographics								
Age, years, median (IQR, range)	64.5 (53-77.75, 1-92)*	53 (35-72, 2-93)*	65.5 (53-77.25, 1-92)*	68 (52-78, 0-96)*	1.03 (1.01-1.05)	**<0.001**	1.00 (0.98-1.02)	0.916
Age>60 years old	44 (62.9)	91 (43.3)	35 (62.5)	81 (66.9)	2.55 (1.37-4.77)	**0.003**	0.74 (0.37-1.47)	0.394
Gender, male	43 (61.4)	91 (43.3)	38 (67.9)	64 (52.9)	2.11 (1.20-3.70)	**0.009**	2.16 (1.06-4.37)	**0.033**
Comorbidities								
Neoplasms and diseases of the blood and blood-forming organs	24 (34.3)	30 (14.3)	19 (33.9)	32 (26.4)	3.28 (1.70-6.32)	**<0.001**	1.58 (0.75-3.34)	0.231
Malignancy	15 (21.4)	20 (9.5)	12 (21.4)	24 (19.8)	2.86 (1.30-6.28)	**0.009**	1.37 (0.53-3.50)	0.516
Solid	5 (7.1)	16 (7.6)	3 (5.4	15 (12.4)	0.93 (0.33-2.63)	0.896	0.42 (0.11-1.57)	0.195
Hematologic	10 (14.3)	3 (1.4)	9 (16.1)	9 (7.4)	26.15 (3.32-205.92)	**0.002**	4.73 (1.20-18.71)	**0.027**
Anaemia	6 (8.6)	2 (1.0)	6 (10.7)	3 (2.5)	9.00 (1.82-44.59)	**0.007**	3.42 (0.82-14.34)	0.093
Endocrine, nutritional and metabolic diseases	14 (20.0)	23 (11.0)	10 (17.9)	18 (14.9)	1.93 (0.96-3.90)	0.065	1.13 (0.46-2.81)	0.785
Diabetes mellitus	7 (10.0)	10 (4.8)	6 (10.7)	12 (9.9)	2.18 (0.81-5.91)	0.125	1.02 (0.37-2.85)	0.965
With complications	1 (1.4)	0 (0.0)	1 (1.8)	3 (2.5)	/	0.250¶	0.60 (0.06-5.95)	0.660
Diseases of the circulatory system	17 (24.3)	41 (19.5)	14 (25.0)	35 (28.9)	1.41 (0.69-2.87)	0.350	0.84 (0.41-1.72)	0.632
Heart failure	1 (1.4)	1 (0.5)	1 (1.8)	3 (2.5)	3.00 (0.19-47.96)	0.437	0.69 (0.06-8.04)	0.764
Diseases of the respiratory system	20 (28.6)	28 (13.3)	16 (28.6)	38 (31.4)	2.56 (1.33-4.94)	**0.005**	0.65 (0.28-1.53)	0.326
Respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	/	1.000¶	/	1.000¶
Diseases of the digestive system	13 (18.6)	39 (18.6)	13 (23.2)	30 (24.8)	1.00 (0.50-1.99)	1.000	0.90 (0.36-2.22)	0.818
Diseases of the genitourinary system	33 (47.1)	27 (12.9)	24 (42.9)	51 (42.1)	8.38 (3.81-18.47)	**<0.001**	0.81 (0.36-1.83)	0.613
Renal failure	9 (12.9)	7 (3.3)	7 (12.5)	13 (10.7)	5.48 (1.65-18.16)	**0.005**	1.09 (0.40-2.94)	0.865
Diseases of the nervous system	10 (14.3)	12 (5.7)	7 (12.5)	11 (9.1)	2.84 (1.14-7.10)	**0.026**	1.39 (0.52-3.77)	0.512
Diseases of the skin and subcutaneous tissue	4 (5.7)	9 (4.3)	3 (5.4)	10 (8.3)	1.36 (0.40-4.57)	0.623	0.39 (0.08-1.92)	0.245
Diseases of the musculoskeletal system and connective tissue	8 (11.4)	17 (8.1)	5 (8.9)	10 (8.3)	1.50 (0.60-3.77)	0.388	1.15 (0.38-3.51)	0.808
External causes of morbidity	21 (30.0)	32 (15.2)	18 (32.1)	15 (12.4)	2.31 (1.23-4.34)	**0.009**	2.96 (1.40-6.26)	**0.005**
Injury, poisoning and certain other consequences of external causes	19 (27.1)	29 (13.8)	16 (28.6)	13 (10.7)	2.27 (1.18-4.36)	**0.014**	3.38 (1.50-7.60)	**0.003**
Immunocompromised status	21 (30.0)	20 (9.5)	17 (30.4)	25 (20.7)	4.53 (2.14-9.58)	**<0.001**	2.07 (0.91-4.71)	0.081
Healthcare exposure								
Emergency admission	51 (72.9)	117 (55.7)	39 (69.6)	98 (81.0)	2.15 (1.19-3.91)	**0.012**	0.46 (0.20-1.06)	0.070
Admission from healthcare facilities	6 (8.6)	10 (4.8)	5 (8.9)	9 (7.4)	1.92 (0.65-5.65)	0.235	1.65 (0.49-5.58)	0.419
Surgical Specialty	35 (50.0)	97 (46.2)	30 (53.6)	46 (38.0)	1.16 (0.68-1.99)	0.583	1.87 (0.96-3.64)	0.068

Variables	Cases vs. Demographic controls		Cases vs. Culture positive controls		Cases vs. Demographic controls		Cases vs. Culture positive controls	
	Cases (%)§ N=70	Controls (%)§ N=210	Cases (%)§ N=56	Controls (%)§ N=121	OR (95%CI)	*P*	OR (95%CI)	*P*
Time at risk, days, median (IQR, range)	11 (1-32.5, 0-88)*	1 (0-4, 0-69)*	7 (0.75-37, 0-85)*	1 (0-12, 0-142)*	1.07 (1.04-1.09)	**<0.001**	1.02 (1.00-1.03)	**0.042**
HDU stay	28 (40.0)	9 (4.3)	20 (35.7)	19 (15.7)	18.92 (6.60-54.20)	**<0.001**	2.95 (1.35-6.48)	**0.007**
Duration of HDU stay, days, median (IQR, range)	0 (0-2, 0-28)*	0 (0-0, 0-6)*	0 (0-2, 0-28)*	0 (0-0, 0-14)*	1.82 (1.26-2.64)	**0.001**	1.16 (1.04-1.28)	**0.006**
ICU stay	21 (30.0)	6 (2.9)	16 (28.6)	15 (12.4)	19.10 (5.67-64.32)	**<0.001**	2.67 (1.18-6.06)	**0.019**
Duration of ICU stay, days, median (IQR, range)	0 (0-0, 0-39)*	0 (0-0, 0-7)*	0 (0-0, 0-39)*	0 (0-0, 0-27)*	1.49 (1.09-2.04)	**0.012**	1.06 (0.97-1.15)	0.176
Hospitalisation	34 (48.6)	29 (13.8)	28 (50.0)	38 (31.4)	6.14 (3.13-12.04)	**<0.001**	3.08 (1.42-6.70)	**0.004**
Duration of hospitalisation, days, median (IQR, range)	19 (8-44, 0-85)*	1 (0-4, 0-69)*	17.5 (5.5-47.5, 0-85)*	5 (0-15, 0-142)*	1.08 (1.05-1.11)	**<0.001**	1.02 (1.01-1.04)	**0.003**
Hospital transfer	13 (18.6)	5 (2.4)	9 (16.1)	5 (4.1)	11.77 (3.33-41.60)	**<0.001**	5.57 (1.44-21.48)	**0.013**
Ward transfer	40 (57.1)	41 (19.5)	31 (55.4)	49 (40.5)	6.59 (3.38-12.85)	**<0.001**	1.65 (0.86-3.14)	0.131
Invasive procedures								
Any	35 (50.0)	57 (27.1)	28 (50.0)	45 (37.2)	2.65 (1.51-4.65)	**0.001**	1.78 (0.92-3.43)	0.087
Transplantation	4 (5.7)	0 (0.0)	4 (7.1)	1 (0.8)	/	**0.004¶**	7.67 (0.82-71.32)	0.073
Centesis	5 (7.1)	5 (2.4)	3 (5.4)	4 (3.3)	3.36 (0.89-12.73)	0.074	2.35 (0.46-12.02)	0.304
Ectomy	10 (14.3)	17 (8.1)	9 (16.1)	8 (6.6)	1.95 (0.82-4.61)	0.129	2.72 (1.04-7.15)	**0.042**
Catheterisation	9 (12.9)	3 (1.4)	6 (10.7)	10 (8.3)	9.00 (2.44-33.24)	**0.001**	1.46 (0.49-4.35)	0.501
Urinary catheter	1 (1.4)	1 (0.5)	1 (1.8)	1 (0.8)	3.00 (0.19-47.96)	0.437	1.73 (0.10-30.76)	0.708
CVC	8 (11.4)	2 (1.0)	5 (8.9)	9 (7.4)	12.00 (2.55-56.51)	**0.002**	1.41 (0.43-4.62)	0.566
Dialysis or drainage	5 (7.1)	1 (0.5)	5 (8.9)	4 (3.3)	15.00 (1.75-128.39)	**0.013**	3.21 (0.85-12.18)	0.086
Endoscopic operation	7 (10.0)	10 (4.8)	6 (10.7)	12 (9.9)	2.18 (0.81-5.91)	0.125	1.00 (0.33-3.03)	1.000
Invasive ventilation	4 (5.7)	2 (1.0)	3 (5.4)	8 (6.6)	6.00 (1.10-32.76)	**0.039**	0.84 (0.20-3.51)	0.813
Other surgical procedures	9 (12.9)	24 (11.4)	6 (10.7)	19 (15.7)	1.15 (0.50-2.63)	0.745	0.60 (0.21-1.67)	0.328

§, number of cases/controls with exposure to the variable (percentage of cases/controls with exposure to the variable among the cases/controls investigated);
*, median (interquartile range, range);
¶, Fisher's exact test;
/, not applicable;
OR (95%CI), odds ratio (95% confidence interval); IQR, interquartile range; ICU, intensive care unit; HDU, high dependency unit; CVC, central venous catheter.

Table 4-6. Univariate analysis of risk factors associated with carbapenemase-producing organisms (CPO) colonisation

Variables	Cases vs. Demographic controls		Cases vs. Culture positive controls		Cases vs. Demographic controls		Cases vs. Culture positive controls	
	Cases (%)[§] N=34	Controls (%)[§] N=102	Cases (%)[§] N=32	Controls (%)[§] N=60	OR (95%CI)	*P*	OR (95%CI)	*P*
Demographics								
Age, years, median (IQR, range)	64.5 (58-78, 19-91)*	51.5 (33.25-63, 0-95)*	65 (58.75-78, 19-91)*	73 (59-81.25, 0-94)*	1.03 (1.01-1.06)	**0.002**	0.99 (0.96-1.01)	0.318
Age>60 years old	21 (61.8)	67 (65.7)	21 (65.6)	43 (71.7)	0.85 (0.38-1.88)	0.680	0.71 (0.27-1.85)	0.482
Gender, male	15 (44.1)	50 (49.0)	15 (46.9)	28 (46.7)	0.83 (0.39-1.77)	0.629	0.98 (0.40-2.39)	0.970
Comorbidities								
Neoplasms and diseases of the blood and blood-forming organs	7 (20.6)	14 (13.7)	7 (21.9)	8 (13.3)	1.61 (0.60-4.34)	0.349	2.00 (0.59-6.73)	0.263
Malignancy	5 (14.7)	8 (7.8)	5 (15.6)	4 (6.7)	1.95 (0.61-6.24)	0.258	2.90 (0.66-12.83)	0.160
Solid	3 (8.8)	7 (6.9)	3 (9.4)	4 (6.7)	1.31 (0.32-5.36)	0.706	1.45 (0.27-7.81)	0.665
Hematologic	2 (5.9)	1 (1.0)	2 (6.3)	0 (0.0)	6.00 (0.54-66.17)	0.143	/	0.119[¶]
Anaemia	2 (5.9)	2 (2.0)	2 (6.3)	1 (1.67)	3.00 (0.42-21.30)	0.272	4.00 (0.36-44.11)	0.258
Endocrine, nutritional and metabolic diseases	12 (35.3)	11 (10.8)	12 (37.5)	8 (13.3)	5.52 (1.89-16.14)	**0.002**	4.08 (1.40-11.92)	**0.010**
Diabetes mellitus	5 (14.7)	4 (3.9)	5 (15.6)	3 (5.0)	5.79 (1.09-30.83)	**0.039**	3.62 (0.85-15.41)	0.082
With complications	3 (8.8)	0 (0.0)	3 (9.4)	1 (1.7)	/	**0.015**[¶]	6.69 (0.69-67.78)	0.101
Diseases of the circulatory system	14 (41.2)	26 (25.5)	13 (40.6)	24 (40.0)	2.29 (0.93-5.64)	0.071	1.02 (0.39-2.64)	0.968
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	/	1.000[¶]	/	1.000[¶]
Diseases of the respiratory system	5 (14.7)	17 (16.7)	5 (15.6)	12 (20.0)	0.87 (0.30-2.51)	0.793	0.66 (0.21-2.08)	0.475
Respiratory failure	2 (5.9)	0 (0.0)	2 (6.3)	3 (5.0)	/	0.061[¶]	1.00 (0.16-6.14)	1.000
Diseases of the digestive system	1 (2.9)	11 (10.8)	1 (3.1)	16 (26.7)	0.26 (0.03-2.06)	0.201	0.10 (0.01-0.80)	**0.030**
Diseases of the genitourinary system	8 (23.5)	10 (9.8)	8 (25.0)	13 (21.7)	2.64 (0.98-7.13)	0.056	1.28 (0.44-3.73)	0.651
Renal failure	4 (11.8)	4 (3.9)	4 (12.5)	3 (5.0)	3.00 (0.75-12.00)	0.120	3.35 (0.59-18.88)	0.171
Diseases of the nervous system	2 (5.9)	5 (4.9)	2 (6.3)	3 (5.0)	1.20 (0.23-6.19)	0.827	1.15 (0.19-7.03)	0.876
Diseases of the skin and subcutaneous tissue	3 (8.8)	8 (7.8)	3 (9.4)	2 (3.3)	1.13 (0.30-4.24)	0.862	3.54 (0.59-21.38)	0.168
Diseases of the musculoskeletal system and connective tissue	3 (8.8)	7 (6.9)	3 (9.4)	7 (11.7)	1.31 (0.32-5.36)	0.706	0.95 (0.21-4.26)	0.949
External causes of morbidity	10 (29.4)	20 (19.6)	9 (28.1)	14 (23.3)	1.61 (0.70-3.72)	0.261	1.19 (0.44-3.26)	0.731
Injury, poisoning and certain other consequences of external causes	10 (29.4)	15 (14.7)	9 (28.1)	12 (20.0)	2.10 (0.91-4.83)	0.081	1.48 (0.53-4.12)	0.453
Immunocompromised status	5 (14.7)	8 (7.8)	5 (15.6)	5 (8.3)	1.95 (0.61-6.24)	0.258	2.17 (0.55-8.48)	0.266
Healthcare exposure								
Emergency admission	23 (67.6)	59 (57.8)	22 (68.8)	45 (75.0)	1.61 (0.67-3.92)	0.290	0.84 (0.29-2.44)	0.750
Admission from healthcare facilities	2 (5.9)	3 (2.9)	1 (3.1)	2 (3.3)	2.00 (0.33-11.97)	0.448	0.62 (0.05-7.00)	0.697
Surgical Specialty	18 (52.9)	39 (38.2)	16 (50.0)	28 (46.7)	1.70 (0.81-3.55)	0.158	1.00 (0.36-2.76)	1.000

Variables	Cases vs. Demographic controls		Cases vs. Culture positive controls		Cases vs. Demographic controls		Cases vs. Culture positive controls	
	Cases (%)§ N=34	Controls (%)§ N=102	Cases (%)§ N=32	Controls (%)§ N=60	OR (95%CI)	*P*	OR (95%CI)	*P*
Time at risk, days, median (IQR, range)	4 (0-22.75, 0-91)*	1 (0-2, 0-81)*	3 (0-23, 0-91)*	3 (0-16, 0-139)*	1.03 (1.01-1.06)	**0.007**	1.01 (0.99-1.03)	0.499
HDU stay	7 (20.6)	2 (2.0)	7 (21.9)	6 (10.0)	19.1 (2.33-156.45)	**0.006**	2.62 (0.64-10.77)	0.183
Duration of HDU stay, days, median (IQR, range)	0 (0-0, 0-5)*	0 (0-0, 0-5)*	0 (0-0, 0-5)*	0 (0-0, 0-20)*	2.01 (1.16-3.51)	**0.014**	0.97 (0.81-1.17)	0.762
ICU stay	9 (26.5)	0 (0.0)	8 (25.0)	8 (13.3)	/	**<0.001¶**	2.22 (0.65-7.57)	0.203
Duration of ICU stay, days, median (IQR, range)	0 (0-0, 0-9)*	/	0 (0-0, 0-9)*	0 (0-0, 0-28)*	/	**<0.001¶**	0.90 (0.69-1.16)	0.409
Hospitalisation	10 (29.4)	13 (12.7)	10 (31.3)	21 (35.0)	2.89 (1.11-7.56)	**0.030**	0.87 (0.37-2.03)	0.748
Duration of hospitalisation, days, median (IQR, range)	6 (0-24.75, 0-91)*	1 (0-2, 0-81)*	7.5 (0-27, 0-91)*	7 (1-24, 0-139)*	1.04 (1.01-1.06)	**0.003**	1.01 (0.99-1.02)	0.529
Hospital transfer	6 (17.6)	3 (2.9)	6 (18.8)	14 (23.3)	6.00 (1.50-23.99)	**0.011**	0.86 (0.29-2.55)	0.783
Ward transfer	19 (55.9)	20 (19.6)	19 (59.4)	26 (43.3)	4.84 (2.06-11.37)	**<0.001**	2.00 (0.78-5.13)	0.147
Invasive procedures								
Any	14 (41.2)	30 (29.4)	14 (43.8)	26 (43.3)	1.62 (0.74-3.54)	0.224	1.04 (0.41-2.60)	0.938
Transplantation	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	/	1.000¶	/	1.000¶
Centesis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	/	1.000¶	/	1.000¶
Ectomy	3 (8.8)	8 (7.8)	3 (9.4)	9 (15.0)	1.13 (0.29-4.47)	0.858	0.53 (0.12-2.24)	0.385
Catheterisation	1 (2.9)	0 (0.0)	1 (3.1)	3 (5.0)	/	0.250¶	0.71 (0.04-11.79)	0.809
Urinary catheter	1 (2.9)	0 (0.0)	1 (3.1)	0 (0.0)	/	0.250¶	/	0.348¶
CVC	1 (2.9)	0 (0.0)	1 (3.1)	2 (3.3)	/	0.250¶	1.41 (0.08-23.57)	0.809
Dialysis or drainage	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	/	1.000¶	/	1.000¶
Endoscopic operation	6 (17.6)	3 (2.9)	6 (18.8)	6 (10.0)	8.11 (1.62-40.67)	**0.011**	1.97 (0.58-6.68)	0.274
Invasive ventilation	1 (2.9)	0 (0.0)	1 (3.1)	2 (3.3)	/	0.250¶	1.14 (0.10-12.66)	0.917
Other surgical procedures	7 (20.6)	21 (20.6)	7 (21.9)	10 (16.7)	1.00 (0.40-2.52)	1.000	1.41 (0.45-4.36)	0.555

§, number of cases/controls with exposure to the variable (percentage of cases/controls with exposure to the variable among the cases/controls investigated);
*, median (interquartile range, range);
¶, Fisher's exact test;
/, not applicable;
OR (95%CI), odds ratio (95% confidence interval); IQR, interquartile range; ICU, intensive care unit; HDU, high dependency unit; CVC, central venous catheter.

Table 4-7. Multivariate analysis of risk factors associated with carbapenemase-producing organisms (CPO) infection and colonisation

Variables	CPO infection				CPO colonisation			
	Cases vs. Demographic controls		Cases vs. Culture positive controls		Cases vs. Demographic controls		Cases vs. Culture positive controls	
	aOR (95%CI)	*P*	aOR (95%CI)	*P*	aOR (95%CI)	*P*	aOR (95%CI)	*P*
Demographics								
Age, years					1.02 (1.00-1.05)	0.114		
Comorbidities								
Immunocompromised status	3.68 (1.16-11.66)	**0.027**						
Endocrine, nutritional and metabolic diseases					3.41 (1.02-11.33)	**0.046**	3.03 (0.69-13.31)	0.142
Diabetes mellitus							1.24 (0.16-9.61)	0.836
Diseases of the digestive system							0.12 (0.01-1.04)	0.054
Healthcare exposure								
Hospitalisation	4.05 (1.52-10.78)	**0.005**						
Duration of hospitalisation, days	1.07 (1.04-1.10)	**<0.001**	1.02 (1.00-1.03)	**0.038**	1.01 (0.99-1.04)	0.306		
Duration of ICU stay, days	1.41 (1.01-1.98)	**0.045**						
HDU stay					11.46 (1.27-103.09)	**0.030**		
Duration of HDU stay, days			1.13 (1.02-1.26)	**0.024**				

aOR (95%CI), adjusted odds ratio (95% confidence interval); ICU, intensive care unit; HDU, high dependency unit.

4.4 Discussion

Carbapenemase encoding genes are usually located on mobile genetic elements which can be easily transferred between bacterial species and individuals. Therefore, identifying patients colonised or infected with CPO is key to limiting potential transmission. Moreover, it has been reported that patients colonised with CPO were more likely than those colonised with non-CPO to develop infections during their hospitalisation (Tamma et al., 2019) and CPO infection was associated with 4 times the risk of 14-day mortality compared with non-CPO infection (Tamma et al., 2017a). Given low numbers of CPO risk factor studies conducted in low incidence settings and that the current Scottish recommendations only focus screening efforts on CPE, there is a need to identify the patients at highest risk of CPO infection/colonisation to guide screening strategies. Although the sample size is small when analyses were conducted for infection and colonisaiton respectively, I did not combine them together to increase the statistical depth given that (1) there were some statistically significant results showing clearly enough statistical power for the comparisons; (2) infection and colonisation have biologically different implications from clinical and public health perspectives and the findings of this study identified some different risk factors for CPO infection and colonisation. This is the first risk factor study for CPO among hospitalised patients in Scotland.

4.4.1 Control selection

In risk factor analyses for antimicrobial resistance, there has been considerable debate regarding control group selection (Harris et al., 2001; Harris et al., 2002a; Zavascki, 2004; Harris et al., 2004). However, the main principles are the same. The appropriate choice of controls should depend on the questions being asked and be representative of the same source population (Harris et al., 2001; Wacholder et al., 1992a; Wacholder et al., 1992b). In this study, I attempted to answer two questions. First, what are the risk factors for acquiring CPO infection or colonisation among hospitalised

patients? Namely what are the risk factors for being infected or colonised by the resistant organism CPO? Second, what are the risk factors for carbapenemase production among hospitalised patients with known pathogens? Namely what are the risk factors for the resistance (carbapenemase production) for one patient infected or colonised by a known bacterial pathogen. Therefore, I selected two control groups those would best allow me to answer these two specific questions. For the first question, I compared patients colonised or infected by CPO with randomly selected hospitalised patients (no patients with CPO and not limited to patients tested positive for other pathogens, therefore similar to all admissions, namely demographic controls). For the second question, I compared patients colonised or infected by CPO with those colonised or infected by non-CPO (namely culture positive controls). This was to help to ensure that risk factors identified in this comparison were not merely risk factors for the pathogen. To minimise selection bias and confounding effects, the cases and controls were matched by participating hospital, admission date, specimen site and organism classification (Enterobacteriaceae or non-fermenters). Admission to the same hospital at a similar time could help to eliminate geographical and temporal impact on infection control policies and microbiological methodology. Patients with the same category of organism from the same specimen site are more likely to have similar disease severity and status (colonisation or infection). Some may argue that not controlling for length of hospital stay which might be a surrogate marker of comorbidities and extensive healthcare exposure between cases and controls may introduce bias and confounding for analyses. I did not use length of hospital stay as a matching criterion because: (1). length of hospital stay is a potential risk factor of interest in this study and I checked the correlation between it and other variables, and the only highly correlated factor was removed from the analyses (Figure 4-6, 4-7 and 4-8). (2) the number of controls available would be quite small if length of hospital stay is used as a matching criterion, which would make the analyses infeasible. Additionally, infection and colonisation represent different medical conditions with different implications for both clinical therapy and infection control and

prevention strategies. Therefore, risk factors analyses were conducted for CPO infection and colonisation separately.

Culture positive controls were colonised or infected by bacterial non-CPO pathogens while demographic controls represented the general hospitalised patients who are not necessarily infected or colonised by pathogens. Therefore, culture positive controls tended to be more debilitated, more likely to be treated with antibiotics, intensive care or invasive procedures which were similar to cases. Therefore, a weaker association (smaller OR) was expected using culture positive controls than using demographic controls for the same risk factors of interest. The univariate analyses demonstrated that the ORs using culture positive controls were generally smaller than those using demographic controls for most potential risk factors of interest (Table 4-5 and Table 4-6, Appendix 4-2 and Appendix 4-3). Additionally, more risk factors were identified using demographic controls than using culture positive controls, implying that some of the risk factors were associated with infections in general.

4.4.2 Risk factors for CPO infection

Regardless of what the controls were chosen, the majority of healthcare exposure variables were associated with CPO infection at a univariate level. Time at risk (time interval between index hospital admission and pathogen isolation for cases/culture positive controls or discharge from hospitals for demographic controls) was highly correlated with length of hospital stay in the preceding 90 days as time at risk equalled to length of hospital stay for 53.6% of cases, 91.9% of demographic controls and 73.6% of culture positive controls, respectively. This indicated that more controls had not been admitted to a hospital before the index admission compared with cases, making the prior hospitalisation a risk factor for CPO infection. Moreover, the independent risk factors for CPO infection among hospitalised patients determined by comparing cases and both control groups in a multivariate analysis were mainly healthcare exposure variables, including prior hospital stay, length of

prior hospital stay, length of HDU stay and length of ICU stay. Prior hospital stay was independently related to CPO infection (aOR 4.05, 95%CI 1.52-10.78, *P*=0.005) among general hospitalised patients. Risk of infected by CPO increased as the patient stayed longer in the hospital for both general hospitalised patients (aOR 1.07, 95%CI 1.04-1.10, *P*<0.001) and patients with infections (aOR 1.02, 95%CI 1.00-1.03, *P*=0.038). These findings are in agreement with previous studies (Baran et al., 2008; Furtado et al., 2010; Patel et al., 2008). On one hand, prior hospital stay and longer duration of hospital stay means more healthcare exposure including contacting with other patients and healthcare staff, medical devices and antimicrobial treatment, and thereby more opportunities to be colonised or infected subsequently by CPO. On the other hand, this may reflect the selection of resistant strains under antimicrobial pressure due to the body flora changes over time during a longer hospitalisation period.

Prolonged ICU stay is a well-documented risk factor for multidrug-resistant organisms as these patients are usually exposed to the resistant flora, have multiple comorbidities and are subject to invasive life support devices or procedures, and hence they are at higher risk of acquiring multidrug-resistant organisms due to cross transmission mediated by these factors (Mittal et al., 2016; Zavascki et al., 2006a). In 2000 the UK Department of Health issued the report “Comprehensive Critical Care” which defined HDU care as “more detailed observations or intervention including support for a single failing organ system or postoperative care and those ‘stepping down’ from higher levels of care” (UK Government: Department of Health, 2000). Therefore, patients in HDU usually require more intensive observation, treatment and nursing care than can be provided on a general ward and have one organ failure, while patients in ICU usually have multiple organ failure. HDU would not normally accept patients requiring mechanical ventilation but could manage those receiving invasive monitoring. It is interesting that duration of HDU stay was an independent risk factor specifically for CPO among infected patients (Table 4-7) while duration of ICU stay was not related with CPO even in the univariate analysis when cases were compared with culture positive controls (Table 4-5).

To exclude the similarity and substitutability between HDU and ICU, duration of HDU stay was replaced respectively by duration of ICU stay and ICU stay in the multivariate model, the latter (duration of ICU stay and ICU stay) were not independently associated with CPO. No previous studies reported (prolonged) HDU stay as a risk factor for CPO and there is no obvious explanation for such an association but it might be possible that an unknown factor could mediate it. Patient and unit characteristics and their association with CPO warrants more research. Hospital and ward transfer might represented an indirect measure of complex diseases or a greater amount of time at risk as described in other studies (Djordjevic et al., 2016; Fortaleza et al., 2006; Torres-Gonzalez et al., 2015).

Compared with demographic controls, CPO infection cases were more likely to have some comorbidities, comprising malignancies (hematologic malignancies in particular), anaemia, respiratory diseases, genitourinary diseases (including renal failure), nervous diseases, injuries and immunocompromised status. By contrast, CPO infection cases were just more likely to have hematologic malignancies and injuries when compared with non-CPO infection controls, and neither was found to be an independent risk factor. Again, this indicated that culture positive controls had more severe but similar illness severity to cases than demographic controls. Hematologic malignancies were highly correlated with immunocompromised status (Figure 4-6). Patients with hematologic malignancies have been reported to be more likely to acquire CRO/CPO, and CRO/CPO were likely to be pathogenic in those patients who were more immunocompromised such as hematologic malignancy patients (Huang et al., 2012; Torres-Gonzalez et al., 2015; Tumbarello et al., 2014). Furthermore, hematologic malignancy patients are subject to multiple readmissions to hospital, treatment with broad-spectrum antibiotics and chemotherapy agents that may disrupt the gastrointestinal microbiota, thus rendering them prone to resistant pathogens (Husni et al., 2002; Wingard et al., 1986). Anaemia has been reported as a risk factor for CROs from univariate analyses in several studies but they were not independently associated with CRO (Li and Ye, 2017; Zilberberg et al., 2017; Zilberberg et

al., 2019) a result reproduced by this study. Six of the 10 cases with anaemia in this study had acute renal failure as well. Acute renal failure could cause various slow poisoning phenomena, such as inhibition of bone marrow function resulting in anaemia, haemorrhage and reduced leukocyte production, and thus lead to immunocompromised status. Therefore, anaemia is believed to be a surrogate marker of an immunocompromised condition. This study also identified immunocompromised status as an independent risk factor for CPO infection among general hospitalised patients (aOR 3.68, 95%CI 1.16-11.66, *P*=0.027). The comorbidity 'injury, poisoning and certain other consequences of external causes' is highly correlated with 'external causes of morbidity' (Figure 4-6 and Figure 4-7) as the former indicates the causes of injury listed in the latter, including injuries, burns, corrosions, complications of trauma and complications of surgical and medical care. Cutaneous wounds from these external causes account for a higher proportion of samples where isolates were taken and have been linked with bacterial colonisation and subsequent infections (Cheng et al., 2015; Cheng et al., 2016b; Gregory et al., 2010; Kaase et al., 2016). Wounds are favourable sites for micro-organism colonisation until they are closed and are prone to subsequent infections. In addition, 70.0% (14/20) of cases with respiratory diseases were respiratory infections and 69.7% (23/33) with genitourinary diseases were urinary tract infections while the numbers for demographic controls were 60.7% (17/28) and 18.5% (5/27) respectively. So respiratory diseases and genitourinary diseases were associated with CPO cases more than demographic controls. Again these factors might also represented more critical illness of cases as more cases than these controls were discharged to healthcare facilities or died in hospital (Table 4-3).

Interestingly, some of invasive procedure related factors were identified as risk factors using demographic controls while just one factor was a risk factor using culture positive controls (Table 4-5). This finding indicated that there might be a possibility of acquiring pathogens due to cross transmission resulting from invasive procedures. Nonetheless, no invasive procedure related factors were risk factors in multivariate analysis using either of the control groups.

In summary, healthcare exposure related factors were most frequently associated with CPO infection using both control groups. Demographics, some comorbidities and invasive procedure related factors were associated with CPO infection when compared with demographic controls while very few of these factors were related with CPO infection when compared with non-CPO infected controls. Extensive healthcare exposure (prior hospital stay and prolonged hospital/ICU/HDU stay) and being immunocompromised were independently associated with CPO infection.

4.4.3 Risk factors for CPO colonisation

Similar to risk factors for CPO infection, a majority of healthcare exposure related factors were associated with CPO colonisation using demographic controls while HDU stay was an independent risk factor. However, no such factors increased CPO colonisation risk when compared with non-CPO colonisation controls (Table 4-6).

The unique risk factor for CPO colonisation was 'endocrine, nutritional and metabolic diseases', diabetes mellitus (with complications) in particular. Endocrine, nutritional and metabolic diseases including diabetes mellitus with complications such as peripheral vascular complications and ketoacidosis as an independent risk factor might come from the effects of such disorders on the immune system (Lodise et al., 2007; Kim et al., 2014b). A previous study has investigated decreased cellular innate immunity such as chemotaxis, phagocytosis, and killing in diabetic polymorphonuclear cells and monocytes/macrophages (Geerlings and Hoepelman, 1999). Furthermore, nutritional and metabolic diseases is linked with heart disease, diabetes, and a wide range of other clinical concerns. A previous study reported that metabolic disease was an independent risk factor for carbapenem-resistant *Klebsiella pneumoniae* infection in patients colonized with carbapenem-resistant *Klebsiella pneumonia* (Akturk et al., 2016). Interestingly, non-CPO colonised patients were more likely to have digestive system diseases than patients colonised by CPO but this was not independently protective for CPO

colonisation (Table 4-7). This finding agrees with some studies reporting that digestive system diseases were more common in patients with carbapenem-susceptible organisms (CSO) but they were not independent protective factors for CRO/CPO (Freire et al., 2016b; Freire et al., 2016c; Orsi et al., 2013).

Endoscopic operation was the only invasive procedure related factor that increased the risk of CPO colonisation comparing with demographic controls. Some studies reported that exposure to endoscopes was associated with apparent acquisition and transmission of CPO due to bacterial contamination (Naas et al., 2010; Epstein et al., 2014). However, the 6 cases with endoscopic operation in this study came from 5 hospitals in 4 NHS Boards between 2013 and 2016, indicating no evidence of possible transmission via contaminated endoscopes, and awareness of the potential transmission via this route and regular reviews of endoscope reprocessing procedures are still required.

For both CPO infection and colonisation, age was a risk factor when compared with demographic controls. Greater age or advanced age is a well-recognised risk factor for multidrug-resistant organisms including CPO (Bleumin et al., 2012; Cezario et al., 2009; Cheng et al., 2015). Some studies argued that advanced age was associated with severity of illness and thus a surrogate marker of such condition (Bleumin et al., 2012; Tuon et al., 2012b). This study is consistent with this as increase of age was a risk factor using demographic controls but not a risk factor when compared with culture positive controls (Table 4-5 and Table 4-6).

In summary, comparing with risk factors for CPO infection, fewer risk factors were related to CPO colonisation. A history of HDU stay and ‘endocrine, nutritional and metabolic diseases’ independently associated with CPO colonisation comparing with general hospitalised patients. No risk factors were independently associated with an increased risk of CPO colonisation comparing with non-CPO controls.

4.4.4 Comparison of outcomes between cases and controls

The prognostic impact of CPO remains controversial and conflicting. An interesting finding of this study is that there was no difference of 30-day or 1-year survival between hospitalised patients infected or colonised by bacterial pathogens regardless of carbapenemase production (Figure 4-2 and Figure 4-4, Table 4-3). However, hospital mortality rate was significantly higher among hospitalised patients with CPO infection (cases) than those with non-CPO infection (culture positive controls) (Table 4-3). This finding agrees with a previous study reporting that patients with carbapenem-resistant gram-negative organisms had higher hospital mortality than patients with carbapenem-susceptible gram-negative organisms, but the 30-day mortality did not differ between groups (Bal et al., 2018). This could be explained as more severe comorbid conditions of cases who might die not because of CPO infections but complications developed during hospital stay, such as hematologic malignancies which usually accompanied by multiple complications, which was associated with CPO infection in this study (Table 4-5). Also, this could be explained by significant longer duration between pathogen isolation and discharge from hospital (including death in hospital) (Table 4-3) and higher proportion of ICU/HDU stay (cases vs. culture positive controls: 46.4% vs 23.1%) and immunocompromised status (cases vs. culture positive controls: 30.4% vs 20.7%). A prospective multicentre study found that the difference of 30-day mortality between CRO and CSO bacteremia diminished as the number of comorbidities increased (Pena et al., 2012). For hospitalised patients with bacterial infections, bacterial family had no impact on survival (Figure 4-4).

Another concern is the longer hospital stay after CPO isolation for infection cases and more CPO colonisation cases discharged to healthcare facilities (Table 4-3), might result in more medical expense and opportunities for further CPO transmission.

4.4.5 Comparison of antimicrobial susceptibility between cases and controls

Although complete antimicrobial resistance profiles were not available, the isolates involved in these analyses were from 13 hospitals located in 8 NHS Boards between 2010 and 2016 including both Enterobacteriaceae and non-fermenters isolates and these should reflect antimicrobial resistance patterns in general. *In vitro* resistance to all tested antibiotics was higher in CPO isolates than their matched controls, i.e. non-CPO (Table 4-4, Figure 4-5). Carbapenemases encoding genes are frequently carried on genetic elements such as plasmids and transposons that also carry genes encoding for other resistance determinants and tend to accumulate resistance genes to different antibiotics. In particular, CPE isolates presented a significant higher *in vitro* resistant profile to all tested antibiotics than Enterobacteriaceae without carbapenemase production isolates (Table 4-4). Compared with non-fermenters without carbapenemase production isolates, carbapenemase-producing non-fermenters isolates presented a significant higher *in vitro* resistant profile to meropenem and gentamicin. An interesting finding was that 11 (36.7%) of the 30 CPO isolates were susceptible to meropenem and all of them were Enterobacteriaceae isolates. The susceptibility rate to carbapenems among CPE isolates was 45.8% (11/24) which were similar to other studies (16%-55%) (De Laveleye et al., 2017; Mittal et al., 2016). Two explanations might accounted for this. Given the identification process of CPO in Scotland (if the isolate was non-susceptible to ≥1 carbapenem, the diagnostic laboratory would refer the isolate to the reference unit for confirmation of carbapenemase prouction) (Trepanier et al., 2017), these meropenem susceptible isolates might be non-susceptible to other carbapenems but there is paucity of antimicrobial susceptibility data for other carbapenems. On the other hand, it had been widely reported that the automated systems routinely used in microbiology laboratories might not detect 6-87% of the β-lactamases associated with carbapenem resistance in known resistant isolates (Tenover et al., 2006; Gasink et al., 2009; Orsi et al.,

2011), especially for OXA-48 producers as carbapenem resistance is not consistently phenotypically expressed and showed lower carbapenem minimum inhibitory concentration values than other carbapenemase producers (Gupta et al., 2011; Nordmann et al., 2012b; Huang et al., 2014b; Dautzenberg et al., 2016; De Laveleye et al., 2017). In line with these studies, the 11 imipenem/meropenem susceptible CPO isolates in this study comprised 7 OXA-48, 3 KPC and 1 NDM producers, illustrating the challenges of identification of OXA-48-producing carbapenem-susceptible isolates by routine microbiological laboratory methods. By contrast, 5 non-CPO isolates showed resistance to imipenem/meropenem including 4 non-fermenters isolates and 1 Enterobacteriaceae isolate, indicating that other mechanisms rather than dissemination of carbapenemases resulted in carbapenem resistance. Previous studies reported that approximately half of CRO tested for carbapenemase production appeared to not be carbapenemase producing (Chiotos et al., 2017; Mittal et al., 2016). Whether systematic genotypic carbapenemase testing should be performed warrants consideration.

There were some unknown or missing data such as prior antibiotic usage at individual level, travel history and complete antimicrobial susceptibility profiles which reflected difficulty to obtain or lack of attention on such information. Despite this limitation, this study is the first and largest matched case-control-control study of CPO at national level in Scotland to date, and it identified a subgroup of hospitalised patients at higher risk of CPO infection and colonisation in whom enhanced infection prevention and control measures might be of benefit given that the overall low incidence of CPO in Scotland.

4.5 Conclusion

Carbapenemase production had no negative impact on survival among hospitalised patients with positive cultures, but resulted in worse survival than general hospitalised patients. Patients with CPO infection had higher hospital mortality and longer hospital stay than both patients with non-CPO infection

and general hospitalised patients. CPO isolates had higher resistance rates than non-CPO isolates to all the tested antibiotics. A history of (prolonged) hospitalisation, prolonged ICU/HDU stay and being immunocompromised independently increased risk for CPO infection. A history of HDU stay and ‘endocrine, nutritional and metabolic diseases’ were independent risk factors for CPO colonisation among general hospitalised patients. As the first national risk factor study for CPO infection and colonisation in a low incidence setting, this study sheds light on identifying patients at high risk of being infected or colonised by CPO among hospitalised patients and thus will help to inform and refine local screening and infection control policies for CPO.

Chapter 5 Discussion

5.1 Overview

Carbapenem resistance, mainly among Gram-negative bacteria including Enterobacteriaceae and non-fermenters, is an on-going global public health threat. Carbapenem resistance, especially when mediated by easily transferable carbapenemase-encoding genes, is increasing and spreading rapidly causing serious outbreaks and dramatically limiting treatment options (Nordmann, 2014; Meletis, 2016). Therefore, it is urgent and important to understand the epidemiology, including who is at risk of acquiring CRO including CPO. Compared with other antimicrobial resistant organisms (e.g., Methicillin-resistant *Staphylococcus Aureus*, vancomycin-resistant *Enterococci*) (Health Protection Scotland, 2014; Health Protection Scotland, 2019b), CPO is still rare. However, as shown in this thesis CPO are increasing rapidly. In addition there are few published papers on CPO in Scotland (Toner et al., 2019; Trepanier et al., 2017). Yet there has been no critical review of the data in Scotland. Only with such a review can we assess the extent of the situation/problem in Scotland and offer suggestions to public health officials regarding the control of CPO. Therefore, there are two main aims in this thesis: (1) to summarise risk factors for CRO infection and colonisation in heathcare facilities from published work; (2) to describe and interpret the epidemiology patterns of CPO in Scotland.This thesis has two main parts accordingly.

In the first part, a systematic review and meta-analyses was conducted to investigate risk factors for acquiring CRO in healthcare facilities worldwide using raw data extracted from published papers between 1986 and 2016 (Chapter 2). Meta-regression analyses were performed to explore potential sources of heterogeneity for leading risk factors. The findings highlight leading risk factors for CRO infection and colonisation in healthcare settings and study characteristics accounting most for heterogeneity.

The second part of the thesis focused on all CPO reported in Scotland since its first report in 2003 until 2016 by conducting a retrospective epidemiology

study using data extracted from multiple national datasets held by NHS National Services Scotland. The epidemiological analyses (Chapter 3) provided a comprehensive description of spatial and temporal epidemiological patterns of CPO and microbiological characteristics of CPO isolates. Additionally, this thesis evaluated the mortality of CPO and identified patients at higher 30-day mortality risk from CPO. Then hospitalised patients with CPO infection and colonisation between 2010 and 2016 were included in a matched case-control study to identify risk factors for CPO infection and colonisation using conditional logistic models and the clinical outcomes and antimicrobial susceptibility were also compared between cases and controls (Chapter 4).

All the work done in this thesis has not been conducted and published by other researchers, therefore, the findings add new knowledge and implications to the existing literature and will hopefully help to inform and refine local screening and infection control policies for CPO to make a better structured and coordinated national plan in Scotland and elsewhere. Nonetheless, there are also some limitations regarding data and methodology which have implications for future research. These are discussed in the next sections of this chapter.

5.2 Data and methodological critique

5.2.1 Systematic review and meta-analysis

Systematic reviews and meta-analyses have been widely used in the practice of evidence-based medicine since the 1970s (Mallett et al., 2012). They can inform both healthcare professionals in clinical practice and public health policy makers by summarising the findings from individual studies relating to a specific health-related topic in both qualitative and quantitative ways. To summarise the risk factors for acquiring CRO in healthcare facilities, I conducted a systematic review and meta-analysis (Chapter 2). As the data were extracted from published papers, there is a risk of publication bias and

language bias (Higgins et al., 2019). To minimise these biases, I searched the three most widely used and largest Chinese databases in addition to the four main English databases and set no language restrictions for studies. I also contacted the authors when a full-text paper could not be accessed or the data needed in my study were not completely reported in the published text. Egger's test is commonly used to detect the publication bias but the power of this method to detect bias will be low with small numbers of studies (Egger et al., 1997), thereby I performed the test for risk factors being investigated in more than ten studies, and the indicators were significant for few risk factors (9/88), none of which were among the leading risk factors (Appendix 2-7).

To maximise the number of studies included in the meta-analyses, study quality was not an exclusion criterion in my study which may introduce a risk of bias and misleading interpretation of results. The quality of a study reflects the strength of the evidence that can be drawn from it. In other words, it reflects the confidence that one can have that the results of a study reflect the 'truth' (Cochrane Consumers and Communication Review Group, 2013). Given that there is no acknowledged standards for interpretation of studies of high or low quality, I defined studies with the lowest scores as 'low quality'. To examine whether including the low quality studies had significant impact on the pooled estimates, I performed sensitivity analyses for risk factors investigated by no less than five studies when the studies of low quality were included and excluded from meta-analyses and found that the results did not differ substantially (Appendix 2-9), i.e. the results are robust.

A major limitation of the meta-analyses in this thesis is that the pooled estimates were generated from univariate analysis without accounting for any potential confounders, thereby the true association between the risk factors and acquiring CRO might be concealed. Furthermore, some risk factors might be correlated with other risk factors in practice, for example, patients with malignancy are usually treated by chemotherapy and patients in ICU usually require mechanical ventilation, CVC or urinary tract support. Such high correlation between risk factors was observed in Chapter 4 (Figure 4-6, Figure

4-7 and Figure 4-8). Given that the large number of included studies, contacting the authors to ask for individual data of each study would take considerable time, I did not endeavour to perform multivariate analysis for these risk factors in the meta-analysis.

5.2.2 Data limitations

The study of CPO in Scotland (Chapters 3 and 4) was based on data extracted from several national datasets. The limitations regarding the data integrity and availability of such data is discussed below.

5.2.2.1 Clinical manifestations and laboratory tests

The impact of antimicrobial resistant organisms on a patient's prognosis will be different depending on whether the organism is associated with an infection or a colonisation as different intervention measures are required. As a result, from both clinical and public health perspectives, discrimination between infection and colonisation are crucial in antimicrobial resistance studies. Clinical manifestations (signs and symptoms) and results of laboratory tests are important components of infection diagnostics (Garner et al., 1988; Horan et al., 2008). Comorbidity data were extracted from Scottish Morbidity Record-General Acute Inpatients/Day Cases (SMR 01), information regarding clinical manifestations and laboratory tests were recorded as a disease belonging to 'Symptoms, signs and abnormal clinical and laboratory findings' according to International Classification of Diseases (Centers for Disease Control and Prevention, 2017). But the records were not recorded in detail and as a result were often not useful to define an infection (for example 'other specified abnormal immunological findings in serum' and 'tendency to fall'). As a compromise, I worked closely with a consultant physician in infectious diseases and general internal medicine (Dr Meghan Perry, Western General Hospital, Edinburgh) to classify cases as infection and colonisation (Table 3-5) based on the source of specimen with positive cultures and diagnosis as suggested by other researchers (Khadem et al., 2017). Those patients that I could not definitely classify as either infection or colonisation are classified as

unclassifiable for the sake of clinical rigour and significance. Moreover, CPO cases from CPE screening programme (launched since August 2013) are expected to be more likely to be colonisations, but whether the reported CPO cases were from the screening programme is unknown.

Survival analyses of all the 211 CPO cases by status (infection, colonisation and unclassifiable) (Figure 3-24) shows that the survival curve of 48 unclassifiable (either infection or colonisation) cases is quite similar to that of 211 cases regardless of status. This could partially demonstrate that the definitions are practically sensible and sound.

5.2.2.2 Antimicrobial susceptibility testing

Antimicrobial susceptibility testing is important in the steps to identify a CPO as described in Chapter 1 (Section 1.3.3). However, the antimicrobial susceptibility testing results were not available for all CPO isolates (antimicrobial susceptibility testing results were available for only 54 of 243 CPO isolates: 22.2%) which means that the specific carbapenem(s) which the CPO isolate was non-susceptible to was unknown. For the 54 CPO isolates with antimicrobial susceptibility testing results, they were not tested for the same agents (Table 3-11). A possible explanation is that the agents tested in antimicrobial susceptibility testing depends on sample type in Scotland (according to Dr Meghan Perry, personal communication by email, November 15, 2019); for example, VITEK® 2 antimicrobial susceptibility testing-N382 (Standard Urine Card) is used for Enterobacteriaceae isolates from urine and VITEK® 2 antimicrobial susceptibility testing-N381 (Standard Enterobacteriaceae Card) is used for Enterobacteriaceae isolates from other sites.

The 54 CPO isolates involved in the analyses were from 14 hospitals located in 10 NHS Boards between 2008 and 2016 while isolates from culture positive controls were from 13 hospitals located in 8 NHS Boards between 2010 and 2016 including both Enterobacteriaceae and non-fermenters. To exclude possible selection bias, I double checked whether the isolates were mainly

from some specific patients (such as older patients, patients in ICU/HDU and patients with infections), but no obvious bias was noted. Nonetheless, the antimicrobial susceptibility testing results were still not convincing and the results should be interpreted with caution due to the small number of isolates tested.

5.2.2.3 Risk factors investigated for CPO infection and colonisation

The results from the systematic review and meta-analysis in Chapter 2 show that prior administrations with specific antibiotics and longer duration of the presence of some invasive medical devices before CRO isolation were leading risk factors for acquiring CRO in healthcare facilities. However, information on antibiotics usage and length of exposure to invasive medical devices at individual patient level in hospitals were not available in Scotland until the end of 2016. In addition, data at individual level regarding medicines related to certain comorbidities like steroids which were also investigated widely by other risk factor studies were not available from the current national datasets until the end of 2016.

The incompleteness, unavailability or inaccessibility of data mentioned above might generate overestimated associations between some variables investigated and CPO infection and colonisation.

5.2.3 Statistical models selection

Statistic models support medical research for antimicrobial resistance by facilitating individualized outcome prognostication conditional on independent variables or by estimating effects of risk factors adjusted for covariates (Heinze et al., 2018).To investigate CPO incidence in Chapter 3, two statistical models were considered, a nonlinear model (exponential model) and a generalised linear model. I performed analyses using both models and found the exponential model had a better fit (residual standard deviation: 0.091) than the generalised linear model (residual standard deviation: 1.316). To investigate risk factors for 30-day mortality of hospitalised CPO cases in Chapter 3, two

statistical models were considered, a Cox proportional-hazards model (Cox, 1972) and a generalised linear mixed model (Breslow and Clayton, 1993). The former investigates the association between the survival time of individuals and predictors while the latter contains random effect(s) in addition to the fixed effects (i.e. predictors of interest). The outcome I am interested in is whether the patient died within 30 days after CPO isolation rather than how long the patient survived within 30 days after CPO isolation which a Cox proportional-hazards model takes into account. Moreover, previous study specified that patients clustered within the same hospital were more likely to be similar to each other than similar to patients from another hospital (Khadem et al., 2017), and medical conditions varied across different hospitals in different NHS Boards. Given all the above factors, a generalised linear mixed model with the hospital where the patient with CPO was treated being a random effect was fitted to account for differences in study setting and geographic location.

Although the CPO study in this thesis is the first and largest national-level study since its first report as of today, the number of patients enrolled is still relatively low compared with the number of variables of interest, thereby variable selection is necessary for multivariate analyses which attempts to find a simple and appropriate model. Variable selection techniques can be grouped into three categories: 1) filter methods which select variables by ranking them on how useful they are for the model via calculating the usefulness score based on their correlation with the dependent variable, like Chi-square, analysis of variance and Pearson's correlation (Saeys et al., 2007); 2) wrapper methods generates different subsets of variables, each subset is then used to build up a model and train the learning algorithm, the best subset is selected by testing the algorithm (Saeys et al., 2007). To select variables for the subsets different criteria are used, e.g. forward selection and backward selection; 3) embedded methods are combinations between the two previous methods including LASSO (Heinze et al., 2018). There are some advantages using LASSO method over other methods. First, it can provide a very good prediction accuracy since shrinkage and removal of the coefficients can reduce variance without increasing substantial bias. This is especially useful when there is a

small sample size investigated and a large number of variables. Second, it helps to increase the model interpretability by eliminating irrelevant variables that are not related with the response variable and thereby reduce overfitting (Fonti and Belitser, 2017). Therefore LASSO was adopted given its advantages in this scenario.

For risk factor analyses in Chapter 3 and 4, a liberal *P* value criterion (0.10) was used rather than the conventional criterion (0.05) to identify independent variables included in multivariate analyses. It is argued that the traditional level of 0.05 can fail in identifying variables known to be important (Costanza and Afifi, 1979, Mickey and Greenland, 1989) and a liberal criterion could compensate by making it more likely that truly important predictors and confounders will be retained in the model when there are too many candidate predictors for the sample size (Steyerberg et al., 2001). A liberal $0.01 \leq P \leq 0.25$ often perform better (Costanza and Afifi, 1979) and 0.01 was chosen in this thesis given the relatively small sample size.

5.3 Implications and future work

The findings of this thesis answer some key questions regarding risk factors for acquiring CRO (including CPO) in healthcare facilities and epidemiology of CPO in Scotland. These findings have implications for the clinical and policy. Due to time and data constraints there were several questions that could not be answered by this thesis. These unanswered questions warrant more research work in the future.

5.3.1 Who are going to acquire CRO in low income countries and high income countries with low CRO incidence?

This thesis highlights the knowledge gap in risk factor studies for acquiring CRO since no relevant study has been reported from low income countries or high income countries with low CRO incidence (e.g. Canada, New Zealand).

However, high level of carbapenem resistance including CPO has been reported in some low income countries (Manenzhe et al., 2015; Ssekatawa et al., 2018) and rapid increases in CPO in high income countries with low CRO incidence had been noted currently (Australian Commission on Safety and Quality in Health Care, 2017; Ministry of Health New Zealand Goverment, 2018; Government of Canada, 2016). Moreover, it is reported that many CPO in low CPO incidence settings have been imported from overseas (Blakiston et al., 2017) and travel and medical exchange between countries are becoming more frequent and increasing. Besides poor hygiene, there is a lack of financial support and a formal framework for surveillance programmes in low income countries. The above situations would facilitate a rapid spread of CRO across these countries or regions. Therefore, future work conducted in these countries or regions will help to fill the knowledge gap and contribute to combat the public health threat globally. This is also an important motivation for the work done in Chapters 3 and 4 of this thesis.

5.3.2 What else can be done to widen the generalisability of the results of the systematic review and meta-analysis from clinical and epidemiological perspective?

The methodological and data limitations of the systematic review and meta-analysis conducted in this thesis were discussed above. Based on these, further research could be performed to address more clinical and epidemiological orientated questions.

First, univariate analysis investigating one single risk factor without taking other factors (confounders) into account could lead to misleading results and conclusions. Future multivariate analysis considering potential confounding would provide more reliable estimates for risk factors of interest.

Second, I applied modified study quality assessment scales tailored from the common used scales for systematic review and meta-analysis. However, these quality assessment scales did not address all aspects related to study

quality, such as risk of bias, sample size and analysis method. More detailed study quality assessment tools should be designed and applied to evaluate the quality of included studies focus on risk factors for antimicrobial resistance in the future.

Third, I merged different types of bacteria (Enterobacteriaceae and non-fermenter), patients (adults and the paediatric, ICU patient and non-ICU patients), infections (bloodstream infections, UTI, pneumonia) and resistance mechanisms (carbapenemase production and non-enzymatic mechanisms) in the analysis. Meta-regression analyses show that some of these characteristics accounted for most of the heterogeneity. Future research on these distinctions and stratifications is crucial to provide more meaningful guidance and data for further action by clinicians and public health epidemiologists.

Finally, I evaluated antibiotic exposure as a dichotomous variable and did not fully address the complexities of previous antibiotic exposure such as duration, dosage and route of administration due to the limited number of studies included. Moreover, I did not specify and allow for the time line of risk factors of interest due to the huge variety across studies. The risk factors can be assessed during hospitalisation or within two weeks till one year of hospital admission or CRO isolation. Analyses detailing these variables and distinctions warrant future work.

5.3.3 Does acute hospital admission screening programme for CPE in Scotland work?

The national screening programme was launched in August 2013 (The Scottish Government, 2013). The observed CPO incidence after 2013 was higher than the extrapolations from the model in 2003-2013 (Figure 3-5), indicating that the introduction of CPE screening programme might have had an impact on CPO incidence. However, the number of reported CPO cases from the screening programme is unknown. Therefore, it is hard to tell exactly to what extent the screening programme has contributed to the increased

number of CPO cases. Better records or labels of CPO cases from the screening programme in the national dataset would enable the policy makers to evaluate the programme better.

5.3.4 How many CPO infections developed from colonisation and what are risk factors for the progress from CPO colonisation to infection?

The systematic review and meta-analysis highlights that prior colonisation by CRO was a leading risk factor for CRO infection. A previous systematic review reported an overall 16.5% risk of developing an infection with CRE among patients colonised by CRE and it was associated with a 10% overall mortality (Tischendorf et al., 2016). Given that the reported high risk of infection developing from colonisation, difficulty of treating CRO infections and associated high mortality, it is important to elucidate the CPO infection burden among patients with CPO colonisation in Scotland and the triggers for the progressions from colonisation to infection. Furthermore, the screening programme using urine and rectal swabs is supposed to identify CPO colonisation, and understanding the risk of infection developing from colonisation could help to assess the screening programme. However, I could not evaluate the risk of developing an infection amongst those colonised with CPO. The risk factors for the progress could be the scope of future research. Clear and practical definitions of CPO infection and colonisation should be developed and applied in the future to better address the question.

5.3.5 Are antibiotics usage and duration of invasive devices presence before CPO isolation associated with acquiring CPO in Scotland?

Prior antibiotics usage and duration of treatments with certain invasive medical devices were found to be leading risk factors for CRO presence in Chapter 2 and have been reported as risk factors for unfavourable outcomes (Punpanich et al., 2012; Kim et al., 2012b). However, data for these variables in hospitals

at individual level are not available in Scotland. Although treatments with certain invasive medical devices as a dichotomous variable was included in the analysis, using the variables in a quantitative manner (i.e. taking the duration of exposure into account) would be more informative. Additionally, these variables may correlate with other variables (comorbidities, demographics and healthcare exposure). The true association between these variables and acquiring CPO/mortality risk from CPO should be investigated further in the future.

5.3.6 Is there clonal persistence and spread of CPO in Scotland or between Scotland and elsewhere?

The epidemiological data shows that some CPO cases with the same carbapenemase had been admitted to the same ward in the same hospital at similar time before CPO isolation. All the cases are VIM/IMP producers which are healthcare-associated. Is there clonal spread of CPO in these hospitals? Moreover, cases with NDM/OXA-48 producing isolates are more likely to be colonisation and community-associated and percentage of these isolates among all CPO isolates showed an upward trend over time. Where did the community-associated cases acquire CPO? Are they imported CPO cases? Given that whole-genome sequencing has been demonstrated as a useful approach to elucidate genetic modes of transmission (Martin et al., 2017), a future bioinformatic and phylogenetic study using such genomic data is essential to answer these questions and provide evidence or guidance for infection prevention control measures in both hospitals and the community.

5.3.7 Are there other factors accounting for the impact of certain species or carbapenemases on patient survival?

This thesis highlights that infection with or colonisation by carbapenemase-producing non-fermenters (*Pseudomonas spp.* or *Acinetobacter spp.*) was independently associated with 30-day mortality and that the incidence of carbapenemase-producing non-fermenters increased over time. Cases with

NDM/OXA-48-producing isolates had significantly better survival than those with KPC/IMP-producing isolates (Figure 3-28). Half of IMP-producing isolates are non-fermenters (9/18, 50.0%) while the majority of NDM/OXA-48-producing isolates are Enterobacteriaceae (97/101, 96.0%). The antimicrobial resistance profiles show no significant differences to nearly all antibiotics between Enterobacteriaceae and non-fermenters isolates (Table 3-11, Figure 3-22). However, all the 8 OXA-48-producing isolates that underwent antimicrobial susceptibility testing remained susceptible to meropenem while all the 4 IMP-producing isolates that underwent antimicrobial susceptibility testing were resistant to meropenem or imipenem. Due to the sparse antimicrobial susceptibility testing data available, it is not possible to conclude that the antimicrobial susceptibility of NDM/OXA-48-producing isolates offering potential effective treatment options accounted for the better survival. Moreover, several studies specified that some mechanisms conferring biofilm formation, enhanced virulence and resistance to immunological responses could contribute to antimicrobial resistance and increased mortality (Chiang et al., 2016; Paauw et al., 2009; Xu et al., 2018; Cho et al., 2018). Therefore, a future molecular study offering a comprehensive understanding of the virulence, antimicrobial susceptibility and pathogenicity profiles of CPO isolates would help answer this question.

5.3.8 Are the risk factors identified in this thesis specific for acquiring CRO/CPO?

The results from both the systematic review and meta-analysis worldwide (Chapter 2) and risk factor analyses for CPO in Scotland (Chapter 4) show that severity of illness and extensive healthcare exposure (including prolonged hospitalization, HDU/ICU stay, exposure to invasive devices and exposure to antibiotics) were associated with CRO/CPO acquisition in healthcare settings. However, these factors were also reported by review studies as common risk factors for acquiring other antimicrobial resistant bacteria in hospitals comprising MRSA, VRE, ESBL-producing bacteria and *Clostridium difficile* (Detsis et al., 2017; Eze et al., 2017; Flokas et al., 2017; Li et al., 2017; Pano

Pardo et al., 2014; Sabbagh et al., 2019; Song and Kim, 2019). Although prolonged hospitalisation and HDU stay were identified as independent risk factors for CPO infection comparing with patients infected by non-CPO, no independent risk factor was noted when CPO colonisation cases were compared with patients colonised by non-CPO. Are the independent risk factors for CPO infection associated with exposure to antibiotics in hospitals? Will the independent association disappear when other variables (e.g. exposure to antibiotics, duration of antibiotics exposure, duration of exposure to invasive devices) are taken into account? Are risk factors the same when all cases and controls are selected in HDU/ICU since patients in these wards are usually very ill? This thesis cannot answer these questions. A well-designed prospective study with sufficient sample size conducted in HDU/ICU that take as many as potential risk factors into account and use logically matched controls who are free of colonisation by any antimicrobial resistant bacteria would address these questions.

5.4 Concluding remarks

This thesis made an endeavour to provide a comprehensive epidemiological understanding of CPO in Scotland since its first report. The traditional epidemiological triad model has three components: reservoir, mode of transmission and susceptible population (Centers for Disease Control and Prevention, 2011). The corresponding infection prevention and control measures should be developed based on the three components, including reservoir identification, cutting off transmission routes and susceptible population identification.

First, reservoir identification, namely identification of CPO cases. CPO incidence (both CPO infection and colonisation) increased over time, indicating that: 1) CPO in Scotland is an increasing public health threat; 2) the acute hospital admission screening programme has an impact on finding CPO cases, thereby it is necessary to continue this surveillance. The percentage of some

CPO isolates (NDM/OXA-48 producers) related to community-associated source and colonisation rose over time, highlighting the presence and possible transmission of CPO in the community. In September 2017, HPS issued a guidance containing a set of recommendations and practical advice to reduce the spread of CPE in non-acute and community settings in Scotland (Health Protection Scotland, 2017). The findings of this thesis confirm the necessity of these measures.

Given that all CPO attributed deaths were CPO infection cases, colonisation precedes infections and the high risk of developing an infection among colonised patients, clear and practical definitions of infection and colonisation of a CPO case should be developed at a national level and the patients who are suspected with CPO and underwent the screening programme should be flagged in the medical records. This would help clinicians and hospital infection control teams to notice, isolate and treat the cases and close contacts as quickly as possible. Also, it will help policy makers to accurately evaluate the local disease burden of CPO infection, colonisation and progression from colonisation to infection, thereby guiding efforts to develop more effective strategies for prevention and control CPO.

Second, cut off transmission routes. Although the data shows that some CPO cases with the same carbapenemase had been admitted to the same ward in the same hospital at similar time before CPO isolation, no clonal transmission or spread can be identified without phylogenetic analyses using sequencing data. Additionally, the antimicrobial susceptibility testing results show that some non-CPO isolates were resistant to carbapenems (Table 4-4, Figure 4-5), indicating that there are other carbapenem resistance mechanisms. Carbapenem resistant non-CPO are outside the scope of this thesis, but they are worthy of public health awareness as an important component of CRO. As discussed in Section 5.3, it is unknown whether antimicrobial resistance and virulence profiles contribute to the unfavourable outcomes of cases with non-fermenters and KPC/IMP producers. Therefore, whole genome sequence data providing a wide range of genetic determinants comprising antimicrobial

resistance, non-carbapenemase producing resistance mechanisms and virulence factors (Turton et al., 2018; Martin et al., 2017), together with metadata will provide a whole picture of CRO in Scotland and inform possible transmission or spread of CRO within Scotland or between Scotland and elsewhere. This would help policy makers to determine if travel or hospital transfer information should be taken into account to refine the screening programme and infection prevention and control measures for nosocomial infections.

Third, identification of the susceptible population, namely the population at high risk of acquiring CRO/CPO. Risk factors for CRO/CPO infection and colonisation identified in this thesis are markers of critical illness and extensive healthcare exposure which are the common risk factors for acquiring other multidrug-resistant organisms. Given that previous carriage of other multidrug-resistant organisms was a leading risk factor for acquiring CRO, pre-emptive identification and isolation of individuals with such risk factors for colonisation and infection by any of these multidrug-resistant organisms would very likely reduce the spread of antimicrobial resistance in hospitals. Furthermore, future studies to identify specific risk factors for CRO/CPO are also important since the CPO study in Scotland shows that CPO infections were associated with prolonged hospital stay and higher in-hospital mortality compared with non-CPO infections.

Finally, my supervisors and myself worked together with HPS, electronic Data Research and Innovation Service and the university staff to apply for, analyse and release the results of the analyses of the data of CPO in Scotland (data used in Chapters 3 and 4). The whole process from application for the data until the acquisition of all the data I required took 14 months which is almost 40% of my PhD programme (36 months). The unanswered questions in this thesis mainly resulted from the data limitations. Since combating antimicrobial resistance needs collaboration from multiple disciplines (human healthcare, epidemiology, environment ecology, food-producing animals and wildlife),

cooperative and efficient data sharing is essential to benefit both public health bodies and researchers.

Appendices

Appendix 2-1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	39
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	iii-iv
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Section 2.1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Section 2.1, Section 2.2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Section 2.2.1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Section 2.2.3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Section 2.2.2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2-2

Section/topic	#	Checklist item	Reported on page #
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Section 2.2.4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Section 2.2.4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix 2-3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Section 2.2.7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Section 2.2.7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Section 2.2.7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Section 2.2.7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Section 2.2.7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 2-1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 2-3, Appendix 2-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix 2-4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	na

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Appendix 2-7 Figure 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix 2-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression, see Item 16).	Appendix 2-9, Appendix 2-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Section 2.4
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Section 2.4
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Section 2.5
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	x

na, not applicable.

Appendix 2-2. Search strategy of risk factors for the presence of carbapenem-resistant organisms (CRO) among patients in healthcare facilities

Embase

1. exp antibiotic resistance/
2. produc*.mp.
3. (Multi-drug resistan* or Multidrug resistan* or MDR or non susceptib* or resistan*).mp.
4. "not susceptible".mp.
5. carbapenem*.mp. or exp carbapenem/
6. exp carbapenemase/ or carbapenemase*.mp.
7. exp imipenem/ or imipenem.mp.
8. exp meropenem/ or meropenem.mp.
9. ertapenem.mp. or exp ertapenem/
10. doripenem.mp. or exp doripenem/
11. exp metallo beta lactamase/ or metallo beta lactamase*.mp. or MBL.mp.
12. (KPC or Klebsiella pneumoniae Carbapenemase).mp.
13. (SME or Serratia marcescens enzyme).mp.
14. (IMI or imipenem hydrolyzing beta lactamase).mp.
15. (NMC or not-metalloenzyme carbapenemase).mp.
16. (IBC or integrin-borne cephalosporinase or GES or Guiana extended spectrum).mp.
17. (IMP or active on imipenem).mp.
18. (VIM or Verona integron encoded metallo beta lactamase).mp.
19. (SPM or Sao Paulo metallo beta lactamase).mp.
20. (GIM or German imipenemase).mp.
21. (SIM or Seoul imipenemase).mp.
22. (OXA or oxacillin hydrolysing).mp.
23. (NDM or New Delhi metallo beta lactamase).mp.
24. KHM.mp.
25. 1 or 2 or 3 or 4
26. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
27. 25 and 26
28. exp risk factor/ or risk factor*.mp.
29. exp prediction/ or predict*.mp.
30. outbreak*.mp.
31. exp association/ or associat*.mp.
32. emergence.mp.
33. exp bacterial transmission/ or transmission*.mp.
34. protect*.mp.
35. exp prevalence/ or exp epidemiology/ or epidemiolog*.mp.
36. age/
37. exp "gender and sex"/ or sex.mp.
38. (underlying disease* or underlying condition*).mp. or exp comorbidity/

39. exp hospitalization/ or previous hospitalization.mp.
40. exp intensive care unit/ or previous ICU stay.mp.
41. exp patient transport/ or patient transport.mp.
42. exp invasive procedure/ or invasive intervention*.mp.
43. exp catheter/ or catheter.mp.
44. ventilation.mp.
45. exp dialysis/ or dialysis.mp.
46. drainage.mp.
47. endoscopy.mp. or exp endoscopy/
48. parenteral nutrition.mp. or exp parenteral nutrition/
49. exp surgical technique/ or surgical procedure*.mp.
50. transplantation*.mp. or exp transplantation/
51. blood transfusion.mp. or exp blood transfusion/
52. exp intubation/ or intubation.mp.
53. travel history.mp.
54. antibiotic exposure*.mp.
55. quinolones.mp. or exp quinolone derivative/
56. extended spectrum cephalosporins.mp. or exp cephalosporin/
57. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
58. 27 and 57
59. Limit 58 to (human and yr=”1986 – 2016”)

MEDLINE

1. (Multi-drug resistan* or Multidrug resistan* or MDR).mp. or exp drug resistance, bacterial/ or exp drug resistance, multiple, bacterial/ or "not susceptible".mp. or non susceptib*.mp. or resistan*.mp.
2. (producer* or producing or production).mp.
3. 1 or 2
4. exp Carbapenems/ or carbapenem*.mp.
5. imipenem.mp. or exp Imipenem/
6. (meropenem or ertapenem or doripenem).mp.
7. (carbapenemase* or metallo beta lactamase* or MBL).mp.
8. (KPC or Klebsiella pneumoniae Carbapenemase).mp.
9. (SME or Serratia marcescens enzyme).mp.
10. (IMI or imipenem hydrolyzing beta lactamase).mp.
11. (NMC or not-metalloenzyme carbapenemase).mp.
12. (IBC or integrin-borne cephalosporinase or GES or Guiana extended spectrum).mp.
13. (IMP or active on imipenem).mp.
14. (VIM or Verona integron encoded metallo beta lactamase).mp.
15. (SPM or Sao Paulo metallo beta lactamase).mp.
16. (GIM or German imipenemase).mp.
17. (SIM or Seoul imipenemase).mp.

18. (OXA or oxacillin hydrolysing).mp.
19. (NDM or New Delhi metallo beta lactamase).mp.
20. KHM.mp.
21. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 3 and 21
23. exp Risk Factors/ or risk factor*.mp.
24. (predict* or determinant*).mp. or exp Disease Outbreaks/ or outbreak*.mp. or exp Epidemiology/ or epidemio*.mp. or spread*.mp. or exp Prevalence/ or prevalen*.mp. or occurrenc*.mp. or emergenc*.mp. or exp Association/ or associat*.mp. or transmission*.mp. or exp Disease Transmission, Infectious/ or protect*.mp.
25. age.mp. or exp Sex/ or sex.mp. or exp Ethnic Groups/ or ethnic.mp.
26. (underlying disease* or underlying condition*).mp. or exp Comorbidity/
27. (ICU stay or hospitalization).mp. or exp hospitalization/ or exp "length of stay"/ or exp patient readmission/ or exp patient transfer/
28. invasive intervention*.mp. or exp catheters/ or exp cannula/ or exp catheters, indwelling/ or exp urinary catheters/ or exp vascular access devices/ or exp cardiac catheters/ or exp central venous catheters/
29. ventilation.mp. or exp Ventilation/ or exp Dialysis/ or dialysis.mp. or drainage.mp. or exp Drainage/
30. endoscopy.mp. or exp Endoscopy/
31. parenteral nutrition.mp. or exp Parenteral Nutrition/
32. surgical procedure*.mp. or exp surgical procedures, operative/
33. transplantation*.mp. or exp transplantation/
34. blood transfusion.mp. or exp Blood Transfusion/
35. intubation.mp. or exp intubation/ or exp intubation, gastrointestinal/ or exp intubation, intratracheal/
36. travel history.mp.
37. antibiotic exposure*.mp.
38. quinolones.mp. or exp quinolones/ or exp fluoroquinolones/
39. exp Carbapenems/ or carbapenem*.mp. or imipenem.mp. or exp Imipenem/ or meropenem.mp. or ertapenem.mp. or doripenem.mp.
40. extended spectrum cephalosporins.mp. or exp Cephalosporins/ or cephalosporins.mp.
41. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42. 22 and 41
43. limit 42 to yr="1986 - 2016"
44. limit 43 to humans

Global Health

1. (carbapenemase* or metallo beta lactamase* or MBL).mp.

2. (KPC or Klebsiella pneumoniae Carbapenemase or SME or Serratia marcescens enzyme or IMI or imipenem hydrolyzing beta lactamase).mp.
3. (NMC or not-metalloenzyme carbapenemase).mp.
4. (IBC or integrin-borne cephalosporinase or GES or Guiana extended spectrum).mp.
5. (IMP or active on imipenem or VIM or Verona integron encoded metallo beta lactamase or SPM or Sao Paulo metallo beta lactamase or GIM or German imipenemase or SIM or Seoul imipenemase or OXA or oxacillin hydrolysing or NDM or New Delhi metallo beta lactamase or KHM).mp.
6. exp carbapenems/ or exp doripenem/ or exp ertapenem/ or exp imipenem/ or exp meropenem/ or carbapenem*.mp. or imipenem.mp. or meropenem.mp. or ertapenem.mp. or doripenem.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp drug resistance/ or resistan*.mp.
9. "not susceptible".mp.
10. "non susceptib*".mp.
11. (producer* or producing or production).mp.
12. 8 or 9 or 10 or 11
13. exp risk factors/ or risk factor*.mp.
14. predict*.mp. or epidemiology.sh. or prediction.sh.
15. outbreak*.mp. or exp outbreaks/
16. prevalen*.mp. or disease incidence.sh. or disease prevalence.sh.
17. exp transmission/ or transmission*.mp.
18. age.mp. or exp age/
19. sex.mp. or exp sex/
20. ethnic group*.mp. or ethnic groups.sh.
21. (underlying disease* or underlying condition* or comorbidit*).mp.
22. previous hospital stay.mp. or hospital stay.sh.
23. ICU stay.mp. or intensive care units.sh.
24. patient transfer.mp.
25. (invasive procedure* or invasive intervention*).mp.
26. catheter*.mp. or exp catheters/ or catheterization.sh.
27. ventilation.mp. or exp ventilation/
28. dialysis.mp. or exp dialysis/
29. exp drainage/ or drainage.mp.
30. endoscopy.mp. or exp endoscopy/
31. parenteral nutrition.mp. or exp parenteral feeding/
32. surgical procedure*.mp. or surgical operations.sh.
33. transplantation*.mp. or exp transplantation/
34. blood transfusion.mp. or exp blood transfusion/
35. intubation.mp.
36. travel history.mp.
37. antibiotic exposure*.mp.
38. quinolones.mp. or exp quinolones/
39. extended spectrum cephalosporins.mp. or cephalosporins.sh.

40. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. 7 and 12 and 40
42. limit 41 to yr="1986 - 2016"

Web of Science

1. TOPIC: (multidrug resistan* or multiple drug resistan* or multidrug resistan* or MDR)
2. TOPIC: (producer* or producing or production)
3. TOPIC: (resistant or resistance)
4. TOPIC: (“not susceptib”)
5. TOPIC: (“non susceptib*)
6. TOPIC: (carbapenem* or imipenem or meropenem or ertapenem or doripenem)
7. TOPIC: (carbapenemase* or metallo beta lactamase* or MBL)
8. TOPIC: (KPC or Klebsiella pneumoniae Carbapenemase or SME or Serratia marcescens enzyme or IMI or imipenem hydrolysing beta lactamase)
9. TOPIC: (NMC or not-metalloenzyme carbapenemase)
10. TOPIC: (IBC or integrom-borne cephalosporinase or GES or Guiana extended spectrum)
11. TOPIC: (IMP or active on imipenem or VIM or Verona integrin encoded metallo beta lactamase or SPM or Sao Paulo metallo beta lactamase or GIM or German imipenemase or SIM or Seoul imipenemase or OXA or oxacillin hydrolysing or NDM or NEW Delhi metallo beta lactamase or KHM)
12. 11 OR 10 OR 9 OR 8 OR 7 OR 6
13. 5 OR 4 OR 3 OR 2 OR 1
14. 12 AND 13
15. TOPIC: (risk factor* or predict* or determinant* or outbreak* or epidemiolog* or prevalence or associate* or transmission* or protect*)
16. TOPIC: (age or sex or ethnic or underlying disease* or underlying condition* or comorbidity or ICU stay or hospitalization or hospital stay or patient transfer or invasive intervention* or invasive procedure* or catheter* or ventilation or dialysis or drainage or endoscopy or parenteral nutrition or surgical procedure* or transplantation* or blood transfusion or intubation or travel history or antibiotic exposure* or quinolones or cephalosporin*)
17. 16 OR 15
18. 17 AND 14
19. limit 18 to Timespan=1986-2016

China National Knowledge Infrastructure

Topic: carbapenem (vague)
OR Topic: carbapenemase (vague)
AND Topic: risk factor (vague)
Publication time: 1st January 1986-31st December 2016

Chongqing VIP databases

Title/Key word: carbapenem
OR Title/Key word: carbapenemase
AND Title/Key word: risk factor
Time: 1989-2016

Wanfang Data

Topic: carbapenem (vague)
OR Topic: carbapenemase (vague)
AND Topic: risk factor (vague)
Publication time: 1986-2016

Appendix 2-3. Definition of extracted data and explanatory variables considered as a potential source of heterogeneity

Explanatory variable	Definition of explanatory variable
World bank income group	As defined by The World Bank in 2017 (https://datahelpdesk.worldbank.org): high income countries lower-middle income countries upper-middle income countries low income countries
Sample Size	Sum of cases and controls
Status	As specified by the authors: acquisition infection colonisation (including asymptomatic nasal/gastrointestinal carriage)
Study Type	case-control study matched case-control study cohort study cross-sectional study
Study Setting	multi-centre single-centre
Healthcare Type	tertiary care hospital other
Specialty	Whether the study was conducted in intensive care unit (ICU) (including any type of ICU and High Dependency Unit) specifically: ICU Non-ICU
Study Population	As specified by the authors: adult patients paediatric patients (including neonates) other

Explanatory variable	Definition of explanatory variable
Organism	Enterobacteriaceae non-fermenters other
Resistance Mechanism	As specified by the authors: carbapenemase production specifically carbapenem resistant
Case-control selection	CR-CS (carbapenem resistance-carbapenem susceptible, including CRX-CSX, CRX-CSO, CPX-non CP organisms) CR-no CR (carbapenem resistance-no carbapenem resistance, the control group is only defined by the absence of CRO or CPO, including CRX-no CRX, CPX-no CPX and CRX-no MDRO) CR-no pathogenic bacteria (carbapenem resistance-no pathogenic bacteria, including CRX/CPX- no pathogenic bacteria and CRX/CPX-no X) CR infection-CR colonisation

CR, carbapenem resistant; CS, carbapenem susceptible; CP, carbapenemase producing; CRO, carbapenem-resistant organisms; CPO, carbapenemase-producing organisms; X, one specific genus or organism; MDRO, multidrug-resistant organisms.

Appendix 2-4. Quality assessment for included studies in the systematic review and meta-analysis

(1) Quality assessment for case-control study according to the modified Newcastle-Ottawa quality assessment scale

Included study	Selection										Comparability		Exposure									Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls				Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Ahn et al., 2014)	√			√			√			√	√	√				√		√		na			4
(Akgul et al., 2016)	√			√			√			√	√	√				√		√		na			4
(Akinci et al., 2005)	√			√			√			√				√				√		na			4
(Armand-Lefevre et al., 2013)	√			√			√			√	√	√				√		√		na			5
(Armand-Lefevre et al., 2013)	√			√			√			√	√	√				√		√		na			5
(Banach et al., 2014)	√			√			√			√	√						√	√		na			4
(Baran et al., 2008)	√			√			√			√							√	√		na			3
(Ben-David et al., 2011)	√			√			√		√		√						√	√		na			5

Included study	Selection									Comparability		Exposure								Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Bhargava et al., 2014)	√			√			√			√	√	√				√		√		na			5
(Bleumin et al., 2012)	√			√			√			√						√		√		na			3
(Borer et al., 2012)	√			√			√			√						√		√		na			3
(Borer et al., 2012)	√			√			√			√						√		√		na			3
(Cezario et al., 2009)	√			√			√			√						√		√		na			3
(Chang et al., 2011)	√			√			√			√	√	√				√		√		na			5
(Chen et al., 2014)	√			√			√			√	√	√				√		√		na			5
(Cheng et al., 2015)	√			√			√			√							√	√		na			3
(Chitnis et al., 2012)	√			√			√			√						√		√		na			3
(Chusri et al., 2015)	√			√			√			√	√	√				√		√		na			5

Included study	Selection									Comparability		Exposure									Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Correa et al., 2013)	√			√			√			√	√	√				√		√		na			5
(Cunha et al., 2016)	√			√			√			√						√		√		na			3
(da Silva et al., 2016)	√			√			√			√	√	√				√		√		na			5
(Da kos et al., 2010)	√			√			√			√						√		√		na			3
(Dautzenberg et al., 2016)	√				√		√			√	√	√				√		√		na			4
(De Jager et al., 2015)	√			√			√			√	√	√				√		√		na			5
(del Mar Tomas et al., 2005)	√			√			√			√	√	√					√	√		na			5
(Deris et al., 2011)	√			√			√			√							√	√		na			3
(Dirajlal-Fargo et al., 2014)	√			√			√			√	√	√					√	√		na			5
(Eagye et al., 2009)	√			√			√			√	√	√				√		√		na			5

Included study	Selection									Comparability		Exposure								Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Eagye et al., 2009)	√			√			√			√	√	√				√		√		na			5
(Epstein et al., 2014)	√			√			√			√						√		√		na			3
(Falagas et al., 2007)	√			√			√			√	√	√				√		√		na			5
(Fortaleza et al., 2006)	√			√			√			√	√	√				√		√		na			5
(Freire et al., 2016a)	√			√			√			√	√	√					√	√		na			5
(Furtado et al., 2009)	√			√			√			√	√	√				√		√		na			5
(Furtado et al., 2010)	√			√			√			√	√	√					√	√		na			5
(Gagliotti et al., 2014)	√			√			√		√		√	√				√		√		na			6
(Garbati et al., 2016)	√			√			√			√	√	√				√		√		na			5
(Garlantezec et al., 2011)	√			√			√			√	√					√		√		na			4

Included study	Selection									Comparability		Exposure									Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Gasink et al., 2009)	√			√			√			√						√		√		na			3
(Gaviria et al., 2011)	√			√			√			√	√	√					√	√		na			5
(Giuffre et al., 2013)	√			√			√			√							√	√		na			3
(Gomez Rueda and Zuleta Tobon, 2014)	√			√			√			√	√	√				√		√		na			5
(Gregory et al., 2010)	√			√			√		√							√		√		na			4
(Gregory et al., 2010)	√			√			√		√							√		√		na			4
(Harris et al., 2002b)	√			√			√			√	√					√		√		na			4
(Henig et al., 2015)	√			√			√			√	√	√				√		√		na			5
(Henig et al., 2015)	√			√			√			√	√	√				√		√		na			5
(Hu et al., 2016)	√			√			√			√	√	√					√	√		na			5

Included study	Selection									Comparability		Exposure									Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Hussein et al., 2013)	√			√			√			√							√	√		na			3
(Hussein et al., 2009)	√			√			√			√						√		√		na			3
(Hyle et al., 2010)	√			√			√			√						√		√		na			3
(Jamulitrat et al., 2007)	√			√			√			√						√		√		na			3
(Jeon et al., 2008)	√			√			√			√	√	√				√		√		na			5
(Kaase et al., 2016)	√			√			√			√							√	√		na			3
(Karaaslan et al., 2016)	√			√			√			√	√						√	√		na			4
(Katragkou et al., 2006)	√			√			√			√	√					√		√		na			4
(Kim et al., 2014a)	√			√			√			√	√					√		√		na			4
(Kim et al., 2012a)	√			√			√			√							√	√		na			3

Included study	Selection									Comparability		Exposure									Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Kim et al., 2014b)	√			√			√			√							√	√		na			3
(Kim et al., 2008)	√			√			√			√						√		√		na			3
(Kim et al., 2008)	√			√			√			√						√		√		na			3
(Kofteridis et al., 2014)	√			√			√			√	√					√		√		na			4
(Kohlenberg et al., 2010)	√			√			√			√							√	√		na			3
(Kritsotakis et al., 2011)	√			√			√			√	√					√		√		na			4
(Lautenbach et al., 2009)	√			√			√			√						√		√		na			3
(Lautenbach et al., 2010)	√			√			√			√						√		√		na			3
(Lautenbach et al., 2006)	√			√			√			√						√		√		na			3
(Lee et al., 2013a)	√			√			√			√	√	√				√		√		na			5

Included study	Selection									Comparability		Exposure								Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Lee et al., 2016)	√			√			√			√	√	√				√		√		na			5
(Lee et al., 2016)	√			√			√			√	√					√		√		na			4
(Lee et al., 2004)	√			√			√			√	√					√		√		na			4
(Leroy et al., 2005)	√			√			√			√						√		√		na			3
(Lin et al., 2016)	√			√			√			√	√						√	√		na			4
(Ling et al., 2015)	√			√			√			√	√	√				√		√		na			5
(Liu et al., 2012)	√			√			√			√	√	√				√		√		na			5
(Marchaim et al., 2012)	√			√			√			√	√	√				√		√		na			5
(Marchaim et al., 2008)	√			√			√			√	√	√				√		√		na			5
(Meradji et al., 2015)	√			√			√			√						√		√		na			3
(Miller and Johnson, 2016)	√			√			√			√	√	√				√		√		na			5

Included study	Selection									Comparability		Exposure								Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Mills et al., 2016)	√			√			√			√						√		√		na			3
(Mittal et al., 2016)	√			√			√			√						√		√		na			3
(Mouloudi et al., 2014)	√			√			√			√							√	√		na			3
(Mouloudi et al., 2010)	√			√			√			√						√		√		na			3
(Mouloudi et al., 2010)	√			√			√			√						√		√		na			3
(Nouer et al., 2005)	√			√			√			√						√		√		na			3
(Nouvenne et al., 2014)	√			√			√			√						√		√		na			3
(Orsi et al., 2013)	√			√			√			√						√		√		na			3
(Orsi et al., 2013)	√			√			√			√						√		√		na			3
(Orsi et al., 2011)	√			√			√			√						√		√		na			3

Included study	Selection									Comparability		Exposure									Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Patel et al., 2008)	√			√			√			√	√	√				√		√		na			5
(Patel et al., 2011)	√			√			√			√	√	√				√		√		na			5
(Playford et al., 2007)	√			√			√			√	√	√					√	√		na			5
(Poole et al., 2016)	√			√			√			√						√		√		na			3
(Pouch et al., 2015)	√			√			√			√	√					√		√		na			4
(Routsi et al., 2013)	√			√			√			√							√	√		na			3
(Routsi et al., 2013)	√			√			√			√							√	√		na			3
(Sanchez-Romero et al., 2012)	√			√			√			√							√	√		na			3
(Satlin et al., 2016)	√			√			√			√	√	√					√	√		na			5
(Satlin et al., 2016)	√			√			√			√	√	√					√	√		na			5

Included study	Selection									Comparability		Exposure								Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Sbrana et al., 2016)	√			√			√			√	√	√				√		√		na			5
(Schechner et al., 2011)	√			√			√			√						√		√		na			3
(Schwaber et al., 2008)	√			√			√			√						√		√		na			3
(Shilo et al., 2013)	√			√			√			√						√		√		na			3
(Simkins et al., 2014)	√			√			√			√						√		√		na			3
(Swaminathan et al., 2013)	√			√			√			√	√	√				√		√		na			5
(Tam et al., 2007)	√			√			√			√							√	√		na			3
(Teo et al., 2012)	√			√			√		√							√		√		na			4
(Thatrimontrichai et al., 2013)	√			√			√			√						√		√		na			3
(Thatrimontrichai et al., 2013)	√			√			√			√						√		√		na			3

Included study	Selection									Comparability		Exposure								Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Thatrimontrichai et al., 2016)	√			√			√			√	√					√		√		na			4
(Thatrimontrichai et al., 2016)	√			√			√			√	√					√		√		na			4
(Torres-Gonzalez et al., 2016)	√			√			√			√	√	√				√		√		na			5
(Torres-Gonzalez et al., 2016)	√			√			√			√	√	√				√		√		na			5
(Troillet et al., 1997)	√			√			√			√						√		√		na			3
(Tumbarello et al., 2014)	√			√			√			√	√	√				√		√		na			5
(Tumbarello et al., 2014)	√			√			√			√	√	√				√		√		na			5
(Tuon et al., 2012a)	√			√			√			√							√	√		na			3
(Tuon et al., 2012b)	√			√			√			√							√	√		na			3

Included study	Selection									Comparability		Exposure								Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Wang et al., 2016b)	√			√			√			√	√					√		√		na			4
(Wiener-Well et al., 2010)	√			√			√			√						√		√		na			3
(Wu et al., 2011)	√			√			√			√	√	√				√		√		na			5
(Yang et al., 2016a)	√			√			√			√	√	√					√	√		na			5
(Ye et al., 2015)	√			√			√			√						√		√		na			3
(Ye et al., 2010)	√			√			√			√						√		√		na			3
(Ye et al., 2010)	√			√			√			√	√	√				√		√		na			5
(Zavascki et al., 2006a)	√			√			√			√							√	√		na			3
(Zavascki et al., 2005a)	√			√			√			√	√					√		√		na			4
(Zavascki et al., 2005a)	√			√			√			√	√					√		√		na			4
(Zhao et al., 2014)	√			√			√			√						√		√		na			3
(Hirakata et al., 2003)	√			√			√			√	√					√		√		na			4

Included study	Selection									Comparability		Exposure								Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Kwak et al., 2005)	√			√			√			√	√					√		√		na			4
(Ma et al., 2014)	√			√			√		√							√		√		na			4
(Peng et al., 2005)	√			√			√			√	√					√		√		na			4
(Saavedra-Trujillo et al., 2016)	√			√			√			√						√		√		na			3
(Zhang et al., 2011)	√			√			√			√	√	√				√		√		na			5
(Zhang et al., 2009)	√			√			√			√							√	√		na			3
(Valderrama et al., 2016)	√			√			√			√							√	√		na			3
(Liu et al., 2011a)	√			√			√			√	√	√				√		√		na			5
(Liu et al., 2006)	√			√			√			√	√					√		√		na			4
(Lu et al., 2009)	√			√			√			√	√					√		√		na			4
(Lv et al., 2015)	√			√			√			√	√	√				√		√		na			5
(Cai et al., 2015)	√			√			√			√	√	√				√		√		na			5

Included study	Selection									Comparability		Exposure									Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Li et al., 2016)	√			√			√			√	√	√					√	√		na			5
(Guo and Sun, 2010)	√			√			√			√	√						√	√		na			4
(Cao et al., 2015)	√			√			√		√		√					√		√		na			5
(Chen and Zhao, 2009)	√			√			√			√	√					√		√		na			4
(Guo et al., 2008)	√			√			√			√						√		√		na			3
(Fei et al., 2014)	√			√			√			√	√					√		√		na			4
(Fei et al., 2012)	√			√			√			√	√					√		√		na			4
(Chen et al., 2010)	√			√			√			√	√					√		√		na			4
(Fei et al., 2013)	√			√			√			√	√					√		√		na			4
(Kong et al., 2016)	√			√			√			√	√	√					√	√		na			5
(Huang et al., 2015)	√			√			√			√	√						√	√		na			4
(Wang et al., 2011)	√			√			√			√						√	√	√		na			3

Included study	Selection									Comparability		Exposure									Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Xu et al., 2015)	√			√			√			√							√	√		na			3
(Sun et al., 2016)	√			√			√			√	√						√	√		na			4
(Deng et al., 2016)	√			√			√			√						√		√		na			3
(Wang et al., 2014)	√			√			√			√	√					√		√		na			4
(Sheng et al., 2010)	√			√			√			√						√		√		na			3
(Sheng et al., 2010)	√			√			√			√						√		√		na			3
(Sheng et al., 2010)	√			√			√			√						√		√		na			3
(Kim et al., 2012c)	√			√			√			√							√	√		na			3
(Le Hello et al., 2010)	√			√			√			√						√		√		na			3
(Ozkurt et al., 2005)	√			√			√			√							√	√		na			3
(Aydemir et al., 2012)	√			√			√			√							√	√		na			3

Included study	Selection									Comparability		Exposure									Score
	Is the case definition adequate			Representativeness of the cases		Selection of Controls			Definition of Controls			Ascertainment of exposure					Same method of ascertainment for cases/controls		Non-Response rate			
	yes, with independent validation★	yes, e.g., record linkage or based on self reports	no description	consecutive or obviously representative series of cases★	potential for selection biases or not stated	community controls★	hospital controls	no description	no history of disease★	no description of source	study controls for the most important factor★	study controls for any additional factor★	secure record★	structured interview where blind to case/control status★	interview not blinded to case/control status	written self report or medical record only	no description	Yes★	no	same rate for both groups★	non respondents described	rate different and no designation	
(Onguru et al., 2008)	√			√			√			√							√	√		na			3
(Sonmezer et al., 2016)	√			√			√			√							√	√		na			3
(Sonmezer et al., 2016)	√			√			√			√							√	√		na			3
(Jiao et al., 2015)	√			√			√			√	√					√		√		na			4
(Hayakawa et al., 2014)	√			√			√			√	√	√				√		√		na			5
(Cekin et al., 2013)	√			√			√			√						√		√		na			3

na, not applicable

(2) Quality assessment for cohort study according to the modified Newcastle-Ottawa quality assessment scale

Included study	Selection												Comparability		Outcome								Score
	Representativeness of the exposed cohort				Selection of the non-exposed cohort			Ascertainment of exposure				Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis		Assessment of outcome				Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts				
	truly representative of the average★	somewhat representative of the average★	selected group of users	no description of the derivation of the cohort	drawn from the same community as the exposed cohort★	drawn from a different source	no description of the derivation of the non-exposed cohort	secure record★	structured interview★	written self report	no description	yes★	no	study controls for the most important factor★	study controls for any additional factor★	independent blind assessment★	record linkage★	self report	no description	yes★	no	complete follow up all subjects accounted for★	subjects lost to follow up unlikely to introduce bias★	follow up rate < % (select an adequate %) and no description of those lost	no statement	
(Candevir Ulu et al., 2015)	√				√			√				√			√		√			na		na				6
(Cavalcante Rde et al., 2014)	√				√			√				√			√		√			na		na				6
(Corbella et al., 2000)	√				√						√		√		√		√			na		na				4

Included study	Selection												Comparability		Outcome								Score
	Representativeness of the exposed cohort				Selection of the non-exposed cohort			Ascertainment of exposure				Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis		Assessment of outcome				Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts				
	truly representative of the average★	somewhat representative of the average★	selected group of users	no description of the derivation of the cohort	drawn from the same community as the exposed cohort★	drawn from a different source	no description of the derivation of the non-exposed cohort	secure record★	structured interview★	written self report	no description	yes★	no	study controls for the most important factor★	study controls for any additional factor★	independent blind assessment★	record linkage★	self report	no description	yes★	no	complete follow up all subjects accounted for★	subjects lost to follow up unlikely to introduce bias★	follow up rate < % (select an adequate %) and no description of those lost	no statement	
(Ganor et al., 2012)	√				√						√	√			√		√			na		na				5
(Dickstein et al., 2016)	√				√			√				√			√		√			na		na				6
(Djordjevic et al., 2016)	√				√			√				√			√		√			na		na				6
(Freire et al., 2015)	√				√						√	√			√		√			na		na				5
(Freire et al., 2016b)	√				√						√	√			√		√			na		na				5
(Freire et al., 2016b)	√				√						√	√			√		√			na		na				5

Included study	Selection												Comparability		Outcome								Score
	Representativeness of the exposed cohort				Selection of the non-exposed cohort			Ascertainment of exposure				Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis		Assessment of outcome				Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts				
	truly representative of the average★	somewhat representative of the average★	selected group of users	no description of the derivation of the cohort	drawn from the same community as the exposed cohort★	drawn from a different source	no description of the derivation of the non-exposed cohort	secure record★	structured interview★	written self report	no description	yes★	no	study controls for the most important factor★	study controls for any additional factor★	independent blind assessment★	record linkage★	self report	no description	yes★	no	complete follow up all subjects accounted for★	subjects lost to follow up unlikely to introduce bias★	follow up rate < % (select an adequate %) and no description of those lost	no statement	
(Freire et al., 2016c)	√				√						√	√			√		√			na		na				5
(Freire et al., 2016c)	√				√						√	√			√		√			na		na				5
(Giannella et al., 2015)	√				√			√				√			√		√			na		na				6
(Harris et al., 2011)	√				√						√	√			√		√			na		na				5
(Huang et al., 2012)	√				√			√					√		√		√			na		na				5
(Kalam et al., 2014)	√				√			√					√		√		√			na		na				5

Included study	Selection												Comparability		Outcome								Score
	Representativeness of the exposed cohort				Selection of the non-exposed cohort			Ascertainment of exposure				Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis		Assessment of outcome				Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts				
	truly representative of the average★	somewhat representative of the average★	selected group of users	no description of the derivation of the cohort	drawn from the same community as the exposed cohort★	drawn from a different source	no description of the derivation of the non-exposed cohort	secure record★	structured interview★	written self report	no description	yes★	no	study controls for the most important factor★	study controls for any additional factor★	independent blind assessment★	record linkage★	self report	no description	yes★	no	complete follow up all subjects accounted for★	subjects lost to follow up unlikely to introduce bias★	follow up rate < % (select an adequate %) and no description of those lost	no statement	
(Kopterides et al., 2007)	√				√			√					√		√		√			na		na				5
(Latibeaudiere et al., 2015)	√				√			√				√			√		√			na		na				6
(Lepelletier et al., 2009)	√				√						√	√			√		√			na		na				5
(Lepelletier et al., 2009)	√				√						√	√			√		√			na		na				5
(Mantzarlis et al., 2013)	√				√			√					√		√		√			na		na				5

Included study	Selection												Comparability		Outcome								Score
	Representativeness of the exposed cohort				Selection of the non-exposed cohort			Ascertainment of exposure				Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis		Assessment of outcome				Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts				
	truly representative of the average★	somewhat representative of the average★	selected group of users	no description of the derivation of the cohort	drawn from the same community as the exposed cohort★	drawn from a different source	no description of the derivation of the non-exposed cohort	secure record★	structured interview★	written self report	no description	yes★	no	study controls for the most important factor★	study controls for any additional factor★	independent blind assessment★	record linkage★	self report	no description	yes★	no	complete follow up all subjects accounted for★	subjects lost to follow up unlikely to introduce bias★	follow up rate < % (select an adequate %) and no description of those lost	no statement	
(Mantzarlis et al., 2013)	√				√			√					√		√		√			na		na				5
(Marchenay et al., 2015)	√				√			√				√			√		√			na		na				6
(Ny et al., 2015)	√				√			√				√		√	√		√			na		na				7
(Ny et al., 2015)	√				√			√				√		√	√		√			na		na				7
(Ny et al., 2015)	√				√			√				√		√	√		√			na		na				7

Included study	Selection												Comparability		Outcome								Score
	Representativeness of the exposed cohort				Selection of the non-exposed cohort			Ascertainment of exposure				Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis		Assessment of outcome				Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts				
	truly representative of the average★	somewhat representative of the average★	selected group of users	no description of the derivation of the cohort	drawn from the same community as the exposed cohort★	drawn from a different source	no description of the derivation of the non-exposed cohort	secure record★	structured interview★	written self report	no description	yes★	no	study controls for the most important factor★	study controls for any additional factor★	independent blind assessment★	record linkage★	self report	no description	yes★	no	complete follow up all subjects accounted for★	subjects lost to follow up unlikely to introduce bias★	follow up rate < % (select an adequate %) and no description of those lost	no statement	
(Sharaf and Gerges, 2016)	√				√			√				√			√		√			na		na				6
(Torres-Gonzalez et al., 2015)	√				√			√					√		√		√			na		na				5
(Vardakas et al., 2015)	√				√			√					√		√		√			na		na				5
(Zheng et al., 2013)	√				√			√					√		√		√			na		na				5
(Petrikkos et al., 2009)	√				√					√			√		√		√			na		na				4

Included study	Selection												Comparability		Outcome								Score
	Representativeness of the exposed cohort				Selection of the non-exposed cohort			Ascertainment of exposure				Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis		Assessment of outcome				Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts				
	truly representative of the average★	somewhat representative of the average★	selected group of users	no description of the derivation of the cohort	drawn from the same community as the exposed cohort★	drawn from a different source	no description of the derivation of the non-exposed cohort	secure record★	structured interview★	written self report	no description	yes★	no	study controls for the most important factor★	study controls for any additional factor★	independent blind assessment★	record linkage★	self report	no description	yes★	no	complete follow up all subjects accounted for★	subjects lost to follow up unlikely to introduce bias★	follow up rate < % (select an adequate %) and no description of those lost	no statement	
(Cisneros et al., 2005)	√				√						√		√		√		√			na		na				4
(Liu et al., 2011b)	√				√			√					√		√		√			na		na				5
(Guo et al., 2016)	√				√			√					√		√		√			na		na				5
(Zhang et al., 2004)	√				√			√				√			√		√			na		na				6
(Lou et al., 2013)	√				√			√					√		√		√			na		na				5
(Jiang et al., 2015)	√				√			√					√		√		√			na		na				5

Included study	Selection												Comparability		Outcome								Score
	Representativeness of the exposed cohort				Selection of the non-exposed cohort			Ascertainment of exposure				Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis		Assessment of outcome				Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts				
	truly representative of the average★	somewhat representative of the average★	selected group of users	no description of the derivation of the cohort	drawn from the same community as the exposed cohort★	drawn from a different source	no description of the derivation of the non-exposed cohort	secure record★	structured interview★	written self report	no description	yes★	no	study controls for the most important factor★	study controls for any additional factor★	independent blind assessment★	record linkage★	self report	no description	yes★	no	complete follow up all subjects accounted for★	subjects lost to follow up unlikely to introduce bias★	follow up rate < % (select an adequate %) and no description of those lost	no statement	
(Wang et al., 2013)	√				√			√					√		√		√			na		na				5
(Zhang et al., 2012)	√				√						√		√		√		√			na		na				4
(Wang et al., 2016a)	√				√			√					√		√		√			na		na				5
(Wu et al., 2016)	√				√						√		√		√		√			na		na				4
(Jia et al., 2016)	√				√						√		√		√		√			na		na				4
(Yang et al., 2016b)	√				√			√					√		√		√			na		na				5

Included study	Selection												Comparability		Outcome								Score
	Representativeness of the exposed cohort				Selection of the non-exposed cohort			Ascertainment of exposure				Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis		Assessment of outcome				Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts				
	truly representative of the average★	somewhat representative of the average★	selected group of users	no description of the derivation of the cohort	drawn from the same community as the exposed cohort★	drawn from a different source	no description of the derivation of the non-exposed cohort	secure record★	structured interview★	written self report	no description	yes★	no	study controls for the most important factor★	study controls for any additional factor★	independent blind assessment★	record linkage★	self report	no description	yes★	no	complete follow up all subjects accounted for★	subjects lost to follow up unlikely to introduce bias★	follow up rate < % (select an adequate %) and no description of those lost	no statement	
(Wang et al., 2016c)	√				√						√		√		√		√			na		na				4
(Hang and Zhang, 2016)	√				√			√					√		√		√			na		na				5
(Pan et al., 2016)	√				√						√		√		√		√			na		na				4
(Li et al., 2015)	√				√						√		√		√		√			na		na				4
(Borer et al., 2009)	√				√			√					√	√	√		√			na		na				6

Included study	Selection												Comparability		Outcome								Score
	Representativeness of the exposed cohort				Selection of the non-exposed cohort			Ascertainment of exposure				Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis		Assessment of outcome				Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts				
	truly representative of the average★	somewhat representative of the average★	selected group of users	no description of the derivation of the cohort	drawn from the same community as the exposed cohort★	drawn from a different source	no description of the derivation of the non-exposed cohort	secure record★	structured interview★	written self report	no description	yes★	no	study controls for the most important factor★	study controls for any additional factor★	independent blind assessment★	record linkage★	self report	no description	yes★	no	complete follow up all subjects accounted for★	subjects lost to follow up unlikely to introduce bias★	follow up rate < % (select an adequate %) and no description of those lost	no statement	
(Chusri et al., 2015)	√				√			√				√					√			na		na				5
(Hoxha et al., 2016)	√				√			√				√		√	√		√			na		na				7
(Trecarichi et al., 2016)	√				√			√				√					√			na		na				5
(Villegas et al., 2016)	√				√			√					√				√			na		na				4
(Yogeesha Babu et al., 2011)	√				√			√					√				√			na		na				4

Included study	Selection												Comparability		Outcome								Score
	Representativeness of the exposed cohort				Selection of the non-exposed cohort			Ascertainment of exposure				Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis		Assessment of outcome				Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts				
	truly representative of the average★	somewhat representative of the average★	selected group of users	no description of the derivation of the cohort	drawn from the same community as the exposed cohort★	drawn from a different source	no description of the derivation of the non-exposed cohort	secure record★	structured interview★	written self report	no description	yes★	no	study controls for the most important factor★	study controls for any additional factor★	independent blind assessment★	record linkage★	self report	no description	yes★	no	complete follow up all subjects accounted for★	subjects lost to follow up unlikely to introduce bias★	follow up rate < % (select an adequate %) and no description of those lost	no statement	
(Debby et al., 2012)	√				√			√					√				√			na		na				4
(Ben-David et al., 2014)	√				√			√					√				√			na		na				4
(Salsano et al., 2016)	√				√			√				√					√			na		na				5
(Tian et al., 2016)	√				√			√					√				√			na		na				4
(Vitkauskiene et al., 2013)	√				√			√					√				√			na		na				4

Included study	Selection												Comparability		Outcome								Score
	Representativeness of the exposed cohort				Selection of the non-exposed cohort			Ascertainment of exposure				Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis		Assessment of outcome				Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts				
	truly representative of the average★	somewhat representative of the average★	selected group of users	no description of the derivation of the cohort	drawn from the same community as the exposed cohort★	drawn from a different source	no description of the derivation of the non-exposed cohort	secure record★	structured interview★	written self report	no description	yes★	no	study controls for the most important factor★	study controls for any additional factor★	independent blind assessment★	record linkage★	self report	no description	yes★	no	complete follow up all subjects accounted for★	subjects lost to follow up unlikely to introduce bias★	follow up rate < % (select an adequate %) and no description of those lost	no statement	
(Wannaro et al., 2012)	√				√			√					√				√			na		na				4
(Huang et al., 2014a)	√				√			√					√				√			na		na				4
(Punpanich et al., 2012)	√				√			√					√				√			na		na				4
(Kumar et al., 2014)	√				√			√					√				√			na		na				4
(Kim et al., 2012b)	√				√			√					√				√			na		na				4
(Al Otaibi and Al-	√				√			√					√				√			na		na				4

Included study	Selection												Comparability		Outcome								Score
	Representativeness of the exposed cohort				Selection of the non-exposed cohort			Ascertainment of exposure				Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis		Assessment of outcome				Was follow-up long enough for outcomes to occur		Adequacy of follow up of cohorts				
	truly representative of the average★	somewhat representative of the average★	selected group of users	no description of the derivation of the cohort	drawn from the same community as the exposed cohort★	drawn from a different source	no description of the derivation of the non-exposed cohort	secure record★	structured interview★	written self report	no description	yes★	no	study controls for the most important factor★	study controls for any additional factor★	independent blind assessment★	record linkage★	self report	no description	yes★	no	complete follow up all subjects accounted for★	subjects lost to follow up unlikely to introduce bias★	follow up rate < % (select an adequate %) and no description of those lost	no statement	
Hulaily, 2012)																										
(Barron et al., 2016)	√				√			√					√				√				na		na			4

na, not applicable

(3) Quality assessment for cross-sectional study according to Agency for Healthcare Research and Quality guidelines

Included study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Total items reported
	Source of Information	Inclusion/Exclusion Criteria	Time Period for Identity	Subjects consecutive	Evaluators Masked	Quality Assurance Assessments	Patient Exclusions	Confounding assessed/controlled	Missing Data	Response Rates	Follow-up	
(Adibhesami et al., 2016)	√	√	√	√	√	√						6
(Ben-David et al., 2011)	√	√	√	√	√	√						6
(Budak et al., 2014)	√	√	√	√	√	√						6
(Cheng et al., 2016a)	√		√		√	√	√		√	√		7
(Horianopoulou et al., 2006)	√	√	√	√	√	√				√		7
(Lodise et al., 2007)	√	√	√	√	√	√	√					7
(Otter et al., 2016)	√	√	√	√	√	√	√			√		8
(Papadimitriou-Olivgeris et al., 2014)	√	√	√	√	√	√						6
(Papadimitriou-Olivgeris et al., 2012)	√	√	√	√	√	√						6
(Papadimitriou-Olivgeris et al., 2013)	√	√	√	√	√	√					√	7
(Pena et al., 2007)	√	√	√	√	√	√					√	7
(Prasad et al., 2016)	√	√	√	√	√	√	√			√		8
(Rosa et al., 2014)	√	√	√	√	√	√						6
(Rossini et al., 2016)	√	√	√	√	√	√						6

Included study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Total items reported
	Source of Information	Inclusion/Exclusion Criteria	Time Period for Identity	Subjects consecutive	Evaluators Masked	Quality Assurance Assessments	Patient Exclusions	Confounding assessed/controlled	Missing Data	Response Rates	Follow-up	
(Routsi et al., 2010)	√	√	√	√	√	√						6
(Zarakolu et al., 2016)	√	√	√	√	√	√					√	7
(Cheng et al., 2016b)	√	√	√	√	√	√						6
(Dizbay et al., 2014)	√	√	√	√	√	√						6
(Dizbay et al., 2010)	√	√	√	√	√	√	√					7

na, not applicable

Appendix 2-5. Definitions of risk factors for the presence of carbapenem-resistant organisms (CRO) included in the systematic review and meta-analysis

Risk factors	Definition
Demography	
Gender	Male
Age (>65yrs)	Older than 65 years old
Age, years	Age in years
Prior healthcare exposure	
ICU stay	ICU stay during a time frame defined by authors before CRO isolation
Length of ICU stay, days	Duration of ICU stay in days during a time frame defined by authors before CRO isolation
Prior hospitalisation	History of admission to a hospital during a time frame defined by authors before the index hospitalisation
Length of hospitalisation, days	Duration of hospital stay in days during a time frame defined by authors before the index hospitalisation
Hospital transfer	Hospital transfer before CRO isolation
Prior presence of CRO	CRO carriage before CRO infection or presence of CRO before the index CRO infection
Presence of ESBL producers	Prior or current acquisition with ESBL producers
Presence of MRSA	Prior or current acquisition with MRSA
Presence of VRE	Prior or current acquisition with VRE
Comorbidities	
Diabetes mellitus	Confirmed diagnosis of diabetes mellitus
Malignancy	Confirmed diagnosis of malignancy or cancer
Hematologic malignancy	Confirmed diagnosis of hematologic malignancy
Liver diseases	Confirmed diagnosis of liver diseases, including cirrhosis, fulminant hepatitis, hepatocellular carcinoma, hepatitis C virus infection, alcohol liver diseases, liver dysfunction/failure and other liver diseases

Risk factors	Definition
Renal failure	Confirmed diagnosis of renal failure
COPD	Confirmed diagnosis of COPD
Steroid treatment	Confirmed steroid administration
Trauma	Confirmed diagnosis of trauma
Heart failure	Confirmed diagnosis of heart failure
Neurological diseases	Confirmed diagnosis of neurological diseases, including nervous system diseases, chronic cerebral disease, cognitive impairment, nerve damage and other neurological diseases
HIV	Confirmed diagnosis of HIV infection
Neutropenia	Confirmed diagnosis of neutropenia
Hypertension	Confirmed diagnosis of hypertension
Stroke	Confirmed diagnosis of stroke/cerebrovascular accident
Chemotherapy	Confirmed chemotherapy
Coronary artery diseases	Confirmed diagnosis of coronary artery diseases
Decubitus ulcer	Confirmed diagnosis of decubitus ulcer
CCI score	Charlson Comorbidity Index scores
APACHE II score	Acute Physiology, Age and Chronic Health Evaluation II scores
SOFA score	Sequential Organ Failure Assessment scores
Prior invasive procedures/devices	
Intravascular catheter	Presence of intravascular catheter during a time frame defined by authors before CRO isolation
CVC	Presence of CVC during a time frame defined by authors before CRO isolation
Duration of CVC, days	Duration of CVC in days during a time frame defined by authors before CRO isolation
Arterial catheter	Presence of arterial catheter during a time frame defined by authors before CRO isolation
Urinary catheter	Presence of urinary catheter during a time frame defined by authors before CRO isolation

Risk factors	Definition
Duration of urinary catheter, days	Duration of urinary catheter in days during a time frame defined by authors before CRO isolation
Mechanical ventilation	Presence of mechanical ventilation during a time frame defined by authors before CRO isolation
Duration of mechanical ventilation, days	Duration of mechanical ventilation in days during a time frame defined by authors before CRO isolation
Dialysis	Dialysis performed during a time frame defined by authors before CRO isolation
Hemodialysis	Hemodialysis performed during a time frame defined by authors before CRO isolation
Tracheostomy	Tracheostomy performed during a time frame defined by authors before CRO isolation
Parenteral nutrition	Parenteral nutrition performed during a time frame defined by authors before CRO isolation
Transplantation	Solid organ or hematopoietic stem cell transplantation performed during a time frame defined by authors before CRO isolation
Drainage	Drainage performed during a time frame defined by authors before CRO isolation, including chest, ventricular, surgical, abdominal and biliary drainage
Endoscopy	Endoscopic procedures or examination performed during a time frame defined by authors before CRO isolation
Endotracheal tube	Presence of endotracheal tube during a time frame defined by authors before CRO isolation
Enteral nutrition	Enteral nutrition performed during a time frame defined by authors before CRO isolation
Gastrostomy	Gastrostomy performed during a time frame defined by authors before CRO isolation
Blood transfusion	Blood transfusion during a time frame defined by authors before CRO isolation, including fresh frozen plasma and red blood cell
Prior antibiotic exposure	
Aminoglycoside	Aminoglycoside administration during a time frame defined by authors before CRO isolation

Risk factors	Definition
Amikacin	Amikacin administration during a time frame defined by authors before CRO isolation
Antifungal	Antifungal drugs administration during a time frame defined by authors before CRO isolation
β-lactam/β-lactamase inhibitor	β-lactam/β-lactamase inhibitor administration during a time frame defined by authors before CRO isolation
AMC	AMC administration during a time frame defined by authors before CRO isolation
AMS	AMS administration during a time frame defined by authors before CRO isolation
SCF	SCF administration during a time frame defined by authors before CRO isolation
TZP	TZP administration during a time frame defined by authors before CRO isolation
Carbapenem	Carbapenem administration during a time frame defined by authors before CRO isolation
Duration of carbapenem therapy, days	Duration of carbapenem therapy in days during a time frame defined by authors before CRO isolation
Ertapenem	Ertapenem administration during a time frame defined by authors before CRO isolation
Imipenem	Imipenem administration during a time frame defined by authors before CRO isolation
Meropenem	Meropenem administration during a time frame defined by authors before CRO isolation
Cephalosporin	Cephalosporin administration during a time frame defined by authors before CRO isolation
Duration of cephalosporin therapy, days	Duration of cephalosporin therapy in days during a time frame defined by authors before CRO isolation
I	Cephalosporin I administration during a time frame defined by authors before CRO isolation
II	Cephalosporin II administration during a time frame defined by authors before CRO isolation
III	Cephalosporin III administration during a time frame defined by authors before CRO isolation

Risk factors	Definition
IV	Cephalosporin IV administration during a time frame defined by authors before CRO isolation
Cefepime	Cefepime administration during a time frame defined by authors before CRO isolation
I/II	Cephalosporin I/II administration during a time frame defined by authors before CRO isolation
III/IV	Cephalosporin III/IV administration during a time frame defined by authors before CRO isolation
Combination therapy	Combined antibiotics therapy during a time frame defined by authors before CRO isolation
Glycopeptide	Glycopeptide administration during a time frame defined by authors before CRO isolation
Vancomycin	Vancomycin administration during a time frame defined by authors before CRO isolation
Clindamycin	Clindamycin administration during a time frame defined by authors before CRO isolation
Macrolide	Macrolide administration during a time frame defined by authors before CRO isolation
Metronidazole	Metronidazole administration during a time frame defined by authors before CRO isolation
Oxazolidinone	Oxazolidinone administration during a time frame defined by authors before CRO isolation
Penicillin	Penicillin administration during a time frame defined by authors before CRO isolation
Extended spectrum penicillin	Extended spectrum penicillin administration during a time frame defined by authors before CRO isolation
Polymyxin	Polymyxin administration during a time frame defined by authors before CRO isolation
Fluoroquinolone	Fluoroquinolone administration during a time frame defined by authors before CRO isolation
Ciprofloxacin	Ciprofloxacin administration during a time frame defined by authors before CRO isolation

Risk factors	Definition
Tigecycline	Tigecycline administration during a time frame defined by authors before CRO isolation
TMP-SMX	TMP-SMX administration during a time frame defined by authors before CRO isolation

CRO, carbapenem-resistant organisms; ICU, intensive care unit; ESBL, extended-spectrum beta-lactamases; MRSA, Methicillin-resistant *Staphylococcus aureus*; VRE, Vancomycin-resistant *Enterococci*; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; CVC, central venous catheter; AMC, amoxicillin-clavulanate; AMS, ampicillin-sulbactam; SCF, cefoperazone-sulbactam; TZP, piperacillin-tazobactam; I, first generation cephalosporins; II, second generation cephalosporins; III, third generation cephalosporins; IV, fourth generation cephalosporins; TMP-SMX, trimethoprim sulfamethoxazole.

Appendix 2-6. Studies included in the systematic review

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(Adibhesami et al., 2016)	2016	Iran	Eastern Mediterranean	UMI	168	3	infection	cross-sectional	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Ahn et al., 2014)	2014	South Korea	Western Pacific	HI	57	114	acquisition	matched case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Akgul et al., 2016)	2016	Turkey	European	UMI	95	100	infection	case-control	Single-centre	Hospital	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-no CR
(Akinci et al., 2005)	2005	Turkey	European	UMI	42	86	infection	case-control	Single-centre	TCH	ICU	patients	other	CARB	CR-CS
(Al Otaibi and Al-Hulaily, 2012)	2012	Saudi Arabia	Eastern Mediterranean	HI	60	321	infection	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Armand-Lefevre et al., 2013)	2013	France	European	HI	36	36	colonization	case-control	Single-centre	SCH	ICU	patients	other	CARB	CR-no CR
(Armand-Lefevre et al., 2013)	2013	France	European	HI	22	22	colonization	case-control	Single-centre	SCH	ICU	patients	Non-fermenters	CARB	CR-no CR
(Banach et al., 2014)	2014	USA	the Americas	HI	25	75	colonization	matched case-control	Multi-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Baran et al., 2008)	2008	Turkey	European	UMI	66	57	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Barron et al., 2016)	2016	USA	the Americas	HI	21	59	infection	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Ben-David et al., 2014)	2014	Israel	European	HI	294	2686	colonization	cohort	Multi-centre	PACH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Ben-David et al., 2011)	2011	Israel	European	HI	121	883	colonization	cross-sectional	Multi-centre	PACH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Ben-David et al., 2011)	2011	Israel	European	HI	118	149	colonization	matched case-control	Multi-centre	PACH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Bhargava et al., 2014)	2014	USA	the Americas	HI	48	144	colonization	matched case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Bleumin et al., 2012)	2012	Israel	European	HI	43	150	acquisition	case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-no CR

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(Borer et al., 2012)	2012	Israel	European	HI	42	84	infection	matched case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CRinf-CRcol
(Borer et al., 2012)	2012	Israel	European	HI	464	464	colonization	matched case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Budak et al., 2014)	2014	Turkey	European	UMI	13	95	infection	cross-sectional	Single-centre	Hospital	ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Candevir Ulu et al., 2015)	2015	Turkey	European	UMI	47	51	infection	cohort	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Cavalcante Rde et al., 2014)	2014	Brazil	the Americas	UMI	29	179	acquisition	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no CR
(Cezario et al., 2009)	2009	Brazil	the Americas	UMI	47	122	infection	case-control	Single-centre	TCH	ICU	adult patients	Non-fermenters	CARB	CR-no CR
(Chang et al., 2011)	2011	China-Taiwan	Western Pacific	HI	17	34	infection	matched case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Chen et al., 2014)	2014	China-Taiwan	Western Pacific	HI	73	73	infection	matched case-control	Single-centre	TCH	Non-ICU	adult patients	Non-fermenters	CARB	CR-no
(Cheng et al., 2015)	2015	China-Hong Kong	Western Pacific	HI	244	488	colonization	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no CR
(Cheng et al., 2016a)	2016	China-Hong Kong	Western Pacific	HI	92	914	colonization	cross-sectional	Multi-centre	Nursing home	Non-ICU	patients	Non-fermenters	CARB	CR-no CR
(Cheng et al., 2016b)	2016	China-Hong Kong	Western Pacific	HI	100	400	colonization	cross-sectional	Multi-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Chitnis et al., 2012)	2012	USA	the Americas	HI	34	34	acquisition	case-control	Single-centre	Long-term acute care hospital	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Chusri et al., 2015)	2015	Thailand	South-East Asia	UMI	139	197	infection	case-control	Single-centre	TCH	Non-ICU	adult patients	Non-fermenters	CARB	CR-no
(Cisneros et al., 2005)	2005	Spain	European	HI	88	115	acquisition	cohort	Multi-centre	Hospital	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Corbella et al., 2000)	2000	Spain	European	HI	39	84	acquisition	cohort	Single-centre	TCH	ICU	adult patients	Non-fermenters	CARB	CR-CS
(Correa et al., 2013)	2013	Brazil	the Americas	UMI	20	40	infection	matched case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Cunha et al., 2016)	2016	USA	the Americas	HI	7	14	colonization	case-control	Multi-centre	Hospital	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(da Silva et al., 2016)	2016	Brazil	the Americas	UMI	47	47	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CP	CR-CS
(Daikos et al., 2010)	2010	Greece	European	HI	67	111	infection	case-control	Multi-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CP	CR-CS
(Dautzenberg et al., 2016)	2016	Netherlands	European	HI	71	211	acquisition	matched case-control	Single-centre	Hospital	Non-ICU	patients	Enterobacteriaceae	CP	CR-no CR
(De Jager et al., 2015)	2015	South Africa	African	UMI	38	68	infection	matched case-control	Single-centre	Hospital	Non-ICU	patients	other	CP	CR-no CR
(Debby et al., 2012)	2012	Israel	European	HI	48	132	colonization	cohort	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(del Mar Tomas et al., 2005)	2005	Spain	European	HI	30	31	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Deris et al., 2011)	2011	Malaysia	Western Pacific	UMI	15	41	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Dickstein et al., 2016)	2016	Israel	European	HI	146	292	colonization	cohort	Single-centre	TCH	ICU	adult patients	Enterobacteriaceae	CARB	CR-no CR
(Dirajlal-Fargo et al., 2014)	2014	USA	the Americas	HI	13	52	acquisition	case-control	Single-centre	Hospital	Non-ICU	paediatric patients	Enterobacteriaceae	CARB	CR-no CR
(Dizbay et al., 2014)	2014	Turkey	European	UMI	42	798	infection	cross-sectional	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Dizbay et al., 2010)	2010	Turkey	European	UMI	524	401	infection	cross-sectional	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Djordjevic et al., 2016)	2016	Serbia	European	UMI	95	42	infection	cohort	Single-centre	TCH	ICU	adult patients	Non-fermenters	CARB	CR-CS
(Eagye et al., 2009)	2009	USA	the Americas	HI	58	125	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Eagye et al., 2009)	2009	USA	the Americas	HI	58	57	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no
(Epstein et al., 2014)	2014	USA	the Americas	HI	8	27	colonization	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CP	CR-no CR
(Falagas et al., 2007)	2007	Greece	European	HI	53	53	infection	matched case-control	Multi-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Fortaleza et al., 2006)	2006	Brazil	the Americas	UMI	108	216	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no CR
(Freire et al., 2015)	2015	Brazil	the Americas	UMI	25	1076	infection	cohort	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CP	CR-no CR
(Freire et al., 2016a)	2016	Brazil	the Americas	UMI	26	52	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(Freire et al., 2016b)	2016	Brazil	the Americas	UMI	119	206	acquisition	cohort	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Freire et al., 2016b)	2016	Brazil	the Americas	UMI	54	324	infection	cohort	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Freire et al., 2016c)	2016	Brazil	the Americas	UMI	81	91	colonization	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no CR
(Freire et al., 2016c)	2016	Brazil	the Americas	UMI	56	138	infection	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no CR
(Furtado et al., 2009)	2009	Brazil	the Americas	UMI	63	182	infection	matched case-control	Single-centre	TCH	ICU	adult patients	Non-fermenters	CARB	CR-no CR
(Furtado et al., 2010)	2010	Brazil	the Americas	UMI	58	237	infection	matched case-control	Single-centre	TCH	ICU	adult patients	Non-fermenters	CARB	CR-no
(Gagliotti et al., 2014)	2014	Italy	European	HI	50	100	colonization	matched case-control	Multi-centre	Hospital	Non-ICU	patients	Enterobacteriaceae	CP	CR-no CR
(Garbati et al., 2016)	2016	Saudi Arabia	Eastern Mediterranean	HI	29	58	infection	matched case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS
(Garlantezec et al., 2011)	2011	France	European	HI	5	28	acquisition	case-control	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-no CR
(Gasink et al., 2009)	2009	USA	the Americas	HI	56	863	acquisition	case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CP	CR-CS
(Gaviria et al., 2011)	2011	USA	the Americas	HI	19	38	infection	matched case-control	Single-centre	Hospital	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Giannella et al., 2015)	2015	Italy	European	HI	20	217	infection	cohort	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-no CR
(Giuffre et al., 2013)	2013	Italy	European	HI	10	44	colonization	case-control	Single-centre	TCH	ICU	paediatric patients-neonates	Enterobacteriaceae	CP	CR-no
(Gomez Rueda and Zuleta Tobon, 2014)	2014	Colombia	the Americas	UMI	61	122	infection	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no
(Gregory et al., 2010)	2010	Puerto Rico	the Americas	HI	26	26	infection	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no
(Gregory et al., 2010)	2010	Puerto Rico	the Americas	HI	26	26	infection	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Harris et al., 2011)	2011	USA	the Americas	HI	118	3028	colonization	cohort	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-no CR

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(Harris et al., 2002b)	2002	USA	the Americas	HI	120	770	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no CR
(Henig et al., 2015)	2015	Israel	European	HI	1190	1190	acquisition	matched case-control	Multi-centre	Hospital	Non-ICU	adult patients	Non-fermenters	CARB	CR-no
(Henig et al., 2015)	2015	Israel	European	HI	241	241	infection	matched case-control	Multi-centre	Hospital	Non-ICU	adult patients	Non-fermenters	CARB	CR-no
(Horianopoulou et al., 2006)	2006	Greece	European	HI	6	23	colonization	cross-sectional	Single-centre	TCH	ICU	patients	other	CP	CR-no CR
(Hu et al., 2016)	2016	China-mainland	Western Pacific	UMI	65	65	infection	case-control	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Huang et al., 2012)	2012	China-Taiwan	Western Pacific	HI	62	164	infection	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Hussein et al., 2013)	2013	Israel	European	HI	103	214	infection	case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS
(Hussein et al., 2009)	2009	Israel	European	HI	88	373	infection	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Hyle et al., 2010)	2010	USA	the Americas	HI	62	62	acquisition	case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS
(Jamulitrat et al., 2007)	2007	Thailand	South-East Asia	UMI	260	639	acquisition	case-control	Single-centre	Hospital	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Jeon et al., 2008)	2008	South Korea	Western Pacific	HI	46	138	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Kaase et al., 2016)	2016	Germany	European	HI	22	43	acquisition	case-control	Multi-centre	Hospital	Non-ICU	patients	Enterobacteriaceae	CP	CR-CS
(Kalam et al., 2014)	2014	Pakistan	Eastern Mediterranean	LMI	22	43	infection	cohort	Single-centre	TCH	Non-ICU	adult patients	other	CARB	CR-CS
(Karaaslan et al., 2016)	2016	Turkey	European	UMI	176	222	colonization	case-control	Single-centre	TCH	Non-ICU	paediatric patients	other	CARB	CR-no CR
(Katragkou et al., 2006)	2006	Greece	European	HI	26	52	acquisition	case-control	Single-centre	TCH	ICU	paediatric patients	Non-fermenters	CARB	CR-no CR
(Kim et al., 2014a)	2014	South Korea	Western Pacific	HI	19	38	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no
(Kim et al., 2012a)	2012	South Korea	Western Pacific	HI	106	205	infection	case-control	Single-centre	TCH	ICU	adult patients	Non-fermenters	CARB	CR-CS
(Kim et al., 2014b)	2014	South Korea	Western Pacific	HI	82	122	infection	case-control	Multi-centre	TCH	Non-ICU	adult patients	other	CARB	CR-CS
(Kim et al., 2008)	2008	South Korea	Western Pacific	HI	27	41	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Kim et al., 2008)	2008	South Korea	Western Pacific	HI	7	41	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CP	CR-CS

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(Kim et al., 2012b)	2012	South Korea	Western Pacific	HI	53	42	infection	cohort	Single-centre	TCH	Non-ICU	adult patients	Non-fermenters	CARB	CR-no CR
(Kim et al., 2012c)	2012	South Korea	Western Pacific	HI	24	51	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CRinf-CRcol
(Kofteridis et al., 2014)	2014	Greece	European	HI	83	161	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no
(Kohlenberg et al., 2010)	2010	Germany	European	HI	15	18	acquisition	case-control	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-CS
(Kopterides et al., 2007)	2007	Greece	European	HI	25	14	infection	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Kritsotakis et al., 2011)	2011	Greece	European	HI	96	151	infection	case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-no CR
(Kumar et al., 2014)	2014	India	South-East Asia	LMI	33	32	infection	cohort	Single-centre	Hospital	ICU	paediatric patients-neonates	Non-fermenters	CARB	CR-CS
(Latibeaudiere et al., 2015)	2015	USA	the Americas	HI	60	304	infection	cohort	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-no CR
(Lautenbach et al., 2009)	2009	USA	the Americas	HI	89	297	acquisition	case-control	Multi-centre	Hospital	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Lautenbach et al., 2010)	2010	USA	the Americas	HI	253	2289	acquisition	case-control	Multi-centre	Hospital	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Lautenbach et al., 2006)	2006	USA	the Americas	HI	142	737	infection	case-control	Single-centre	TCH	Non-ICU	adult patients	Non-fermenters	CARB	CR-CS
(Le Hello et al., 2010)	2010	France	European	HI	50	152	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CP	CR-CS
(Lee et al., 2013a)	2013	USA	the Americas	HI	25	50	acquisition	matched case-control	Multi-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no
(Lee et al., 2016)	2016	South Korea	Western Pacific	HI	37	37	acquisition	case-control	Single-centre	SCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS (same species)
(Lee et al., 2016)	2016	South Korea	Western Pacific	HI	37	37	acquisition	case-control	Single-centre	SCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS (different species)
(Lee et al., 2004)	2004	South Korea	Western Pacific	HI	104	416	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no CR
(Lepelletier et al., 2009)	2009	France	European	HI	38	738	colonization	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no
(Lepelletier et al., 2009)	2009	France	European	HI	38	112	colonization	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Leroy et al., 2005)	2005	France	European	HI	42	126	infection	case-control	Single-centre	TCH	ICU	patients	other	CARB	CR-CS

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(Lin et al., 2016)	2016	China-Taiwan	Western Pacific	HI	82	82	acquisition	case-control	Multi-centre	Hospital	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Ling et al., 2015)	2015	Singapore	Western Pacific	HI	203	203	acquisition	matched case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-no CR
(Liu et al., 2012)	2012	China-Taiwan	Western Pacific	HI	25	50	infection	matched case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Lodise et al., 2007)	2007	USA	the Americas	HI	154	197	infection	cross-sectional	Single-centre	TCH	Non-ICU	adult patients	Non-fermenters	CARB	CR-CS
(Mantzarlis et al., 2013)	2013	Greece	European	HI	25	18	infection	cohort	Single-centre	TCH	ICU	adult patients	Enterobacteriaceae	CARB	CR-CS
(Mantzarlis et al., 2013)	2013	Greece	European	HI	25	39	infection	cohort	Single-centre	TCH	ICU	adult patients	Enterobacteriaceae	CARB	CR-no
(Marchaim et al., 2012)	2012	USA	the Americas	HI	91	91	acquisition	matched case-control	Multi-centre	Hospital	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no
(Marchaim et al., 2008)	2008	Israel	European	HI	33	33	acquisition	matched case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Marchenay et al., 2015)	2015	France	European	HI	23	324	acquisition	cohort	Single-centre	TCH	ICU	adult patients	other	CARB	CR-no CR
(Meradji et al., 2015)	2015	Algeria	African	UMI	15	65	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Miller and Johnson, 2016)	2016	USA	the Americas	HI	41	123	infection	matched case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS
(Mills et al., 2016)	2016	USA	the Americas	HI	99	123	acquisition	case-control	Single-centre	Long-term acute care hospital	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Mittal et al., 2016)	2016	India	South-East Asia	LMI	26	74	colonization	case-control	Single-centre	Hospital	ICU	patients	Enterobacteriaceae	CP	CR-no CR
(Mouloudi et al., 2014)	2014	Greece	European	HI	17	34	infection	case-control	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CP	CR-no CR
(Mouloudi et al., 2010)	2010	Greece	European	HI	18	22	infection	case-control	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CP-metallo	CR-CS
(Mouloudi et al., 2010)	2010	Greece	European	HI	19	22	infection	case-control	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CP-*bla*KPC	CR-CS
(Nouer et al., 2005)	2005	Brazil	the Americas	UMI	14	28	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CP	CR-CS

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(Nouvenne et al., 2014)	2014	Italy	European	HI	133	400	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Ny et al., 2015)	2015	USA	the Americas	HI	48	48	Infection-pneumonia and UTI	cohort	Single-centre	SCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS
(Ny et al., 2015)	2015	USA	the Americas	HI	21	21	Infection-pneumonia	cohort	Single-centre	SCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS
(Ny et al., 2015)	2015	USA	the Americas	HI	27	27	Infection-UTI	cohort	Single-centre	SCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS
(Orsi et al., 2013)	2013	Italy	European	HI	39	60	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB-non-carbapenemase production	CR-CS
(Orsi et al., 2013)	2013	Italy	European	HI	44	60	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CP-*bla*KPC	CR-CS
(Orsi et al., 2011)	2011	Italy	European	HI	38	62	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Otter et al., 2016)	2016	UK	European	HI	5	4006	colonization	cross-sectional	Single-centre	Hospital	Non-ICU	adult patients	Enterobacteriaceae	CP	CR-no CR
(Ozkurt et al., 2005)	2005	Turkey	European	UMI	40	93	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Papadimitriou-Olivgeris et al., 2014)	2014	Greece	European	HI	48	225	infection	cross-sectional	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CP	CR-no
(Papadimitriou-Olivgeris et al., 2012)	2012	Greece	European	HI	52	353	colonization	cross-sectional	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CP	CR-no CR
(Papadimitriou-Olivgeris et al., 2013)	2013	Greece	European	HI	164	62	colonization	cross-sectional	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CP	CR-no CR
(Patel et al., 2008)	2008	USA	the Americas	HI	99	99	infection	matched case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Patel et al., 2011)	2011	USA	the Americas	HI	102	102	infection	matched case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS
(Pena et al., 2007)	2007	Spain	European	HI	30	224	colonization	cross-sectional	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-no CR
(Playford et al., 2007)	2007	Australia	Western Pacific	HI	65	131	acquisition	matched case-control	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-no CR
(Poole et al., 2016)	2016	UK	European	HI	26	592	colonization	case-control	Single-centre	Hospital	Non-ICU	adult patients	Enterobacteriaceae	CP	CR-no CR

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(Pouch et al., 2015)	2015	USA	the Americas	HI	20	80	colonization	case-control	Multi-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS
(Prasad et al., 2016)	2016	USA	the Americas	HI	57	244	colonization	cross-sectional	Single-centre	Long-term care facility	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-no CR
(Punpanich et al., 2012)	2012	Thailand	South-East Asia	UMI	91	85	infection	cohort	Single-centre	TCH	Non-ICU	paediatric patients	Non-fermenters	CARB	CR-CS
(Rosa et al., 2014)	2014	USA	the Americas	HI	61	501	acquisition	cross-sectional	Single-centre	TCH	ICU	adult patients	Non-fermenters	CARB	CR-no CR
(Rossini et al., 2016)	2016	Italy	European	HI	145	1019	colonization	cross-sectional	Single-centre	Rehabilitation hospital	Non-ICU	patients	Enterobacteriaceae	CP	CR- no CR
(Routsi et al., 2010)	2010	Greece	European	HI	30	66	infection	cross-sectional	Single-centre	TCH	ICU	adult patients	Non-fermenters	CARB	CR-CS
(Routsi et al., 2013)	2013	Greece	European	HI	85	84	infection	case-control	Single-centre	TCH	ICU	adult patients	other	CARB	CR-CS
(Routsi et al., 2013)	2013	Greece	European	HI	85	630	infection	case-control	Single-centre	TCH	ICU	adult patients	other	CARB	CR-no
(Salsano et al., 2016)	2016	Italy	European	HI	32	521	infection	cohort	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Sanchez-Romero et al., 2012)	2012	Spain	European	HI	55	55	acquisition	case-control	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CP	CR-no CR
(Satlin et al., 2016)	2016	USA	the Americas	HI	43	129	infection	case-control	Multi-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Satlin et al., 2016)	2016	USA	the Americas	HI	43	129	infection	case-control	Multi-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Sbrana et al., 2016)	2016	Italy	European	HI	30	60	infection	matched case-control	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CP	CR-no
(Schechner et al., 2011)	2011	Israel	European	HI	23	43	colonization	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Schwaber et al., 2008)	2008	Israel	European	HI	48	59	acquisition	case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-no
(Sharaf and Gerges, 2016)	2016	Egypt	Eastern Mediterranean	LMI	11	135	infection	cohort	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-CS
(Sheng et al., 2010)	2010	China-Taiwan	Western Pacific	HI	30	30	colonization	case-control	Multi-centre	Hospital	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Sheng et al., 2010)	2010	China-Taiwan	Western Pacific	HI	91	97	infection	case-control	Multi-centre	Hospital	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Sheng et al., 2010)	2010	China-Taiwan	Western Pacific	HI	63	60	Infection-BSI	case-control	Multi-centre	Hospital	Non-ICU	patients	Non-fermenters	CARB	CR-CS

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(Shilo et al., 2013)	2013	Israel	European	HI	135	127	acquisition	case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS
(Simkins et al., 2014)	2014	USA	the Americas	HI	13	39	infection	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Swaminathan et al., 2013)	2013	USA	the Americas	HI	104	104	colonization	matched case-control	Multi-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Tam et al., 2007)	2007	USA	the Americas	HI	18	33	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Teo et al., 2012)	2012	Singapore	Western Pacific	HI	29	87	acquisition	case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-no
(Thatrimontrichai et al., 2013)	2013	Thailand	South-East Asia	UMI	14	44	infection	case-control	Single-centre	TCH	ICU	paediatric patients-neonates	Non-fermenters	CARB	CR-no
(Thatrimontrichai et al., 2013)	2013	Thailand	South-East Asia	UMI	14	38	infection	case-control	Single-centre	TCH	ICU	paediatric patients-neonates	Non-fermenters	CARB	CR-CS
(Thatrimontrichai et al., 2016)	2016	Thailand	South-East Asia	UMI	63	25	infection	case-control	Single-centre	TCH	ICU	paediatric patients-neonates	Non-fermenters	CARB	CR-no
(Thatrimontrichai et al., 2016)	2016	Thailand	South-East Asia	UMI	63	13	infection	case-control	Single-centre	TCH	ICU	paediatric patients-neonates	Non-fermenters	CARB	CR-CS
(Tian et al., 2016)	2016	China-mainland	Western Pacific	UMI	33	81	infection	cohort	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Torres-Gonzalez et al., 2015)	2015	Mexico	the Americas	UMI	55	275	colonization	cohort	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-no CR
(Torres-Gonzalez et al., 2016)	2016	Mexico	the Americas	UMI	27	54	infection	matched case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CP	CR-CS
(Torres-Gonzalez et al., 2016)	2016	Mexico	the Americas	UMI	27	54	infection	matched case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CP	CR-CS (ESBL)
(Troillet et al., 1997)	1997	USA	the Americas	HI	40	387	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Tumbarello et al., 2014)	2014	Italy	European	HI	657	1314	acquisition	matched case-control	Multi-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CP	CR-no CR
(Tumbarello et al., 2014)	2014	Italy	European	HI	426	852	infection	matched case-control	Multi-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CP	CR-no CR

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(Tuon et al., 2012a)	2012	Brazil	the Americas	UMI	29	48	infection	case-control	Single-centre	TCH	Non-ICU	adult patients	Non-fermenters	CARB	CR-CS
(Tuon et al., 2012b)	2012	Brazil	the Americas	UMI	18	67	infection	case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CP	CR-no CR
(Vardakas et al., 2015)	2015	Greece	European	HI	73	18	infection	cohort	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Vitkauskiene et al., 2013)	2013	Lithuania	European	HI	40	59	infection	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Wang et al., 2016b)	2016	China-mainland	Western Pacific	UMI	94	93	infection	matched case-control	Multi-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no
(Wannaro et al., 2012)	2012	Thailand	South-East Asia	UMI	13	9	infection	cohort	Single-centre	Hospital	ICU	paediatric patients-neonates	Non-fermenters	CARB	CR-CS
(Wiener-Well et al., 2010)	2010	Israel	European	HI	16	32	colonization	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Wu et al., 2011)	2011	China-mainland	Western Pacific	UMI	39	78	infection	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Yang et al., 2016a)	2016	China-mainland	Western Pacific	UMI	370	740	infection	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Ye et al., 2015)	2015	China-mainland	Western Pacific	UMI	11	14	infection	case-control	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-no CR
(Ye et al., 2010)	2010	China-Taiwan	Western Pacific	HI	49	160	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Ye et al., 2010)	2010	China-Taiwan	Western Pacific	HI	20	20	acquisition	matched case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Zarakolu et al., 2016)	2016	Turkey	European	UMI	8	271	infection	cross-sectional	Multi-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CRinf-CRcol
(Zavascki et al., 2006a)	2006	Brazil	the Americas	UMI	86	212	infection	case-control	Multi-centre	TCH	Non-ICU	adult patients	Non-fermenters	CP	CR-CS
(Zavascki et al., 2005a)	2005	Brazil	the Americas	UMI	93	93	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no
(Zavascki et al., 2005a)	2005	Brazil	the Americas	UMI	93	65	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Zhao et al., 2014)	2014	China-mainland	Western Pacific	UMI	20	283	colonization	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Zheng et al., 2013)	2013	China-mainland	Western Pacific	UMI	97	145	infection	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Hirakata et al., 2003)	2003	Japan	Western Pacific	HI	69	247	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CP	CR-no CR
(Huang et al., 2014a)	2014	China-Taiwan	Western Pacific	HI	67	262	infection	cohort	Single-centre	TCH	Non-ICU	adult patients	Non-fermenters	CARB	CR-CS

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(Kwak et al., 2005)	2005	South Korea	Western Pacific	HI	30	120	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Ma et al., 2014)	2014	China-mainland	Western Pacific	UMI	9	18	colonization	case-control	Single-centre	TCH	ICU	paediatric patients-neonates	Enterobacteriaceae	CP	CR-no CR
(Peng et al., 2005)	2005	China-mainland	Western Pacific	UMI	67	200	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no
(Petrikkos et al., 2009)	2009	Greece	European	HI	67	111	infection	cohort	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CP	CR-CS
(Saavedra-Trujillo et al., 2016)	2016	Colombia	the Americas	UMI	135	30	infection	case-control	Multi-centre	Hospital	ICU	adult patients	Non-fermenters	CARB	CR-CS
(Zhang et al., 2011)	2011	China-mainland	Western Pacific	UMI	32	64	infection	case-control	Single-centre	TCH	Non-ICU	paediatric patients	Non-fermenters	CARB	CR-CS
(Zhang et al., 2009)	2009	China-mainland	Western Pacific	UMI	24	10	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Valderrama et al., 2016)	2016	Colombia	the Americas	UMI	42	126	infection	case-control	Single-centre	TCH	Non-ICU	adult patients	Non-fermenters	CARB	CR-CS
(Liu et al., 2011a)	2011	China-mainland	Western Pacific	UMI	40	20	infection	case-control	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-CS
(Liu et al., 2011b)	2011	China-mainland	Western Pacific	UMI	44	58	acquisition	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CP	CR-CS
(Liu et al., 2006)	2006	China-mainland	Western Pacific	UMI	90	90	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Lu et al., 2009)	2009	China-mainland	Western Pacific	UMI	44	66	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Lv et al., 2015)	2015	China-mainland	Western Pacific	UMI	32	64	infection	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Guo et al., 2016)	2016	China-mainland	Western Pacific	UMI	49	76	infection	cohort	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Zhang et al., 2004)	2004	China-mainland	Western Pacific	UMI	17	38	acquisition	cohort	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-CS
(Cai et al., 2015)	2015	China-mainland	Western Pacific	UMI	11	33	infection	case-control	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Lou et al., 2013)	2013	China-mainland	Western Pacific	UMI	135	381	infection	cohort	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-CS
(Jiang et al., 2015)	2015	China-mainland	Western Pacific	UMI	81	24	infection	cohort	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-CS
(Li et al., 2016)	2016	China-mainland	Western Pacific	UMI	35	36	infection	case-control	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-no CR
(Wang et al., 2013)	2013	China-mainland	Western Pacific	UMI	155	46	infection	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(Zhang et al., 2012)	2012	China-mainland	Western Pacific	UMI	65	61	infection	cohort	Single-centre	TCH	Non-ICU	patients	other	CP	CR-CS
(Wang et al., 2016a)	2016	China-mainland	Western Pacific	UMI	130	151	acquisition	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Guo and Sun, 2010)	2010	China-mainland	Western Pacific	UMI	30	30	infection	case-control	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-CS
(Cao et al., 2015)	2015	China-mainland	Western Pacific	UMI	23	85	colonization	case-control	Single-centre	TCH	Non-ICU	paediatric patients-neonates	Enterobacteriaceae	CARB	CR-CS
(Wu et al., 2016)	2016	China-mainland	Western Pacific	UMI	65	122	infection	cohort	Single-centre	TCH	Non-ICU	paediatric patients	Enterobacteriaceae	CARB	CR-CS
(Jia et al., 2016)	2016	China-mainland	Western Pacific	UMI	48	37	infection	cohort	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Chen and Zhao, 2009)	2009	China-mainland	Western Pacific	UMI	48	104	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Yang et al., 2016b)	2016	China-mainland	Western Pacific	UMI	8	110	infection	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no CR
(Guo et al., 2008)	2008	China-mainland	Western Pacific	UMI	195	195	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Fei et al., 2014)	2014	China-mainland	Western Pacific	UMI	30	30	infection	case-control	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Fei et al., 2012)	2012	China-mainland	Western Pacific	UMI	30	30	infection	case-control	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-CS
(Chen et al., 2010)	2010	China-mainland	Western Pacific	UMI	30	30	infection	case-control	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-CS
(Fei et al., 2013)	2013	China-mainland	Western Pacific	UMI	30	30	infection	case-control	Single-centre	TCH	ICU	patients	Non-fermenters	CARB	CR-CS
(Wang et al., 2016c)	2016	China-mainland	Western Pacific	UMI	97	145	infection	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Kong et al., 2016)	2016	China-mainland	Western Pacific	UMI	68	68	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-no
(Huang et al., 2015)	2015	China-mainland	Western Pacific	UMI	163	68	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Wang et al., 2011)	2011	China-mainland	Western Pacific	UMI	30	62	infection	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Hang and Zhang, 2016)	2016	China-mainland	Western Pacific	UMI	30	30	infection	cohort	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Xu et al., 2015)	2015	China-mainland	Western Pacific	UMI	80	80	infection	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Sun et al., 2016)	2016	China-mainland	Western Pacific	UMI	114	101	infection	case-control	Multi-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Deng et al., 2016)	2016	China-mainland	Western Pacific	UMI	40	80	infection	case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS

Study	Year	Country/ Region	WHO region	World Bank Income group	Number of cases	Number of controls	Status	Study Design	Study Setting	Health-care Type	Specialty	Study Population	Organism	Resistance mechanism	Case-Control
(Wang et al., 2014)	2014	China-mainland	Western Pacific	UMI	103	103	infection	case-control	Multi-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Pan et al., 2016)	2016	China-mainland	Western Pacific	UMI	26	164	infection	cohort	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Li et al., 2015)	2015	China-mainland	Western Pacific	UMI	401	294	infection	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Aydemir et al., 2012)	2012	Turkey	European	UMI	110	55	infection	case-control	Single-centre	TCH	Non-ICU	adult patients	Non-fermenters	CARB	CR-CS
(Borer et al., 2009)	2009	Israel	European	HI	32	32	infection	cohort	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-no
(Cekin et al., 2013)	2013	Turkey	European	UMI	20	22	acquisition	case-control	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Chusri et al., 2014)	2014	Thailand	South-East Asia	UMI	139	25	infection	cohort	Single-centre	Hospital	Non-ICU	adult patients	Non-fermenters	CARB	CR-no
(Hoxha et al., 2016)	2016	Italy	European	HI	49	49	infection	cohort	Multi-centre	Hospital	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS
(Onguru et al., 2008)	2008	Turkey	European	UMI	75	95	infection	case-control	Single-centre	TCH	Non-ICU	adult patients	Non-fermenters	CARB	CR-CS
(Sonmezer et al., 2016)	2016	Turkey	European	UMI	56	64	infection	case-control	Single-centre	TCH	ICU	patients	Non-fermenters	CARB-imipenem	CR-CS
(Sonmezer et al., 2016)	2016	Turkey	European	UMI	52	68	infection	case-control	Single-centre	TCH	ICU	patients	Non-fermenters	CARB-meropenem	CR-CS
(Trecarichi et al., 2016)	2016	Italy	European	HI	161	117	infection	cohort	Multi-centre	Hospital	Non-ICU	patients	Enterobacteriaceae	CARB	CR-CS
(Ganor et al., 2012)	2012	Israel	European	HI	48	132	colonization	cohort	Single-centre	TCH	ICU	patients	Enterobacteriaceae	CARB	CR-no CR
(Villegas et al., 2016)	2016	Argentina, Colombia, Ecuador, Guatemala, Mexico, Peru, Venezuela	the Americas	UMI	53	202	infection	cohort	Multi-centre	Hospital	Non-ICU	patients	Enterobacteriaceae	CP	CR-no CR
(Yogeesha Babu et al., 2011)	2011	India	South-East Asia	LMI	24	86	infection	cohort	Single-centre	TCH	Non-ICU	patients	Non-fermenters	CARB	CR-CS
(Jiao et al., 2015)	2015	China-mainland	Western Pacific	UMI	30	30	acquisition	case-control	Single-centre	TCH	Non-ICU	adult patients	Enterobacteriaceae	CARB	CR-CS
(Hayakawa et al., 2014)	2014	Japan	Western Pacific	HI	15	45	acquisition	matched case-control	Single-centre	TCH	Non-ICU	patients	Enterobacteriaceae	CP	CR-no

HI, high income; UMI, upper-middle income; LMI, lower-middle income; TCH, tertiary care hospital; SCH, secondary care hospital; PACH, post-acute care hospital; ICU, intensive care unit; CARB, carbapenem resistance; CP, carbapenemase production; CR-CS, carbapenem resistance-carbapenem susceptible; CR-no CR, carbapenem resistance-no carbapenem resistance; CR-no, carbapenem resistance-no organisms; CRinf-CRcol, carbapenem resistance infection-carbapenem resistance colonisation; ESBL, extended spectrum beta-lactamases.

Appendix 2-7. Pooled estimates of risk factors investigated for carbapenem-resistant organisms (CRO) presence, infection and colonisation

(1) Pooled estimates of risk factors for CRO presence, infection and colonisation

Risk Factors	Number (a, b, c)*			Pooled OR (95%CI)			Heterogeneity, I^2 (%)			Publication bias, $P^{\S}$		
	All	Inf	Col	All	Inf	Col	All	Inf	Col	All	Inf	Col
Demography												
Age (>65yrs)	1, 9, 11.11%	na, 4, na	na, 2, na	1.11 (0.75-1.63)	na	na	72	na	na	na	na	na
Age, years	27, 176, 15.34%	13, 101, 12.87%	3, 32, 9.38%	0.08 (-0.01, 0.18)¶	0.13 (-0.01, 0.27)¶	-0.16 (-0.33, 0.02)¶	93	94	92	0.00	0.03	0.43
Gender-male	19, 217, 8.76%	3, 124, 2.42%	8, 36, 22.22%	1.12 (1.06-1.20)	1.06 (0.97-1.16)	1.29 (1.12-1.48)	45	44	45	0.62	0.86	0.66
Prior healthcare exposure												
Prior hospitalisation	21, 62, 33.87%	10, 32, 31.25%	4, 11, 36.36%	1.87 (1.56-2.25)	1.72 (1.38-2.15)	1.75 (1.24-2.48)	73	56	60	0.40	0.77	0.59
Length of hospitalisation, days	51, 112, 45.54%	24, 65, 36.92%	na, 1, na	0.41 (0.30, 0.51)¶	0.29 (0.20, 0.38)¶	na	90	73	na	0.00	0.57	na
Hospital transfer	11, 22, 50.00%	4, 8, 50.00%	na, 3, na	2.15 (1.79-2.59)	2.17 (1.66-2.85)	na	39	30	na	0.67	na	na
ICU stay	69, 114, 60.53%	44, 70, 62.86%	8, 12, 66.67%	3.26 (2.73-3.90)	3.03 (2.46-3.73)	5.14 (2.47-10.69)	86	82	91	0.80	0.93	0.92
Length of ICU stay, days	14, 27, 51.85%	11, 22, 50.00%	na, 0, na	0.48 (0.33, 0.64)¶	0.49 (0.30, 0.67)¶	na	78	81	na	0.99	0.89	na
Prior presence of CRO	6, 7, 85.71%	5, 6, 83.33%	na, 0, na	7.14 (3.68-13.85)	5.82 (3.03-11.20)	na	41	31	na	na	na	na
Presence of ESBL producers	4, 9, 44.44%	na, 4, na	na, 3, na	3.97 (2.32-6.81)	na	na	50	na	na	na	na	na
Presence of MRSA	3, 8, 37.50%	na, 1, na	na, 2, na	2.75 (1.68-4.50)	na	na	59	na	na	na	na	na
Presence of VRE	3, 7, 42.86%	na, 0, na	na, 2, na	6.93 (3.90-12.32)	na	na	0	na	na	na	na	na
Comorbidities												
Chemotherapy	3, 17, 17.65%	2, 12, 16.67%	na, 0, na	1.23 (0.75-2.02)	1.23 (0.71-2.13)	na	91	78	na	0.18	0.43	na
Steroid treatment	14, 45, 31.11%	8, 29, 27.59%	1, 5, 20.00%	2.06 (1.62-2.61)	2.49 (1.73-3.59)	1.72 (0.79-3.78)	77	81	77	0.48	0.19	na
Decubitus ulcer	5, 10, 50.00%	4, 5, 80.00%	na, 1, na	3.08 (1.90-4.99)	5.08 (1.98-13.05)	na	63	82	na	0.09	na	na
Diabetes mellitus	20, 149, 13.42%	12, 89, 13.48%	3, 18, 16.67%	1.36 (1.25-1.47)	1.34 (1.20-1.50)	1.47 (1.16-1.85)	27	34	29	0.53	0.26	0.56
HIV	0, 26, 0.00%	0, 13, 0.00%	na, 3, na	1.10 (0.76-1.58)	1.24 (0.60-2.59)	na	6	34	na	0.11	0.22	na
Liver diseases	8, 75, 10.67%	6, 40, 15.00%	0, 9, 0.00%	1.34 (1.14-1.58)	1.42 (1.11-1.82)	0.91 (0.60-1.37)	45	55	0	0.12	0.41	na
COPD	13, 46, 28.26%	8, 36, 22.22%	na, 4, na	1.53 (1.27-1.85)	1.46 (1.22-1.75)	na	59	33	na	0.46	0.20	na
Malignancy	18, 124, 14.52%	12, 70, 17.14%	2, 14, 14.29%	1.18 (1.05-1.33)	1.25 (1.05-1.48)	1.11 (0.76-1.64)	51	52	61	0.29	0.90	0.42

Risk Factors	Number (a, b, c)*			Pooled OR (95%CI)			Heterogeneity, I^2 (%)			Publication bias, $P^§$		
	All	Inf	Col	All	Inf	Col	All	Inf	Col	All	Inf	Col
Hematologic malignancy	7, 25, 28.00%	4, 15, 26.67%	na, 2, na	1.58 (1.22-2.05)	1.58 (1.19-2.10)	na	46	18	na	0.99	0.12	na
Neurological disease	9, 33, 27.27%	4, 14, 28.57%	2, 5, 40.00%	1.49 (1.18-1.87)	1.56 (1.10-2.21)	1.57 (0.85-2.90)	63	59	80	0.15	0.91	na
Neutropenia	7, 23, 30.43%	5, 16, 31.25%	na, 1, na	1.78 (1.32-2.38)	1.75 (1.18-2.59)	na	27	38	na	0.13	0.74	na
Renal failure	14, 47, 29.79%	7, 27, 25.93%	1, 8, 12.50%	1.73 (1.44-2.09)	1.67 (1.37-2.03)	1.64 (0.98-2.73)	47	23	44	0.72	0.74	na
Trauma	8, 43, 18.60%	4, 30, 13.33%	2, 5, 40.00%	1.50 (1.15-1.95)	1.23 (0.91-1.68)	2.38 (1.34-4.22)	67	55	75	0.33	0.30	na
Hypertension	2, 23, 8.70%	2, 21, 9.52%	na, 1, na	1.24 (1.07-1.45)	1.26 (1.08-1.48)	na	0	0	na	0.47	0.38	na
Heart failure	3, 43, 6.98%	0, 20, 0.00%	2, 12, 16.67%	1.50 (1.29-1.75)	1.51 (1.20-1.90)	1.28 (0.83-1.97)	13	0	64	0.10	0.21	0.07
Coronary artery disease	1, 14, 7.14%	1, 11, 9.09%	na, 1, na	1.16 (0.83-1.62)	1.24 (0.77-1.99)	na	39	51	na	0.20	0.25	na
Stroke	2, 20, 10.00%	2, 10, 20.00%	0, 6, 0.00%	1.50 (1.04-2.17)	1.89 (0.98-3.64)	1.06 (0.72-1.55)	68	79	0	0.14	0.22	na
CCI score	9, 29, 31.03%	4, 12, 33.33%	2, 6, 33.33%	0.26 (0.10, 0.43)¶	0.33 (0.01, 0.66)¶	0.13 (-0.09, 0.34)¶	86	91	71	0.01	0.053	na
APACHE II score	11, 33, 33.33%	8, 27, 29.63%	na, 4, na	0.22 (0.09, 0.35)¶	0.22 (0.10, 0.34)¶	na	73	59	na	0.89	0.83	na
SOFA score	2, 12, 16.67%	1, 8, 12.50%	na, 3, na	0.27 (-0.15, 0.69)¶	0.01 (-0.21, 0.23)¶	na	93	56	na	0.87	na	na
Prior invasive procedures/devices												
Blood transfusion	3, 14, 21.43%	2, 9, 22.22%	na, 0, na	1.84 (1.26-2.67)	1.41 (0.94-2.13)	na	38	26	na	0.80	na	na
Intravenous catheter	59, 124, 47.58%	36, 79, 45.57%	4, 12, 33.33%	2.52 (2.16-2.95)	2.31 (1.91-2.80)	2.31 (1.39-3.84)	77	78	67	0.82	0.31	0.38
CVC	36, 89, 40.45%	25, 59, 42.37%	4, 11, 36.36%	2.25 (1.87-2.70)	2.07 (1.66-2.59)	2.36 (1.32-4.21)	79	80	73	0.19	0.10	0.39
Duration of CVC, days	4, 9, 44.44%	4, 7, 57.14%	na, 0, na	0.33 (-0.33, 0.99)¶	0.36 (-0.51, 1.22)¶	na	93	95	na	na	na	na
Arterial catheter	7, 19, 36.84%	3, 13, 23.08%	na, 0, na	2.26 (1.52-3.36)	1.82 (1.12-2.96)	na	64	69	na	0.15	0.48	na
Dialysis	18, 55, 32.73%	12, 35, 34.29%	2, 8, 25.00%	2.12 (1.76-2.56)	2.05 (1.59-2.66)	1.98 (1.41-2.79)	44	52	0	0.10	0.03	na
Hemodialysis	8, 30, 26.67%	6, 20, 30.00%	na, 4, na	1.98 (1.52-2.59)	1.73 (1.22-2.46)	na	54	62	na	0.00	0.00	na
Drainage	9, 32, 28.13%	3, 19, 15.79%	na, 4, na	2.10 (1.65-2.68)	1.79 (1.29-2.48)	na	56	54	na	0.44	0.40	na
Enteral nutrition	5, 20, 25.00%	3, 14, 21.43%	na, 4, na	2.00 (1.47-2.72)	1.80 (1.27-2.56)	na	47	28	na	0.71	0.85	na
Parenteral nutrition	17, 53, 32.08%	11, 35, 31.43%	3, 5, 60.00%	1.75 (1.47-2.08)	1.67 (1.36-2.06)	3.41 (2.22-5.25)	44	37	0	0.34	0.56	na
Endoscopy	8, 17, 47.06%	3, 9, 33.33%	na, 1, na	2.10 (1.58-2.79)	1.56 (1.13-2.17)	na	56	49	na	0.70	na	na
Endotracheal tube	6, 21, 28.57%	4, 15, 26.67%	na, 3, na	2.40 (1.78-3.23)	1.96 (1.56-2.46)	na	48	0	na	0.70	0.33	na
Gastrostomy	4, 17, 23.53%	0, 6, 0.00%	2, 5, 40.00%	2.25 (1.39-3.66)	1.20 (0.59-2.41)	4.66 (1.82-11.98)	52	11	56	0.43	na	na
Mechanical ventilation	63, 98, 64.29%	48, 70, 68.57%	5, 6, 83.33%	3.42 (2.87-4.09)	3.77 (3.03-4.68)	3.17 (1.75-5.72)	80	81	70	0.07	0.06	na
Duration of mechanical ventilation, days	12, 16, 75.00%	11, 15, 73.33%	na, 1, na	0.70 (0.47, 0.93)¶	0.70 (0.43, 0.97)¶	na	76	77	na	0.93	0.69	na
Nasogastric tube	22, 36, 61.11%	11, 19, 57.89%	7, 11, 63.64%	3.33 (2.50-4.44)	2.92 (1.85-4.60)	3.83 (2.34-6.27)	86	89	82	0.66	0.93	0.47
Tracheostomy	24, 55, 43.64%	17, 35, 48.57%	3, 7, 42.86%	2.55 (2.09-3.09)	2.52 (1.98-3.21)	2.75 (1.59-4.73)	57	57	73	0.06	0.02	na

Risk Factors	Number (a, b, c)*			Pooled OR (95%CI)			Heterogeneity, I^2 (%)			Publication bias, $P^§$		
	All	Inf	Col	All	Inf	Col	All	Inf	Col	All	Inf	Col
Transplantation	9, 44, 20.45%	4, 21, 19.05%	0, 5, 0.00%	1.70 (1.33-2.16)	1.95 (1.44-2.63)	0.82 (0.42-1.58)	37	33	19	0.76	0.83	na
Urinary catheter	54, 113, 47.79%	32, 71, 45.07%	7, 13, 53.85%	2.41 (2.05-2.83)	2.28 (1.83-2.85)	2.09 (1.62-2.69)	79	81	48	0.11	0.21	0.43
Duration of urinary catheter, days	3, 6, 50.0%	na, 3, na	na, 0, na	0.52 (0.16, 0.87)¶	na	na	67	na	na	na	na	na
Prior antibiotic exposure												
Aminoglycoside	40, 116, 34.48%	19, 70, 27.14%	5, 13, 38.46%	1.86 (1.62-2.14)	1.58 (1.34-1.86)	3.03 (1.80-5.09)	58	53	64	0.57	0.93	0.89
Amikacin	6, 10, 60.00%	4, 5, 80.00%	na, 1, na	2.60 (1.75-3.86)	2.18 (1.21-3.93)	na	37	57	na	0.79	na	na
Antifungal	3, 7, 42.86%	1, 5, 20.00%	na, 2, na	2.94 (1.95-4.43)	2.04 (1.27-3.30)	na	18	0	na	na	na	na
β-lactam/β-lactamase inhibitor	53, 104, 50.96%	30, 60, 50.00%	10, 21, 47.62%	2.32 (2.03-2.64)	2.31 (1.94-2.75)	2.06 (1.50-2.85)	64	61	77	0.76	0.56	0.14
AMC	3, 11, 27.27%	1, 5, 20.00%	na, 4, na	1.29 (0.70-2.35)	1.30 (0.32-5.24)	na	78	88	na	0.57	na	na
AMS	2, 11, 18.18%	1, 5, 20.00%	na, 0, na	1.26 (0.82-1.94)	1.10 (0.55-2.17)	na	60	63	na	0.36	na	na
SCF	5, 10, 50.00%	3, 7, 42.86%	na, 1, na	2.71 (1.50-4.91)	2.34 (1.23-4.46)	na	55	52	na	0.23	na	na
TZP	19, 45, 42.22%	12, 26, 46.15%	2, 6, 33.33%	2.15 (1.79-2.58)	2.22 (1.75-2.82)	1.63 (1.20-2.23)	39	36	22	0.15	0.02	na
Carbapenem	133, 173, 76.88%	77, 102, 75.49%	21, 28, 75.00%	4.79 (4.17-5.51)	4.34 (3.60-5.24)	4.47 (3.22-6.21)	76	77	75	0.51	0.27	0.67
Duration of carbapenem therapy, days	5, 14, 35.71%	1, 7, 14.29%	na, 0, na	0.42 (0.09, 0.76)¶	0.14 (-0.10, 0.39)¶	na	90	62	na	0.28	na	na
Ertapenem	2, 7, 28.57%	1, 6, 16.67%	na, 0, na	2.81 (1.68-4.71)	2.64 (1.56-4.45)	na	0	0	na	na	na	na
Imipenem	20, 26, 76.92%	8, 14, 57.14%	5, 5, 100.00%	6.60 (4.67-9.33)	4.24 (2.66-6.78)	6.55 (3.90-10.99)	74	63	50	0.85	0.70	na
Meropenem	9, 12, 75.00%	7, 9, 77.78%	na, 1, na	4.33 (3.03-6.19)	4.19 (2.78-6.31)	na	0	0	na	0.48	na	na
Cephalosporin	55, 153, 35.95%	32, 89, 35.96%	8, 29, 27.59%	1.76 (1.52-2.02)	1.68 (1.37-2.06)	1.56 (1.12-2.17)	78	81	75	0.35	0.38	0.49
Duration of cephalosporin therapy, days	2, 11, 18.18%	1, 7, 14.29%	na, 0, na	-0.02 (-0.19, 0.15)¶	-0.13 (-0.35, 0.09)¶	na	72	75	na	0.72	na	na
I	1, 12, 8.33%	1, 6, 16.67%	na, 1, na	0.73 (0.42-1.26)	0.60 (0.19-1.88)	na	78	86	na	0.73	na	na
II	2, 21, 9.52%	0, 12, 0.00%	na, 2, na	1.06 (0.59-1.91)	0.90 (0.44-1.82)	na	84	85	na	0.00	0.00	na
III	18, 63, 28.57%	13, 42, 30.95%	0, 7, 0.00%	1.56 (1.31-1.87)	1.58 (1.29-1.95)	0.85 (0.46-1.57)	61	54	68	0.57	0.78	na
IV	16, 42, 38.10%	8, 28, 28.57%	na, 4, na	2.44 (1.79-3.32)	2.02 (1.36-3.00)	na	72	74	na	0.30	0.76	na
Cefepime	9, 19, 47.37%	3, 11, 27.27%	na, 2, na	2.55 (1.61-4.04)	1.71 (0.87-3.39)	na	80	84	na	0.71	0.24	na
I/II	0, 11, 0.00%	0, 9, 0.00%	na, 1, na	0.91 (0.58-1.43)	0.80 (0.49-1.30)	na	37	37	na	0.05	na	na
III/IV	8, 17, 47.06%	5, 14, 35.71%	na, 2, na	2.12 (1.47-3.08)	1.92 (1.30-2.82)	na	64	56	na	0.46	0.99	na
Combination therapy	8, 11, 72.73%	8, 10, 80.00%	na, 0, na	2.94 (1.96-4.43)	3.04 (1.96-4.71)	na	67	70	na	0.40	0.35	na
Glycopeptide	48, 82, 58.54%	18, 40, 45.00%	10, 17, 58.82%	2.95 (2.48-3.50)	2.36 (1.94-2.88)	3.37 (2.12-5.35)	71	49	78	0.43	0.98	0.67

Risk Factors	Number (a, b, c)*			Pooled OR (95%CI)			Heterogeneity, I^2 (%)			Publication bias, $P^§$		
	All	Inf	Col	All	Inf	Col	All	Inf	Col	All	Inf	Col
Vancomycin	29, 46, 63.04%	10, 20, 50.00%	6, 11, 54.55%	3.10 (2.46-3.91)	2.63 (1.98-3.49)	3.02 (1.92-4.77)	48	48	67	0.95	0.74	0.85
Clindamycin	2, 11, 18.18%	1, 7, 14.29%	na, 2, na	1.65 (1.04-2.61)	1.51 (0.95-2.39)	na	26	17	na	0.39	na	na
Macrolide	1, 16, 6.25%	1, 8, 12.50%	na, 3, na	1.67 (1.15-2.43)	1.56 (0.86-2.81)	na	42	67	na	0.12	na	na
Metronidazole	11, 35, 31.43%	3, 18, 16.67%	3, 9, 33.33%	1.99 (1.52-2.61)	1.50 (1.09-2.06)	2.91 (1.26-6.72)	62	43	81	0.71	0.36	na
Oxazolidinone	11, 17, 64.71%	4, 5, 80.00%	3, 6, 50.00%	4.40 (3.08-6.29)	4.00 (2.23-7.19)	5.03 (1.97-12.88)	49	51	73	0.55	na	na
Penicillin	18, 58, 31.03%	8, 34, 23.53%	4, 8, 50.00%	1.90 (1.55-2.33)	1.60 (1.29-1.99)	2.30 (1.02-5.18)	68	54	86	0.84	0.64	na
Extended spectrum penicillin	7, 21, 33.33%	4, 14, 28.57%	na, 2, na	2.07 (1.46-2.94)	1.75 (1.21-2.54)	na	72	56	na	0.93	0.51	na
Polymyxin	9, 23, 39.13%	7, 15, 46.67%	2, 7, 28.57%	2.97 (2.02-4.37)	2.44 (1.61-3.69)	5.75 (2.88-11.48)	62	62	32	0.20	0.21	na
Fluoroquinolone	39, 102, 38.24%	20, 55, 36.36%	7, 19, 36.84%	1.97 (1.68-2.32)	1.99 (1.52-2.60)	1.75 (1.32-2.31)	74	81	49	0.39	0.97	0.60
Ciprofloxacin	5, 15, 33.33%	2, 7, 28.57%	na, 1, na	2.18 (1.62-2.94)	1.89 (1.21-2.96)	na	16	30	na	0.11	na	na
Tigecycline	4, 12, 33.33%	2, 7, 28.57%	na, 4, na	3.51 (1.84-6.68)	2.05 (1.08-3.89)	na	46	17	na	0.65	na	na
TMP-SMX	4, 9, 44.44%	3, 5, 60.00%	na, 2, na	2.55 (1.43-4.54)	2.78 (1.45-5.35)	na	61	60	na	na	na	na

(2) Pooled estimates of risk factors investigated for hospital acquired CRO infection

Risk Factors	Number (a,b,c)*	Pooled OR (95%CI)	Heterogeneity, I^2 (%)	Publication bias, $P^{\S}$
Demography				
Age (>65yrs)	na, 1, na	na	na	na
Age, years	8, 55, 14.55%	0.18 (-0.04, 0.40)¶	96	0.15
Gender-male	2, 68, 2.94%	1.06 (0.93-1.22)	53	0.10
Prior healthcare exposure				
Prior hospitalisation	3, 12, 25.00%	1.90 (1.29-2.80)	61	0.11
Length of hospitalisation, days	14, 35, 40.00%	0.21 (0.09, 0.34)¶	77	0.58
Hospital transfer	na, 4, na	na	na	na
ICU stay	19, 31, 61.29%	2.91 (2.11-4.01)	86	0.77
Length of ICU stay, days	8, 15, 53.33%	0.56 (0.35, 0.76)¶	73	**0.01**
Prior presence of CRO	na, 2, na	na	na	na
Presence of ESBL producers	na, 0, na	na	na	na
Presence of MRSA	na, 0, na	na	na	na
Presence of VRE	na, 0, na	na	na	na
Comorbidities				
Chemotherapy	1, 6, 16.67%	1.55 (1.23-1.96)	0	na
Steroid treatment	7, 20, 35.00%	3.07 (1.76-5.37)	85	0.37
Decubitus ulcer	na, 0, na	na	na	na
Diabetes mellitus	6, 48, 12.50%	1.35 (1.15-1.59)	37	0.17
HIV	0, 6, 0.00%	1.85 (0.40-8.63)	58	na
Liver diseases	2, 21, 9.52%	1.14 (0.87-1.50)	25	0.49
COPD	4, 19, 21.05%	1.45 (1.07-1.98)	34	0.20
Malignancy	8, 45, 17.78%	1.36 (1.10-1.69)	56	0.71
Hematologic malignancy	2, 6, 33.33%	1.99 (1.37-2.88)	0	na
Neurological disease	3, 8, 37.50%	1.52 (0.89-2.66)	76	na
Neutropenia	4, 12, 33.33%	1.73 (1.07-2.80)	45	0.75
Renal failure	3, 16, 18.75%	1.46 (1.11-1.90)	27	0.57
Trauma	3, 20, 15.00%	1.19 (0.80-1.79)	66	0.30

Risk Factors	Number (a,b,c)*	Pooled OR (95%CI)	Heterogeneity, I^2 (%)	Publication bias, $P^{§}$
Hypertension	1, 10, 10.00%	1.18 (0.89-1.56)	7	0.32
Heart failure	0, 9, 0.00%	1.41 (0.92-2.16)	0	na
Coronary artery disease	1, 7, 14.29%	1.46 (0.65-3.32)	69	na
Stroke	2, 6, 33.33%	2.66 (1.21-5.86)	83	na
CCI score	2 ,6, 33.33%	0.48 (-0.10, 1.07)¶	95	na
APACHE II score	6, 18, 33.33%	0.20 (0.03, 0.35)¶	70	0.91
SOFA score	1, 8, 12.50%	0.01 (-0.21, 0.23)¶	56	na
Prior invasive procedures/devices				
Blood transfusion	1, 5, 20.00%	1.49 (0.91-2.44)	0	na
Intravenous catheter	22, 43, 51.16%	2.35 (1.86-2.97)	75	0.43
CVC	15, 29, 51.72%	2.07 (1.56-2.75)	79	0.09
Duration of CVC, days	3, 5, 60.00%	0.38 (-0.80, 1.57)¶	96	na
Arterial catheter	1, 9, 11.11%	1.32 (0.93-1.89)	28	na
Dialysis	8, 19, 42.11%	2.21 (1.66-2.96)	43	**<0.01**
Hemodialysis	4, 14, 28.57%	1.88 (1.34-2.64)	38	**<0.01**
Drainage	1, 8, 12.50%	1.70 (0.97-2.98)	64	na
Enteral nutrition	2, 9, 22.22%	1.94 (1.41-2.66)	0	na
Parenteral nutrition	8, 22, 36.36%	1.79 (1.39-2.31)	39	0.29
Endoscopy	na, 4, na	na	na	na
Endotracheal tube	5, 14, 35.71%	1.96 (1.55-2.48)	0	0.34
Gastrostomy	na, 2, na	na	na	na
Mechanical ventilation	23, 34, 67.65%	3.88 (2.76-5.45)	87	0.31
Duration of mechanical ventilation, days	9, 11, 81.82%	0.80 (0.49, 1.11)¶	77	0.36
Nasogastric tube	9, 14, 64.29%	2.88 (1.57-5.28)	92	0.99
Tracheostomy	10, 20, 50.00%	2.59 (1.94-3.48)	61	**0.01**
Transplantation	1, 12, 8.33%	1.47 (1.09-1.97)	0	0.58
Urinary catheter	13, 34, 38.24%	1.87 (1.35-2.59)	81	0.08
Prior antibiotic exposure				
Aminoglycoside	11, 41, 26.83%	1.51 (1.22-1.87)	53	0.24
Amikacin	na, 2, na	na	na	na

Risk Factors	Number (a,b,c)*	Pooled OR (95%CI)	Heterogeneity, I^2 (%)	Publication bias, $P^{§}$
Antifungal	na, 2, na	na	na	na
β-lactam/β-lactamase inhibitor	17, 40, 42.50%	2.18 (1.74-2.73)	62	0.80
AMC	na, 1, na	na	na	na
AMS	na, 2, na	na	na	na
SCF	3, 6, 50.00%	2.70 (1.23-5.94)	52	na
TZP	7, 16, 43.75%	2.35 (1.74-3.17)	33	0.09
Carbapenem	41, 54, 75.93%	4.28 (3.27-5.59)	80	0.79
Duration of carbapenem therapy, days	1, 5, 20.00%	0.19 (-0.08, 0.46)[¶]	68	na
Ertapenem	na, 1, na	na	na	na
Imipenem	4, 7, 57.14%	4.04 (2.15-7.60)	58	na
Meropenem	na, 4, na	na	na	na
Cephalosporin	20, 52, 38.46%	1.82 (1.33-2.50)	85	0.46
Duration of cephalosporin therapy, days	1, 6, 16.67%	-0.06 (-0.26, 0.14)[¶]	67	na
I	1, 5, 20.00%	1.01 (0.48-2.12)	56	na
II	0, 9, 0.00%	0.96 (0.42-2.24)	88	na
III	10, 26, 38.46%	1.56 (1.19-2.05)	65	0.92
IV	5, 17, 29.41%	2.31 (1.43-3.73)	73	0.94
Cefepime	2, 5, 40.00%	3.93 (2.23-6.93)	54	na
I/II	na, 3, na	na	na	na
III/IV	4, 9, 44.44%	1.98 (1.32-2.97)	50	na
Combination therapy	4, 6, 66.67%	3.58 (1.54-8.33)	81	na
Glycopeptide	10, 28, 35.71%	2.22 (1.67-2.95)	60	0.88
Vancomycin	6, 14, 42.86%	2.64 (1.78-3.93)	61	0.69
Clindamycin	na, 2, na	na	na	na
Macrolide	1, 6, 16.67%	1.88 (0.85-4.15)	72	na
Metronidazole	3, 9, 33.33%	1.50 (0.91-2.48)	65	na
Oxazolidinone	na, 2, na	na	na	na
Penicillin	4, 17, 23.53%	1.56 (1.11-2.20)	63	0.38
Extended spectrum penicillin	1, 5, 20.00%	1.46 (0.73-2.92)	47	na
Polymyxin	6, 11, 54.55%	3.00 (1.91-4.72)	49	0.70

Risk Factors	Number (a,b,c)*	Pooled OR (95%CI)	Heterogeneity, I^2 (%)	Publication bias, $P^{\S}$
Fluoroquinolone	8, 27, 29.63%	1.76 (1.12-2.78)	87	0.45
Ciprofloxacin	na, 3, na	na	na	na
Tigecycline	na, 4, na	na	na	na
TMP/SMX	na, 2, na	na	na	na

*, frequency of being a risk factor, frequency of being a candidate risk factor, percentage of being a risk factor (i.e. percentage significant);
¶, standardised mean difference (95% confidence interval);
§, statistically significant results in bold;
na, not applicable; All, infection, colonisation or acquisition; Inf, infection; Col, colonisation; OR (95%CI), odds ratio (95% confidence interval); CRO, carbapenem-resistant organisms; ICU, intensive care unit; ESBL, extended-spectrum beta-lactamases; MRSA, Methicillin-resistant *Staphylococcus aureus*; VRE, Vancomycin-resistant *Enterococci*; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; CCI, Charlson Comorbidity Index; APACHE II, Acute Physiology, Age and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CVC, central venous catheter; AMC, amoxicillin-clavulanate; AMS, ampicillin-sulbactam; SCF, cefoperazone-sulbactam; TZP, piperacillin-tazobactam; I, first generation cephalosporins; II, second generation cephalosporins; III, third generation cephalosporins; IV, fourth generation cephalosporins; TMP-SMX, trimethoprim sulfamethoxazole.

Appendix 2-8. Evaluation of two estimation methods of standard deviation

No	Study	Risk factors	Median (Range)		SD-Wan (Wan et al., 2014)		SD-Walter (Walter and Yao, 2007)		SMD (95%CI)-Wan (Wan et al., 2014)[§]	SMD (95%CI)-Walter (Walter and Yao, 2007)[§]
			Cases	Controls	Cases	Controls	Cases	Controls		
1	(Akgul et al., 2016)	Age, years	66 (19-94)	58 (21-87)	15.119	13.207	15.038	13.134	0.37 (0.09, 0.65)	0.37 (0.09, 0.65)
2	(Al Otaibi and Al-Hulaily, 2012)	Age, years	50 (0.1-98)	47.5 (0-94)	21.171	16.274	21.151	16.260	0.13 (-0.14, 0.41)	0.13 (-0.14, 0.41)
3	(Armand-Lefevre et al., 2013)	Age, years	58.3 (30-86)	59.9 (37-86)	13.243	11.587	13.250	11.593	-0.20 (-0.67, 0.26)	-0.20 (-0.67, 0.26)
4	(Armand-Lefevre et al., 2013)	Age, years	57.3 (30-74)	60.9 (37-80)	11.521	11.259	11.546	11.283	-0.44 (-1.03, 0.16)	-0.43 (-1.03, 0.16)
5	(Barron et al., 2016)	Age, years	57 (26-77)	55 (22-88)	13.496	14.309	13.525	14.296	-0.05 (-0.55, 0.45)	-0.05 (-0.55, 0.45)
6	(Borer et al., 2012)	Age, years	72 (19-91)	72.5 (21-95)	16.547	15.187	16.488	15.126	-0.11 (-0.48, 0.26)	-0.11 (-0.48, 0.26)
7	(Borer et al., 2012)	Age, years	72.5 (21-59)	72 (19-91)	6.331	11.996	6.332	11.997	-0.76 (-0.89, -0.62)	-0.76 (-0.89, -0.62)
8	(Candevir Ulu et al., 2015)	Age, years	38 (0-83)	8 (0-86)	18.698	19.103	18.650	19.040	0.75 (0.34, 1.16)	0.75 (0.34, 1.16)
9	(Chitnis et al., 2012)	Age, years	75 (43-88)	68 (43-98)	10.759	13.149	10.773	13.167	0.08 (-0.39, 0.56)	0.08 (-0.39, 0.56)
10	(Cunha et al., 2016)	Age, years	72 (38-85)	76 (47-98)	17.223	14.934	17.390	14.994	-0.46 (-1.38, 0.46)	-0.46 (-1.38, 0.46)
11	(Fortaleza et al., 2006)	Age, years	45 (0-88)	44 (0-90)	17.421	16.304	17.371	16.265	0.00 (-0.23, 0.23)	0.00 (-0.23, 0.23)
12	(Freire et al., 2015)	Age, years	59 (21-73)	47 (6-79)	13.237	11.238	13.208	11.238	0.73 (0.33, 1.13)	0.73 (0.33, 1.13)
13	(Freire et al., 2016a)	Age, years	56 (18-69)	47 (22-72)	12.874	11.070	12.862	11.040	0.23 (-0.24, 0.71)	0.23 (-0.24, 0.71)
14	(Freire et al., 2016b)	Age, years	52 (14-71)	54 (16-52)	11.135	6.559	11.126	6.535	0.38 (0.15, 0.61)	0.38 (0.15, 0.61)
15	(Freire et al., 2016b)	Age, years	52 (17-70)	54 (14-72)	11.660	10.036	11.639	10.029	-0.07 (-0.36, 0.22)	-0.07 (-0.36, 0.22)
16	(Freire et al., 2016c)	Age, years	50.0 (16-70)	53.5 (18-73)	11.142	11.156	11.102	11.094	-0.27 (-0.57, 0.03)	-0.27 (-0.57, 0.03)
17	(Freire et al., 2016c)	Age, years	51.5 (16-70)	53 (16-73)	11.808	10.918	11.794	10.910	-0.13 (-0.44, 0.18)	-0.13 (-0.44, 0.18)
18	(Furtado et al., 2009)	Age, years	50 (16-92)	54 (14-93)	16.303	14.610	16.279	14.577	-0.12 (-0.40, 0.17)	-0.12 (-0.40, 0.17)
19	(Garlantezec et al., 2011)	Age, years	62 (50-79)	64 (16-86)	12.291	17.398	12.470	17.402	0.33 (-0.62, 1.29)	0.33 (-0.62, 1.29)
20	(Gregory et al., 2010)	Age, years	70 (52-86)	62 (24-96)	8.583	18.175	8.575	18.158	0.59 (0.03, 1.15)	0.59 (0.03, 1.15)
21	(Gregory et al., 2010)	Age, years	70 (52-86)	70 (21-96)	8.583	18.932	8.575	18.915	0.35 (-0.20, 0.90)	0.35 (-0.20, 0.90)
22	(Kaase et al., 2016)	Age, years	60 (4-86)	66 (0-91)	21.470	20.826	21.517	20.775	-0.15 (-0.67, 0.36)	-0.15 (-0.67, 0.36)
23	(Kofteridis et al., 2014)	Age, years	79 (28-101)	75 (18-100)	15.008	15.398	14.950	15.372	0.31 (0.04, 0.58)	0.31 (0.04, 0.58)
24	(Lee et al., 2016)	Age, years	68 (31-90)	66 (42-88)	13.880	10.822	13.877	10.819	-0.10 (-0.56, 0.36)	-0.10 (-0.56, 0.36)
25	(Lee et al., 2016)	Age, years	68 (31-90)	65 (16-91)	13.880	17.644	13.877	17.640	0.31 (-0.15, 0.77)	0.31 (-0.15, 0.77)
26	(Marchaim et al., 2008)	Age, years	64 (45-83)	73.5 (44-94)	11.620	11.824	11.666	11.830	-0.61 (-1.27, 0.06)	-0.60 (-1.27, 0.06)

No	Study	Risk factors	Median (Range)		SD-Wan (Wan et al., 2014)		SD-Walter (Walter and Yao, 2007)		SMD (95%CI)-Wan (Wan et al., 2014)§	SMD (95%CI)-Walter (Walter and Yao, 2007)§
			Cases	Controls	Cases	Controls	Cases	Controls		
27	(Mouloudi et al., 2014)	Age, years	54 (44-66)	55 (26-66)	6.124	9.563	6.138	9.576	0.46 (-0.13, 1.05)	0.46 (-0.13, 1.05)
28	(Mouloudi et al., 2010)	Age, years	56 (17-81)	50.5 (15-78)	17.566	16.495	17.600	16.531	0.23 (-0.39, 0.86)	0.23 (-0.39, 0.86)
29	(Mouloudi et al., 2010)	Age, years	47 (25-79)	50.5 (15-78)	14.629	16.495	14.634	16.531	0.06 (-0.55, 0.68)	0.06 (-0.55, 0.68)
30	(Nouer et al., 2005)	Age, years	48.5 (11-88)	50 (12-97)	22.547	21.126	22.638	21.131	-0.15 (-0.79, 0.49)	-0.15 (-0.79, 0.49)
31	(Ny et al., 2015)	Age, years	70 (36-95)	78 (29-95)	13.243	14.814	13.204	14.771	-0.16 (-0.56, 0.24)	-0.16 (-0.56, 0.24)
32	(Ny et al., 2015)	Age, years	69 (41-90)	62 (29-91)	12.966	16.406	12.995	16.442	0.41 (-0.20, 1.03)	0.41 (-0.20, 1.03)
33	(Ny et al., 2015)	Age, years	71 (36-95)	80 (36-95)	14.775	14.775	14.774	14.774	-0.30 (-0.84, 0.24)	-0.30 (-0.84, 0.24)
34	(Poole et al., 2016)	Age, years	75 (35-98)	68 (17-99)	15.903	13.336	15.889	13.364	0.58 (0.18, 0.97)	0.57 (0.18, 0.97)
35	(Sheng et al., 2010)	Age, years	61 (5-93)	64 (7-88)	21.566	19.850	21.560	19.845	-0.04 (-0.54, 0.47)	-0.04 (-0.54, 0.47)
36	(Sheng et al., 2010)	Age, years	67 (<1-89)	61 (10-97)	18.052	17.485	17.951	17.391	-0.08 (-0.37, 0.20)	-0.08 (-0.37, 0.20)
37	(Sheng et al., 2010)	Age, years	61 (<1-93)	57 (8-92)	19.950	18.162	19.921	18.144	0.01 (-0.34, 0.37)	0.01 (-0.34, 0.37)
38	(Teo et al., 2012)	Age, years	55 (22-91)	65 (18-100)	17.026	16.742	17.029	16.662	-0.37 (-0.79, 0.05)	-0.37 (-0.79, 0.05)
39	(Tumbarello et al., 2014)	Age, years	70 (57-78)	66 (49-77)	3.382	4.237	3.392	4.237	1.07 (0.97, 1.17)	1.07 (0.97, 1.17)
40	(Tumbarello et al., 2014)	Age, years	68.5 (56-78)	66 (50-77)	3.698	4.244	3.703	4.246	0.74 (0.62, 0.86)	0.74 (0.62, 0.86)
41	(Yang et al., 2016a)	Age, years	85 (80-87)	74 (59-84)	1.194	3.981	1.196	3.993	3.46 (3.27, 3.65)	3.45 (3.26, 3.64)
42	(Zhang et al., 2011)	Age, years	0.1 (0-16)	0.2 (0-15)	3.871	3.210	3.891	3.204	0.06 (-0.36, 0.49)	0.06 (-0.36, 0.49)
43	(Valderrama et al., 2016)	Age, years	60 (22-88)	64.5 (19-91)	15.168	13.957	15.114	13.954	-0.16 (-0.51, 0.19)	-0.16 (-0.51, 0.19)
44	(Villegas et al., 2016)	Age, years	59 (0.1-91)	60 (0.1-99)	11.379	14.571	11.404	14.512	-0.75 (-1.24, -0.26)	-0.75 (-1.24, -0.26)
45	(Akgul et al., 2016)	Length of hospitalisation, days	31 (4-160)	16 (4-150)	31.446	29.216	31.278	29.054	0.33 (0.05, 0.61)	0.33 (0.05, 0.61)
46	(Armand-Lefevre et al., 2013)	Length of hospitalisation, days	13.5 (3-52)	12.5 (3-52)	11.587	11.587	11.593	11.593	0.04 (-0.42, 0.50)	0.04 (-0.42, 0.50)
47	(Armand-Lefevre et al., 2013)	Length of hospitalisation, days	13 (4-37)	13 (3-37)	8.640	8.902	8.659	8.922	0.03 (-0.56, 0.62)	0.03 (-0.56, 0.62)
48	(Candevir Ulu et al., 2015)	Length of hospitalisation, days	19 (1-280)	11 (3-682)	62.853	150.827	62.691	150.331	-0.82 (-1.23, -0.41)	-0.82 (-1.24, -0.41)
49	(Chitnis et al., 2012)	Length of hospitalisation, days	23 (6-71)	18 (5-69)	15.540	15.301	15.561	15.322	0.21 (-0.27, 0.69)	0.21 (-0.27, 0.68)
50	(Daikos et al., 2010)	Length of hospitalisation, days	21 (0-299)	8 (0-246)	63.519	48.515	63.328	48.413	0.36 (0.05, 0.67)	0.36 (0.06, 0.67)
51	(Freire et al., 2016a)	Length of hospitalisation, days	10 (1-43)	18 (3-160)	10.602	34.760	10.592	34.666	-1.15 (-1.65, -0.64)	-1.15 (-1.66, -0.64)
52	(Furtado et al., 2009)	Length of hospitalisation, days	25 (4-107)	15 (2-129)	22.095	23.487	22.063	23.434	0.00 (-0.29, 0.29)	0.00 (-0.29, 0.29)
53	(Giuffre et al., 2013)	Length of hospitalisation, days	12 (4-135)	12 (4-118)	42.350	25.982	42.575	25.924	0.14 (-0.55, 0.83)	0.14 (-0.55, 0.83)

No	Study	Risk factors	Median (Range)		SD-Wan (Wan et al., 2014)		SD-Walter (Walter and Yao, 2007)		SMD (95%CI)-Wan (Wan et al., 2014)§	SMD (95%CI)-Walter (Walter and Yao, 2007)§
			Cases	Controls	Cases	Controls	Cases	Controls		
54	(Gregory et al., 2010)	Length of hospitalisation, days	14 (6-109)	8 (3-45)	26.000	10.602	25.977	10.592	0.98 (0.40, 1.56)	0.98 (0.40, 1.56)
55	(Mouloudi et al., 2010)	Length of hospitalisation, days	13 (7-36)	12 (5-52)	7.959	12.306	7.975	12.333	-0.28 (-0.90, 0.35)	-0.28 (-0.90, 0.35)
56	(Mouloudi et al., 2010)	Length of hospitalisation, days	18 (6-29)	12 (5-52)	6.231	12.306	6.233	12.333	-0.25 (-0.86, 0.37)	-0.25 (-0.86, 0.37)
57	(Nouer et al., 2005)	Length of hospitalisation, days	21.5 (1-69)	17 (0-89)	19.912	22.120	19.992	22.125	-0.11 (-0.76, 0.53)	-0.11 (-0.76, 0.53)
58	(Ny et al., 2015)	Length of hospitalisation, days	13 (4-211)	9 (3-71)	46.462	15.263	46.327	15.218	1.07 (0.64, 1.50)	1.07 (0.64, 1.50)
59	(Ny et al., 2015)	Length of hospitalisation, days	14 (14-105)	13 (5-55)	24.080	13.231	24.133	13.260	0.77 (0.14, 1.40)	0.77 (0.14, 1.40)
60	(Ny et al., 2015)	Length of hospitalisation, days	10 (4-211)	6 (3-71)	51.839	17.029	51.647	16.966	0.95 (0.39, 1.52)	0.96 (0.39, 1.52)
61	(Teo et al., 2012)	Length of hospitalisation, days	17 (1-85)	6 (1-40)	20.728	7.963	20.731	7.925	1.34 (0.89, 1.80)	1.35 (0.89, 1.80)
62	(Wannaro et al., 2012)	Length of hospitalisation, days	34 (2-105)	36 (13-57)	30.784	14.724	30.900	14.828	0.31 (-0.55, 1.17)	0.31 (-0.55, 1.16)
63	(Zarakolu et al., 2016)	Length of hospitalisation, days	68 (21-432)	48 (1-524)	143.285	92.298	144.261	92.215	-0.08 (-0.79, 0.62)	-0.08 (-0.79, 0.62)
64	(Valderrama et al., 2016)	Length of hospitalisation, days	26 (3-115)	16 (1-161)	25.740	31.017	25.670	31.008	-0.20 (-0.55, 0.15)	-0.20 (-0.55, 0.15)
65	(Sanchez-Romero et al., 2012)	Length of hospitalisation, days	18 (5-63)	7 (3-110)	12.721	23.468	12.702	23.433	-0.30 (-0.68, 0.07)	-0.30 (-0.68, 0.07)
66	(Sbrana et al., 2016)	Length of hospitalisation, days	9 (7-14)	10 (8-14)	1.715	1.297	1.715	1.296	-0.51 (-0.96, -0.07)	-0.51 (-0.96, -0.07)
67	(Sheng et al., 2010)	Length of hospitalisation, days	40 (6-214)	24 (5-179)	50.973	42.641	50.960	42.630	0.36 (-0.15, 0.87)	0.36 (-0.15, 0.87)
68	(Sheng et al., 2010)	Length of hospitalisation, days	48 (3-264)	21 (6-367)	52.940	72.554	52.644	72.164	-0.20 (-0.49, 0.08)	-0.20 (-0.49, 0.08)
69	(Sheng et al., 2010)	Length of hospitalisation, days	49 (3-264)	23 (5-151)	55.989	31.567	55.906	31.536	0.89 (0.51, 1.26)	0.89 (0.52, 1.26)
70	(Qureshi et al., 2014)	Length of hospitalisation, days	2 (1-79)	8.5 (1-346)	20.640	70.803	20.686	70.518	-1.08 (-1.58, -0.58)	-1.09 (-1.59, -0.59)
71	(Freire et al., 2016b)	Length of ICU stay, days	10.5 (1-46)	7.0 (1-102)	9.900	17.475	9.882	17.465	-0.74 (-1.03, -0.44)	-0.74 (-1.03, -0.44)
72	(Garlantezec et al., 2011)	Length of ICU stay, days	14 (6-17)	5 (2-25)	4.662	5.716	4.730	5.7178	0.61 (-0.35, 1.58)	0.61 (-0.35, 1.57)
73	(Gregory et al., 2010)	Length of ICU stay, days	4 (0-42)	0 (0-37)	10.602	9.340	10.592	9.331	0.32 (-0.23, 0.87)	0.32 (-0.23, 0.87)
74	(Valderrama et al., 2016)	Length of ICU stay, days	12.5 (0-106)	8 (0-161)	24.361	31.210	24.274	31.202	-0.39 (-0.74, -0.03)	-0.39 (-0.74, -0.03)
75	(Teo et al., 2012)	CCI score	4 (0-13)	4 (0-13)	3.208	1.852	3.255	2.642	0.00 (-0.42, 0.42)	0.00 (-0.42, 0.42)
76	(Qureshi et al., 2014)	CCI score	2 (0-7)	4 (0-13)	2.654	2.668	1.856	2.657	-0.93 (-1.43, -0.44)	-0.98 (-1.48, -0.49)
77	(Furtado et al., 2009)	APACHE II score	20 (4-28)	13 (0-31)	5.148	5.733	5.141	5.720	0.67 (0.38, 0.96)	0.67 (0.38, 0.96)
78	(Mouloudi et al., 2014)	APACHE II score	14 (10-23)	15 (7-28)	3.619	5.021	3.627	5.027	-0.21 (-0.80, 0.37)	-0.21 (-0.80, 0.37)

No	Study	Risk factors	Median (Range)		SD-Wan (Wan et al., 2014)		SD-Walter (Walter and Yao, 2007)		SMD (95%CI)-Wan (Wan et al., 2014)§	SMD (95%CI)-Walter (Walter and Yao, 2007)§
			Cases	Controls	Cases	Controls	Cases	Controls		
79	(Mouloudi et al., 2010)	APACHE II score	20 (4-33)	17.5 (10-37)	7.959	7.069	7.975	7.085	-0.16 (-0.79, 0.46)	-0.16 (-0.79, 0.46)
80	(Mouloudi et al., 2010)	APACHE II score	26 (10-36)	17.5 (10-37)	7.043	7.069	7.046	7.085	0.56 (-0.07, 1.18)	0.56 (-0.07, 1.18)
81	(Ny et al., 2015)	APACHE II score	22 (7-38)	14 (2-39)	6.958	8.305	6.938	8.281	0.65 (0.24, 1.06)	0.65 (0.24, 1.06)
82	(Ny et al., 2015)	APACHE II score	24 (7-38)	19 (6-39)	8.203	8.732	8.221	8.752	0.29 (-0.32, 0.90)	0.29 (-0.32, 0.90)
83	(Ny et al., 2015)	APACHE II score	17 (7-33)	11 (2-27)	6.511	6.261	6.510	6.260	0.89 (0.33, 1.45)	0.89 (0.33, 1.45)
84	(Teo et al., 2012)	APACHE II score	15 (2-30)	9 (0-32)	6.909	6.533	7.314	6.502	0.45 (0.03, 0.87)	0.44 (0.02, 0.87)
85	(Valderrama et al., 2016)	APACHE II score	14.5 (0-29)	11.5 (0-33)	6.665	6.397	6.641	6.395	0.08 (-0.27, 0.43)	0.08 (-0.27, 0.43)
86	(Freire et al., 2016a)	SOFA score	4 (1-6)	4 (0-7)	1.262	1.550	1.261	1.546	0.00 (-0.47, 0.47)	0.00 (-0.47, 0.47)
87	(Mouloudi et al., 2014)	SOFA score	10.5 (7-14)	9 (6-13)	1.949	1.674	1.953	1.676	0.70 (0.10, 1.30)	0.69 (0.10, 1.29)
88	(Furtado et al., 2009)	Duration of MV, days	15 (2-60)	5 (0-39)	12.442	7.213	12.424	7.196	1.21 (0.91, 1.52)	1.21 (0.91, 1.52)
89	(Garlantezec et al., 2011)	Duration of MV, days	11 (6-16)	1 (0-32)	4.238	7.953	4.300	7.955	0.32 (-0.63, 1.28)	0.32 (-0.63, 1.28)
90	(Thatrimontrichai et al., 2016)	Duration of MV, days	9 (3-69)	8 (4-26)	14.158	5.600	14.137	5.588	0.88 (0.40, 1.36)	0.88 (0.40, 1.36)
91	(Thatrimontrichai et al., 2016)	Duration of MV, days	9 (3-69)	16 (5-61)	14.158	16.737	14.137	16.800	-0.14 (-0.73, 0.46)	-0.14 (-0.73, 0.46)
92	(Freire et al., 2016c)	Duration of CVC, days	8 (1-68)	4 (1-54)	13.825	10.750	13.775	10.690	0.45 (0.14, 0.75)	0.45 (0.14, 0.75)
93	(Freire et al., 2016c)	Duration of CVC, days	10 (1-49)	6 (1-91)	10.496	17.238	10.483	17.226	-0.54 (-0.86, -0.23)	-0.54 (-0.86, -0.23)
94	(Freire et al., 2016a)	Duration of UC, days	6 (0-25)	5 (0-29)	6.311	6.421	6.305	6.403	-0.08 (-0.55, 0.39)	-0.08 (-0.55, 0.39)
95	(Freire et al., 2016c)	Duration of UC, days	7 (1-28)	5 (1-47)	5.571	9.330	5.5512	9.278	-0.48 (-0.78, -0.18)	-0.48 (-0.79, -0.18)
96	(Freire et al., 2016c)	Duration of UC, days	7.5 (3-35)	6.5 (3-56)	6.997	10.151	6.989	10.144	-0.51 (-0.82, -0.19)	-0.51 (-0.82, -0.19)
97	(Freire et al., 2016c)	Duration of carbapenem therapy, days	6 (0-40)	0 (0-72)	8.747	13.791	8.736	13.781	-0.40 (-0.71, -0.08)	-0.40 (-0.71, -0.08)
98	(Teo et al., 2012)	Duration of carbapenem therapy, days	0 (0-25)	0 (0-9)	6.169	1.838	6.170	1.829	1.15 (0.71, 1.60)	1.15 (0.71, 1.60)
99	(Freire et al., 2016c)	Duration of cephalosporin therapy, days	1.5 (0-15)	2 (0-21)	3.280	4.022	3.276	4.019	-0.46 (-0.77, -0.14)	-0.46 (-0.77, -0.14)
100	(Teo et al., 2012)	Duration of cephalosporin therapy, days	3 (0-14)	0 (0-15)	3.455	3.063	3.455	3.048	0.39 (-0.03, 0.82)	0.39 (-0.03, 0.82)
101	(Teo et al., 2012)	Duration of cephalosporin therapy, days	0 (0-11)	0 (0-6)	2.714	1.225	2.715	1.219	0.72 (0.29, 1.15)	0.29, 1.16)

§ different results of Wan's and Walter's methods in bold;

SD-Wan, standard deviation estimated from Wan's method; SD-Walter, standard deviation estimated from Walter's method; SMD (95%CI)-Wan, standardised mean difference (95% confidence interval) calculated with standard deviation estimated from Wan's method; SMD (95%CI)-Walter, standardised mean difference calculated with standard deviation estimated from Walter's method; ICU, intensive care unit; CCI, Charlson Comorbidity Index; APACHE II, Acute Physiology, Age and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; MV, mechanical ventilation; CVC, central venous catheter; UC, urinary catheter.

Appendix 2-9. Sensitivity analysis of risk factors for carbapenem-resistant organisms (CRO) presence, infection and colonisation when studies of low quality were excluded or included

(1) Sensitivity analysis of risk factors for CRO presence

Risk Factors#	Excluding studies of low quality				Including studies of low quality			
	Number (a, b, c)*	Rank¶	Pooled OR (95%CI)	Rank§	Number (a, b, c)*	Rank¶	Pooled OR (95%CI)	Rank§
Prior presence of CRO	6, 6, 100.00%	1	8.24 (4.17-16.29)	1	6, 7, 85.71%	1	7.14 (3.68-13.85)	1
Imipenem	13, 16, 81.25%	2	7.04 (4.34-11.41)	2	20, 26, 76.92%	2	6.60 (4.67-9.33)	2
Carbapenem	81, 105, 77.14%	4	4.64 (3.83-5.62)	3	133, 173, 76.88%	2	4.79 (4.17-5.51)	3
Meropenem	7, 10, 70.00%	6	4.17 (2.74-6.36)	4	9, 12, 75.00%	4	4.33 (3.03-6.19)	5
Tigecycline	3, 9, 33.33%	32	3.89 (2.08-7.27)	5	4, 12, 33.33%	34	3.51 (1.84-6.68)	7
Presence of ESBL producers	4, 8, 50.00%	15	3.88 (2.14-7.06)	6	4, 9, 44.44%	22	3.97 (2.32-6.81)	6
Vancomycin	21, 28, 75.00%	5	3.65 (2.77-4.80)	7	29, 46, 63.04%	8	3.10 (2.46-3.91)	11
Mechanical ventilation	42, 64, 65.63%	9	3.63 (2.90-4.56)	8	63, 98, 64.29%	7	3.42 (2.87-4.09)	8
Decubitus ulcer	4, 8, 50.00%	15	3.52 (1.83-6.76)	9	5, 10, 50.00%	14	3.08 (1.90-4.99)	12
Oxazolidinone	7, 10, 70.00%	6	3.50 (2.49-4.92)	10	11, 17, 64.71%	6	4.40 (3.08-6.29)	4
Nasogastric tube	13, 22, 59.09%	10	3.47 (2.33-5.19)	11	22, 36, 61.11%	9	3.33 (2.50-4.44)	9
ICU stay	46, 78, 58.97%	11	3.31 (2.64-4.15)	12	69, 114, 60.53%	10	3.26 (2.73-3.90)	10
Ertapenem	2, 5, 40.00%	25	3.31 (1.73-6.35)	12	2, 7, 28.57%	44	2.81 (1.68-4.71)	16
Glycopeptide	35, 52, 67.31%	8	3.23 (2.63-3.96)	14	48, 82, 58.54%	12	2.95 (2.48-3.50)	14
Combination therapy	7, 9, 77.78%	3	3.21 (1.98-5.21)	15	8, 11, 72.73%	5	2.94 (1.96-4.43)	15
Cefepime	6, 11, 54.55%	12	2.98 (1.66-5.36)	16	9, 19, 47.37%	19	2.55 (1.61-4.04)	19
Endotracheal tube	5, 16, 31.25%	36	2.76 (1.87-4.07)	17	6, 21, 28.57%	44	2.40 (1.78-3.23)	24
TMP-SMX	3, 8, 37.50%	27	2.72 (1.30-5.69)	18	4, 9, 44.44%	22	2.55 (1.43-4.54)	19
Cephalosporin-IV	13, 32, 40.63%	24	2.69 (1.91-3.80)	19	16, 42, 38.10%	29	2.44 (1.79-3.32)	23
Arterial catheter	4, 11, 36.36%	30	2.69 (1.50-4.82)	19	7, 19, 36.84%	30	2.26 (1.52-3.36)	27
Intravenous catheter	36, 69, 52.17%	13	2.66 (2.15-3.29)	21	59, 124, 47.58%	18	2.52 (2.16-2.95)	22
Tracheostomy	12, 26, 46.15%	21	2.63 (1.96-3.53)	22	24, 55, 43.64%	24	2.55 (2.09-3.09)	19
Polymyxin	4, 15, 26.67%	45	2.42 (1.73-3.39)	23	9, 23, 39.13%	27	2.97 (2.02-4.37)	13
Am kacin	3, 7, 42.86%	22	2.41 (1.29-4.50)	24	6, 10, 60.00%	11	2.60 (1.75-3.86)	18
CVC	25, 51, 49.02%	18	2.38 (1.86-3.05)	25	36, 89, 40.45%	26	2.25 (1.87-2.70)	28
β-lactam/β-lactamase inhibitor	36, 70, 51.43%	14	2.37 (2.03-2.77)	26	53, 104, 50.96%	13	2.32 (2.03-2.64)	26
TZP	14, 30, 46.67%	19	2.36 (1.88-2.96)	27	19, 45, 42.22%	25	2.15 (1.79-2.58)	31

Risk Factors[#]	Excluding studies of low quality				Including studies of low quality			
	Number (a, b, c)[*]	Rank[¶]	Pooled OR (95%CI)	Rank[§]	Number (a, b, c)[*]	Rank[¶]	Pooled OR (95%CI)	Rank[§]
Enteral nutrition	4, 13, 30.77%	39	2.36 (1.61-3.47)	27	5, 20, 25%	53	2.00 (1.47-2.72)	39
Hemodialysis	6, 20, 30.00%	41	2.33 (1.73-3.13)	29	8, 30, 26.67%	52	1.98 (1.52-2.59)	41
Dialysis	13, 36, 36.11%	31	2.30 (1.87-2.82)	30	18, 55, 32.73%	37	2.12 (1.76-2.56)	33
Hospital transfer	7, 15, 46.67%	19	2.26 (1.70-2.99)	31	11, 22, 50.00%	14	2.15 (1.79-2.59)	31
Urinary catheter	30, 72, 41.67%	23	2.26 (1.80-2.83)	31	54, 113, 47.79%	17	2.41 (2.05-2.83)	25
Blood transfusion	2, 10, 20.00%	52	2.19 (1.47-3.26)	33	3, 14, 21.43%	55	1.84 (1.26-2.67)	46
Ciprofloxacin	2, 10, 20.00%	52	2.13 (1.59-2.87)	34	5, 15, 33.33%	34	2.18 (1.62-2.94)	30
Neutropenia	3, 10, 30.00%	41	2.12 (1.55-2.91)	35	7, 23, 30.43%	42	1.78 (1.32-2.38)	47
Drainage	6, 20, 30.00%	41	2.10 (1.61-2.73)	36	9, 32, 28.13%	48	2.10 (1.65-2.68)	35
Prior hospitalisation	15, 40, 37.50%	27	1.98 (1.59-2.48)	37	21, 62, 33.87%	33	1.87 (1.56-2.25)	44
Renal failure	7, 27, 25.93%	46	1.93 (1.56-2.39)	38	14, 47, 29.79%	43	1.73 (1.44-2.09)	50
Steroid treatment	7, 28, 25.00%	47	1.93 (1.45-2.56)	38	14, 45, 31.11%	40	2.06 (1.62-2.61)	38
Aminoglycoside	22, 66, 33.33%	32	1.91 (1.60-2.28)	40	40, 116, 34.48%	32	1.86 (1.62-2.14)	45
Endoscopy	5, 10, 50.00%	15	1.90 (1.36-2.66)	41	8, 17, 47.06%	20	2.10 (1.58-2.79)	35
Cephalosporin	33, 90, 36.67%	29	1.86 (1.53-2.27)	42	55, 153, 35.95%	31	1.76 (1.52-2.02)	48
Fluoroquinolone	22, 66, 33.33%	32	1.83 (1.46-2.31)	43	39, 102, 38.24%	28	1.97 (1.68-2.32)	42
Penicillin	11, 35, 31.43%	35	1.81 (1.37-2.40)	44	18, 58, 31.03%	41	1.90 (1.55-2.33)	43
Metronidazole	8, 26, 30.77%	39	1.80 (1.43-2.27)	45	11, 35, 31.43%	39	1.99 (1.52-2.61)	40
Extended spectrum penicillin	3, 13, 23.08%	50	1.80 (1.24-2.61)	45	7, 21, 33.33%	34	2.07 (1.46-2.94)	37
Cephalosporin-III/IV	4, 10, 40.00%	25	1.77 (1.15-2.72)	47	8, 17, 47.06%	20	2.12 (1.47-3.08)	33
Parenteral nutrition	9, 30, 30.00%	41	1.77 (1.39-2.25)	47	17, 53, 32.08%	38	1.75 (1.47-2.08)	49
SCF	1, 5, 20.00%	52	1.73 (0.95-3.15)	49	5, 10, 50%	14	2.71 (1.50-4.91)	17
Stroke	1, 12, 8.33%	67	1.66 (1.05-2.64)	50	2, 20, 10%	65	1.50 (1.04-2.17)	57
Gastrostomy	1, 9, 11.11%	63	1.60 (1.01-2.54)	51	4, 17, 23.53%	54	2.25 (1.39-3.66)	28
Neurological disease	4, 21, 19.05%	56	1.58 (1.27-1.97)	52	9, 33, 27.27%	50	1.49 (1.18-1.87)	60
Hematologic malignancy	5, 16, 31.25%	36	1.57 (1.12-2.18)	53	7, 25, 28%	49	1.58 (1.22-2.05)	54
Heart failure	2, 27, 7.41%	68	1.57 (1.31-1.88)	53	3, 43, 6.98%	71	1.50 (1.29-1.75)	57
Transplantation	5, 30, 16.67%	57	1.53 (1.15-2.04)	55	9, 44, 20.45%	56	1.70 (1.33-2.16)	51
Cephalosporin-III	10, 43, 23.26%	49	1.52 (1.22-1.87)	56	18, 63, 28.57%	44	1.56 (1.31-1.87)	55
COPD	9, 29, 31.03%	38	1.50 (1.23-1.82)	57	13, 46, 28.26%	47	1.53 (1.27-1.85)	56
Macrolide	0, 12, 0.00%	70	1.48 (1.04-2.11)	58	1, 16, 6.25%	72	1.67 (1.15-2.43)	52
Diabetes mellitus	12, 87, 13.79%	62	1.42 (1.29-1.55)	59	20, 149, 13.42%	62	1.36 (1.25-1.47)	61

Risk Factors[#]	Excluding studies of low quality				Including studies of low quality			
	Number (a, b, c)[*]	Rank[¶]	Pooled OR (95%CI)	Rank[§]	Number (a, b, c)[*]	Rank[¶]	Pooled OR (95%CI)	Rank[§]
Liver diseases	4, 45, 8.89%	66	1.40 (1.12-1.75)	60	8, 75, 10.67%	64	1.34 (1.14-1.58)	62
AMS	1, 6, 16.67%	57	1.39 (0.80-2.41)	61	2, 11, 18.18%	58	1.26 (0.82-1.94)	64
Clindamycin	1, 9, 11.11%	63	1.39 (0.89-2.15)	61	2, 11, 18.18%	58	1.65 (1.04-2.61)	53
Hypertension	2, 12, 16.67%	57	1.33 (1.03-1.71)	63	2, 23, 8.7%	68	1.24 (1.07-1.45)	65
Chemotherapy	3, 14, 21.43%	51	1.32 (0.78-2.25)	64	3, 17, 17.65%	60	1.23 (0.75-2.02)	66
Trauma	4, 24, 16.67%	57	1.32 (0.90-1.93)	64	8, 43, 18.6%	57	1.50 (1.15-1.95)	57
Age (>65yrs)	1, 5, 20.00%	52	1.27 (0.70-2.30)	66	1, 9, 11.11%	63	1.11 (0.75-1.63)	70
Malignancy	11, 73, 15.07%	61	1.22 (1.07-1.39)	67	18, 124, 14.52%	61	1.18 (1.05-1.33)	67
AMC	2, 8, 25.00%	47	1.20 (0.51-2.83)	68	3, 11, 27.27%	50	1.29 (0.70-2.35)	63
Gender-male	11, 123, 8.94%	65	1.16 (1.06-1.26)	69	19, 217, 8.76%	67	1.12 (1.06-1.20)	69
HIV	0, 20, 0.00%	70	1.09 (0.76-1.58)	70	0, 26, 0%	73	1.10 (0.76-1.58)	71
Coronary artery disease	0, 9, 0.00%	70	1.07 (0.82-1.39)	71	1, 14, 7.14%	70	1.16 (0.83-1.62)	68
Cephalosporin-II	1, 17, 5.88%	69	0.94 (0.49-1.81)	72	2, 21, 9.52%	66	1.06 (0.59-1.91)	72
Cephalosporin-I/II	0, 8, 0.00%	70	0.70 (0.38-1.29)	73	0, 11, 0%	73	0.91 (0.58-1.43)	73
Cephalosporin-I	0, 9, 0.00%	70	0.63 (0.35-1.13)	74	1, 12, 8.33%	69	0.73 (0.42-1.26)	74

(2) Sensitivity analysis of risk factors for CRO infection

Risk Factors[#]	Excluding studies of low quality				Including studies of low quality			
	Number (a, b, c)[*]	Rank[¶]	Pooled OR (95%CI)	Rank[§]	Number (a, b, c)[*]	Rank[¶]	Pooled OR (95%CI)	Rank[§]
Prior presence of CRO	5, 6, 83.33%	2	5.82 (3.03-11.20)	1	5, 6, 83.33%	1	5.82 (3.03-11.20)	1
Decubitus ulcer	4, 5, 80.00%	3	5.08 (1.98-13.05)	2	4, 5, 80.00%	2	5.08 (1.98-13.05)	2
Carbapenem	47, 63, 74.60%	4	3.94 (3.02-5.14)	3	77, 102, 75.49%	4	4.34 (3.60-5.24)	3
Mechanical ventilation	31, 46, 67.39%	5	3.70 (2.80-4.90)	4	48, 70, 68.57%	5	3.77 (3.03-4.68)	5
Combination therapy	7, 8, 87.50%	1	3.37 (1.99-5.72)	5	8, 10, 80.00%	2	3.04 (1.96-4.71)	6
Imipenem	3, 6, 50.00%	10	3.25 (1.49-7.10)	6	8, 14, 57.14%	8	4.24 (2.66-6.78)	4
ICU stay	26, 42, 61.90%	6	2.92 (2.19-3.88)	7	44, 70, 62.86%	6	3.03 (2.46-3.73)	7
Nasogastric tube	8, 13, 61.54%	7	2.92 (1.68-5.05)	7	11, 19, 57.89%	7	2.92 (1.85-4.60)	8
TZP	10, 17, 58.82%	8	2.70 (2.00-3.65)	9	12, 26, 46.15%	14	2.22 (1.75-2.82)	17
Vancomycin	6, 12, 50.00%	10	2.66 (1.69-4.18)	10	10, 20, 50.00%	9	2.63 (1.98-3.49)	9
β-lactam/β-lactamase inhibitor	21, 38, 55.26%	9	2.64 (2.15-3.23)	11	30, 60, 50.00%	9	2.31 (1.94-2.75)	14
Tracheostomy	9, 20, 45.00%	14	2.64 (1.87-3.72)	11	17, 35, 48.57%	12	2.52 (1.98-3.21)	10
Tigecycline	2, 5, 40.00%	19	2.63 (1.07-6.45)	13	2, 7, 28.57%	28	2.05 (1.08-3.89)	20
Hospital transfer	3, 7, 42.86%	16	2.35 (1.73-3.20)	14	4, 8, 50.00%	9	2.17 (1.66-2.85)	18
Steroid treatment	3, 16, 18.75%	43	2.35 (1.43-3.86)	14	8, 29, 27.59%	32	2.49 (1.73-3.59)	11
Glycopeptide	11, 24, 45.83%	12	2.34 (1.76-3.13)	16	18, 40, 45.00%	17	2.36 (1.94-2.88)	13
Cephalosporin-IV	7, 20, 35.00%	25	2.33 (1.47-3.70)	17	8, 28, 28.57%	28	2.02 (1.36-3.00)	22
Dialysis	8, 22, 36.36%	23	2.32 (1.75-3.09)	18	12, 35, 34.29%	22	2.05 (1.59-2.66)	20
Enteral nutrition	2, 8, 25.00%	31	2.20 (1.35-3.60)	19	3, 14, 21.43%	42	1.80 (1.27-2.56)	29
Transplantation	3, 12, 25.00%	31	2.14 (1.40-3.26)	20	4, 21, 19.05%	44	1.95 (1.44-2.63)	25
Endotracheal tube	3, 11, 27.27%	30	2.05 (1.52-2.76)	21	4, 15, 26.67%	35	1.96 (1.56-2.46)	24
Intravenous catheter	18, 42, 42.86%	16	2.03 (1.56-2.65)	22	36, 79, 45.57%	15	2.31 (1.91-2.80)	14
Hemodialysis	4, 13, 30.77%	27	2.02 (1.36-3.01)	23	6, 20, 30.00%	27	1.73 (1.22-2.46)	32
Stroke	1, 6, 16.67%	46	2.02 (0.86-4.74)	23	2, 10, 20.00%	43	1.89 (0.98-3.64)	27
Polymyxin	3, 9, 33.33%	26	2.00 (1.30-3.08)	25	7, 15, 46.67%	13	2.44 (1.61-3.69)	12
Urinary catheter	17, 47, 36.17%	24	1.97 (1.46-2.67)	26	32, 71, 45.07%	16	2.28 (1.83-2.85)	16
Cefepime	2, 5, 40.00%	19	1.96 (0.68-5.60)	27	3, 11, 27.27%	33	1.71 (0.87-3.39)	34
CVC	16, 35, 45.71%	13	1.94 (1.44-2.61)	28	25, 59, 42.37%	18	2.07 (1.66-2.59)	19
Prior hospitalisation	9, 21, 42.86%	16	1.94 (1.52-2.48)	28	10, 32, 31.25%	25	1.72 (1.38-2.15)	33
Renal failure	5, 17, 29.41%	29	1.91 (1.49-2.44)	30	7, 27, 25.93%	37	1.67 (1.37-2.03)	36

Risk Factors[#]	Excluding studies of low quality				Including studies of low quality			
	Number (a, b, c)[*]	Rank[¶]	Pooled OR (95%CI)	Rank[§]	Number (a, b, c)[*]	Rank[¶]	Pooled OR (95%CI)	Rank[§]
Cephalosporin-III/IV	4, 9, 44.44%	15	1.87 (1.18-2.97)	31	5, 14, 35.71%	21	1.92 (1.30-2.82)	26
Cephalosporin	19, 52, 36.54%	22	1.87 (1.41-2.50)	31	32, 89, 35.96%	20	1.68 (1.37-2.06)	35
Fluoroquinolone	11, 37, 29.73%	28	1.81 (1.26-2.62)	33	20, 55, 36.36%	19	1.99 (1.52-2.60)	23
Drainage	2, 11, 18.18%	45	1.77 (1.20-2.61)	34	3, 19, 15.79%	48	1.79 (1.29-2.48)	30
Parenteral nutrition	5, 20, 25.00%	31	1.69 (1.30-2.21)	35	11, 35, 31.43%	24	1.67 (1.36-2.06)	36
Endoscopy	3, 8, 37.50%	21	1.61 (1.12-2.31)	36	3, 9, 33.33%	23	1.56 (1.13-2.17)	42
Liver diseases	3, 22, 13.64%	49	1.60 (1.10-2.32)	37	6, 40, 15.00%	49	1.42 (1.11-1.82)	48
Metronidazole	3, 13, 23.08%	35	1.57 (1.07-2.32)	38	3, 18, 16.67%	46	1.50 (1.09-2.06)	46
Neurological disease	2, 10, 20.00%	40	1.57 (1.20-2.06)	38	4, 14, 28.57%	28	1.56 (1.10-2.21)	42
Blood transfusion	1, 5, 20.00%	40	1.57 (0.90-2.73)	38	2, 9, 22.22%	40	1.41 (0.94-2.13)	49
Extended spectrum penicillin	2, 9, 22.22%	37	1.53 (1.05-2.23)	41	4, 14, 28.57%	28	1.75 (1.21-2.54)	31
Aminoglycoside	8, 38, 21.05%	39	1.53 (1.25-1.87)	42	19, 70, 27.14%	34	1.58 (1.34-1.86)	39
Cephalosporin-III	5, 27, 18.52%	44	1.51 (1.17-1.95)	43	13, 42, 30.95%	26	1.58 (1.29-1.95)	39
Heart failure	0, 12, 0.00%	54	1.49 (1.12-1.97)	44	0, 20, 0.00%	56	1.51 (1.20-1.90)	44
COPD	5, 22, 22.73%	36	1.48 (1.17-1.88)	45	8, 36, 22.22%	40	1.46 (1.22-1.75)	47
Arterial catheter	1, 6, 16.67%	46	1.48 (0.85-2.59)	45	3, 13, 23.08%	39	1.82 (1.12-2.96)	28
Gastrostomy	0, 5, 0.00%	54	1.45 (0.76-2.77)	47	0, 6, 0.00%	56	1.20 (0.59-2.41)	57
Hematologic malignancy	2, 8, 25.00%	31	1.44 (0.95-2.17)	48	4, 15, 26.67%	35	1.58 (1.19-2.10)	39
Chemotherapy	2, 9, 22.22%	37	1.39 (0.76-2.54)	49	2, 12, 16.67%	46	1.23 (0.71-2.13)	55
Hypertension	2, 10, 20.00%	40	1.39 (1.06-1.84)	49	2, 21, 9.52%	53	1.26 (1.08-1.48)	51
Diabetes mellitus	5, 50, 10.00%	52	1.37 (1.20-1.57)	51	12, 89, 13.48%	51	1.34 (1.20-1.50)	50
Penicillin	3, 20, 15.00%	48	1.34 (1.05-1.72)	52	8, 34, 23.53%	38	1.60 (1.29-1.99)	38
Malignancy	4, 37, 10.81%	51	1.29 (1.09-1.52)	53	12, 70, 17.14%	45	1.25 (1.05-1.48)	52
Clindamycin	0, 6, 0.00%	54	1.21 (0.79-1.87)	54	1, 7, 14.29%	50	1.51 (0.95-2.39)	44
HIV	0, 9, 0.00%	54	1.17 (0.60-2.27)	55	0, 13, 0.00%	56	1.24 (0.60-2.59)	53
Gender-male	4, 69, 5.80%	53	1.07 (0.93-1.22)	56	3, 124, 2.42%	55	1.06 (0.97-1.16)	58
Coronary artery disease	0, 6, 0.00%	54	1.06 (0.74-1.52)	57	1, 11, 9.09%	54	1.24 (0.77-1.99)	53
Trauma	2, 16, 12.50%	50	1.03 (0.67-1.58)	58	4, 30, 13.33%	52	1.23 (0.91-1.68)	55
Cephalosporin-II	0, 11, 0.00%	54	0.89 (0.42-1.92)	59	0, 12, 0.00%	56	0.90 (0.44-1.82)	59
Cephalosporin-I/II	0, 7, 0.00%	54	0.65 (0.32-1.30)	60	0, 9, 0.00%	56	0.80 (0.49-1.30)	60

(3) Sensitivity analysis of risk factors for CRO colonisation

Risk Factors[#]	Excluding studies of low quality				Including studies of low quality			
	Number (a, b, c)[*]	Rank[¶]	Pooled OR (95%CI)	Rank[§]	Number (a, b, c)[*]	Rank[¶]	Pooled OR (95%CI)	Rank[§]
Imipenem	5, 5, 100%	1	6.55 (3.90-10.99)	1	5, 5, 100.00%	1	6.55 (3.90-10.99)	1
Carbapenem	15, 18, 83.33%	3	4.91 (3.78-6.38)	2	21, 28, 75.00%	3	4.47 (3.22-6.21)	5
ICU stay	6, 8, 75.00%	5	4.16 (1.73-10.02)	3	8, 12, 66.67%	4	5.14 (2.47-10.69)	3
CVC	3, 5, 60.00%	7	4.12 (2.08-8.19)	4	4, 11, 36.36%	13	2.36 (1.32-4.21)	11
Polymyxin	1, 5, 20.00%	19	4.10 (2.18-7.70)	5	2, 7, 28.57%	17	5.75 (2.88-11.48)	2
Mechanical ventilation	5, 5, 100.00%	1	4.02 (2.53-6.39)	6	5, 6, 83.33%	2	3.17 (1.75-5.72)	7
Intravenous catheter	3, 6, 50.00%	9	3.91 (2.15-7.08)	7	4, 12, 33.33%	15	2.31 (1.39-3.84)	12
Vancomycin	5, 6, 83.33%	3	3.25 (1.92-5.50)	8	6, 11, 54.55%	6	3.02 (1.92-4.77)	9
Oxazolidinone	2, 5, 40.00%	12	3.09 (1.87-5.13)	9	3, 6, 50.00%	8	5.03 (1.97-12.88)	4
Glycopeptide	8, 11, 72.73%	6	2.83 (1.88-4.26)	10	10, 17, 58.82%	5	3.37 (2.12-5.35)	6
Aminoglycoside	2, 8, 25.00%	16	2.49 (1.81-3.43)	11	5, 13, 38.46%	11	3.03 (1.80-5.09)	8
Urinary catheter	3, 6, 50.00%	9	2.27 (1.35-3.82)	12	7, 13, 53.85%	7	2.09 (1.62-2.69)	14
Dialysis	2, 5, 40.00%	12	2.22 (1.49-3.29)	13	2, 8, 25.00%	19	1.98 (1.41-2.79)	16
Metronidazole	1, 6, 16.67%	22	1.81 (1.22-2.67)	14	3, 9, 33.33%	15	2.91 (1.26-6.72)	10
β-lactam/β-lactamase inhibitor	6, 14, 42.86%	11	1.74 (1.22-2.48)	15	10, 21, 47.62%	10	2.06 (1.50-2.85)	15
Penicillin	3, 5, 60.00%	7	1.60 (0.68-3.78)	16	4, 8, 50.00%	8	2.30 (1.02-5.18)	13
Fluoroquinolone	4, 12, 33.33%	14	1.53 (1.01-2.33)	17	7, 19, 36.84%	12	1.75 (1.32-2.31)	17
Diabetes mellitus	3, 11, 27.27%	15	1.44 (1.00-2.07)	18	3, 18, 16.67%	21	1.47 (1.16-1.85)	20
Prior hospitalisation	1, 5, 20.00%	19	1.41 (0.84-2.36)	19	4, 11, 36.36%	13	1.75 (1.24-2.48)	17
Malignancy	2, 8, 25.00%	16	1.38 (0.76-2.49)	20	2, 14, 14.29%	23	1.11 (0.76-1.64)	23
Gender-male	4, 21, 19.05%	21	1.36 (1.11-1.65)	21	8, 36, 22.22%	20	1.29 (1.12-1.48)	21
Cephalosporin	4, 17, 23.53%	18	1.33 (0.86-2.05)	22	8, 29, 27.59%	18	1.56 (1.12-2.17)	19
Heart failure	1, 7, 14.29%	23	1.31 (0.71-2.41)	23	2, 12, 16.67%	21	1.28 (0.83-1.97)	22
Liver diseases	0, 7, 0.00%	24	0.84 (0.53-1.33)	24	0, 9, 0.00%	24	0.91 (0.60-1.37)	24
Transplantation	0, 5, 0.00%	24	0.82 (0.42-1.58)	25	0, 5, 0.00%	24	0.82 (0.42-1.58)	26
Cephalosporin-III	0, 6, 0.00%	24	0.72 (0.40-1.29)	26	0, 7, 0.00%	24	0.85 (0.46-1.57)	25

[#], the list of risk factors is ordered by the pooled OR estimates from high to low after excluding studies of low quality;
*, frequency of being a risk factor, frequency of being a candidate risk factor, percentage of being a risk factor (i.e. percentage significant);

¶, the rank ordered by percentage of being a risk factor (i.e. percentage significant) from high to low;
§, the rank ordered by pooled OR estimates from high to low, factors with different interpretations of results in bold;
na, not applicable; OR (95%CI), odds ratio (95% confidence interval); CRO, carbapenem-resistant organisms; ICU, intensive care unit; ESBL, extended-spectrum beta-lactamases; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; CVC, central venous catheter; AMC, amoxicillin-clavulanate; AMS, ampicillin-sulbactam; SCF, cefoperazone-sulbactam; TZP, piperacillin-tazobactam; I, first generation cephalosporins; II, second generation cephalosporins; III, third generation cephalosporins; IV, fourth generation cephalosporins; TMP-SMX, trimethoprim sulfamethoxazole.

Appendix 2-10. Exploration of heterogeneity for top ten risk factors with highest pooled odds ratio (OR) estimates and/or most likely significant

(1) Results of risk factors for CRO presence

Explanatory variable	Mechanical ventilation (I^2=80%)		Nasogastric tube (I^2=86%)		ICU stay (I^2=86%)		Urinary catheter (I^2=79%)	
	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*
World bank income group	0%	na	0%	na	2.59%	Upper-middle income [48, 2.47 (1.93; 3.18), 84.7%] High income [66, 3.97 (3.11; 5.07), 85.7%]	0%	na
Sample Size	0%	na	0%	na	0%	na	14.75%	Weak evidence that OR increases with larger sample size
Status	0%	na	0%	na	0%	na	0%	na
Study Type	2.70%	Cohort [24, 5.17 (3.63; 7.35), 75.9%] Matched case-control [15, 3.52 (2.36; 5.24), 77.5%] Cross-sectional [5, 3.72, (2.07; 6.69), 79.6%] Case-control [53, 2.79 (2.17; 3.59), 80.4%]	7.03%	Matched case-control [9, 2.68 (1.84; 3.92), 73.7%] Cohort [7, 3.07, (1.61; 5.84), 78.1%] Case-control [16, 4.11 (2.39; 7.07), 84.5%] Cross-sectional [4, 3.23 (1.49; 6.95), 89.6%]	0%	na	0%	na
Study Setting	1.15%	Multi-centre [15, 2.65 (1.90; 3.70), 71.1%] Single-centre [82, 3.58 (2.93; 4.39), 80.8%]	0%	na	0%	na	2.22%	Single-centre [90, 2.36 (1.96; 2.85), 77.1%] Multi-centre [21, 2.58 (1.91; 3.50), 81.6%]
Healthcare type	0%	na	0%	na	0%	na	0%	na

Explanatory variable	Mechanical ventilation (I^2=80%)		Nasogastric tube (I^2=86%)		ICU stay (I^2=86%)		Urinary catheter (I^2=79%)	
	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*
Specialty	0%	na	0%	na	0%	na	3.13%	ICU [19, 1.62 (0.79; 3.33), 74.5%] Non-ICU [92, 2.53 (2.15; 2.97), 79.3%]
Study Population	9.08%	Paediatric patients [3, 16.54 (8.27; 33.09), 0.0%] Adult patients [23, 2.91 (2.15; 3.92, 77.1%] Other [71, 3.42 (2.77; 4.23), 79.7%]	0%	na	0%	na	0%	na
Organism	0%	na	12.13%	Non-fermenters [16, 3.11 (1.98; 4.89), 81.4%] Enterobacteriaceae [19, 3.21 (2.26; 4.58), 84.1%] Other [1, 14.09 (8.35; 23.76), /]	5.52%	Non-fermenters [49, 3.00 (2.38; 3.78), 83.3%] Enterobacteriaceae [62, 3.33 (2.55; 4.34), 86.2%] Other [3, 6.82 (4.59; 10.15), 0.0%]	8.01%	Non-fermenters [50, 2.07 (1.68; 2.56), 68.3%] Enterobacteriaceae [59, 2.67 (2.14; 3.34), 81.8%] Other [2, 5.29 (2.28; 12.25), 6.0%]
Resistance Mechanism	0%	na	0%	na	7.65%	Carbapenem resistant [94, 3.05 (2.54; 3.67), 84.0%] Carbapenemase producers [20, 4.19 (2.66; 6.59), 86.9%]	5.55%	Carbapenem resistant [99, 2.34 (1.97; 2.79), 76.6%] Carbapenemase producers [12, 2.94 (2.02; 4.26), 81.5%]

Explanatory variable	Mechanical ventilation (I^2=80%)		Nasogastric tube (I^2=86%)		ICU stay (I^2=86%)		Urinary catheter (I^2=79%)	
	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*
Case-control selection	0%	na	20.56%	CR-no pathogenic bacteria [4, 3.60 (1.72; 7.53), 41.8%] CR-CS [15, 2.37 (1.60; 3.50), 75.3%] CR-no CR [17, 4.36 (2.96; 6.43), 86.7%]	15.64%	CR-CS [74, 2.89 (2.45; 3.40), 72.1%] CR-no pathogenic bacteria [13, 5.05 (2.50; 10.19), 87.3%] CR-no CR [26, 3.87 (2.52; 5.96), 91.9%] CR infection-CR colonisation [1, 0.69 (0.17; 2.83), /]	13.84%	CR-CS [69, 2.38 (1.97; 2.87), 67.0%] CR infection-CR colonisation [3, 1.97 (0.44; 8.71), 82.3%] CR-no CR [27, 2.63 (1.97; 3.50), 83.7%] CR-no pathogenic bacteria [12, 2.16 (1.21; 3.85), 83.8%]

(2) Results of risk factors for CRO infection

Explanatory variable	Mechanical ventilation (I^2=81%)		Nasogastric tube (I^2=89%)		ICU stay (I^2=82%)		Urinary catheter (I^2=81%)		Central Venous Catheter (I^2=80%)	
	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*
World bank income group	0%	na	0%	na	0%	na	0%	na	0%	na
Sample Size	0%	na	0%	na	6.63%	Weak evidence that OR increases with larger sample size	15.18%	Weak evidence that OR increases with larger sample size	9.30%	Weak evidence that OR increases with larger sample size
Study Type	0%	na	0%	na	0%	na	0%	na	0%	na
Study Setting	0%	na	0%	na	0%	na	0%	na	0%	na
Healthcare type	0%	na	0%	na	0%	na	0%	na	0%	na
Specialty	0%	na	0%	na	0%	na	3.82%	ICU [14, 1.52 (0.62; 3.70), 81.4%] Non-ICU [55, 2.49 (1.99; 3.13), 80.1%]	9.44%	ICU [15, 1.46 (0.82; 2.59), 71.6%] Non-ICU [42, 2.29 (1.82; 2.89), 80.2%]
Study Population	7.64%	Paediatric patients [2, 16.66 (8.15; 34.05), 0.0%] Adult patients [17, 3.30 (2.21; 4.92), 78.5%] Other [50, 3.72 (2.89; 4.79), 80.4%]	0%	na	3.59%	Adult patients [23, 2.12 (1.56; 2.89), 76.1%] Other [46, 3.58 (2.73; 4.69), 83.1%] Paediatric patients [1, 8.20 (3.85; 17.47), /]	0%	na	0%	na
Organism	0%	na	15.55%	Non-fermenters [11, 2.50 (1.50; 4.169), 78.4%] Enterobacteriaceae [8, 3.37 (1.68; 6.75), 90.7%]	7.38%	Non-fermenters [34, 2.82 (2.21; 3.59), 75.4%] Enterobacteriaceae [34, 3.12 (2.23; 4.39), 84.6%] Other [2, 5.08 (2.24; 11.53), 0.0%]	13.85%	Non-fermenters [35, 1.87 (1.44; 2.43), 70.0%] Enterobacteriaceae [34, 2.90 (2.07; 4.06), 82.5%]	0%	na

Explanatory variable	Mechanical ventilation (I^2=81%)		Nasogastric tube (I^2=89%)		ICU stay (I^2=82%)		Urinary catheter (I^2=81%)		Central Venous Catheter (I^2=80%)	
	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*
Resistance Mechanism	0%	na	0%	na	1.17%	Carbapenem resistant [59, 2.93 (2.35; 3.65), 81.5%] Carbapenemase producers [11, 3.64 [2.01; 6.59], 82.9%]	0%	na	0%	na
Case-control selection	0%	na	0%	na	31.27%	CR-CS [56, 3.08 (2.53; 3.77), 73.4%] CR-no pathogenic bacteria [7, 1.93 (1.08; 3.46), 75.9%] CR-no CR [6, 4.75 (2.47; 9.11), 86.1%] CR infection-CR colonisation [1, 0.69 (0.17; 2.83), /]	35.81%	CR-no pathogenic bacteria [7, 1.08 (0.66; 1.76), 61.8%] CR-no CR [6, 4.63 (2.98; 7.18), 69.7%] CR-CS [53, 2.38 (1.89; 3.01), 71.6%] CR infection-CR colonisation [3, 1.97 (0.44; 8.71), 82.3%]	8.07%	CR infection-CR colonisation [1, 1.50 (0.50; 4.47), /] CR-no pathogenic bacteria [6, 2.18 (1.32; 3.59), 58.8%] CR-CS [43, 2.01 (1.58; 2.55), 73.0%] CR-no CR [7, 2.37 (1.12; 5.01), 91.3%]

(3) Results of risk factors for CRO colonisation

Explanatory variable	ICU stay (I^2=91%)		Nasogastric tube (I^2=82%)		Glycopeptide usage (I^2=78%)	
	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*	Proportion explained	Subgroup analysis [N, Pooled OR (95%CI), I^2]*
World bank income group	0%	na	0%	na	0%	na
Sample Size	0%	na	0%	na	0%	na
Study Type	0%	na	0%	na	0%	na
Study Setting	0%	na	10.48%	Multi-centre [5, 2.61 (1.24; 5.48), 76.2%] Single-centre [6, 5.21 (2.79; 9.73), 82.2%]	0%	na
Healthcare type	0%	na	0%	na	0%	na
Specialty	10.22%	ICU [2, 22.85 (1.45; 358.93), 94.2%] Non-ICU [10, 3.81 (1.84; 7.87), 89.4%]	4.16%	ICU [2, 1.91 (0.89; 4.07), 0.0%] Non-ICU [9, 4.37 (2.56; 7.46), 84.0%]	0%	na
Study Population	0%	na	16.03%	Other [9, 3.57 (2.26; 5.63), 74.7%] Paediatric patients [2, 4.71 (0.46; 47.82), 90.0%]	0%	na
Organism	0%	na	44.05%	Non-fermenters [2, 6.26 (3.71; 10.59), 39.2%] Enterobacteriaceae [8, 2.71 (1.61; 4.54), 70.5%] Other [1, 14.09 (8.35; 23.76), /]	0%	na
Resistance Mechanism	2.44%	Carbapenem resistant [9, 3.92 (1.76; 8.72), 88.7%] Carbapenemase producers [3, 12.18 (1.87; 79.37), 91.6%]	0%	na	2.85%	Carbapenem resistant [14, 2.80 (1.88; 4.16), 65.3%] Carbapenemase producers [3, 9.18 (0.76; 111.09), 93.5%]
Case-control selection	0%	na	2.03%	CR-no CR [10, 4.12 (2.49; 6.82), 82.8%] CR-no pathogenic bacteria [1, 1.32 (0.33; 5.21), /]	0%	na

*, N number of studies investigated the risk factor;

OR, odds ratio; 95%CI, 95% confidence interval; na, not applicable; ICU, intensive care unit; CR-CS, carbapenem resistance-carbapenem susceptible; CR-no CR, carbapenem resistance-no carbapenem resistance.

Appendix 3-1. Application form of Public Benefit and Privacy Panel for Health and Social Care

Application Control *Applicants should not complete the "submitted date" field*			
Application Coordinator	Mark Macartney		
Application Number	1617-0328	Submitted Date	06/07/2017
Applicant Name	Shengyuan Zhao		
Proposal Name	Epidemiology of Carbapenamase producing organisms (CPOs) in Scotland		
Project End Date	March 31st 2020		
Pre-submission checklist *Applicants should not fill out this section – **to be completed by the eDRIS coordinator***			
Approved Information Governance Training	☒ Approved training complete and certificates received ☐ Approved training complete and certificates pending		
Use of recognised safe haven	☒Yes ☐ No		
NHSCR Involvement	☐ Yes ☐ Reference number:..... ☐ Email Confirmation of approval supplied:		

	☒ No
Is project covered by National Safe Haven generic ethics approval?	☒ Yes ☐ No ☐ N/A
Supporting Documents	
Please list *only* supporting documents which you have clearly referenced in your application – the name of each should clearly indicate what the document/file/reference is about. Appendix I. Flow chart of the study Appendix II. Carbapenemase Producing Organisms (CPOs) of interest Appendix III. Antimicrobial agents included in prescription and resistance rate analysis Appendix IV. Supporting document of NHS ethical approval absence Appendix V. Supporting document of R&D approval absence Appendix VI. Departmental ethical approval	

Note to Applicants

Prior to completing your application form you should:

Contact the eDRIS Team, who will assist you - Nss.edris@nhs.net or by phone on 0131 275 7333

Read and understand the separate Guidance for Applicants

Your application should be typed, not handwritten. Your eDRIS application coordinator will inform you of how to submit your application form and any supporting evidence. Before submitting your completed application, you should ensure that:

All relevant sections of the application are complete

Relevant supporting evidence is attached

Individuals named on the form have read and approved its submission

Please note that submitted applications may be circulated to panel members, administrative colleagues, NHSScotland information governance and information security colleagues, Caldicott Guardians, the CHI Advisory Group and, where appropriate, non-NHS Scotland colleagues from a variety of participating partner bodies, in the course of processing. You must make your eDRIS application coordinator aware of any confidential or sensitive information contained in your application which you would consider inappropriate for circulation in such a manner. Your application could be subject to disclosure or partial disclosure under the Freedom of Information (Scotland) Act, and will be retained in line with NHSScotland information policy.

Section 1 – People

1.1	**Applicant** *Please read section 1.1 of the guidance*	
1.1.01	Full Name:	Shengyuan Zhao
1.1.02	Title:	Ms
1.1.03	Position (if PhD researcher, please also complete section 1.2):	PhD student
1.1.04	Professional Registration No.:	
1.1.05	Organisation Name:	University of Edinburgh
1.1.06	Address (incl. postcode):	Centre for Immunity, Infection and Evolution, Usher Institute of Population Health Sciences & Informatics, Ashworth Laboratories, King's Buildings, Edinburgh EH9 3JT
1.1.07	Email:	
1.1.08	Do you have an NHS contract/honorary contract?	No
1.1.09	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A of guidance notes	
	Name and institution of course:	MRC Research Data and Confidentiality online module

	Date completed:	12/3/17
1.2	**PhD Supervisor** *Please read section 1.2 of the guidance*	
1.2.01	Full Name:	Mark Woolhouse
1.2.02	Title:	Professor
1.2.03	Position:	Chair of Infectious Diseases Epidemiology
1.2.04	Professional Registration No.:	n/a
1.2.05	Organisation Name:	University of Edinburgh
1.2.06	Address (incl. postcode):	Centre for Immunity, Infection and Evolution, Usher Institute of Population Health Sciences & Informatics, Ashworth Laboratories, King's Buildings, Edinburgh EH9 3JT
1.2.07	Email:	
1.2.08	Does this person have an NHS contract/honorary contract?	No
1.2.09	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A of guidance notes	

	Name and institution of course:	MRC Research Data and Confidentiality online module
	Date completed:	15/3/17
1.3	**Clinical Sponsor/Lead** *Please read section 1.3 of the guidance*	
1.3.01	Full Name:	Mark Woolhouse
1.3.02	Title:	Professor
1.3.03	Position:	Chair of Infectious Diseases Epidemiology
1.3.04	Professional Registration No.:	n/a
1.3.05	Organisation Name:	University of Edinburgh
1.3.06	Address (incl. postcode):	Centre for Immunity, Infection and Evolution, Usher Institute of Population Health Sciences & Informatics, Ashworth Laboratories, King's Buildings, Edinburgh EH9 3JT
1.3.07	Email:	
1.3.08	Does this person have an NHS contract/honorary contract?	No

1.3.09	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A of guidance notes	
	Name and institution of course:	MRC Research Data and Confidentiality online module
	Date completed:	15/3/17
1.4	**Information/Data Custodian** *Please read section 1.4 of the guidance*	
1.4.01	Full Name:	Eleanor Anderson
1.4.02	Title:	Dr
1.4.03	Position:	CPHM
1.4.04	Professional Registration No.:	*GMC3323119*
1.4.05	Organisation Name:	Health Protection Scotland
1.4.06	Address (incl. postcode):	Meridian Court, 5 Cadogan Street, Glasgow G2 6QE
1.4.07	Email:	
1.4.08	Does this person have an NHS contract/honorary contract?	Yes

1.4.09	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A of guidance notes	
	Name and institution of course:	NHS Scotland Information Governance eLearning, NHS NSS
	Date completed:	6/3/17, 1/6/17
1.5 Others with access to identifiable or potentially identifiable data *Please read section 1.5 of the guidance*		
1.5.01	Full Name:	Margo Chase-Topping
1.5.02	Title:	Ms.
1.5.03	Position:	Statistical Epidemiologist
1.5.04	Professional Registration No.:	n/a
1.5.05	Organisation Name:	University of Edinburgh
1.5.06	Address (incl. postcode):	
1.5.07	Email:	
1.5.08	Does this person have an NHS contract/honorary contract?	No
1.5.09	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A of guidance notes	
	Name and institution of course:	MRC Research Data and Confidentiality online module
	Date completed:	15/5/17

1.5.01	Full Name:	Gail Robertson
1.5.02	Title:	Ms.
1.5.03	Position:	Statistical Epidemiologist
1.5.04	Professional Registration No.:	n/a
1.5.05	Organisation Name:	University of Edinburgh
1.5.06	Address (incl. postcode):	
1.5.07	Email:	
1.5.08	Does this person have an NHS contract/honorary contract?	No
1.5.09	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A of guidance notes	
	Name and institution of course:	MRC Research Data and Confidentiality online module
	Date completed:	4/5/17
1.5.01	Full Name:	Sharon Kennedy
1.5.02	Title:	Ms.
1.5.03	Position:	Principle Analyst/Statistician
1.5.04	Professional Registration No.:	n/a

1.5.05	Organisation Name:	NHS NSS
1.5.06	Address (incl. postcode):	Meridian Court 5 Cadogan Street Glasgow G2 6QE
1.5.07	Email:	Sharon.kennedy2@nhs.net
1.5.08	Does this person have an NHS contract/honorary contract?	Yes
1.5.09	Provide details of the most recent information governance training undertaken - a list of training courses is included at Appendix A of guidance notes	
	Name and institution of course:	NSS Safe Information Handling (foundation) NSS Information Handling in Practice (intermediate)
	Date completed:	25/4/2016 (foundation) 29/1/2015 (intermediate)

1.6 Others *Please read section 1.6 of the guidance*

Complete this section if applicable – for each additional person

Full Name:		Involvement in Proposal:	
Organisation:		Position:	

Section 2 – Organisations & Bodies

2.1	**Organisation or Body Leading Proposal** *Please read section 2.1 of the guidance*	
2.1.01	Organisation or Body Name: *If the organisation here is an NHSScotland board, note this and go directly to question 2.1.3*	*University of Edinburgh*
2.1.02	Is this a commercial organisation or body?	No
2.1.02a	If 'Yes', please provide a full explanation of the organisation or body's activity and industry sector, including any previous experience of using NHSScotland data - append supporting documentation as appropriate	
2.1.03	Is this organisation or body wholly funding or paying for the costs of conducting the proposal?	Yes
2.2	**Organisation or Body Funding Proposal** *Please read section 2.2 of the guidance*	
Complete the following section if you answered 'No' to question 2.1.3		
2.2.01	Organisation or Body Name: *If the organisation here is an NHSScotland board note this and, go directly to section 2.3*	

2.2.02	Is this organisation or body a commercial organisation?	Choose an item.
2.2.02a	If 'Yes', please provide a full explanation of the organisation or body's activity and industry sector, including any previous experience of using NHSScotland data - append supporting documentation as appropriate	

2.3 Other Relevant Organisations or Bodies *Please read section 2.3 of the guidance*		
Complete this section if applicable		
Organisation Name	Nature of Business/Sector	Nature of interest in proposal
Health Protection Scotland	Public Health	Collaborators

Section 3 – Overview

3.1	**Proposal Essentials** *Please read section 3.1 of the guidance*	
3.1.01	Please specify the proposal end date	**March 31, 2020**
3.1.02	Is this proposal: • an extension • a renewal of an existing approval • related to a previous application (approved or not)	No

	Please provide details, include the reference number of the original application, and summarise the changes requested	
3.1.03	Does this proposal require updates of information or to be repeated at regular intervals? If yes please advise of the frequency	No
3.1.04	What is the substantive purpose of the proposal? (please choose **one** option from below that best matches your proposal) ☐ Patient Care ☒ Research ☐ Audit ☐ Performance Monitoring/Management ☐ Service Planning/Improvement ☐ Health/Social Care Administration ☐ Systems Implementation/Testing ☐ Training/Education ☐ Other	
	If other clearly defined purpose, please give details:	
3.1.05	Access is being requested to data from which sources? (tick as many as are relevant)	

	☐ A single NHS Scotland Board (excluding NSS) including any system/database ☒ NHS National Services Scotland ☒ More than one NHS Scotland Board including any system/database ☒ Community Health Index (CHI) database ☐ NHS Central Registry ☐ Other
	If other, please give details:
3.1.06	Provide a full, clear concise *lay* outline of the proposal (max. 500 words)
	As β-lactam antibiotics, carbapenems provide enhanced Gram-negative coverage as compared with other β-lactams and stability against extended-spectrum β-lactamases (ESBLs). Accordingly, carbapenems are often used as last resort antibiotics for treatment of multi-drug resistant (MDR) infections caused by Gram-negative bacilli (GNB). Carbapenemase producing is the main mechanism of carbapenem resistance. The rates of carbapenemase producing organisms (CPOs) have been gradually increasing worldwide over the last 10 years, leaving few effective therapeutic options available to MDR infections. In 2017, The World Health Organization developed a global priority pathogens list (global PPL) of antibiotic-resistant bacteria and carbapenem-resistant *Acinetobacter baumannii/Pseudomonas aeruginosa/Enterobacteriaceae* were listed as the top three pathogens of critical priority. Increases in carbapenemase producers among GNB can be attributed to multiple potential risk factors. Notably, antibiotic exposure has been reported as a factor independently associated with CPOs acquisition in healthcare facilities worldwide. Nevertheless, risk factors for CROs acquisition have not been completely characterized and conflict results are reported in various studies owing to the great heterogeneity between these studies conducting in different countries.

	In Scotland, the first carbapenemase was identified in an *Enterobacter cloacae* complex blood culture isolate in 2003, carrying KPC-4. Afterwards, more and more CPOs were reported from nearly all parts of Scotland, showing a worrying upward trend. Additionally, there has been a 9.3% increase in carbapenem usage in Scottish acute hospitals since 2012. The epidemiology of Scottish CPO isolates, however, remains unclear. To date, no relevant data is available to the public in terms of morbidity and mortality rates, prescribing rates of clinically routine used antibiotics and risk factors for acquisition of CPOs in Scotland. This study aims to provide an indepth epidemiological analysis of CPOs in Scotland hence to provide a comprehensive understanding of characteristics underlying factors and related morbidity and mortality associated with CPOs. Insights based on these findings will further the development of effective and appropriate prevention and infection control strategies, thus curbing future emergence and spread of carbapenem resistance in Scotland. We intend to conduct a retrospective study of epidemiology of CPOs (as listed in Appendix II) among inpatients in Scotland between 2003 and 2016. This study will involve descriptive analysis of the temporal and spatial patterns of all CPOs cases in terms of morbidity and mortality and association between antibiotic prescription and morbidity from 2003 to 2016 as well as a matched case-control study to identify risk factors associated with CPOs acquisition among inpatients between 2010 and 2016.
3.1.07	Provide a description of the aims and objectives of the proposal
	The proposal has 5 aims: 1. To evaluate morbidity and mortality associated with CPOs acquisition in Scotland and to compare temporal trends of both rates at national, NHS board and hospital level and spatial trends of both rates between NHS boards from 2003 to 2016. 2. To evaluate risk factors for CPOs acquisition among inpatients from 2010 to 2016 in Scotland. We will conduct a matched 3:1 case-control study with two control groups (test control and demographic control). Cases will be inpatients carrying CPOs isolates, control group 1 (test control) will be a random selection of inpatients carrying non-CPOs isolates matched with cases by participating hospital, admission date (± 2 months), specimen site and organism

	species, control group 2 (demographic control) will be a random selection of all inpatients without CPOs isolation matched with cases by participating hospital and admission date (± 2 months). Variables of all cases and controls during study period, including demographic characteristics (age, sex), underlying diseases/comorbidity, exposure to operations and interventions, exposure to antibiotics in both the present indexing and 12 months prior to present indexing (listed in section 4.3) will be analysed using a regression model to identify independent risk factors for CPOs acquisition. 3. To compare antimicrobial resistance rates to routine clinical tested antimicrobials (as listed in Appendix II) among cases and control group 1 isolates from 2010 to 2016. 1) Results of antimicrobial susceptibility test (AST) of CPOs and non-CPOs isolates will be used to calculate resistance rates; 2) Differences of resistance rates between CPOs and non-CPOs isolates will be evaluated. 4. To examine temporal and spatial trends of relevant antimicrobial (as listed in Appendix II) prescribing rates in primary and secondary care from 2003 to 2016. 1) At Scottish national level and NHS board level, yearly prescribing rates of each antimicrobial in primary (2003-2016) and secondary care (2007-2016) will be calculated; in addition, at hospital level, in hospitals where CPOs isolates were identified, prescribing rates of each relevant antimicrobial will be calculated (2007-2016). 2) At NHS board level, temporal trends of each relevant antimicrobial prescribing rates in primary (2003-2016) and secondary care (2007-2016) will be examined and temporal trends of each antimicrobial prescribing rate in different hospitals (2007-2016) will be examined. 3) Trends of each antimicrobial prescribing rate between NHS boards in primary (2003-2016) and secondary care (2007-2016) will be examined. 5. To investigate associations between antimicrobial prescribing rates in primary and secondary care and CPOs morbidity and antimicrobial resistance from 2003 to 2016. 1) Associations between antimicrobial prescribing rates and morbidity of CPOs acquisition in primary care by year and NHS board will be examined from 2003 to 2016; 2) Associations between antimicrobial prescribing rates and morbidity of CPOs acquisition in secondary care by year and NHS board will be examined from 2007 to 2016;

	3) Associations between antimicrobial prescribing rates and antimicrobial resistance rates in primary care by year and NHS board will be examined from 2003 to 2016; 4) Associations between antimicrobial prescribing rates and antimicrobial resistance rates in secondary care by year and NHS board will be examined from 2007 to 2016; 5) Associations between antimicrobial prescribing rates and antimicrobial resistance rates at hospital level by year will be examined from 2007 to 2016.
3.1.08	Provide a description of the envisaged benefits to the public and/or patients
	The intended study will provide an in-depth epidemiological analysis of CPOs in Scotland hence to provide a comprehensive understanding of characteristics underlying factors and related morbidity and mortality associated with CPOs. Better knowledge of risk factors and association between antibiotic prescription and morbidity and mortality of CPOs will help Scottish healthcare workers to identify cases and take corresponding precautions among patients of high risk for CPOs carriage and to optimise stewardship of clinical antibiotics. These will help local healthcare workers and public health policy makers to assess the impact of carbapenem resistance on disease burden and then to develop effective and appropriate prevention and infection control strategies, thus curbing future emergence and spread of carbapenem resistance in Scotland.
3.1.09	Provide a concise description of: the research study design (sample size, inclusion criteria, time period); data collection; data processing or other means required to achieve the aims of your proposal.
	We intend to conduct a retrospective study of epidemiology of CPOs (as listed in Appendix II) among patients hospitalised in Scotland between 2003 and 2016. **Study 1: epidemiology of CPOs (2003-2016)** Inclusion criteria: All patients hospitalized in Scottish hospitals (including travel related cases) from whom a CPO was isolated from any type of

	samples (i.e. isolation sites) during hospitalization from 2003 to 2016. Exclusion criteria: If two or more CPO isolates of the same species were isolated from the same patient during the same hospitalisation, only the first isolate and corresponding episode will be included. Where more than one organism were present in a sample (a rare event) each organism will separately represent a case. **Study 2: case-control study (2010-2016)** For the 3:1 matched case-control study, controls are matched to cases of CPOs by participating hospital, admission date (± 2 months), specimen site and organism species as appropriate. Admission date will be identified by comparison with specimen date within two weeks pre/post. Inclusion criteria: Cases (n=x): These are a subset of patients that were identified for study 1. Patients hospitalized in Scottish hospitals testing positive for CPOs isolated from any site from January 2010 to December 2016. Controls are defined as: Control Group 1 (n=3x): Randomly selected patients hospitalized in Scottish hospitals testing positive for organisms that did not produce carbapenemases from January 2010 to December 2016. These controls match with cases by participating hospital, admission date (± 2 months), specimen site and organism species. Control Group 2 (n=3x): Randomly selected patients hospitalized in Scottish hospitals who did not have CPOs isolated during their hospital stay from January 2010 to December 2016. These controls match with cases by participating hospital and admission date (± 2 months). Exclusion criteria: If two or more CPOs isolates of the same species were isolated from the same patient during the same hospitalisation, only the first isolate and corresponding episode will be included. Where more than one organism were present in a sample (a rare event) each organism will separately represent a case.

	Data sources: 1. SMR01 Inpatients and Day Cases: variables of potential risk factors of our interest, including demographic characteristics, underlying diseases/comorbidity, exposure to operations and interventions, hospital admission, separate hospital episode records of admission to Intensive Care Unit (ICU) and hospital transfer in both the present indexing and all previous records during 12 months prior to indexing from 2010 to 2016. 2. PIS (Prescribing Information System): 1) quarterly and yearly prescribing data of antimicrobials dispensed in the community at both national and NHS board level from 2003 to 2016 2) quarterly and yearly prescribing data of antimicrobials dispensed in the community at individual patient level from 2009 to 2016 in the course of preceding 12 months prior to indexing. 3. HMUD (Hospital Medicines Utilisation Database): quarterly and yearly prescribing data of antimicrobials dispensed in hospitals at national/NHS board/hospital level from 2007 to 2016. 4. ECOSS (The Electronic Communication of Surveillance in Scotland): CPO records including organism, specimen date, specimen site and results of AST from January 2003 to December 2016. 5. NRS Deaths Data: date and causes of death for all cases and controls from 2003 to 2016. 6. ISD(S)1 (Hospital Activity Statistics): Quarterly and yearly data of total occupied bed days at national/NHS board/hospital level from 2003 to 2016. 7. Publicly available data being added to Safe Haven for statistic analysis: NRS Health Board Population Estimates-midyear population estimates from 2003 to 2016 by NHS board, age and sex.
3.1.10	Provide a clear and concise outline of any statistical methods that will be used in the project (if applicable)
	1. Spatial trends of morbidity and mortality rates between NHS boards will be evaluated with appropriate regression analysis or analysis of variance (ANOVA). Temporal and spatial trends of routine clinical tested antimicrobials (see Appendix III) prescribing rates in primary and secondary care will be evaluated with ANOVA. Additionally, associations between antimicrobial prescribing rates in primary and secondary care and CPOs morbidity and

	antimicrobial resistance will be evaluated with linear regression analysis. **2.** For the case-control study, univariate analysis will be performed: chi-square or Fisher's exact test for dichotomous variables will be used to test the significance of categorical covariates. Parametric (ANOVA) and non-parametric test, the Wilcoxon signed-rank test, will be used to assess the significance of continuous covariates. Logistic regression analysis was used to examine the independent risk factors associated with CPOs acquisition.
3.1.11	Provide a diagram/description to illustrate the data flow or data linkage process envisaged (if applicable)
	Data linkage Linkage of datasets held at Health Protection Scotland (HPS) for all inpatients testing positive for CPOs confirmed by AMRHAI reference unit PHE and Information Services Division (ISD) held datasets providing information on hospitalizations, deaths, and relevant risk factors will be performed via HPS/PHI's HPS Statistics Support Team. Community Health Index (CHI) number will be replaced with an anonymised patient identifier in the file made available for analysis. Age at admission would be derived from date of birth and hospital admission dates. Sex would be retained for analysis. Age and sex are potential risk factors of our interest and would be used as adjust factors as well while performing risk factor analysis. Please also find a flow chart attached (Appendix I).
3.1.12	Does the proposal have implications for, or target, sensitive groups or vulnerable populations? Please give details.
	No
3.1.13	Does the proposal seek to use information exclusively about deceased persons? Please give details
	No
3.1.14	Describe how you have included public input / lay representation in your proposal design.

	Not applicable
3.1.15	Describe any peer review undertaken, with details (for example formal review by a peer organisation or funding body, informal internal review, and review by a third party).
	No
3.1.16	Has a Privacy Impact Assessment been carried out which supports your proposal? Provide details and attach as supporting documentation (e.g. screening questions, full signed PIA etc)
	No
3.1.17	Is there *any* commercial aspect or dimension to the proposal or its outcomes? If yes, give details.
	No
3.2	**Statutory and Regulatory Context** *Please read section 3.2 of the guidance*
3.2.01	Does your proposal have a statutory or regulatory justification - is the proposal responding to a statutory or regulatory instruction, duty or order? Please give details
	No
3.2.02	Explain which of the Data Protection Act schedule 2 and schedule 3 conditions are relevant to this project and why? (a list of conditions can be found at Appendix B of guidance notes)
	Schedule 2 (6) Schedule 3 (8)

3.2.03	Are there any relevant information sharing agreements, protocols or contracts in place which support your proposal? Please give details and attach as supporting documentation	
	No	
3.2.04	Has Caldicott approval been given for your proposal at a local level? Please give details	
	No	
3.2.05	Are regulatory approvals from outside Scotland pending or received? Please give details	
	No	
3.3	**Research and Ethics Governance** *Please read section 3.5 of the guidance*	
3.3.01	Has your proposal sought NHS or university research/ethics approval?	No
3.3.01a	If yes, provide committee details and status of approval (ie pending, approved, etc). Please attach as supporting documentation if available	
3.3.01b	If no, explain why NHS or university research/ethics approval is not sought:	
	Clinical Research Governance of College of Medicine & Veterinary Medicine of University of Edinburgh and NHS Lothian R&D team: not need R&D approval; West of Scotland Research Ethics Service: not need NHS ethical approval;	

	Usher Institute of Population Health Sciences & Informatics of University of Edinburgh: not require formal ethical review	
3.4	**Safe Havens** *Please read section 3.4 of the guidance*	
3.4.01	Do you intend to access the data requested exclusively through a safe haven listed at Appendix A of guidance notes? Please provide details of which safe haven/s *If you have answered 'Yes' you do not need to complete sections 5.1 or 5.2*	
	Yes NHS NSS ISD Electronic Data Research Innovation Service(@Farr Institute)	
3.4.02	If you applying to use NHS NSS data and you do not intend to do this through the National Safe Haven, please explain why then proceed to Section 4	
3.4.03	Will you be accessing the safe haven remotely?	Yes
3.4.04	How and at what location will you be accessing the safe haven? E.g. on a university-provided laptop from a university office.	
	We will be accessing the safe haven on the desk computers provided by the University of Edinburgh from the university office located in Room 138, Ashworth Laboratories, King's Buildings, Edinburgh, EH9 3JT	

Section 4 – Data & Data Subjects

4.1 Data yet to be collected *Please read section 4.1 of the guidance*		
Dataset/source Name	Collection by (whom)?	Has explicit consent been sought? If Yes, describe how explicit consent has been sought – provide copies of participant consent/registration forms, etc. If No, explain why consent is not being sought (eg impractical, risk associated with seeking consent, etc)

4.2 All Other Datasets / sources *Please read section 4.2 of the guidance*

Please note that contact should be established as early in the process as possible with NHS Scotland boards/Data providers to discuss data provisioning requirements for any of the applicable sources listed below.

Dataset/source Name	Data Controller (Organisation) **For existing dataset/sources for which the data controller is not an NHSScotland board, please append evidence of the data controllers permission to use the data**	Original purpose compatible with proposal?
Electronic Communications of Surveillance in Scotland system (ECOSS)	**HPS**	**Yes**
SMR01	**NSS**	**Yes**

NRS Deaths	**NRS**	**Yes**
ISD(S)1	**NSS**	**Yes**
PIS	**NSS**	**Yes**
HMUD	**NSS**	**Yes**

4.2.01	How were individuals originally informed of the use of their data? You should ensure that you include an appropriate explanation for each of the data sources which you have listed above.
	Patients have been informed of the use of their data via two main routes. The first involves the publication of generic leaflets explaining how NSS uses patient data and these are available in a wide range of healthcare premises. The second method is the NSS privacy notice which is published on the NSS website (https://nhsnss.org/how-nss-works/data-protection/). This notice provides information to persons on how NSS stores and uses NHS Scotland data.

4.3 Data Variables *Please read section 4.3 of the guidance*

Dataset/source Name	Variable	Time Period/Range	Please check to indicate if this item is used for processing only and will not be part of the output
ECOSS	Anonymous ID	For all cases and controls	☐

ECOSS	Date of Birth	For all cases and controls	☒
ECOSS	Sex	For all cases and controls	☐
ECOSS	Specimen site	For all cases and controls	☐
ECOSS	Specimen date	For all cases and controls	☐
ECOSS	Result of antimicrobial suseptibillity test	For all CPOs from 2003 to 2016, for control group 1 from 2010 to 2016	No
ECOSS	Organism	For all cases and controls	No
ECOSS	Specimen	For all cases and controls	No
ECOSS	Enzyme	For all cases and controls	No
SMR01	CIS marker	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No

SMR01	Location (of treatment	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SMR01	NHS Board of treatment and residence	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SMR01	Admission date	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SMR01	Admission type	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1	No

		and admission date for control group 2	
SMR01	Admission/ transfer from - location	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SM01	Admission transfer from	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SMR01	Specialty	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SMR01	Significant facility	For the present indexing record and all records during 12	No

		months prior to specimen date for cases/control group 1 and admission date for control group 2	
SMR01	Discharge date	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SMR01	Discharge type	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SMR01	Discharge/ transfer to	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No

SMR01	Discharge/Transfer To-Location	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SMR01	Main condition	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SMR01	Other condition (all)	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SMR01	Other condition (all)	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1	No

		and admission date for control group 2	
SMR01	Main Operation	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SMR01	Date Main Operation	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SMR01	Other Operation (all)	For the present indexing record and all records during 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
SMR01	Date Other Operation (all)	For the present indexing record and all records during 12	No

		months prior to specimen date for cases/control group 1 and admission date for control group 2	
Hospital Activity Statistics: ISD(S)1	Total/Acute Occupied Bed Days (TOBDs/AOBDs)	Quarterly and yearly data from 2003 to 2016	No
Hospital Activity Statistics: ISD(S)1	Health Board Treatment name		No
Hospital Activity Statistics: ISD(S)1	Location name (Hospital)		No
NRS- deaths	Date of Death	For all CRGNB carriers from 2003 to 2016 and control group 1	No
NRS- deaths	Causes (all) of Death	For all CRGNB carriers from 2003 to 2016 and control group 1	No
PIS (Prescribing	Antimicrobial name and group- at patient level	Records in the 12 months prior to specimen date for	No

Information System)		cases/control group 1 and admission date for control group 2	
PIS (Prescribing Information System)	Daily defined doses (DDDs)- at patient level	Records in the 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
PIS (Prescribing Information System)	NHS Board (HB)- at patient level	Records in the 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
PIS (Prescribing Information System)	Date, and calendar year and quarter dispensed - at patient level	Records in the 12 months prior to specimen date for cases/control group 1 and admission date for control group 2	No
PIS (Prescribing Information System)	Antimicrobial name and group	Quarterly and yearly data from 2003 to 2016	No
PIS (Prescribing	Daily defined doses (DDDs)	Quarterly and yearly data from 2003 to 2016	No

Information System)			
PIS (Prescribing Information System)	NHS Board (HB)	Quarterly and yearly data from 2003 to 2016	No
PIS (Prescribing Information System)	Calendar Year	Quarterly and yearly data from 2003 to 2016	No
PIS (Prescribing Information System)	Calendar Quarter	Quarterly and yearly data from 2003 to 2016	No
HMUD (Hospital Medicines Utilisation Database)	Antimicrobial name and group	Quarterly and yearly data from 2007 to 2016	No
HMUD (Hospital Medicines Utilisation Database)	Daily defined doses (DDDs)	Quarterly and yearly data from 2007 to 2016	No
HMUD (Hospital Medicines	NHS Board (HB)	Quarterly and yearly data from 2007 to 2016	No

Utilisation Database)			
HMUD (Hospital Medicines Utilisation Database)	Hospital	Quarterly and yearly data from 2007 to 2016	No
HMUD (Hospital Medicines Utilisation Database)	Calendar Year	Quarterly and yearly data from 2007 to 2016	No
HMUD (Hospital Medicines Utilisation Database)	Calendar Quarter	Quarterly and yearly data from 2007 to 2016	No

4.3.01	Please justify your need for identifiable or potentially identifiable variables
	An ECOSS extract will be provided from HPS to PHI's HPS Statistical Support Team for all organisms as defined in the appended list from 2003-2016 and will include all available patient identifiers (CHI, forename, surname, date of birth, sex, address/postcode) in order to facilitate CHI seeding, linkage and identification of matched cases/controls. All linkage and identification of cases/controls will be performed by PHI's HPS statistical Support Team and required variables (e.g. age, DDDs) will be derived prior to the file being anonymised and made available for analysis via eDRIS in the safe haven identified. For the aggregated study covering 2003-2016, an ECOSS extract will be provided by PHI's HPS statistical support team and made

	available to the safe haven via eDRIS giving the total number of isolates by quarter, hospital and NHS Board. For the case control study covering 2010-2016, a separate extract will be provided at patient level with an anonymised patient identifier used in place of CHI. Age will be derived from date of birth and hospital admission dates by PHI's HPS Statistical Support Team. Sex will be retained for analysis. Age and sex are potential risk factors of our interest and would be included in risk factor analysis. Dates of admission (SMR01) will be used to identify the hospital episode record(s) that are likely to correspond with the specimen being taken, and to identify previous hospitalisations and corresponding risk factors. Dispensed date (PIS) will be retained to enable a measure of antibiotic prescribing history to be defined in periods prior to indexing.
4.4	**Methodology** *Please read section 4.1 of the guidance*
4.4.01	Does the proposal require any of the following: ☒ Data matching ☐ Single anonymised data extract ☒ Data linking ☒ Use of matched controls ☐ Other (please specify):
4.4.02	If the proposal requires data linkage, who is undertaking the linkage e.g. eDRIS team, local analysts etc..? *All data will be linked by PHI's HPS Statistical Support Team and an anonymised file provided to PHI's eDRIS team, based at the FARR institute, to enable provision of data via the safe haven identified.*

4.4.03	What variables will be processed for linkage? ☒ CHI Number ☒ Forename ☒ Surname ☒ Date of Birth ☒ Address ☐ NHS Number ☒ Postcode ☐ Other Please Specify:
4.5	**NRS/NHSCR Data Sources** *Please read section 4.4 of the guidance*
Complete this section if access to NHSCR is required, or if there is any National Records of Scotland involvement	
4.5.01	Does the proposal require access to NHS Central Registry as a sampling frame for cohorts? — No
4.5.02	Does the proposal involve flagging of individuals on the NHSCR for long term follow up? — No
4.5.03	If yes, is flagging necessary: ☐ To trace and contact individuals throughout the UK? ☐ To be informed of fact and cause of death? ☐ To be informed of the incidence of on-going cancers? ☐ To be informed of emigrations prospectively and retrospectively?

4.5.04	Is any other NRS/NHSCR involvement required? Please provide details No				
4.6	**Making Contact with Individuals** *Please read section 4.5 of the guidance*				
4.6.01	Is any direct contact with any group of individuals required? If Yes, please provide details below				No
	Contact Group and Method of contact				Contact by (whom)
	☐ Hospital Consultants	☐ Letter	☐ Phone	☐ Other (specify) :	
	☐ Other NHSS Staff	☐ Letter	☐ Phone	☐ Other (specify) :	
	☐ General Practitioners	☐ Letter	☐ Phone	☐ Other (specify) :	
	☐ Patients/Public	☐ Letter	☐ Phone	☐ Other (specify) :	
	☐ Relatives of participants	☐ Letter	☐ Phone	☐ Other (specify):	

	☐ Others (please specify):	☐ Letter	☐ Phone	☐ Other (specify) :	
4.6.02	Please explain why contact is being made – append copies of relevant correspondence as supporting evidence				
4.7	**Community Health Index (CHI) Database** *Please read section 4.6 of the guidance*				
Complete this section if access to CHI Database is required					
4.7.01	What monitoring and audit of the use of CHI is planned? Please provide details				
	n/a				
4.7.02	What technical method will be used to access CHI (online read-only, download, other extract, anonymised extract, etc)? Please provide details				
	n/a				
4.7.03	Have any risks been identified in the proposal which relate specifically to CHI?				
	n/a				

Section 5 – Data Processing

5.1	**Access** *Please read section 5.2 of the guidance*

Complete the following section if you answered 'No' to question 3.4.1		
5.1.01	At what location is identifiable or potentially identifiable data being accessed?	
5.1.02	Please provide details of security policy/procedure governing access to this physical and technical environment – append supporting documentation referencing appropriate sections	
5.1.03	Does this policy/procedure cover password policy in detail? Please provide details/ append supporting documentation referencing appropriate sections	
5.1.04	Does this policy/procedure cover user account management, including review or removal of access to sensitive/personal data, in detail? Please provide details/ append supporting documentation referencing appropriate sections	
5.1.05	Will individuals with access to data have individual or shared accounts?	
5.1.06	Will the data be accessed by staff working off site eg staff working from home at any time during the duration of the proposal?	Choose an item.

5.1.06b	If yes, are policies/procedures in place to facilitate, monitor and audit this access? Please provide details/ append supporting documentation	
5.1.07	Provide any additional detail of how data is protected from unauthorised access	
5.2	**Store & Use** *Please read section 5.3 of the guidance*	
Complete the following section if you answered 'No' to question 3.4.1		
5.2.01	Where is data being stored and used? (location, organisation, address – refer to addresses in previous sections if appropriate)	
5.2.02	Data Protection Registration Number	
5.2.03	ISO 27001 Cert. No.	
5.2.04	Please provide details of security policy/procedure governing storage and use of data within this physical and technical environment – append supporting documentation referencing appropriate sections	
5.2.05	Does this policy/procedure cover the implementation of up-to-date controls for the detection and prevention of malware? Please provide details/ append supporting documentation	

5.2.06	Does this policy/procedure cover access control and auditing of system administrator activity? Please provide details/ append supporting documentation referencing appropriate sections
5.2.07	Does this policy/procedure cover the production of backups and the controls in place around these? Please provide details/ append supporting documentation
5.2.08	Does this policy/procedure describe the controls in place to prohibit unauthorised copying of data? Please provide details/ append supporting documentation referencing appropriate sections
5.2.09	Does this policy/procedure describe physical and site controls? Please provide details/ append supporting documentation referencing appropriate sections
5.2.10	Does this policy/procedure cover hardware repair, replacement or disposal and protection of data from inappropriate access during such procedures? Please provide details/ append supporting documentation
5.2.11	Describe the systems, software and security used to store and use data - please provide details/ append supporting documentation

5.2.12	Is outsourced IT in use? If yes, please give details	
Please repeat section 5.2 above for each relevant location in the proposal – see guidance		
5.3	**Transfer** *Please read section 5.3 of the guidance*	
5.3.01	Please provide details of security policy/procedure to ensure that data will be transferred in such a way that it is protected from inappropriate or unauthorised access (mention email encryption, secure file transfer protocols SFTP, device encryption, physical controls, etc, as appropriate) - append supporting documentation	
	Data will be transferred between ECOSS, PHI's HPS Statistical Support Team and eDRIS using nhs.net accounts	
5.3.02	At what intervals/ trigger points will data transfer take place? E.g. one of transfer, monthly intervals	
	A transfer of ECOSS data from HPS to the HPS Statistical Support Team to perform linkage and data preparation. Then a transfer of the anonymised extracts from the HPS Statistical Support Team to eDRIS for storage in the safe haven. This will be performed once for the purposes of this study alone.	
5.3.03	Will any identifiable or potentially identifiable data be transferred outside of the UK?	No
5.3.03b	If yes, please provide details of the country of destination, the method of transfer, the proposed location and method of storage outside of the UK, and details of any further onward transfer	

5.3.04	Other than initial transfers from source systems, is there any copying of data required within the proposal? If yes, please give details	
	No	
5.4	**Dissemination** *Please read section 5.4 of the guidance*	
5.4.01	Will proposal findings be published or disseminated beyond those listed in Section 1? (*If you have answered 'No', go directly to section 5.5)*	Yes
5.4.01a	If yes, how will proposal findings be published or disseminated, to what audience and in what format? Please give details	
	Peer-review journals, Conference, Presentations/Proceedings, PhD thesis of the University of Edinburgh	
5.4.01b	If yes, what steps will be taken to ensure that persons cannot be identified in published Please give details and confirm what disclosure control policy will be applied	
	All data will be aggregated prior to publication and issues around deductive disclosure will be taken into account. The risk will be based on the following: the cell values and table design, the topic in question (i.e. how 'sensitive' the topic is), populations, geographies and institutions involved, the likelihood of an	

	attempt to identify an individual, and the level of impact of any disclosure
5.4.01c	If yes, are there any circumstances where a living or dead individual would be cited? (E.g. where a person consented to their data being used as a case study)? Please give details
	No
5.4.01d	If yes, were any permissions to publish data required or sought (for example from data controllers)? Please provide details
	No
5.5	**Retain/Dispose** *Please read section 5.5 of the guidance*
5.5.01	Which information/data/records retention policy will you be applying to the proposal data (details of the policy and the organisation to which it belongs)?
	The National Safe Haven uses the NSS Document Storage, Retention and Disposal Policy.
5.5.02	How long do you intend to retain identifiable or potentially identifiable data after the conclusion of the proposal (including archive/backup copies)?
	Data to be archived will not contain identifiable information. The study data will be archived for 5 years
5.5.03	Who will retain the data and where?
	NSS National Safe Haven
5.5.04	What is the purpose for retaining the data for the specified time? Data will be retained to enable checking of results during and immediately following publication.

5.5.05	What method of disposal or destruction will be used when this period has expired (including archive/backup copies)?
	The National Safe Haven uses NHS Scotland Information Security Policy for guidance for destruction of data.
5.5.06	What evidence will be obtained that destruction has occurred (eg IT supplier certificate of destruction, etc)?
	The National Safe Haven uses NHS Scotland Information Security Policy for guidance for evidence of destruction of data.
5.6	**Review** *Please read section 5.6 of the guidance*
5.6.01	Describe how the mechanisms which safeguard data security will be audited and reviewed at regular intervals to ensure their continued efficacy
	Access to the safe haven is logged. Logs are monitored for unusual activity. Each person who accesses the data in the safe haven will have signed the eDRIS User Agreement which details acceptable use and penalties for misuse.
5.6.02	Describe any resource implications to any of the proposed measures for the protection of physical or technical security of information which are unresolved at the time of this application? (for example encryption of devices is an intention not yet fulfilled, training is not yet undertaken, etc)
	Not applicable

5.6.03	Describe the breach reporting mechanisms to be invoked in the event of any inappropriate access to data or other information security incident
	As per the eDRIS User Agreement (section 2.1), researchers will inform the safe haven research co-ordinator of any breaches.

Section 6 – Declaration

- I DECLARE THAT this application is accurate, and that, should it be successful, any health data made accessible will be used for no other purpose, and in no other way, than as described above.
- I UNDERTAKE TO notify the Public Benefit and Privacy Panel of any future changes to the purpose or manner in which data is processed in accordance with this application.
- I UNDERSTAND THAT any future applications by me, or my employing or sponsoring organisation, may be refused should any health data made accessible be used for any other purpose or in any other way than that described above.
- I CERTIFY THAT all those who have access to health data in this proposal are aware of the requirements of confidentiality and understand that any breach (eg disclosure of confidential information to a person not authorised to receive it) will be reported to the data controller, and in the case of NHS Scotland originated data to Scottish Government eHealth division.
- I GUARANTEE THAT no publication will appear in any form in which an individual may be identified without the written permission of that individual, and that I will apply appropriate disclosure control when planning publications involving the data requested.
- I UNDERSTAND THAT the Data Controller, and agents acting on its behalf, reserves the right to inspect the data on the sites where it is being processed.

To be signified by the APPLICANT

Name (in Capitals):	Date:
SHENGYUAN ZHAO SHENGYUAN ZHAO	08/06/2017

To be signified by the PhD SUPERVISOR (if applicable)

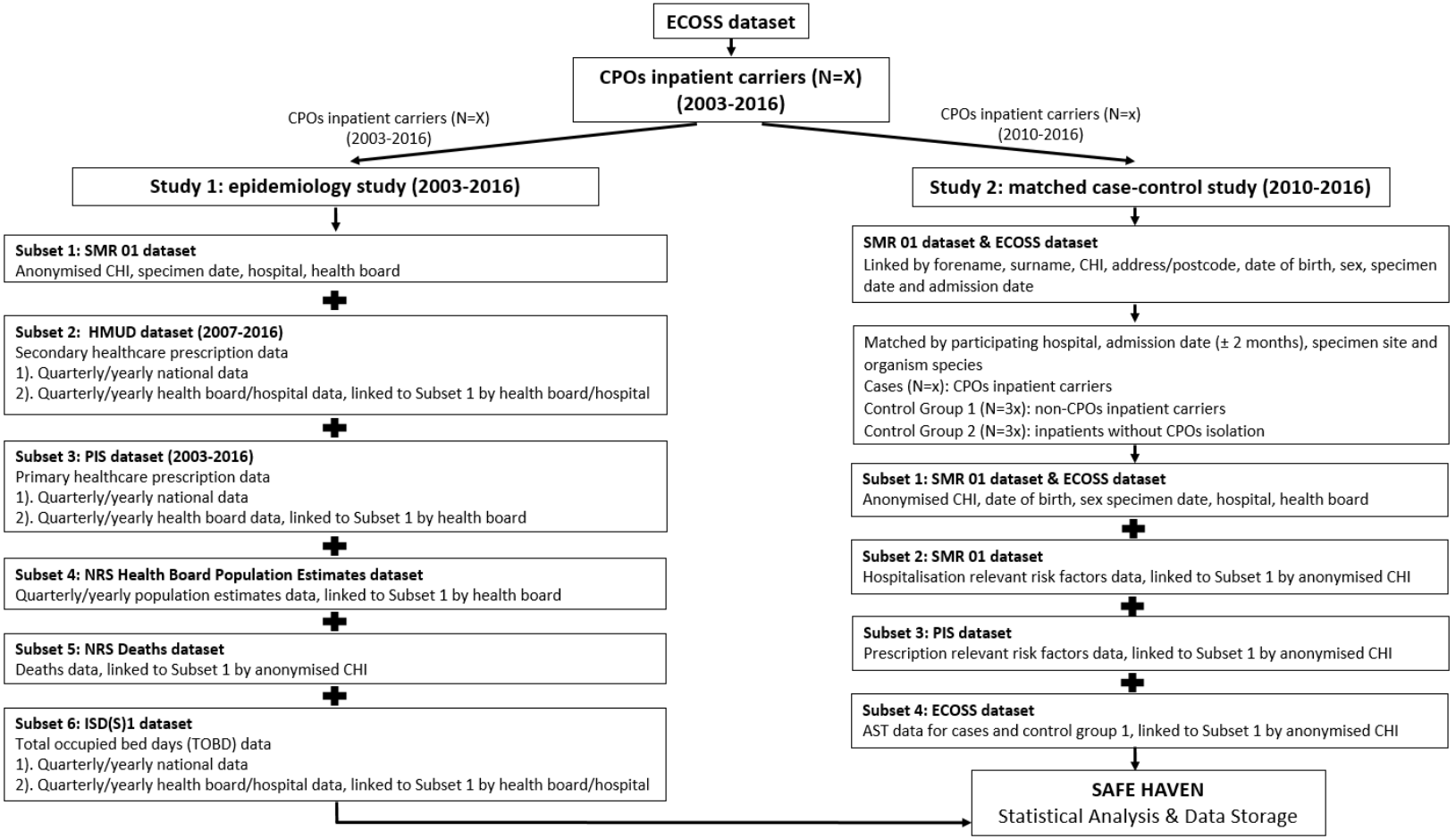
Name (in Capitals):	Date: 08/06/2017
MARK WOOLHOUSE	

- I DECLARE THAT (the applicant named above) is a *bona fide* worker engaged in a reputable project and that the data he/she asks for can be entrusted to him/her in the knowledge that he/she will conscientiously discharge his/her obligations, including in regard to confidentiality of the data, as stated in the declaration above.

To be signified by the INFORMATION CUSTODIAN named in Section 1.4 above (where the Information Custodian is not the applicant).

Name (in Capitals):	Date: 08/06/2017
ELEANOR ANDERSON	

Appendix I. Flow chart of the study



Appendix II. Carbapenemase Producing Organisms (CPOs) of interest

Enterobacteriaceae	Non-fermenting bacteria
Escherichia coli	***Pseudomonas spp.***
Klebsiella spp.	P. aeruginosa
K. pneumoniae	P. fluorescens
K. oxytoca	P. putida
K. granulomatis	P. stutzeri
K. terrigena	***Acinetobacter spp.***
K. variicola	A. baumannii
Enterobacter spp.	A. lwoffii
Enterobacter cloacae complex	A. Junii
E. cloacae	
E. asburiae	
E. hormaechei	
E. kobei	
E. ludwigii	
E. nimipressuralis	
E. aerogenes	
E. agglomerans	
Other Enterobacter species	
Citrobacter spp.	
C. freundii	
C. diversus	
C. koseri	
Other Citrobacter species	
Providencia spp.	
P. stuartii	
P. rettgeri	
Proteus spp.	
P. mirabilis	
P. vulgaris	

Appendix III. Antimicrobial agents included in prescription and resistance rate analysis

Antimicrobial Class	Antimicrobial Subclass	Agents	Enterobacteriaceae	Non-fermenting bacteria
Penicillin	Penicillinase-labile penicillins	Amoxicillin	√	√
		Ampicillin	√	√
β-Lactam/β-lactamase inhibitor combinations		Co-amoxiclav (i.e. Amoxicillin-clavulanate)	√	√
		Piperacillin-tazobactam	√	√
Cephems	Cephalosporin II	Cefuroxime	√	√
	Cephalosporin III	Cefotaxime	√	√
		Ceftazidime	√	√
		Ceftriaxone	√	√
	Cephamycin	Cefoxitin	√	
Monobactams		Aztreonam	√	
Penems	Carbapenem	Imipenem (i.e. imipenem with cilastatin)	√	√
		Meropenem	√	√
Aminoglycosides		Amikacin	√	√
		Gentamicin	√	√
Folate pathway inhibitors		Trimethoprim	√	√
		Trimethoprim-sulfamethoxazole	√	√
Pseudomonic acid	Fluoroquinolone	Ciprofloxacin	√	√
		Levofloxacin	√	√

Cephalosporin II, III are referred to as second- and third-generation cephalosporins, respectively.

Appendix IV. Supporting document of NHS ethical approval absence

RE: Seek Ethics advice for intended study (eDRIS reference no. 1617-0328)

Godden, Judith <Judith.Godden@ggc.scot.nhs.uk>

Thu 09/03/2017 16:26

Inbox

To: ZHAO Shengyuan <Shengyuan.Zhao@ed.ac.uk>;

Dear Shengyuan
As I understand it the data you will be getting has been fully anonymised before you have any access to it. It should also be checked for any possible statistical disclosure. Fully anonymised routine data does not usually require NHS ethical approval. Also as I understand it, eDRIS has the ability through its own generic ethical approval to approve on behalf of ethics (please check this with them).
You may find that your University will want the study to go through the University Ethics Committee. I suggest you do not require to apply for ethics approval through IRAS unless eDRIS specifically require it.

Kind regards

Judith

Dr Judith Godden
Manager/Scientific Officer
West of Scotland Research Ethics Service
Clinical Research & Development
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow G3 8SW

Tel: 0141 232 1784
e-mail:

Appendix V. Supporting document of R&D approval absence

RE: Seek advice on Ethics and R&D research approval of intended study (eDRIS Ref No. 1617-0328)

CONER Chris

Mon 13/03/2017 10:09

To:ZHAO Shengyuan <Shengyuan.Zhao@ed.ac.uk>;

Cc:CHASE-TOPPING Margo <Margo.Chase@ed.ac.uk>;

Dear Shengyuan,

Thank you for your email. If all the data is being processed through eDRIS then the decision on whether NHS ethics is needed falls to the eDRIS team, they should be able to advise you.

Has you study had any sort of departmental ethical review?

I've spoken with the NHS Lothian R&D team, you will not need R&D approval. You will however need to seek approval from HPS for the use of their data/resources.

Hope this helps, please let me know if you have any questions.

Many thanks,

Chris

Christopher Coner

Clinical Research Governance Coordinator

Email:

tel: 0131 2423326 (ext. 23326) ***Note new number.

Research Governance
College of Medicine & Veterinary Medicine
University of Edinburgh
The Queen's Medical Research Institute
47 Little France Crescent
Edinburgh, EH16 4TJ

Appendix VI. Departmental ethical approval

THE UNIVERSITY *of* EDINBURGH

Centre for Population Health Sciences
THE USHER INSTITUTE of POPULATION HEALTH SCIENCES AND INFORMATICS
The University of Edinburgh
Medical School
Teviot Place
Edinburgh
EH8 9AG
Tel: +44 (0)131 650 3237
Fax +44 (0)131 650 6909
www.ed.ac.uk
email: cphs.ethics@ed.ac.uk

16 March 2017

Shengyuan Zhao
PhD student
Usher Institute of Population Health Sciences & Informatics
Ashworth Laboratories, Kings Buildings
University of Edinburgh
Charlotte Auerbach Road
Edinburgh
EH9 3FL

Dear Shengyuan

Re: Epidemiology of Carbapenem-Resistant Gram-negative Bacilli (CRGNB) in Scotland

This is to confirm that the Level 1 Ethics Self-Audit undertaken by you with respect to the above study (as submitted on **14/03/2017**) demonstrates that the proposed research poses no reasonably foreseeable ethical risks. Within our research governance process, this means that the research proposed (as outlined on the Level 1 form) does not require formal ethical review by the Review Group – i.e. it can be considered to be 'exempt'.

You may forward this letter to any collaborating data owner who requires reassurance as to ethical oversight of the research proposed, together with the Level 1 form completed.

Yours sincerely

Diane White
Ethics Review Group Administrator

The University of Edinburgh is a charitable body, registered in Scotland, with registration number SC005336

Appendix 3-2. Definition of each independent variable included in risk factors analysis for 30-day mortality of 150 hospitalised carbapenemase-producing organisms (CPO) cases and characteristics of CPO cases

Variables	Definition
Demographics	*According to General Acute Inpatient and Day Case-Scottish Morbidity Record (SMR01) (Information Services Division National Survices Scotland, 2016)*
Age, years	Age at CPO diagnosis
Older (>60 years)	Age>60 years old at CPO diagnosis
Gender, male	As described in section "Sex (Gender)" of the medical records
Microbiological characteristics	
Organism family, Non-fermenter	Carbapenemase producing *Pseudomonas* species and *Acinetobacter* species
Comorbidities	*According to International Classification of Diseases-10th Revision codes (ICD-10) (Centers for Disease Control and Prevention, 2017)*
Certain infectious and parasitic diseases	A00-B99
Sepsis	Name of diseases including the term "Sepsis" and "Septic Shock"
Co-presence with other pathogens	Bacteria (including Clostridium perfringens, Clostridium difficile, Streptococcus, Staphylococcus, Salmonella), fungus (including Aspergillus, Candida), virus (including human immunodeficiency viruses HIV, Hepatitis C virus, Reoviridae)
Neoplasms and diseases of the blood and blood-forming organs	C00-D89
Malignancy	C00-C80, C7A, C81-C96, D00-D09
Solid	Including carcinoma and malignant neoplasm
Hematology	Including lymphoma, leukaemia, multiple myeloma and myelodysplastic syndrome
Anaemia	Neoplasms and diseases of the blood and blood-forming organs with anaemia
Endocrine, nutritional and metabolic diseases	E00-E89
Diabetes mellitus	Including Type 1 and Type 2
With complications	Including circulatory complications, ketoacidosis and multiple complications

Variables	Definition
Diseases of the circulatory system	I00-I99
Heart failure	Circulatory diseases with heart failure
Diseases of the respiratory system	J00-J99
Respiratory tract infection	Including pneumonia and upper/lower respiratory tract infection
Respiratory failure	Circulatory diseases with respiratory failure
Diseases of the digestive system	K00-K95, excluding constipation
Diseases of the genitourinary system	N00-N99
Urinary tract infection	Including cystitis
Renal failure	Diseases of the genitourinary system with renal failure or chronic kidney disease at stage 5
Diseases of the nervous system	G00-G99
Diseases of the skin and subcutaneous tissue	L00-L99
Diseases of the musculoskeletal system and connective tissue	M00-M99
External causes of morbidity	V00-Y99
Injury, poisoning and certain other consequences of external causes	S00-T88
Systemic infection or organ failure	Sepsis or heart failure or respiratory failure or renal failure
Immunocompromised status	Patients with AIDS, malignancy, stem blood cell or organ transplant, chemotherapy or radiotherapy
Healthcare exposure	*According to General Acute Inpatient and Day Case-Scottish Morbidity Record (SMR01) (Information Services Division National Survices Scotland, 2016), healthcare exposure in the prior 90 days before specimen collection date of the first positive culture, unless stated otherwise.*
Emergency admission	For the index hospitalisation, Admission Type: 30-39

Variables	Definition
Admission from healthcare facilities	For the index hospitalisation, Admission/Transfer From: 24, 25, 40-59, 4A-4H, 5A-5H
Surgical Specialty	For the index hospitalisation, Specialty/Discipline: C1, C3, C6, C8, C9, C11-13, C41-42, CA, CB
Time at risk, days	For the index hospitalisation, interval between hospital admission and specimen collection date of the first positive culture
HDU stay	Stayed in HDU
Duration of HDU stay, days	Total days of HDU stay
ICU stay	Stayed in ICU
Duration of ICU stay, days	Total days of ICU stay
Hospitalisation	Admitted to a hospital *in the prior 90 days before the current index admission date*
Duration of hospitalisation, days	Total days of hospital stay
Hospital transfer	Transferred between different hospitals
Ward transfer	Transferred between different significant facilities during hospitalisation
Discharge type, death	For the index hospitalisation: Discharge Type-Death: 40-43
Discharge to healthcare facilities	For the index hospitalisation: Discharge/Transfer To: 24, 25, 40-59, 61, 4A-4H, 5A-5H
Invasive procedures	*According to OPCS Classification of Interventions and Procedures version 4.7 (OPCS-4.7) (National Health Service Digital, 2013), in the prior 90 days before specimen collection date of the first positive culture.*
Any	Any invasive procedures mentioned below
Transplantation	Stem blood cell or solid organ transplantation
Centesis	Extraction of bone marrow, spinal puncture, pleural aspiration or percutaneous needle biopsy
Ectomy	Ectomy, excision, resection, amputation or extirpation surgical operation
Catheterisation	Insertion of indwelling devices, including tunnelled catheter, urinary catheter, CVC and percutaneous transluminal cannulation of artery

Variables	Definition
Urinary catheter	Insertion of urinary catheter
CVC	Insertion of CVC
Dialysis or drainage	Dialysis or drainage requiring catheterisation, including haemodialysis, peritoneal dialysis, drainage of ascites/ventricle of brain/sphenoid sinus/gall bladder/pleural cavity/biliary/cerebrospinal fluid
Endoscopic operation	Endoscopic examination, resection, cauterization, insertion, dilation, aspiration, incision or extirpation
Invasive ventilation	Invasive ventilation
Other surgical procedures	Xenograft replacement, autograft of skin, vein graft, debridement, prosthetic replacement, repair of diaphragmatic hernia, drainage of perianal abscess/lesion of skin, opening of abdomen, posterior instrumented fusion of lumbar spine, open reduction of fracture, internal fixation, ileostomy, tracheostomy, percutaneous insertion of nephrostomy tube, cystostomy, gastrostomy, antrostomy, intubation of stomach, arteriography, stomach bypass, aorta anastomosis, percutaneous transluminal angioplasty, colostomy, evacuation of subdural haematoma, freeing of adhesions of peritoneum, annuloplasty, colporrhaphy, implantation of cardiac pacemaker system, transluminal operations on coronary artery

CPO, carbapenemase-producing organisms; ICU, intensive care unit; HDU, high dependency unit; CVC, central venous catheter.

Appendix 3-3. Characteristics associated with all-cause 30-day mortality of 150 hospitalised carbapenemase-producing organisms (CPO) cases

Characteristics	Survivor (%)§ (N=127)	Non-survivor (%)§ (N=23)	Univariate		Multivariate	
			OR (95%CI)	*P* value	aOR (95%CI)	*P* value
Demographics						
Age, years, median (IQR)	62 (49.5-74)¤	71 (61-78)¤	1.04 (1.00-1.07)	0.024		
Age>60 years old	69 (54.33)	18 (78.26)	3.03 (1.06-8.65)	0.039	3.36 (1.06-10.63)	0.033
Gender, male	73 (57.48)	12 (52.17)	0.81 (0.33-1.97)	0.637		
Microbiological characteristics						
Organism family, Non-fermenter	21 (16.54)	10 (43.48)	3.88 (1.50-10.02)	0.005	4.88 (1.64-14.47)	0.005
Comorbidities						
Certain infectious and parasitic diseases	57 (44.88)	8 (34.78)	0.65 (0.26-1.65)	0.371		
Sepsis	11 (8.66)	6 (26.09)	3.72 (1.22-11.38)	0.021		
Co-presence with other pathogens	20 (15.75)	1 (4.35)	0.24 (0.03-1.91)	0.179		
Neoplasms and diseases of the blood and blood-forming organs	37 (29.13)	10 (43.48)	1.87 (0.75-4.64)	0.177		
Malignancy	24 (18.90)	9 (39.13)	2.76 (1.07-7.12)	0.036	1.57 (0.49-5.09)	0.081
Solid	8 (6.30)	3 (13.04)	2.23 (0.55-9.13)	0.264		
Hematologic	16 (12.60)	6 (26.09)	2.45 (0.84-7.13)	0.100		
Anaemia	7 (5.51)	2 (8.70)	1.63 (0.32-8.40)	0.558		
Endocrine, nutritional and metabolic diseases	31 (24.41)	5 (21.74)	0.86 (0.29-2.51)	0.783		
Diabetes mellitus	20 (15.75)	0 (0.00)	/	0.044¶		
With complications	8 (6.30)	0 (0.00)	/	0.609¶		
Diseases of the circulatory system	38 (29.92)	5 (21.74)	0.65 (0.23-1.88)	0.427		
Heart failure	3 (2.36)	0 (0.00)	/	1.000¶		
Diseases of the respiratory system	35 (27.56)	11 (47.83)	2.41 (0.97-5.96)	0.057		
Respiratory tract infection	21 (16.54)	8 (34.78)	2.69 (1.01-7.15)	0.047	1.41 (0.49-4.04)	0.185
Respiratory failure	2 (1.57)	2 (8.70)	5.95 (0.79-44.59)	0.083	2.12 (0.21-20.96)	0.169
Diseases of the digestive system	17 (13.39)	3 (13.04)	0.97 (0.26-3.62)	0.965		
Diseases of the genitourinary system	35 (27.56)	8 (34.78)	1.40 (0.55-3.60)	0.482		
Urinary tract infection	18 (14.17)	4 (17.39)	1.27 (0.39-4.18)	0.689		
Renal failure	15 (11.81)	4 (17.39)	1.57 (0.47-5.25)	0.462		
Diseases of the nervous system	19 (14.96)	0 (0.00)	/	0.046¶		
Diseases of the skin and subcutaneous tissue	11 (8.66)	3 (13.04)	1.58 (0.41-6.18)	0.509		
Diseases of the musculoskeletal system and connective tissue	17 (13.39)	0 (0.00)	/	0.076¶		

Characteristics	Survivor (%)§ (N=127)	Non-survivor (%)§ (N=23)	Univariate		Multivariate	
			OR (95%CI)	*P* value	aOR (95%CI)	*P* value
External causes of morbidity	44 (34.65)	4 (17.39)	0.40 (0.13-1.24)	0.112		
Injury, poisoning and certain other consequences of external causes	40 (31.50)	4 (17.39)	0.46 (0.15-1.43)	0.180		
Systemic infection or organ failure	24 (18.90)	11 (47.83)	3.93 (1.55-9.98)	0.004	4.21 (1.38-12.81)	0.032
Immunocompromised status	29 (22.83)	9 (39.13)	2.17 (0.85-5.53)	0.104		
Healthcare exposure						
Emergency admission	98 (77.17)	20 (86.96)	1.97 (0.55-7.11)	0.299		
Admission from healthcare facilities	13 (10.24)	3 (13.04)	1.32 (0.34-5.04)	0.689		
Surgical Specialty	60 (47.24)	9 (39.13)	0.72 (0.29-1.78)	0.474		
Time at risk, days, median (IQR)	5 (1-25.5)¤	13 (2-20.5)¤	1.01 (0.98-1.03)	0.593		
HDU stay	47 (37.01)	8 (34.78)	0.91 (0.36-2.30)	0.839		
Duration of HDU stay, days, median (IQR)	0 (0-2.5)¤	0 (0-2.5)¤	1.01 (0.97-1.06)	0.523		
ICU stay	33 (25.98)	9 (39.13)	1.83 (0.72-4.63)	0.201		
Duration of ICU stay, days, median (IQR)	0 (0-0)¤	0 (0-0.5)¤	1.02 (0.94-1.11)	0.636		
Hospitalisation	53 (41.73)	11 (47.83)	1.28 (0.53-3.12)	0.587		
Duration of hospitalisation, days, median (IQR)	17 (1-39)¤	18 (9-38)¤	1.00 (0.98-1.02)	0.799		
Hospital transfer	23 (18.11)	4 (17.39)	0.95 (0.30-3.06)	0.934		
Ward transfer	65 (51.18)	15 (65.22)	1.79 (0.71-4.51)	0.218		
Invasive procedures						
Any	52 (40.94)	12 (52.17)	1.57 (0.65-3.84)	0.319		
Centesis	7 (5.51)	3 (13.04)	2.57 (0.61-10.78)	0.196		
Ectomy	15 (11.81)	3 (13.04)	1.12 (0.30-4.23)	0.867		
Transplantation	4 (3.15)	0 (0.00)	/	1.000¶		
Catheterisation	15 (11.81)	2 (8.70)	0.71 (0.15-3.34)	0.666		
Urinary catheter	3 (2.36)	1 (4.35)	1.88 (0.19-18.89)	0.592		
CVC	12 (9.45)	2 (8.70)	0.91 (0.19-4.38)	0.909		
Dialysis or drainage	6 (4.72)	1 (4.35)	0.92 (0.11-7.99)	0.937		
Endoscopic operation	8 (6.30)	3 (13.04)	2.23 (0.55-9.13)	0.264		
Invasive ventilation	6 (4.72)	2 (8.70)	1.92 (0.36-10.16)	0.443		
Other surgical procedures	17 (13.39)	3 (13.04)	0.97 (0.26-3.62)	0.965		

/, not applicable;
¶, Fisher's exact test;

§, Number of survivors/non-survivors with the characteristics (percentage of survivors/non-survivors with the characteristics among all the survivors/non-survivors investigated), unless stated otherwise;
¤, median (interquartile range);
OR (95%CI), odds ratio (95% confidence interval); aOR (95%CI), adjusted odds ratio (95% confidence interval); CPO, carbapenemase-producing organisms; IQR, interquartile range; ICU, intensive care unit; HDU, high dependency unit; CVC, central venous catheter.

Appendix 4-1. Definition of each independent variable included in risk factors analysis for carbapenemase-producing organisms (CPO) infection and colonisation

Variables	Definition
Demographics	*According to General Acute Inpatient and Day Case-Scottish Morbidity Record (SMR01) (Information Services Division National Survices Scotland, 2016)*
Age, years	Age at diagnosis
Age>60 years old	Age over 40 years old
Gender, male	As described in medical records
Comorbidities	*According to International Classification of Diseases-10th Revision codes (ICD-10) (Centers for Disease Control and Prevention, 2017)*
Neoplasms and diseases of the blood and blood-forming organs	C00-D89 (Centers for Disease Control and Prevention, 2017)
Malignancy	C00-C80, C7A, C81-C96, D00-D09 (Centers for Disease Control and Prevention, 2017)
Solid	Including carcinoma and malignant neoplasm
Hematology	Including lymphoma, leukaemia, multiple myeloma and myelodysplastic syndrome
Anaemia	Neoplasms and diseases of the blood and blood-forming organs with anaemia
Endocrine, nutritional and metabolic diseases	E00-E89 (Centers for Disease Control and Prevention, 2017)
Diabetes mellitus	Including Type 1 and Type 2
With complications	Including circulatory complications, ketoacidosis and multiple complications
Diseases of the circulatory system	I00-I99 (Centers for Disease Control and Prevention, 2017)
Heart failure	Circulatory diseases with heart failure
Diseases of the respiratory system	J00-J99 (Centers for Disease Control and Prevention, 2017)
Respiratory failure	Circulatory diseases with respiratory failure

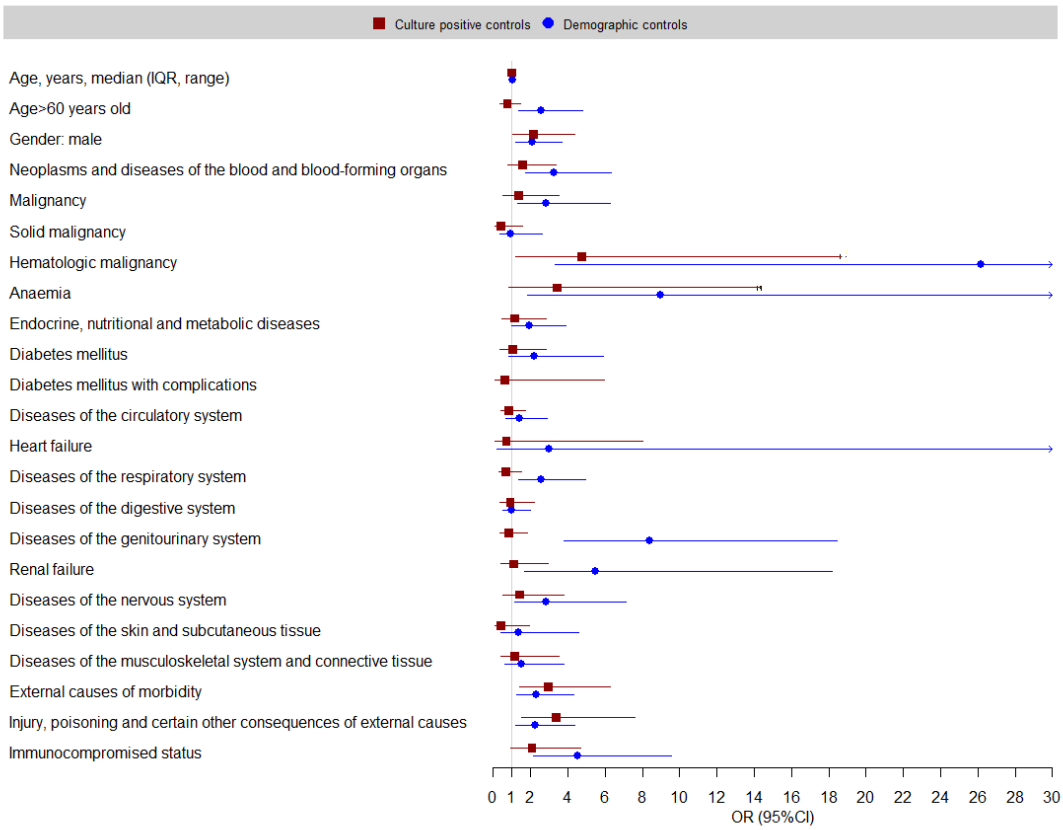
Variables	Definition
Diseases of the digestive system	K00-K95 (Centers for Disease Control and Prevention, 2017), excluding constipation
Diseases of the genitourinary system	N00-N99 (Centers for Disease Control and Prevention, 2017)
Renal failure	Diseases of the genitourinary system with renal failure or chronic kidney disease at stage 5
Diseases of the nervous system	G00-G99 (Centers for Disease Control and Prevention, 2017)
Diseases of the skin and subcutaneous tissue	L00-L99 (Centers for Disease Control and Prevention, 2017)
Diseases of the musculoskeletal system and connective tissue	M00-M99 (Centers for Disease Control and Prevention, 2017)
External causes of morbidity	V00-Y99 (Centers for Disease Control and Prevention, 2017)
Injury, poisoning and certain other consequences of external causes	S00-T88 (Centers for Disease Control and Prevention, 2017)
Immunocompromised status	Patients with AIDS, malignancy, stem blood cell or organ transplant, chemotherapy or radiotherapy
Healthcare exposure	*According to General Acute Inpatient and Day Case-Scottish Morbidity Record (SMR01) (Information Services Division National Survices Scotland, 2016), healthcare exposure in the prior 90 days before specimen collection date of the first positive culture for cases and test controls, before the discharge date of the index hospitalisation for demographic controls, unless stated otherwise.*
Emergency admission	For the index hospitalisation, Admission Type: 30-39 (Information Services Division National Survices Scotland, 2016)
Admission from healthcare facilities	For the index hospitalisation, Admission/Transfer From: 24, 25, 40-59, 4A-4H, 5A-5H (Information Services Division National Survices Scotland, 2016)

Variables	Definition
Surgical Specialty	For the index hospitalisation, Specialty/Discipline: C1, C3, C6, C8, C9, C11-13, C41-42, CA, CB (Information Services Division National Survices Scotland, 2016)
Time at risk, days	For the index hospitalisation, interval between hospital admission and specimen collection date of the first positive culture
HDU stay	Stayed in HDU
Duration of HDU stay, days	Total days of HDU stay
ICU stay	Stayed in ICU
Duration of ICU stay, days	Total days of ICU stay
Hospitalisation	Admitted to a hospital *in the prior 90 days before the current index admission date*
Duration of hospitalisation, days	Total days of hospital stay
Hospital transfer	Transferred between different hospitals
Ward transfer	Transferred between different significant facilities during hospitalisation
Invasive procedures	*According to OPCS Classification of Interventions and Procedures version 4.7 (OPCS-4.7) (National Health Service Digital, 2013), procedures conducted in the prior 90 days before specimen collection date of the first positive culture for cases and test controls, before the discharge date of the index hospitalisation for demographic controls.*
Any	Any invasive procedures mentioned below
Transplantation	Stem blood cell or solid organ transplantation
Centesis	Extraction of bone marrow, spinal puncture, pleural aspiration or percutaneous needle biopsy
Ectomy	Ectomy, excision, resection, amputation or extirpation surgical operation
Catheterisation	Insertion of indwelling devices, including tunnelled catheter, urinary catheter, CVC and percutaneous transluminal cannulation of artery
Urinary catheter	Insertion of urinary catheter
CVC	Insertion of CVC

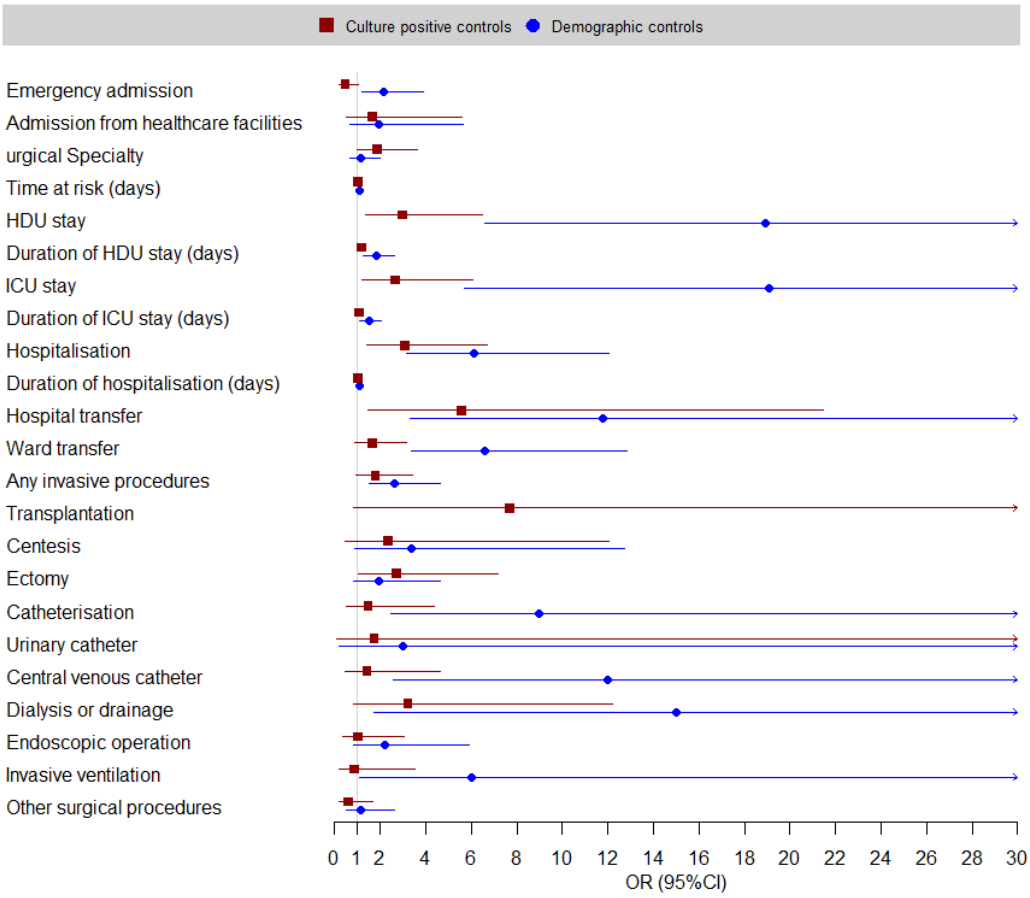
Variables	Definition
Dialysis or drainage	Dialysis or drainage requiring catheterisation, including haemodialysis, peritoneal dialysis, drainage of ascites/ventricle of brain/sphenoid sinus/gall bladder/pleural cavity/biliary/cerebrospinal fluid
Endoscopic operation	Endoscopic examination, resection, cauterization, insertion, dilation, aspiration, incision or extirpation
Invasive ventilation	Invasive ventilation
Other surgical procedures	Xenograft replacement, autograft of skin, vein graft, debridement, prosthetic replacement, repair of diaphragmatic hernia, drainage of perianal abscess/lesion of skin, opening of abdomen, posterior instrumented fusion of lumbar spine, open reduction of fracture, internal fixation, ileostomy, tracheostomy, percutaneous insertion of nephrostomy tube, cystostomy, gastrostomy, antrostomy, intubation of stomach, arteriography, stomach bypass, aorta anastomosis, percutaneous transluminal angioplasty, colostomy, evacuation of subdural haematoma, freeing of adhesions of peritoneum, annuloplasty, colporrhaphy, implantation of cardiac pacemaker system, transluminal operations on coronary artery

CPO, Carbapenemase-producing organisms; ICU, intensive care unit; HDU, high dependency unit; CVC, central venous catheter.

Appendix 4-2. Forest plots of results of univariate analyses of risk factors for carbapenemase-producing organisms (CPO) infection by comparing cases and culture positive controls/demographic controls. (A) Demographics and comorbidities related variables; (B) Healthcare exposure and invasive procedures related variables.

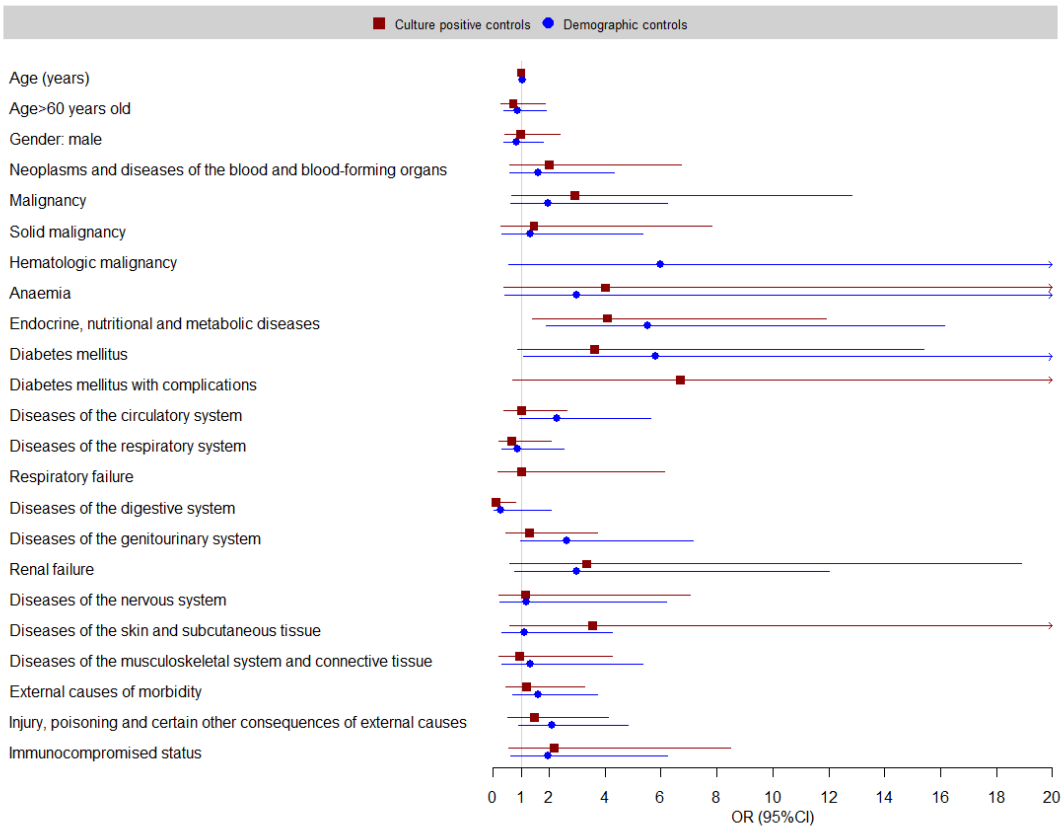


(A)

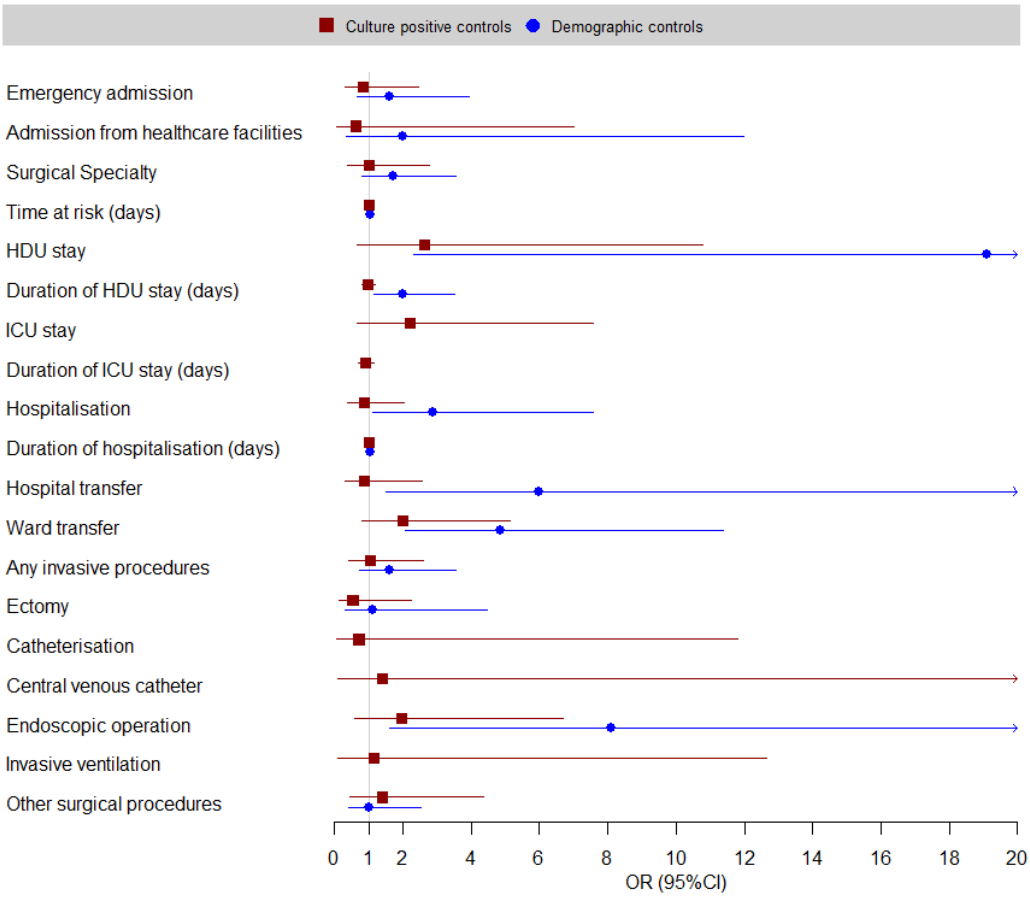

Culture positive controls
Demographic controls
Emergency admission
Admission from healthcare facilities
urgical Specialty
Time at risk (days)
HDU stay
Duration of HDU stay (days)
ICU stay
Duration of ICU stay (days)
Hospitalisation
Duration of hospitalisation (days)
Hospital transfer
Ward transfer
Any invasive procedures
Transplantation
Centesis
Ectomy
Catheterisation
Urinary catheter
Central venous catheter
Dialysis or drainage
Endoscopic operation
Invasive ventilation
Other surgical procedures
0 1 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
OR (95%CI)

(B)

Appendix 4-3. Forest plots of results of univariate analyses of risk factors for carbapenemase-producing organisms (CPO) colonisation by comparing cases and culture positive controls/demographic controls. (A) Demographics and comorbidities related variables; (B) Healthcare exposure and invasive procedures related variables.



(A)


Culture positive controls
Demographic controls
Emergency admission
Admission from healthcare facilities
Surgical Specialty
Time at risk (days)
HDU stay
Duration of HDU stay (days)
ICU stay
Duration of ICU stay (days)
Hospitalisation
Duration of hospitalisation (days)
Hospital transfer
Ward transfer
Any invasive procedures
Ectomy
Catheterisation
Central venous catheter
Endoscopic operation
Invasive ventilation
Other surgical procedures
0
1
2
4
6
8
10
12
14
16
18
20
OR (95%CI)

(B)

References

ADIBHESAMI, H., DOURAGHI, M., ZERAATI, H., BAZMI, F., RAHBAR, M., POURMAND, M. R., TABRIZI, M. S., ALIRAMEZANI, A. & GHOURCHIAN, S. 2016. Carbapenem-resistant Acinetobacter baumannii recovered from burn patients. *Journal of Pharmacy and Pharmaceutical Sciences,* 19**,** 339-348.

AHN, J. Y., SONG, J. E., KIM, M. H., CHOI, H., KIM, J. K., ANN, H. W., KIM, J. H., JEON, Y., JEONG, S. J., KIM, S. B., KU, N. S., HAN, S. H., SONG, Y. G., YONG, D., LEE, K., KIM, J. M. & CHOI, J. Y. 2014. Risk factors for the acquisition of carbapenem-resistant Escherichia coli at a tertiary care center in South Korea: a matched case-control study. *American Journal of Infection Control,* 42**,** 621-625.

AKGUL, F., BOZKURT, I., SUNBUL, M., ESEN, S. & LEBLEBICIOGLU, H. 2016. Risk factors and mortality in the Carbapenem-resistant Klebsiella pneumoniae infection: case control study. *Pathogens and Global Health,* 110**,** 321-325.

AKINCI, E., COLPAN, A., BODUR, H., BALABAN, N. & ERBAY, A. 2005. Risk factors for ICU-acquired imipenem-resistant Gram-negative bacterial infections. *Journal of Hospital Infection,* 59**,** 317-323.

AKTURK, H., SUTCU, M., SOMER, A., AYDIN, D., CIHAN, R., OZDEMIR, A., COBAN, A., INCE, Z., CITAK, A. & SALMAN, N. 2016. Carbapenem-resistant Klebsiella pneumoniae colonization in pediatric and neonatal intensive care units: risk factors for progression to infection. *The Brazilian Journal of Infectious Diseases,* 20**,** 134-140.

AL OTAIBI, F. E. & AL-HULAILY, F. F. 2012. Imipenem-resistant Psedomonas aeruginosa: Epidemiology and susceptibility patterns at a Teaching Hospital in Riyadh, Saudi Arabia. *African Journal of Microbiology Research,* 6**,** 1527-1533.

ALTOPARLAK, U., EROL S FAU - AKCAY, M. N., AKCAY MN FAU - CELEBI, F., CELEBI F FAU - KADANALI, A. & KADANALI, A. 2004. The time-related changes of antimicrobial resistance patterns and predominant bacterial profiles of burn wounds and body flora of burned patients. *Burns,* 30**,** 660-664.

AMBLER, R. P. 1980. The structure of beta-lactamases. *Philosophical Transactions of the Royal Society B: Biological Sciences,* 289**,** 321-331.

ANDERSON, D. R. & BURNHAM, K. P. 2002. *Model selection and inference: a practical information-theoretic approach, Second Edition,* New York, Springer-Verlag.

ANDERSON, D. R., BURNHAM, K. P. & THOMPSON, W. L. 2000. Null hypothesis testing: Problems, prevalence, and an alternative. *Journal of Wildlife Management,* 64**,** 912-923.

ANDERSON, K. F., LONSWAY, D. R., RASHEED, J. K., BIDDLE, J., JENSEN, B., MCDOUGAL, L. K., CAREY, R. B., THOMPSON, A., STOCKER, S., LIMBAGO, B. & PATEL, J. B. 2007. Evaluation of methods to identify the Klebsiella pneumoniae carbapenemase in Enterobacteriaceae. *Journal of Clinical Microbiology,* 45**,** 2723-2725.

ANDERTON, A., NWOGUH, C. E., MCKUNE, I., MORRISON, L., GREIG, M. & CLARK, B. 1993. A Comparative-Study of the Numbers of Bacteria Present in Enteral Feeds Prepared and Administered in Hospital and the Home. *Journal of Hospital Infection,* 23**,** 43-49.

ARMAND-LEFEVRE, L., ANGEBAULT, C., BARBIER, F., HAMELET, E., DEFRANCE, G., RUPPE, E., BRONCHARD, R., LEPEULE, R., LUCET, J. C., EL MNIAI, A., WOLFF, M., MONTRAVERS, P., PLESIAT, P. & ANDREMONT, A. 2013. Emergence of imipenem-resistant gram-negative bacilli in intestinal flora of intensive care patients. *Antimicrobial Agents and Chemotherapy,* 57**,** 1488-1495.

AUSTRALIAN COMMISSION ON SAFETY AND QUALITY IN HEALTH CARE. 2017. *Recommendations for the control of carbapenemase-producing Enterobacteriaceae (CPE). A guide for acute care health facilities.* [Online]. Australian Commission on Safety and Quality in Health Care. Available: https://www.safetyandquality.gov.au/sites/default/files/migrated/Recommendations-for-the-control-of-Carbapenemase-producing-Enterobacteriaceae.pdf [Accessed 24/12/2019].

AYDEMIR, H., CELEBI, G., PISKIN, N., OZTOPRAK, N., KESKIN, A. S., AKTAS, E., SUMBULOGLU, V. & AKDUMAN, D. 2012. Mortality attributable to carbapenem-resistant nosocomial Acinetobacter baumannii infections in a Turkish university hospital. *Japanese Journal of Infectious Diseases,* 65**,** 66-71.

BAL, Z. S., BEKMEZCI, N., SOYLU, M., SEN, S., AVCU, G., AYDEMIR, S. & VARDAR, F. 2018. The prospective evaluation of risk factors and clinical influence of carbapenem resistance in children with gram-negative bacteria infection. *American Journal of Infection Control,* 46**,** 147-153.

BALVINDER, M., AMBER, P., HARSIMRAN, K., VINAYKUMAR, H., NEHA, G. & NEELAM, T. 2017. Fecal carriage of carbapenem-resistant Enterobacteriaceae and risk factor analysis in hospitalised patients: a single centre study from India. *Indian Journal of Medical Microbiology,* 35**,** 555-562.

BANACH, D. B., FRANCOIS, J., BLASH, S., PATEL, G., JENKINS, S. G., LABOMBARDI, V., KREISWIRTH, B. N., SRINIVASAN, A. & CALFEE, D. P. 2014. Active surveillance for carbapenem-resistant Enterobacteriaceae using stool specimens submitted for testing for Clostridium difficile. *Infection Control and Hospital Epidemiology,* 35**,** 82-84.

BAR-YOSEPH, H., COHEN, N., KORYTNY, A., ANDRAWUS, E. R., EVEN DAR, R., GEFFEN, Y., HUSSEIN, K. & PAUL, M. 2019. Risk factors for mortality among carbapenem-resistant enterobacteriaceae carriers with focus on immunosuppression. *Journal of Infection,* 78**,** 101-105.

BARAN, G., ERBAY, A., BODUR, H., ONGURU, P., AKINCI, E., BALABAN, N. & CEVIK, M. A. 2008. Risk factors for nosocomial imipenem-resistant Acinetobacter baumannii infections. *International Journal of Infectious Diseases,* 12**,** 16-21.

BARRON, M. A., RICHARDSON, K., JEFFRES, M. & MCCOLLISTER, B. 2016. Risk factors and influence of carbapenem exposure on the development of carbapenem resistant Pseudomonas aeruginosa bloodstream infections and infections at sterile sites. *Springerplus,* 5**,** 755.

BARSHES, N. R., GOODPASTOR, S. E. & GOSS, J. A. 2004. Pharmacologic immunosuppression. *Frontiers in Bioscience,* 9**,** 411-420.

BARTSCH, S. M., MCKINNELL, J. A., MUELLER, L. E., MILLER, L. G., GOHIL, S. K., HUANG, S. S. & LEE, B. Y. 2017. Potential economic burden of carbapenem-resistant Enterobacteriaceae (CRE) in the United States. *Clinical Microbiology and Infection,* 23**,** 48.e49-48.e16.

BASSETTI, M., NICOLINI, L., ESPOSITO, S., RIGHI, E. & VISCOLI, C. 2009. Current status of newer carbapenems. *Current Medicinal Chemistry,* 16**,** 564-575.

BEDENIC, B., PLECKO, V., SARDELIC, S., UZUNOVIC, S. & GODIC TORKAR, K. 2014. Carbapenemases in gram-negative bacteria: laboratory detection and clinical significance. *BioMed Research International,* 2014**,** 841951.

BEEZHOLD, D. W., SLAUGHTER, S., HAYDEN, M. K., MATUSHEK, M., NATHAN, C., TRENHOLME, G. M. & WEINSTEIN, R. A. 1997. Skin Colonization with Vancomycin-Resistant Enterococci Among Hospitalized Patients with Bacteremia. *Clinical Infectious Diseases,* 24**,** 704-706.

BEN-DAVID, D., MASARWA, S., ADLER, A., MISHALI, H., CARMELI, Y. & SCHWABER, M. J. 2014. A national intervention to prevent the spread of carbapenem-resistant Enterobacteriaceae in Israeli post-acute care hospitals. *Infection Control and Hospital Epidemiology,* 35**,** 802-809.

BEN-DAVID, D., MASARWA, S., NAVON-VENEZIA, S., MISHALI, H., FRIDENTAL, I., RUBINOVITCH, B., SMOLLAN, G., CARMELI, Y. & SCHWABER, M. J. 2011. Carbapenem-resistant Klebsiella pneumoniae in post-acute-care facilities in Israel. *Infection Control and Hospital Epidemiology,* 32**,** 845-853.

BEYROUTHY, R., ROBIN, F., DABBOUSSI, F., MALLAT, H., HAMZE, M. & BONNET, R. 2014. Carbapenemase and virulence factors of Enterobacteriaceae in North Lebanon between 2008 and 2012: evolution via endemic spread of OXA-48. *Journal of Antimicrobial Chemotherapy,* 69**,** 2699-2705.

BHARGAVA, A., HAYAKAWA, K., SILVERMAN, E., HAIDER, S., ALLURI, K. C., DATLA, S., DIVITI, S., KUCHIPUDI, V., MUPPAVARAPU, K. S., LEPHART, P. R., MARCHAIM, D. & KAYE, K. S. 2014. Risk factors for colonization due to carbapenem-resistant Enterobacteriaceae among patients exposed to long-term acute care and acute care facilities. *Infection Control and Hospital Epidemiology,* 35**,** 398-405.

BIRNBAUM, J., KAHAN, F. M., KROPP, H. & MACDONALD, J. S. 1985. Carbapenems, a new class of beta-lactam antibiotics. Discovery and development of imipenem/cilastatin. *The American Journal of Medicine,* 78**,** 3-21.

BLAKISTON, M., HEFFERNAN, H., ROBERTS, S. & FREEMAN, J. 2017. The clear and present danger of carbapenemase-producing Enterobacteriaceae (CPE) in New Zealand: time for a national response plan. *The New Zealand Medical Journal,* 130**,** 72-79.

BLEUMIN, D., COHEN, M. J., MORANNE, O., ESNAULT, V. L., BENENSON, S., PALTIEL, O., TZUKERT, K., MOR-YOSEF LEVI, I., BEN-DOV, I. Z., LEVI, R., BLOCH, A. & HAVIV, Y. S. 2012. Carbapenem-resistant Klebsiella pneumoniae is associated with poor outcome in hemodialysis patients. *Journal of Infection,* 65**,** 318-325.

BORER, A., SAIDEL-ODES, L., ESKIRA, S., NATIV, R., RIESENBERG, K., LIVSHIZ-RIVEN, I., SCHLAEFFER, F., SHERF, M. & PELED, N. 2012. Risk factors for developing clinical infection with carbapenem-resistant Klebsiella pneumoniae in hospital patients initially only colonized with carbapenem-resistant K pneumoniae. *American Journal of Infection Control,* 40**,** 421-425.

BORER, A., SAIDEL-ODES, L., RIESENBERG, K., ESKIRA, S., PELED, N., NATIV, R., SCHLAEFFER, F. & SHERF, M. 2009. Attributable mortality rate for carbapenem-resistant Klebsiella pneumoniae bacteremia. *Infection Control and Hospital Epidemiology,* 30**,** 972-976.

BOU, G., OLIVER, A. & MARTINEZ-BELTRAN, J. 2000. OXA-24, a novel class D beta-lactamase with carbapenemase activity in an Acinetobacter baumannii clinical strain. *Antimicrobial Agents and Chemotherapy,* 44**,** 1556-1561.

BRESLOW, N. E. & CLAYTON, D. G. 1993. Approximate Inference in Generalized Linear Mixed Models. *Journal of the American Statistical Association,* 88**,** 9-25.

BROLUND, A., LAGERQVIST, N., BYFORS, S., STRUELENS, M. J., MONNET, D. L., ALBIGER, B., KOHLENBERG, A. & EUROPEAN ANTIMICROBIAL RESISTANCE GENES SURVEILLANCE NETWORK, E.-N. C. S. G. 2019. Worsening epidemiological situation of carbapenemase-producing Enterobacteriaceae in Europe, assessment by national experts from 37 countries, July 2018. *Eurosurveillance,* 24**,** 1900123.

BROWN, S., YOUNG, H. K. & AMYES, S. G. 2005. Characterisation of OXA-51, a novel class D carbapenemase found in genetically unrelated clinical strains of Acinetobacter baumannii from Argentina. *Clinical Microbiology and Infection,* 11**,** 15-23.

BUDAK, S., ONCUL, O., AKTAS, Z., ACAR, A., OZYURT, M., TURHAN, V., ERDEM, H. & GORENEK, L. 2014. The determination of carbapenem resistance in Escherichia coli and Pneumoniae isolates related to nosocomial infections and the evaluation of risk factors. *Southeast Asian Journal of Tropical Medicine and Public Health,* 45**,** 113-122.

BUEHRLE, D. J., SHIELDS, R. K., CLARKE, L. G., POTOSKI, B. A., CLANCY, C. J. & HONG NGUYEN, M. 2017. Carbapenem-resistant pseudomonas aeruginosa bacteremia: Risk factors for mortality and microbiologic treatment failure. *Antimicrobial Agents and Chemotherapy,* 61**,** e01243-16.

BURCKHARDT, I. & ZIMMERMANN, S. 2011. Using Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry To Detect Carbapenem Resistance within 1 to 2.5 Hours. *Journal of Clinical Microbiology,* 49**,** 3321-3324.

CAI, B. C., GU, Q., SHEN, R. H., LU, F., FU, X. F. & HU, B. J. 2015. Risk factors for Carbapenem-resistant Klebsiella pneumoniae infection in ICU patients. *Chinese Journal of Nosocomiology,* 25**,** 4847-4849.

CANDEVIR ULU, A., KURTARAN, B., INAL, A. S., KOMUR, S., KIBAR, F., YAPICI CICEKDEMIR, H., BOZKURT, S., GUREL, D., KILIC, F., YAMAN, A., AKSU, H. S. & TASOVA, Y. 2015. Risk factors of carbapenem-resistant Klebsiella pneumoniae infection: a serious threat in ICUs. *Medical Science Monitor,* 21**,** 219-224.

CAO, Y., MAO, J. Q., WEI, D. J., LI, X. & CHEN, W. 2015. Drug resistance of Carbapenem-resistant Klebsiella pneumonia colonized in neonates and risk factors of its clonization. *Chinese Journal of Clinical Infectious Diseases,* 8**,** 407-412.

CARDOSO, T., ALMEIDA, M., FRIEDMAN, N. D., ARAGAO, I., COSTA-PEREIRA, A., SARMENTO, A. E. & AZEVEDO, L. 2014. Classification of healthcare-associated infection: a systematic review 10 years after the first proposal. *BMC Medicine,* 12**,** 40.

CARDOSO, T., RIBEIRO, O., ARAGAO, I. C., COSTA-PEREIRA, A. & SARMENTO, A. E. 2012. Additional risk factors for infection by multidrug-resistant pathogens in healthcare-associated infection: a large cohort study. *BMC Infectious Diseases,* 12**,** 375.

CARRER, A., POIREL, L., YILMAZ, M., AKAN, O. A., FERIHA, C., CUZON, G., MATAR, G., HONDERLICK, P. & NORDMANN, P. 2010. Spread of OXA-48-encoding plasmid in Turkey and beyond. *Antimicrobial Agents and Chemotherapy,* 54**,** 1369-1373.

CARVALHO, K. R., CARVALHO-ASSEF, A. P. D. A., PEIRANO, G., SANTOS, L. C. G. D., PEREIRA, M. J. F. & ASENSI, M. D. 2009. Dissemination of multidrug-resistant Acinetobacter baumannii genotypes carrying blaOXA-23 collected from hospitals in Rio de Janeiro, Brazil. *International Journal of Antimicrobial Agents,* 34**,** 25-28.

CASSINI, A., HOGBERG, L. D., PLACHOURAS, D., QUATTROCCHI, A., HOXHA, A., SIMONSEN, G. S., COLOMB-COTINAT, M., KRETZSCHMAR, M. E., DEVLEESSCHAUWER, B., CECCHINI, M., OUAKRIM, D. A., OLIVEIRA, T. C., STRUELENS, M. J., SUETENS, C., MONNET, D. L. & BURDEN OF, A. M. R. C. G. 2019. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infectious Diseases,* 19**,** 56-66.

CASTANHEIRA, M., DESHPANDE, L. M., MATHAI, D., BELL, J. M., JONES, R. N. & MENDES, R. E. 2011. Early dissemination of NDM-1- and OXA-181-producing Enterobacteriaceae in Indian hospitals: report from the SENTRY Antimicrobial Surveillance Program, 2006-2007. *Antimicrobial Agents and Chemotherapy,* 55**,** 1274-1278.

CASTANHEIRA, M., TOLEMAN, M. A., JONES, R. N., SCHMIDT, F. J. & WALSH, T. R. 2004. Molecular characterization of a beta-lactamase gene, blaGIM-1, encoding a new subclass of metallo-beta-lactamase. *Antimicrobial Agents and Chemotherapy,* 48**,** 4654-4661.

CAVALCANTE RDE, S., CANET, P. & FORTALEZA, C. M. 2014. Risk factors for the acquisition of imipenem-resistant Acinetobacter baumannii in a burn unit: An appraisal of the effect of colonization pressure. *Scandinavian Journal of Infectious Diseases,* 46**,** 593-598.

CEKIN, Y., KARAGOZ, A., KIZILATES, F., CEKIN, A. H., OZTOPRAK CUVALCI, N., BULBULLER, N. & DURMAZ, R. 2013. Evaluation of a hospital outbreak related to carbapenem-resistant Pseudomonas aeruginosa. *Mikrobiyoloji Bulteni,* 47**,** 619-627.

CENTERS FOR DISEASE CONTROL AND PREVENTION 2011. *Principles of Epidemiology in Public Health Practice, Third Edition,* Atlanta, Centers for Disease Control and Prevention.

CENTERS FOR DISEASE CONTROL AND PREVENTION. 2013. *Antibiotic resistance threats in the United States, 2013* [Online]. Centers for Disease Control and Prevention. Available: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf [Accessed 24/12/2019].

CENTERS FOR DISEASE CONTROL AND PREVENTION. 2015. *Facility Guidance for Control of CarbapenemResistant Enterobacteriaceae (CRE) November 2015 Update* [Online]. Centers for Disease Control and Prevention. Available: https://www.cdc.gov/hai/pdfs/cre/CRE-guidance-508.pdf [Accessed 30/12/2019].

CENTERS FOR DISEASE CONTROL AND PREVENTION. 2017. *International Classification of Diseases-10th Revision codes* [Online]. Centers for Disease Control and Prevention. [Accessed 24/12/2019].

CENTERS FOR DISEASE CONTROL AND PREVENTION. 2019. *Antibiotic Resistance Threats in the United States, 2019* [Online]. Centers for Disease Control and Prevention. Available: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf [Accessed 24/12/2019].

CEZARIO, R. C., DUARTE DE MORAIS, L., FERREIRA, J. C., COSTA-PINTO, R. M., DA COSTA DARINI, A. L. & GONTIJO-FILHO, P. P. 2009. Nosocomial outbreak by imipenem-resistant metallo-beta-lactamase-producing Pseudomonas aeruginosa in an adult intensive care unit in a Brazilian teaching hospital. *Enfermedades Infecciosas y Microbiologia Clinica,* 27**,** 269-274.

CHANG, H. J., HSU, P. C., YANG, C. C., KUO, A. J., CHIA, J. H., WU, T. L. & LEE, M. H. 2011. Risk factors and outcomes of carbapenem-nonsusceptible Escherichia coli bacteremia: a matched case-control study. *Journal of Microbiology, Immunology and Infection,* 44**,** 125-130.

CHEN, H. H., LI, H. Y., HE, L. X., HU, B. J., CHEN, X. H., ZHOU, C. M. & GAO, X. D. 2010. Analysis of hospital-acquired pneumonia caused by Carbapenem-resistant Acinetobacter baumannii. *Chinese Journal of Infection and Chemotherapy,* 10**,** 94-99.

CHEN, N. & ZHAO, M. 2009. Risk factors and prognosis analysis for hospital acquired pneumonia caused by Carbapenem-resistant Pseudomonas aeruginosa. *Shaanxi Medical Journal,* 38**,** 1655-1657.

CHEN, Y. H., CHIUEH, C. C. & LEE, Y. J. 2014. Risk Factors of Carbapenem-resistant Acinetobacter baumannii Infection among Hospitalized Patients. *Journal of Experimental and Clinical Medicine (Taiwan),* 6**,** 143-146.

CHENG, V. C. C., CHEN, J. H., SO, S. Y., WONG, S. C., YAN, M. K., CHAU, P. H., LEE, W. M., TO, K. K., CHAN, J. F., HUNG, I. F., HO, P. L. & YUEN, K. Y. 2015. Use of fluoroquinolones is the single most important risk factor for the high bacterial load in patients with nasal and gastrointestinal colonization by multidrug-resistant Acinetobacter baumannii. *European Journal of Clinical Microbiology and Infectious Diseases,* 34**,** 2359-2366.

CHENG, V. C. C., CHEN, J. H. K., NG, W. C., WONG, J. Y. H., CHOW, D. M. K., LAW, T. C., SO, S. Y. C., WONG, S. C. Y., CHAN, T. C., CHAN, F. H. W., HO, P. L. & YUEN, K. Y. 2016a. Emergence of Carbapenem-Resistant Acinetobacter baumannii in Nursing Homes with High Background Rates of MRSA Colonization. *Infection Control and Hospital Epidemiology,* 37**,** 983-986.

CHENG, V. C. C., CHEN, J. H. K., SO, S. Y. C., WONG, S. C. Y., CHAU, P. H., WONG, L. M. W., CHING, R. H. C., NG, M. M. L., LEE, W. M., HUNG, I. F. N., HO, P. L. & YUEN, K. Y. 2016b. A Novel Risk Factor Associated with Colonization by Carbapenemase-Producing Enterobacteriaceae: Use of Proton Pump Inhibitors in Addition to Antimicrobial Treatment. *Infection Control and Hospital Epidemiology,* 37**,** 1418-1425.

CHIANG, T. T., YANG, Y. S., YEH, K. M., CHIU, S. K., WANG, N. C., LIN, T. Y., HUANG, L. Y., CHANG, F. Y., SIU, L. K., LIN, J. C. & CHEN, J. H. 2016. Quantification and comparison of virulence and characteristics of different variants of carbapenemase-producing Klebsiella pneumoniae clinical isolates from Taiwan and the United States. *Journal of Microbiology, Immunology and Infection,* 49**,** 83-90.

CHIOTOS, K., TAMMA, P. D., FLETT, K. B., NAUMANN, M., KARANDIKAR, M. V., BILKER, W. B., ZAOUTIS, T. & HAN, J. H. 2017. Multicenter study of the risk factors for colonization or infection with carbapenem-resistant Enterobacteriaceae in children. *Antimicrobial Agents and Chemotherapy,* 61**,** e01440-17.

CHITNIS, A. S., CARUTHERS, P. S., RAO, A. K., LAMB, J., LURVEY, R., BEAU DE ROCHARS, V., KITCHEL, B., CANCIO, M., TOROK, T. J., GUH, A. Y., GOULD, C. V. & WISE, M. E. 2012. Outbreak of carbapenem-resistant enterobacteriaceae at a long-term acute care hospital: sustained reductions in transmission through active surveillance and targeted interventions. *Infection Control and Hospital Epidemiology,* 33**,** 984-992.

CHO, H. H., KWON, K. C., KIM, S., PARK, Y. & KOO, S. H. 2018. Association between Biofilm Formation and Antimicrobial Resistance

in Carbapenem-Resistant Pseudomonas Aeruginosa. *Annals of Clinical and Laboratory Science,* 48**,** 363-368.

CHOI, S. W. & LAM, D. M. 2017. Heterogeneity in meta-analyses. Comparing apples and oranges? *Anaesthesia,* 72**,** 532-534.

CHUANG, Y. C., SHENG, W. H., LAUDERDALE, T. L., LI, S. Y., WANG, J. T., CHEN, Y. C. & CHANG, S. C. 2014. Molecular epidemiology, antimicrobial susceptibility and carbapenemase resistance determinants among Acinetobacter baumannii clinical isolates in Taiwan. *Journal of Microbiology, Immunology and Infection,* 47**,** 324-332.

CHUSRI, S., CHONGSUVIVATWONG, V., RIVERA, J. I., SILPAPOJAKUL, K., SINGKHAMANAN, K., MCNEIL, E. & DOI, Y. 2014. Clinical outcomes of hospital-acquired infection with Acinetobacter nosocomialis and Acinetobacter pittii. *Antimicrobial Agents and Chemotherapy,* 58**,** 4172-4179.

CHUSRI, S., SILPAPOJAKUL, K., MCNEIL, E., SINGKHAMANAN, K. & CHONGSUVIVATWONG, V. 2015. Impact of antibiotic exposure on occurrence of nosocomial carbapenem-resistant Acinetobacter baumannii infection: a case control study. *Journal of Infection and Chemotherapy,* 21**,** 90-95.

CISNEROS, J. M., RODRIGUEZ-BANO, J., FERNANDEZ-CUENCA, F., RIBERA, A., VILA, J., PASCUAL, A., MARTINEZ-MARTINEZ, L., BOU, G., PACHON, J., SPANISH GROUP FOR NOSOCOMIAL INFECTION FOR THE SPANISH SOCIETY OF INFECTIOUS, D. & CLINICAL, M. 2005. Risk factors for the acquisition of imipenem-resistant Acinetobacter baumannii in Spain: a nationwide study. *Clinical Microbiology and Infection,* 11**,** 874-879.

CLINICAL AND LABORATORY STANDARDS INSTITUTE. 2019. *Performance Standards for Antimicrobial Susceptibility Testing. 29th ed. CLSI supplement M100* [Online]. Wayne, PA: Clinical and Laboratory Standards Institute. Available: https://clsi.org/standards/products/microbiology/documents/m100/ [Accessed 24/12/2019].

COCHRANE CONSUMERS AND COMMUNICATION REVIEW GROUP. 2013. *Study quality guide: guide for review atuhors in assessing study quality* [Online]. Cochrane Consumers and Communication Review Group. Available: https://cccrg.cochrane.org/sites/cccrg.cochrane.org/files/public/uploads/StudyQualityGuide_May%202013.pdf [Accessed 15/01/2020].

CODJOE, F. S. & DONKOR, E. S. 2018. Carbapenem Resistance: A Review. *Medical Sciences,* 6**,** E1.

COELHO, J., WOODFORD, N., AFZAL-SHAH, M. & LIVERMORE, D. 2006. Occurrence of OXA-58-like carbapenemases in Acinetobacter spp. collected over 10 years in three continents. *Antimicrobial Agents and Chemotherapy,* 50**,** 756-758.

COLE, M. 1980. Beta-Lactams as Beta-Lactamase Inhibitors. *Philosophical Transactions of the Royal Society B-Biological Sciences,* 289**,** 207-223.

CORBELLA, X., MONTERO, A., PUJOL, M., DOMINGUEZ, M. A., AYATS, J., ARGERICH, M. J., GARRIGOSA, F., ARIZA, J. & GUDIOL, F. 2000. Emergence and rapid spread of carbapenem resistance during a large and sustained hospital outbreak of multiresistant Acinetobacter baumannii. *Journal of Clinical Microbiology,* 38**,** 4086-4095.

CORNAGLIA, G., GIAMARELLOU, H. & ROSSOLINI, G. M. 2011. Metallo-beta-lactamases: a last frontier for beta-lactams? *Lancet Infectious Diseases,* 11**,** 381-393.

CORREA, L., MARTINO, M. D., SIQUEIRA, I., PASTERNAK, J., GALES, A. C., SILVA, C. V., CAMARGO, T. Z., SCHERER, P. F. & MARRA, A. R. 2013. A hospital-based matched case-control study to identify clinical outcome and risk factors associated with carbapenem-resistant Klebsiella pneumoniae infection. *BMC Infectious Diseases,* 13**,** 80.

COSTANZA, M. C. & AFIFI, A. A. 1979. Comparison of Stopping Rules in Forward Stepwise Discriminant-Analysis. *Journal of the American Statistical Association,* 74**,** 777-785.

COUTINHO, A. E. & CHAPMAN, K. E. 2011. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Molecular and Cellular Endocrinology,* 335**,** 2-13.

COX, D. R. 1972. Regression Models and Life-Tables. *Journal of the Royal Statistical Society Series B-Statistical Methodology,* 34**,** 187-220.

CRISTINA, M. L., ALICINO, C., SARTINI, M., FACCIO, V., SPAGNOLO, A. M., BONO, V. D., CASSOLA, G., DE MITE, A. M., CRISALLI, M. P., OTTRIA, G., SCHINCA, E., PINTO, G. L., BOTTARO, L. C., VISCOLI, C., ORSI, A., GIACOBBE, D. R. & ICARDI, G. 2018. Epidemiology, management, and outcome of carbapenem-resistant Klebsiella pneumoniae bloodstream infections in hospitals within the same endemic metropolitan area. *Journal of Infection and Public Health,* 11**,** 171-177.

CUI, X., ZHANG, H. & DU, H. 2019. Carbapenemases in Enterobacteriaceae: Detection and Antimicrobial Therapy. *Frontiers in Microbiology,* 10**,** 1823.

CUNHA, C. B., KASSAKIAN, S. Z., CHAN, R., TENOVER, F. C., ZIAKAS, P., CHAPIN, K. C. & MERMEL, L. A. 2016. Screening of nursing home residents for colonization with carbapenem-resistant Enterobacteriaceae admitted to acute care hospitals: Incidence and risk factors. *American Journal of Infection Control,* 44**,** 126-130.

CUNNINGHAM, S. A., VASOO, S. & PATEL, R. 2016. Evaluation of the Check-Points Check MDR CT103 and CT103 XL Microarray Kits by Use of Preparatory Rapid Cell Lysis. *Journal of Clinical Microbiology,* 54**,** 1368-1371.

CUZON, G., NAAS, T., LESENNE, A., BENHAMOU, M. & NORDMANN, P. 2010. Plasmid-mediated carbapenem-hydrolysing OXA-48 beta-lactamase in Klebsiella pneumoniae from Tunisia. *International Journal of Antimicrobial Agents,* 36**,** 91-93.

DA SILVA, G. J., QUINTEIRA, S., BERTOLO, E., SOUSA, J. C., GALLEGO, L., DUARTE, A. & PEIXE, L. 2004. Long-term dissemination of an

OXA-40 carbapenemase-producing Acinetobacter baumannii clone in the Iberian Peninsula. *Journal of Antimicrobial Chemotherapy,* 54**,** 255-258.

DA SILVA, K. E., MACIEL, W. G., SACCHI, F. P., CARVALHAES, C. G., RODRIGUES-COSTA, F., DA SILVA, A. C., CRODA, M. G., NEGRAO, F. J., CRODA, J., GALES, A. C. & SIMIONATTO, S. 2016. Risk factors for KPC-producing Klebsiella pneumoniae: watch out for surgery. *Journal of Medical Microbiology,* 65**,** 547-553.

DAIKOS, G. L., PETRIKKOS, P., PSICHOGIOU, M., KOSMIDIS, C., VRYONIS, E., SKOUTELIS, A., GEORGOUSI, K., TZOUVELEKIS, L. S., TASSIOS, P. T., BAMIA, C. & PETRIKKOS, G. 2009. Prospective Observational Study of the Impact of VIM-1 Metallo-beta-Lactamase on the Outcome of Patients with Klebsiella pneumoniae Bloodstream Infections. *Antimicrobial Agents and Chemotherapy,* 53**,** 1868-1873.

DAIKOS, G. L., VRYONIS, E., PSICHOGIOU, M., TZOUVELEKIS, L. S., LIATIS, S., PETRIKKOS, P., KOSMIDIS, C., TASSIOS, P. T., BAMIAS, G. & SKOUTELIS, A. 2010. Risk factors for bloodstream infection with Klebsiella pneumoniae producing VIM-1 metallo-beta-lactamase. *Journal of Antimicrobial Chemotherapy,* 65**,** 784-788.

DAROUKH, A., DELAUNAY, C., BIGOT, S., CECI, J. M., SIDDHOUN, N., BUKREYEVA, I., RAISIN, J., PORCHERET, H., MAISONNEUVE, L. & BOULDOUYRE, M. A. 2014. Characteristics and costs of carbapenemase-producing enterobacteria carriers (2012/2013). *Medecine Et Maladies Infectieuses,* 44**,** 321-326.

DAUTZENBERG, M. J. D., OSSEWAARDE, J. M., DE GREEFF, S. C., TROELSTRA, A. & BONTEN, M. J. M. 2016. Risk factors for the acquisition of OXA-48-producing Enterobacteriaceae in a hospital outbreak setting: A matched case-control study. *Journal of Antimicrobial Chemotherapy,* 71**,** 2273-2279.

DE JAGER, P., CHIRWA, T., NAIDOO, S., PEROVIC, O. & THOMAS, J. 2015. Nosocomial outbreak of New Delhi metallobeta-lactamase-1-producing Gram-negative bacteria in South Africa: A case-control study. *PLoS ONE,* 10**,** e0123337.

DE LAVELEYE, M., HUANG, T. D., BOGAERTS, P., BERHIN, C., BAURAING, C., SACRE, P., NOEL, A., GLUPCZYNSKI, Y. & MULTICENTER STUDY, G. 2017. Increasing incidence of carbapenemase-producing Escherichia coli and Klebsiella pneumoniae in Belgian hospitals. *European Journal of Clinical Microbiology and Infectious Diseases,* 36**,** 139-146.

DEBBY, B. D., GANOR, O., YASMIN, M., DAVID, L., NATHAN, K., ILANA, T., DALIT, S., SMOLLAN, G. & GALIA, R. 2012. Epidemiology of carbapenem resistant Klebsiella pneumoniae colonization in an intensive care unit. *European Journal of Clinical Microbiology and Infectious Diseases,* 31**,** 1811-1817.

DEL MAR TOMAS, M., CARTELLE, M., PERTEGA, S., BECEIRO, A., LLINARES, P., CANLE, D., MOLINA, F., VILLANUEVA, R., CISNEROS, J. M. & BOU, G. 2005. Hospital outbreak caused by a carbapenem-resistant strain of Acinetobacter baumannii: patient

prognosis and risk-factors for colonisation and infection. *Clinical Microbiology and Infection,* 11**,** 540-546.

DENG, Q., XU, Q. F., ZHOU, Y., XU, Z., YU, Q., RAO, S. Y., TANG, S. Q. & CAO, X. W. 2016. The risk factors of Carbapenem-resistant Klebsiella pneumonia blood infection. *Chinese Journal of Microecology,* 28**,** 816-818.

DERIS, Z. Z., SHAFEI, M. N. & HARUN, A. 2011. Risk factors and outcomes of imipenem-resistant Acinetobacter bloodstream infection in North-Eastern Malaysia. *Asian Pacific Journal of Tropical Biomedicine,* 1**,** 313-315.

DERSIMONIAN, R. & LAIRD, N. 2015. Meta-analysis in clinical trials revisited. *Contemporary Clinical Trials,* 45**,** 139-145.

DETSIS, M., KARANIKA, S. & MYLONAKIS, E. 2017. ICU Acquisition Rate, Risk Factors, and Clinical Significance of Digestive Tract Colonization With Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae: A Systematic Review and Meta-Analysis. *Critical Care Medicine,* 45**,** 705-714.

DI MODUGNO, E., ERBETTI, I., FERRARI, L., GALASSI, G., HAMMOND, S. M. & XERRI, L. 1994. In vitro activity of the tribactam GV104326 against gram-positive, gram-negative, and anaerobic bacteria. *Antimicrobial Agents and Chemotherapy,* 38**,** 2362-2368.

DICKSTEIN, Y., EDELMAN, R., DROR, T., HUSSEIN, K., BAR-LAVIE, Y. & PAUL, M. 2016. Carbapenem-resistant Enterobacteriaceae colonization and infection in critically ill patients: a retrospective matched cohort comparison with non-carriers. *Journal of Hospital Infection,* 94**,** 54-59.

DIRAJLAL-FARGO, S., DEBIASI, R., CAMPOS, J. & SONG, X. 2014. Carbapenem-resistant Enterobacteriaceae in pediatric patients: epidemiology and risk factors. *Infection Control and Hospital Epidemiology,* 35**,** 447-449.

DIZBAY, M., GUZEL TUNCCAN, O., KARASAHIN, O. & AKTAS, F. 2014. Emergence of carbapenem-resistant Klebsiella spp. infections in a Turkish university hospital: epidemiology and risk factors. *Journal of Infection in Developing Countries,* 8**,** 44-49.

DIZBAY, M., TUNCCAN, O. G., SEZER, B. E. & HIZEL, K. 2010. Nosocomial imipenem-resistant Acinetobacter baumannii infections: epidemiology and risk factors. *Scandinavian Journal of Infectious Diseases,* 42**,** 741-746.

DJORDJEVIC, Z. M., FOLIC, M. M., FOLIC, N. D., GAJOVIC, N., GAJOVIC, O. & JANKOVIC, S. M. 2016. Risk factors for hospital infections caused by carbapanem-resistant Acinetobacter baumannii. *Journal of Infection in Developing Countries,* 10**,** 1073-1080.

DOUMITH, M., ELLINGTON, M. J., LIVERMORE, D. M. & WOODFORD, N. 2009. Molecular mechanisms disrupting porin expression in ertapenem-resistant Klebsiella and Enterobacter spp. clinical isolates from the UK. *Journal of Antimicrobial Chemotherapy,* 63**,** 659-667.

DUARTE, A., BOAVIDA, F., GROSSO, F., CORREIA, M., LITO, L. M., CRISTINO, J. M. & SALGADO, M. J. 2003. Outbreak of GES-1 beta-

lactamase-producing multidrug-resistant Klebsiella pneumoniae in a university hospital in Lisbon, Portugal. *Antimicrobial Agents and Chemotherapy,* 47**,** 1481-1482.

EAGYE, K. J., KUTI, J. L. & NICOLAU, D. P. 2009. Risk factors and outcomes associated with isolation of meropenem high-level-resistant Pseudomonas aeruginosa. *Infection Control and Hospital Epidemiology,* 30**,** 746-752.

EGGER, M., SMITH, G. D., SCHNEIDER, M. & MINDER, C. 1997. Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal,* 315**,** 629-634.

EPSTEIN, L., HUNTER, J. C., ARWADY, M. A., TSAI, V., STEIN, L., GRIBOGIANNIS, M., FRIAS, M., GUH, A. Y., LAUFER, A. S., BLACK, S., PACILLI, M., MOULTON-MEISSNER, H., RASHEED, J. K., AVILLAN, J. J., KITCHEL, B., LIMBAGO, B. M., MACCANNELL, D., LONSWAY, D., NOBLE-WANG, J., CONWAY, J., CONOVER, C., VERNON, M. & KALLEN, A. J. 2014. New Delhi metallo-beta-lactamase-producing carbapenem-resistant Escherichia coli associated with exposure to duodenoscopes. *JAMA,* 312**,** 1447-1455.

EROL, S., ALTOPARLAK, U., AKCAY, M. N., CELEBI, F. & PARLAK, M. 2004. Changes of microbial flora and wound colonization in burned patients. *Burns,* 30**,** 357-361.

EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL. 2014. *Systematic review of the effectiveness of infection control measures to prevent the transmission of extended-spectrum beta-lactamase-producing Enterobacteriaceae through cross-border transfer of patients* [Online]. European Centre for Disease Prevention and Control. Available: https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/ESBL-systematic-review-effectiveness-infection-control-measures.pdf [Accessed 24/12/2019].

EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL. 2018. *Antimicrobial consumption. Annual epidemiological report 2017* [Online]. European centre for Disease Prevention and Control. Available: https://www.ecdc.europa.eu/sites/portal/files/documents/ESAC-NET-reportAER-2017-updated.pdf [Accessed 18/04/2020].

EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL. 2019a. *Guidance on prevention and control of infections by carbapenem-resistant organisms* [Online]. European Centre for Disease Prevention and Control,. Available: https://www.ecdc.europa.eu/en/publications-data/directory-guidance-prevention-and-control/prevention-and-control-infections-1 [Accessed 24/12/2019].

EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL. 2019b. *Surveillance of antimicrobial resistance in Europe 2017* [Online]. European Centre for Disease Prevention and Control. Available: https://ecdc.europa.eu/sites/portal/files/documents/EARS-Net-report-2017-update-jan-2019.pdf [Accessed 24/12/2019].

EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL. 2019c. *Surveillance of antimicrobial resistance in Europe 2018* [Online]. European Centre for Disease Prevention and Control. Available: https://www.ecdc.europa.eu/sites/default/files/documents/surveillance-antimicrobial-resistance-Europe-2018.pdf [Accessed 24/12/2019].

EUROPEAN MEDICINES AGENCY. 2014. *Public statement on Doribax* [Online]. Available: https://www.ema.europa.eu/en/documents/public-statement/public-statement-doribax-withdrawal-marketing-authorisation-european-union_en.pdf [Accessed 06/02/2020].

EZE, P., BALSELLS, E., KYAW, M. H. & NAIR, H. 2017. Risk factors for Clostridium difficile infections - an overview of the evidence base and challenges in data synthesis. *Journal of Global Health,* 7**,** 010417.

FALAGAS, M. E., RAFAILIDIS, P. I., KOFTERIDIS, D., VIRTZILI, S., CHELVATZOGLOU, F. C., PAPAIOANNOU, V., MARAKI, S., SAMONIS, G. & MICHALOPOULOS, A. 2007. Risk factors of carbapenem-resistant Klebsiella pneumoniae infections: a matched case control study. *Journal of Antimicrobial Chemotherapy,* 60**,** 1124-1130.

FALAGAS, M. E., TANSARLI, G. S., KARAGEORGOPOULOS, D. E. & VARDAKAS, K. Z. 2014. Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. *Emerging Infectious Diseases,* 20**,** 1170-1175.

FALCONE, M., MEZZATESTA, M. L., PERILLI, M., FORCELLA, C., GIORDANO, A., CAFISO, V., AMICOSANTE, G., STEFANI, S. & VENDITTI, M. 2009. Infections with VIM-1 metallo-{beta}-lactamase-producing enterobacter cloacae and their correlation with clinical outcome. *Journal of Clinical Microbiology,* 47**,** 3514-3519.

FEI, D. S., CAO, Y. H., MENG, X. L., NAN, C. C., ZHAO, M. Y. & XU, H. Y. 2012. Risk factors for central line-associated blood stream infection caused by Carbapenem-resistant Acinetobacter baumannii. *Chinese Journal of Gerontology,* 32**,** 1605-1608.

FEI, D. S., CAO, Y. H., NAN, C. C., MENG, X. L., ZHAO, M. Y. & XU, H., Y. 2013. The risk factors associated with acquisition of ventilator associated pneumonia caused by carbapenem resistant Acinetobacter baumannii. *Chinese Journal of Gerontology,* 33**,** 4945-4948.

FEI, D. S., CAO, Y. H., NAN, C. C., MENG, X. L., ZHAO, M. Y. & XU, H. Y. 2014. Risk factors for ventilator associated pneumonia caused by Carbapene-resistant Klebsiella pneumoniae. *Chinese Journal of Gerontology,* 34**,** 5973-5976.

FLOKAS, M. E., KARAGEORGOS, S. A., DETSIS, M., ALEVIZAKOS, M. & MYLONAKIS, E. 2017. Vancomycin-resistant enterococci colonisation, risk factors and risk for infection among hospitalised paediatric patients: a systematic review and meta-analysis. *International Journal of Antimicrobial Agents,* 49**,** 565-572.

FONTI, V. & BELITSER, E. 2017. *Feature Selection using LASSO* [Online]. Available: https://beta.vu.nl/nl/Images/werkstuk-fonti_tcm235-836234.pdf [Accessed 10/04/2019].

FORTALEZA, C. M., FREIRE, M. P., FILHO DDE, C. & DE CARVALHO RAMOS, M. 2006. Risk factors for recovery of imipenem- or ceftazidime-resistant pseudomonas aeruginosa among patients admitted to a teaching hospital in Brazil. *Infection Control and Hospital Epidemiology,* 27**,** 901-906.

FREEMAN, R., MOORE, L. S. P., CHARLETT, A., DONALDSON, H. & HOLMES, A. H. 2015. Exploring the epidemiology of carbapenem-resistant Gram-negative bacteria in west London and the utility of routinely collected hospital microbiology data. *Journal of Antimicrobial Chemotherapy,* 70**,** 1212-1218.

FREIRE, M. P., ABDALA, E., MOURA, M. L., DE PAULA, F. J., SPADAO, F., CAIAFFA-FILHO, H. H., DAVID-NETO, E., NAHAS, W. C. & PIERROTTI, L. C. 2015. Risk factors and outcome of infections with Klebsiella pneumoniae carbapenemase-producing K. pneumoniae in kidney transplant recipients. *Infection,* 43**,** 315-323.

FREIRE, M. P., GARCIA, D. D. O., CURY, A. P., SPADAO, F., GIOIA, T. S. R. D., FRANCISCO, G. R., BUENO, M. F. C., TOMAZ, M., PAULA, F. J. D., FARO, L. B. D., PIOVESAN, A. C., ROSSI, F., LEVIN, A. S., DAVID NETO, E., NAHAS, W. C. & PIERROTTI, L. C. 2016a. Outbreak of IMP-producing carbapenem-resistant Enterobacter gergoviae among kidney transplant recipients. *Journal of Antimicrobial Chemotherapy,* 71**,** 2577-2585.

FREIRE, M. P., OSHIRO, I. C. V. S., PIERROTTI, L. C., BONAZZI, P. R., DE OLIVEIRA, L. M., SONG, A. T. W., CAMARGO, C. H., VAN DER HEIJDEN, I. M., ROSSI, F., COSTA, S. F., D'ALBUQUERQUE, L. A. C. & ABDALA, E. 2016b. Carbapenem-Resistant Enterobacteriaceae Acquired before Liver Transplantation: Impact on Recipient Outcomes. *Transplantation,* 101**,** 811-820.

FREIRE, M. P., PIERROTTI, L. C., OSHIRO, I. C. V. S., BONAZZI, P. R., OLIVEIRA, L. M. D., MACHADO, A. S., VAN DER HEIJDEN, I. M., ROSSI, F., COSTA, S. F., D'ALBUQUERQUE, L. A. C. & ABDALA, E. 2016c. Carbapenem-resistant Acinetobacter baumannii acquired before liver transplantation: Impact on recipient outcomes. *Liver Transplantation,* 22**,** 615-626.

FRIEDMAN, J., HASTIE, T. & TIBSHIRANI, R. 2010. Regularization Paths for Generalized Linear Models via Coordinate Descent. *Journal of Statistical Software,* 33**,** 1-22.

FURTADO, G. H., BERGAMASCO, M. D., MENEZES, F. G., MARQUES, D., SILVA, A., PERDIZ, L. B., WEY, S. B. & MEDEIROS, E. A. 2009. Imipenem-resistant Pseudomonas aeruginosa infection at a medical-surgical intensive care unit: risk factors and mortality. *Journal of Critical Care,* 24**,** 625.e629-625.e614.

FURTADO, G. H., GALES, A. C., PERDIZ, L. B., SANTOS, A. E., WEY, S. B. & MEDEIROS, E. A. 2010. Risk factors for hospital-acquired pneumonia caused by imipenem-resistant Pseudomonas aeruginosa in an intensive care unit. *Anaesthesia and Intensive Care,* 38**,** 994-1001.

GAGETTI, P., PASTERAN, F., MARTINEZ, M. P., FATOURAEI, M., GU, J., FERNANDEZ, R., PAZ, L., ROSE, W. E., CORSO, A. & ROSATO, A. E. 2016. Modeling Meropenem Treatment, Alone and in Combination with Daptomycin, for KPC-Producing Klebsiella pneumoniae Strains with Unusually Low Carbapenem MICs. *Antimicrobial Agents and Chemotherapy,* 60**,** 5047-5050.

GAGLIOTTI, C., GIORDANI, S., CICCARESE, V., BAROZZI, A., GIOVINAZZI, A., PIETRANTONIO, A. M., MORO, M. L., PINELLI, G. & SARTI, M. 2014. Risk factors for colonization with carbapenemase-producing Klebsiella pneumoniae in hospital: a matched case-control study. *American Journal of Infection Control,* 42**,** 1006-1008.

GALES, A. C., JONES, R. N. & SADER, H. S. 2011. Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006-09). *Journal of Antimicrobial Chemotherapy,* 66**,** 2070-2074.

GANOR, O., YASMIN, M., DAVID, L., NATHAN, K., ILANA, T., DALIT, S., SMOLLAN, G. & GALIA, R. 2012. Epidemiology of carbapenem resistant Klebsiella pneumoniae colonization in an intensive care unit. *European Journal of Clinical Microbiology and Infectious Diseases,* 31**,** 1811-1817.

GARBATI, M. A., SAKKIJHA, H. & ABUSHAHEEN, A. 2016. Infections due to Carbapenem Resistant Enterobacteriaceae among Saudi Arabian Hospitalized Patients: A Matched Case-Control Study. *BioMed Research International,* 2016**,** 3961684.

GARLANTEZEC, R., BOURIGAULT, C., BOLES, J. M., PRAT, G., BARON, R., TONNELIER, J. M., COSSE, M., LEFEVRE, M., JOURDAIN, S., LELAY, G., DANIEL, L., VIRMAUX, M., LE DU, I., TANDE, D., RENAULT, A. & LEJEUNE, B. 2011. Investigation and management of an imipenem-resistant oxa-23 Acinetobacter baumannii outbreak in an intensive care unit. *Medecine et Maladies Infectieuses,* 41**,** 430-436.

GARNER, J. S., JARVIS, W. R., EMORI, T. G., HORAN, T. C. & HUGHES, J. M. 1988. CDC definitions for nosocomial infections, 1988. *American Journal of Infection Control,* 16**,** 128-140.

GASINK, L. B., EDELSTEIN, P. H., LAUTENBACH, E., SYNNESTVEDT, M. & FISHMAN, N. O. 2009. Risk factors and clinical impact of Klebsiella pneumoniae carbapenemase-producing K. pneumoniae. *Infection Control and Hospital Epidemiology,* 30**,** 1180-1185.

GAVIRIA, D., GREENFIELD, V., BIXLER, D., THOMAS, C. A., IBRAHIM, S. M., KALLEN, A., LIMBAGO, B., KITCHEL, B. & TAYLOR, T. K. 2011. Carbapenem-resistant klebsiella pneumoniae associated with a long-term--care facility - west Virginia, 2009-2011. *Morbidity and Mortality Weekly Report,* 60**,** 1418-1420.

GEERLINGS, S. E. & HOEPELMAN, A. I. 1999. Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunology and Medical Microbiology,* 26**,** 259-265.

GIANNELLA, M., BARTOLETTI, M., MORELLI, M. C., TEDESCHI, S., CRISTINI, F., TUMIETTO, F., PASQUALINI, E., DANESE, I.,

CAMPOLI, C., LAURIA, N. D., FAENZA, S., ERCOLANI, G., LEWIS, R., PINNA, A. D. & VIALE, P. 2015. Risk factors for infection with carbapenem-resistant Klebsiella pneumoniae after liver transplantation: the importance of pre- and posttransplant colonization. *American Journal of Transplantation,* 15**,** 1708-1715.

GISKE, C. G., GEZELIUS, L., SAMUELSEN, O., WARNER, M., SUNDSFJORD, A. & WOODFORD, N. 2011. A sensitive and specific phenotypic assay for detection of metallo-beta-lactamases and KPC in Klebsiella pneumoniae with the use of meropenem disks supplemented with aminophenylboronic acid, dipicolinic acid and cloxacillin. *Clinical Microbiology and Infection,* 17**,** 552-556.

GIUFFRE, M., BONURA, C., GERACI, D. M., SAPORITO, L., CATALANO, R., DI NOTO, S., NOCIFORO, F., CORSELLO, G. & MAMMINA, C. 2013. Successful control of an outbreak of colonization by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae sequence type 258 in a neonatal intensive care unit, Italy. *Journal of Hospital Infection,* 85**,** 233-236.

GNIADEK, T. J., CARROLL, K. C. & SIMNER, P. J. 2016. Carbapenem-Resistant Non-Glucose-Fermenting Gram-Negative Bacilli: the Missing Piece to the Puzzle. *Journal of Clinical Microbiology,* 54**,** 1700-1710.

GOMEZ RUEDA, V. & ZULETA TOBON, J. J. 2014. Risk factors for infection with carbapenem-resistant Klebsiella pneumoniae: a case-case-control study. *Colombia Medica,* 45**,** 54-60.

GOVERNMENT OF CANADA. 2016. *Summary Report on Antimicrobial Resistant Organisms Surveillance Data from January 1, 2011 to December 31, 2015* [Online]. Government of Canada. Available: https://www.canada.ca/content/dam/canada/public-health/services/publications/science-research-data/canadian-nosocomial-infection-summary/cnisp-aro-2011-2015-report-final-eng.pdf [Accessed 24/12/2019].

GREGORY, C. J., LLATA, E., STINE, N., GOULD, C., SANTIAGO, L. M., VAZQUEZ, G. J., ROBLEDO, I. E., SRINIVASAN, A., GOERING, R. V. & TOMASHEK, K. M. 2010. Outbreak of carbapenem-resistant Klebsiella pneumoniae in Puerto Rico associated with a novel carbapenemase variant. *Infection Control and Hospital Epidemiology,* 31**,** 476-484.

GRUNDMANN, H., GLASNER, C., ALBIGER, B., AANENSEN, D. M., TOMLINSON, C. T., ANDRASEVIC, A. T., CANTON, R., CARMELI, Y., FRIEDRICH, A. W., GISKE, C. G., GLUPCZYNSKI, Y., GNIADKOWSKI, M., LIVERMORE, D. M., NORDMANN, P., POIREL, L., ROSSOLINI, G. M., SEIFERT, H., VATOPOULOS, A., WALSH, T., WOODFORD, N., MONNET, D. L., APFALTER, P., HARTL, R., GLUPCZYNSKI, Y., HUANG, T. D., STRATEVA, T., MARTEVA-PROEVSKA, Y., ANDRASEVIC, A. T., BUTIC, I., PIERIDOU-BAGATZOUNI, D., MAIKANTI-CHARALAMPOUS, P., HRABAK, J., ZEMLICKOVA, H., HAMMERUM, A., JAKOBSEN, L., IVANOVA, M., PAVELKOVICH, A., JALAVA, J., OSTERBLAD, M., VAUX, S., DORTET, L., KAASE, M., GATERMANN, S. G., VATOPOULOS, A.,

TRYFINOPOULOU, K., TOTH, A., JANVARI, L., BOO, T. W., MCGRATH, E., PANTOSTI, A., MONACO, M., BALODE, A., SAULE, M., MICIULEVICIENE, J., MIERAUSKAITE, A., PERRIN-WENIGER, M., REICHERT, P., NESTOROVA, N., DEBATTISTA, S., ZABICKA, D., LITERACKA, E., CANICA, M., MANAGEIRO, V., DAMIAN, M., LIXANDRU, B., NIKS, M., SCHRETEROVA, E., PIRS, M., CERAR, T., OTEO, J., ARACIL, B., GISKE, C. G., SJOSTROM, K., WOODFORD, N., HOPKINS, K., WIUFF, C., BROWN, D. J., HARDARSON, H., SAMUELSEN, O., HALDORSEN, B., KORAQI, A., LACEJ, D., RAKA, L., KURTI, A., MIJOVIC, G., LOPICIC, M., JELESIC, Z., TRUDIC, A., KRAFTANDZIEVA, A., TRAJKOVSKA-DOKIC, E., GUR, D., CAKAR, A., CARMELI, Y., ADLER, A. & CARBAPENEMASE-PROD, E. S. 2017. Occurrence of carbapenemase-producing Klebsiella pneumoniae and Escherichia coli in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study. *Lancet Infectious Diseases,* 17**,** 153-163.

GUO, M. F. & SUN, B. L. 2010. Risk factors for hospital aquired pneumonia caused by Carbapenem-resistant Pseudomonas aeruginosa. *Zhejiang Clinical Medicine,* 12**,** 1084-1086.

GUO, X., CAO, Z. & ZHANG, Z. 2016. Dissemination and evolution of blaOXA-23 gene among carbapenem-resistant Acinetobacter baumannii isolates from central China. *Journal of Infection in Developing Countries,* 10**,** 445-448.

GUO, Z. H., LIN, X. H., LI, Y. G., LIANG, W. F. & YAN, Z. M. 2008. Analysis of drug resistance of Imipenem-resistant Pseudomonas aeruginosa and risk factors. *China Tropical Medicine,* 8**,** 933-934,941.

GUPTA, N., LIMBAGO, B. M., PATEL, J. B. & KALLEN, A. J. 2011. Carbapenem-Resistant Enterobacteriaceae: Epidemiology and Prevention. *Clinical Infectious Diseases,* 53**,** 60-67.

GUREVITCH, J., KORICHEVA, J., NAKAGAWA, S. & STEWART, G. 2018. Meta-analysis and the science of research synthesis. *Nature,* 555**,** 175-182.

HAMPRECHT, A., POIREL, L., GOTTIG, S., SEIFERT, H., KAASE, M. & NORDMANN, P. 2013. Detection of the carbapenemase GIM-1 in Enterobacter cloacae in Germany. *Journal of Antimicrobial Chemotherapy,* 68**,** 558-561.

HANG, X. & ZHANG, B. 2016. Analysis of susceptible factors of patients with infections caused by Carbapenem-resistant Klebsiella pneumonia. *Journal of Shanxi Medical University,* 47**,** 450-454.

HARRIS, A. D., JOHNSON, J. K., THOM, K. A., MORGAN, D. J., MCGREGOR, J. C., AJAO, A. O., MOORE, A. C., COMER, A. C. & FURUNO, J. P. 2011. Risk factors for development of intestinal colonization with imipenem-resistant Pseudomonas aeruginosa in the intensive care unit setting. *Infection Control and Hospital Epidemiology,* 32**,** 719-722.

HARRIS, A. D., KARCHMER, T. B., CARMELI, Y. & SAMORE, M. H. 2001. Methodological principles of case-control studies that analyzed risk

factors for antibiotic resistance: A systematic review. *Clinical Infectious Diseases,* 32**,** 1055-1061.

HARRIS, A. D., KAYE, K. S. & CARMELI, Y. 2004. Assessing risk factors for acquiring antimicrobial-resistant pathogens: A time for a comparative approach - Reply to Zavascki. *Clinical Infectious Diseases,* 39**,** 872-873.

HARRIS, A. D., SAMORE, M. H., LIPSITCH, M., KAYE, K. S., PERENCEVICH, E. & CARMELI, Y. 2002a. Control-group selection importance in studies of antimicrobial resistance: Examples applied to Pseudomonas aeruginosa, enterococci, and Escherichia coli. *Clinical Infectious Diseases,* 34**,** 1558-1563.

HARRIS, A. D., SMITH, D., JOHNSON, J. A., BRADHAM, D. D. & ROGHMANN, M. C. 2002b. Risk factors for imipenem-resistant Pseudomonas aeruginosa among hospitalized patients. *Clinical Infectious Diseases,* 34**,** 340-345.

HAYAKAWA, K., MIYOSHI-AKIYAMA, T., KIRIKAE, T., NAGAMATSU, M., SHIMADA, K., MEZAKI, K., SUGIKI, Y., KURODA, E., KUBOTA, S., TAKESHITA, N., KUTSUNA, S., TOJO, M. & OHMAGARI, N. 2014. Molecular and epidemiological characterization of IMP-Type metallo-beta-lactamase-producing enterobacter cloacae in a large tertiary care hospital in Japan. *Antimicrobial Agents and Chemotherapy,* 58**,** 3441-3450.

HEALTH PROTECTION SCOTLAND. 2014. *Scottish MRSA Reference Laboratory (SMRSARL) Annual Report 2013-2014* [Online]. Health Protection Scotland. Available: https://www.hps.scot.nhs.uk/web-resources-container/scottish-mrsa-reference-laboratory-smrsarl-annual-report-2013-2014-1/ [Accessed 24/12/2019].

HEALTH PROTECTION SCOTLAND. 2016a. *Healthcare Associated Infection Annual Report 2015* [Online]. Health Protection Scotland. Available: http://www.hps.scot.nhs.uk/haiic/resourcedetail.aspx?id=1717 [Accessed 24/12/2019].

HEALTH PROTECTION SCOTLAND. 2016b. *Toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae in Scottish acute settings* [Online]. Health Protection Scotland. Available: https://hpspubsrepo.blob.core.windows.net/hps-website/nss/2531/documents/1_cpe-acute-toolkit-v1.2.1.pdf [Accessed 24/12/2019].

HEALTH PROTECTION SCOTLAND. 2017. *Toolkit for managing carbapenemase-producing Enterobacteriaceae (CPE) in Scottish non-acute care settings* [Online]. Health Protection Scotland. Available: https://www.hps.scot.nhs.uk/web-resources-container/toolkit-for-managing-carbapenemase-producing-enterobacteriaceae-cpe-in-scottish-non-acute-care-settings/ [Accessed 24/12/2019].

HEALTH PROTECTION SCOTLAND. 2018a. *Advice leaflet for contacts of a carbapenemase-producing Enterobacteriaceae (CPE) carrier* [Online]. Health Protection Scotland. Available:

https://www.hps.scot.nhs.uk/web-resources-container/advice-leaflet-for-contacts-of-a-carbapenemase-producing-enterobacteriaceae-cpe-carrier/ [Accessed 24/12/2019].

HEALTH PROTECTION SCOTLAND. 2018b. *Advice leaflet for individuals receiving care at home or in the community who have an infection with, or are colonised by carbapenemase-producing Enterobacteriaceae (CPE)* [Online]. Health Protection Scotland. Available: https://www.hps.scot.nhs.uk/web-resources-container/advice-leaflet-for-individuals-receiving-care-at-home-or-in-the-community-who-have-an-infection-with-or-are-colonised-by-carbapenemase-producing-enterobacteriaceae-cpe/ [Accessed 24/12/2019].

HEALTH PROTECTION SCOTLAND. 2018c. *Advice leaflet for the family of a person who is a carrier of carbapenemase-producing Enterobacteriaceae (CPE)* [Online]. Health Protection Scotland. Available: https://www.hps.scot.nhs.uk/web-resources-container/advice-leaflet-for-the-family-of-a-person-who-is-a-carrier-of-carbapenemase-producing-enterobacteriaceae-cpe/ [Accessed 24/12/2019].

HEALTH PROTECTION SCOTLAND. 2018d. *Scottish One Health Antimicrobial Use and Antimicrobial Resistance in 2017* [Online]. Health Protection Scotland. Available: https://hpspubsrepo.blob.core.windows.net/hps-website/nss/2647/documents/1_SONAAR-report-2017-revised-november-2019.pdf [Accessed 24/12/2019].

HEALTH PROTECTION SCOTLAND. 2019a. *Healthcare Associated Infection Annual Report 2018* [Online]. Health Protection Scotland. Available: https://hpspubsrepo.blob.core.windows.net/hps-website/nss/2776/documents/1_HAI-Annual-Report-2018-final-v1%201.pdf [Accessed 24/12/2019].

HEALTH PROTECTION SCOTLAND. 2019b. *Scottish One Health Antimicrobial Use and Antimicrobial Resistance in 2018* [Online]. Health Protection Scotland. Available: https://www.hps.scot.nhs.uk/web-resources-container/scottish-one-health-antimicrobial-use-and-antimicrobial-resistance-in-2018/ [Accessed 24/12/2019].

HEALTHCARE IMPROVEMENT SCOTLAND. 2016. *Carbapenemase-producing Enterobacteriaceae (CPE) in hospital screening samples obtained from patients identified as at risk of CPE colonisation during clinical risk assessment: Advice Statement 005-16* [Online]. Healthcare Improvement Scotland. Available: http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/shtg_advice_statements/advice_statement_005-16.aspx [Accessed 24/12/2019].

HEINZE, G., WALLISCH, C. & DUNKLER, D. 2018. Variable selection - A review and recommendations for the practicing statistician. *Biometrical Journal,* 60**,** 431-449.

HENIG, O., WEBER, G., HOSHEN, M. B., PAUL, M., GERMAN, L., NEUBERGER, A., GLUZMAN, I., BERLIN, A., SHAPIRA, C. & BALICER, R. D. 2015. Risk factors for and impact of carbapenem-resistant Acinetobacter baumannii colonization and infection: matched case-control study. *European Journal of Clinical Microbiology and Infectious Diseases,* 34**,** 2063-2068.

HERITIER, C., POIREL, L., LAMBERT, T. & NORDMANN, P. 2005. Contribution of acquired carbapenem-hydrolyzing oxacillinases to carbapenem resistance in Acinetobacter baumannii. *Antimicrobial Agents and Chemotherapy,* 49**,** 3198-3202.

HIGGINS, J., THOMAS, J., CHANDLER, J., CUMPSTON, M., LI, T., PAGE, M. & WELCH, V. 2019. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)* [Online]. Cochrane. Available: www.training.cochrane.org/handbook [Accessed 14/01/2020].

HIGGINS, J. P., THOMPSON, S. G., DEEKS, J. J. & ALTMAN, D. G. 2003. Measuring inconsistency in meta-analyses. *BMJ,* 327**,** 557-560.

HIRAKATA, Y., YAMAGUCHI, T., NAKANO, M., IZUMIKAWA, K., MINE, M., AOKI, S., KONDOH, A., MATSUDA, J., HIRAYAMA, M., YANAGIHARA, K., MIYAZAKI, Y., TOMONO, K., YAMADA, Y., KAMIHIRA, S. & KOHNO, S. 2003. Clinical and bacteriological characteristics of IMP-type metallo-beta-lactamase-producing Pseudomonas aeruginosa. *Clinical Infectious Diseases,* 37**,** 26-32.

HONG, K. B., OH, H. S., SONG, J. S., LIM, J. H., KANG, D. K., SON, I. S., PARK, J. D., KIM, E. C., LEE, H. J. & CHOI, E. H. 2012. Investigation and Control of an Outbreak of Imipenem-resistant Acinetobacter baumannii Infection in a Pediatric Intensive Care Unit. *Pediatric Infectious Disease Journal,* 31**,** 685-690.

HOOD, J. D., BOX, S. J. & VERRALL, M. S. 1979. Olivanic acids, a family of beta-lactam antibiotics with beta-lactamase inhibitory properties produced by Streptomyces species. II. Isolation and characterisation of the olivanic acids MM 4550, MM 13902 and MM 17880 from Streptomyces olivaceus. *The Journal of Antibiotics,* 32**,** 295-304.

HORAN, T. C., ANDRUS, M. & DUDECK, M. A. 2008. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *American Journal of Infection Control,* 36**,** 309-332.

HORAN, T. C., GAYNES, R. P., MARTONE, W. J., JARVIS, W. R. & EMORI, T. G. 1992. CDC Definitions of Nosocomial Surgical Site Infections, 1992 - a Modification of Cdc Definitions of Surgical Wound Infections. *American Journal of Infection Control,* 20**,** 271-274.

HORIANOPOULOU, M., LEGAKIS, N. J., KANELLOPOULOU, M., LAMBROPOULOS, S., TSAKRIS, A. & FALAGAS, M. E. 2006. Frequency and predictors of colonization of the respiratory tract by VIM-2-producing Pseudomonas aeruginosa in patients of a newly established intensive care unit. *Journal of Medical Microbiology,* 55**,** 1435-1439.

HOXHA, A., KARKI, T., GIAMBI, C., MONTANO, C., SISTO, A., BELLA, A., D'ANCONA, F. & STUDY WORKING, G. 2016. Attributable mortality of carbapenem-resistant Klebsiella pneumoniae infections in a prospective matched cohort study in Italy, 2012-2013. *Journal of Hospital Infection,* 92**,** 61-66.

HU, Y., PING, Y., LI, L., XU, H., YAN, X. & DAI, H. 2016. A retrospective study of risk factors for carbapenem-resistant Klebsiella pneumoniae acquisition among ICU patients. *Journal of Infection in Developing Countries,* 10**,** 208-213.

HUANG, L., CHEN, T. L., LEE, Y. T., LEE, M. H., KUO, S. C., YU, K. W., DOU, H. Y. & FUNG, C. P. 2014a. Risk factors for imipenem-nonsusceptible Acinetobacter nosocomialis bloodstream infection. *Journal of Microbiology, Immunology and Infection,* 47**,** 311-317.

HUANG, S. T., CHIANG, M. C., KUO, S. C., LEE, Y. T., CHIANG, T. H., YANG, S. P., TI, Y., CHEN, T. L. & FUNG, C. P. 2012. Risk factors and clinical outcomes of patients with carbapenem-resistant Acinetobacter baumannii bacteremia. *Journal of Microbiology, Immunology and Infection,* 45**,** 356-362.

HUANG, T. D., POIREL, L., BOGAERTS, P., BERHIN, C., NORDMANN, P. & GLUPCZYNSKI, Y. 2014b. Temocillin and piperacillin/tazobactam resistance by disc diffusion as antimicrobial surrogate markers for the detection of carbapenemase-producing Enterobacteriaceae in geographical areas with a high prevalence of OXA-48 producers. *Journal of Antimicrobial Chemotherapy,* 69**,** 445-450.

HUANG, W. Z., QIAO, F., WANG, Y. T., YIN, W. J. & ZONG, Z. Y. 2015. Risk factors and prognosis of patients with bloodstream infection due to Carbapenem-resistant Acinetobacter baumannii. *Chinese Journal of Infection Control,* 14**,** 668-671.

HUNG, K. H., YAN, J. J., LU, J. J., CHEN, H. M. & WU, J. J. 2013. Characterization of the modified Hodge test-positive isolates of Enterobacteriaceae in Taiwan. *Journal of Microbiology, Immunology and Infection,* 46**,** 35-40.

HUSNI, R., HACHEM, R., HANNA, H. & RAAD, I. 2002. Risk factors for vancomycin-resistant Enterococcus (VRE) infection in colonized patients with cancer. *Infection Control and Hospital Epidemiology,* 23**,** 102-103.

HUSSEIN, K., RAZ-PASTEUR, A., FINKELSTEIN, R., NEUBERGER, A., SHACHOR-MEYOUHAS, Y., OREN, I. & KASSIS, I. 2013. Impact of carbapenem resistance on the outcome of patients' hospital-acquired bacteraemia caused by Klebsiella pneumoniae. *Journal of Hospital Infection,* 83**,** 307-313.

HUSSEIN, K., SPRECHER, H., MASHIACH, T., OREN, I., KASSIS, I. & FINKELSTEIN, R. 2009. Carbapenem resistance among Klebsiella pneumoniae isolates: risk factors, molecular characteristics, and susceptibility patterns. *Infection Control and Hospital Epidemiology,* 30**,** 666-671.

HYLE, E. P., FERRARO, M. J., SILVER, M., LEE, H. & HOOPER, D. C. 2010. Ertapenem-resistant Enterobacteriaceae: risk factors for

acquisition and outcomes. *Infection Control and Hospital Epidemiology,* 31**,** 1242-1249.

IN 'T HOLT, A. F. V., SEVERIN, J. A., LESAFFRE, E. M. E. H. & VOS, M. C. 2014. A Systematic Review and Meta- Analyses Show that Carbapenem Use and Medical Devices Are the Leading Risk Factors for CarbapenemResistant Pseudomonas aeruginosa. *Antimicrobial Agents and Chemotherapy,* 58**,** 2626-2637.

INFORMATION SERVICES DIVISION NATIONAL SURVICES SCOTLAND. 2016. *General Acute Inpatient and Day Case-Scottish Morbidity Record (SMR01)* [Online]. Information Services Division National Survices Scotland. Available: https://www.ndc.scot.nhs.uk/Data-Dictionary/SMR-Datasets//SMR01-General-Acute-Inpatient-and-Day-Case/ [Accessed 24/12/2019].

INFORMATION SERVICES DIVISION SCOTLAND. 2016. *Scottish Antimicrobial Prescribing Group (SAPG) Report on Antimicrobial Use and Resistance in Humans 2015* [Online]. Information Services Division Scotland. Available: http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Publications/2016-08-30/2016-08-30-SAPG-2015-Report.pdf [Accessed 24/12/2019].

INFORMATION SERVICES DIVISION SCOTLAND. 2019. *Current NHS Hospitals in Scotland* [Online]. Information Services Division Scotland. Available: https://www.isdscotland.org/Health-Topics/Hospital-Care/Hospitals/index.asp?Co=Y [Accessed 24/12/2019].

ITO, H., ARAKAWA, Y., OHSUKA, S., WACHAROTAYANKUN, R., KATO, N. & OHTA, M. 1995. Plasmid-mediated dissemination of the metallo-beta-lactamase gene blaIMP among clinically isolated strains of Serratia marcescens. *Antimicrobial Agents and Chemotherapy,* 39**,** 824-829.

JAMULITRAT, S., THONGPIYAPOOM, S. & SUWALAK, N. 2007. An outbreak of imipenem-resistant Acinetobacter baumannii at Songklanagarind Hospital: the risk factors and patient prognosis. *Journal of the Medical Association of Thailand,* 90**,** 2181-2191.

JAPAN NOSOCOMIAL INFECTIONS SURVEILLANCE. 2018. *Japan Nosocomial Infections Surveillance (JANIS) Annual Open Report 2018* [Online]. Japan Nosocomial Infections Surveillance. Available: https://janis.mhlw.go.jp/english/report/open_report/2018/3/1/ken_Open_Report_Eng_201800_clsi2012.pdf [Accessed 24/12/2019].

JEON, B. C., JEONG, S. H., BAE, I. K., KWON, S. B., LEE, K., YOUNG, D., LEE, J. H., SONG, J. S. & LEE, S. H. 2005. Investigation of a nosocomial outbreak of imipenem-resistant Acinetobacter baumannii producing the OXA-23 beta-lactamase in korea. *Journal of Clinical Microbiology,* 43**,** 2241-2245.

JEON, M. H., CHOI, S. H., KWAK, Y. G., CHUNG, J. W., LEE, S. O., JEONG, J. Y., WOO, J. H. & KIM, Y. S. 2008. Risk factors for the acquisition of carbapenem-resistant Escherichia coli among hospitalized patients. *Diagnostic Microbiology and Infectious Disease,* 62**,** 402-406.

JEONG, S. J., YOON, S. S., BAE, I. K., JEONG, S. H., KIM, J. M. & LEE, K. 2014. Risk factors for mortality in patients with bloodstream infections caused by carbapenem-resistant Pseudomonas aeruginosa: clinical impact of bacterial virulence and strains on outcome. *Diagnostic Microbiology and Infectious Disease,* 80**,** 130-135.

JIA, X., DAI, W., MA, W., YAN, J., HE, J., LI, S., LI, C., YANG, S., XU, X., SUN, S., SHI, J. & ZHANG, L. 2018. Carbapenem-resistant E. cloacae in Southwest China: Molecular analysis of resistance and risk factors for infections caused by NDM-1-producers. *Frontiers in Microbiology,* 9**,** 658.

JIA, Y. M., ZHENG, Y. J., YUAN, Y., FAN, Y. C. & YANG, L. 2016. The features and factors analysis of klebsiella pneumoniae infection with carbapenem antibiotic resistance. *Chinese Journal of Clinical Rational Drug Use,* 9**,** 1-2.

JIANG, F. L., DONG, Y. L., LIU, D. & ZHANG, J. 2015. Analysis of risk factors for lung infection of Carbapenem-resistant Acinetobacter baumannii in ICU. *China Pharmacy,* 26**,** 4077-4079.

JIAO, Y., QIN, Y. H., LIU, J. J., LI, Q., DONG, Y. C., SHANG, Y., HUANG, Y. & LIU, R. 2015. Risk factors for carbapenem-resistant Klebsiella pneumoniae infection/colonization and predictors of mortality: a retrospective study. *Pathogens and Global Health,* 109**,** 68-74.

KAASE, M., SCHIMANSKI, S., SCHILLER, R., BEYREISS, B., THURMER, A., STEINMANN, J., KEMPF, V. A., HESS, C., SOBOTTKA, I., FENNER, I., ZIESING, S., BURCKHARDT, I., VON MULLER, L., HAMPRECHT, A., TAMMER, I., WANTIA, N., BECKER, K., HOLZMANN, T., FURITSCH, M., VOLMER, G. & GATERMANN, S. G. 2016. Multicentre investigation of carbapenemase-producing Escherichia coli and Klebsiella pneumoniae in German hospitals. *International Journal of Medical Microbiology,* 306**,** 415-420.

KAHAN, J. S., KAHAN, F. M., GOEGELMAN, R., CURRIE, S. A., JACKSON, M., STAPLEY, E. O., MILLER, T. W., MILLER, A. K., HENDLIN, D., MOCHALES, S., HERNANDEZ, S., WOODRUFF, H. B. & BIRNBAUM, J. 1979. Thienamycin, a new beta-lactam antibiotic. I. Discovery, taxonomy, isolation and physical properties. *The Journal of Antibiotics,* 32**,** 1-12.

KALAM, K., QAMAR, F., KUMAR, S., ALI, S. & BAQI, S. 2014. Risk factors for carbapenem resistant bacteraemia and mortality due to gram negative bacteraemia in a developing country. *Journal of the Pakistan Medical Association,* 64**,** 530-536.

KARAASLAN, A., SOYSAL, A., ALTINKANAT GELMEZ, G., KEPENEKLI KADAYIFCI, E., SOYLETIR, G. & BAKIR, M. 2016. Molecular characterization and risk factors for carbapenem-resistant Gram-negative bacilli colonization in children: emergence of NDM-producing Acinetobacter baumannii in a newborn intensive care unit in Turkey. *Journal of Hospital Infection,* 92**,** 67-72.

KATRAGKOU, A., KOTSIOU, M., ANTACHOPOULOS, C., BENOS, A., SOFIANOU, D., TAMIOLAKI, M. & ROILIDES, E. 2006. Acquisition of imipenem-resistant Acinetobacter baumannii in a pediatric intensive

care unit: A case-control study. *Intensive Care Medicine,* 32**,** 1384-1391.

KELLY, A. M., MATHEMA, B. & LARSON, E. L. 2017. Carbapenem-resistant Enterobacteriaceae in the community: a scoping review. *International Journal of Antimicrobial Agents,* 50**,** 127-134.

KHADEM, T., STEVENS, V., HOLT, K., HOFFMANN, C., DUMYATI, G. & BROWN, J. 2017. Risk factors for carbapenem-nonsusceptible Pseudomonas aeruginosa: Case-control study. *Diagnostic Microbiology and Infectious Disease,* 89**,** 146-150.

KIM, S. B., MIN, Y. H., CHEONG, J. W., KIM, J. S., KIM, S. J., KU, N. S., JEONG, S. J., HAN, S. H., CHOI, J. Y., SONG, Y. G. & KIM, J. M. 2014a. Incidence and risk factors for carbapenem- and multidrug-resistant Acinetobacter baumannii bacteremia in hematopoietic stem cell transplantation recipients. *Scandinavian Journal of Infectious Diseases,* 46**,** 81-88.

KIM, S. Y., JUNG, J. Y., KANG, Y. A., LIM, J. E., KIM, E. Y., LEE, S. K., PARK, S. C., CHUNG, K. S., PARK, B. H., KIM, Y. S., KIM, S. K., CHANG, J. & PARK, M. S. 2012a. Risk factors for occurrence and 30-day mortality for carbapenem-resistant Acinetobacter baumannii bacteremia in an intensive care unit. *Journal of Korean Medical Science,* 27**,** 939-947.

KIM, T., CHONG, Y. P., PARK, S. Y., JEON, M. H., CHOO, E. J., CHUNG, J. W., LEE, H. K., MOON, C., KIM, D. M., PECK, K. R. & KIM, Y. S. 2014b. Risk factors for hospital-acquired pneumonia caused by carbapenem-resistant Gram-negative bacteria in critically ill patients: a multicenter study in Korea. *Diagnostic Microbiology and Infectious Disease,* 78**,** 457-461.

KIM, U. J., KIM, H. K., AN, J. H., CHO, S. K., PARK, K. H. & JANG, H. C. 2014c. Update on the Epidemiology, Treatment, and Outcomes of Carbapenem-resistant Acinetobacter infections. *Chonnam Medical Journal,* 50**,** 37-44.

KIM, Y. A., CHOI, J. Y., KIM, C. K., KIM, C. O., KIM, M. S., CHOI, S. H., CHIN, B. S., HAN, S. H., LEE, H. S., CHOI, H. K., JEOUNG, S. J., SONG, Y. G., YUM, J. H., YONG, D., LEE, K. & KIM, J. M. 2008. Risk factors and outcomes of bloodstream infections with metallo-beta-lactamase-producing Acinetobacter. *Scandinavian Journal of Infectious Diseases,* 40**,** 234-240.

KIM, Y. J., KIM, S. I., HONG, K. W., KIM, Y. R., PARK, Y. J. & KANG, M. W. 2012b. Risk factors for mortality in patients with carbapenem-resistant Acinetobacter baumannii bacteremia: impact of appropriate antimicrobial therapy. *Journal of Korean Medical Science,* 27**,** 471-475.

KIM, Y. J., KIM, S. I., KIM, Y. R., HONG, K. W., WIE, S. H., PARK, Y. J., JEONG, H. & KANG, M. W. 2012c. Carbapenem-resistant Acinetobacter baumannii: diversity of resistant mechanisms and risk factors for infection. *Epidemiology and Infection,* 140**,** 137-145.

KIPNIS, E., SAWA, T. & WIENER-KRONISH, J. 2006. Targeting mechanisms of Pseudomonas aeruginosa pathogenesis. *Médecine et Maladies Infectieuses,* 36**,** 78-91.

KIRATISIN, P., CHONGTHALEONG, A., TAN, T. Y., LAGAMAYO, E., ROBERTS, S., GARCIA, J. & DAVIES, T. 2012. Comparative in vitro activity of carbapenems against major Gram-negative pathogens: results of Asia-Pacific surveillance from the COMPACT II study. *International Journal of Antimicrobial Agents,* 39**,** 311-316.

KLEIN, E. Y., VAN BOECKEL, T. P., MARTINEZ, E. M., PANT, S., GANDRA, S., LEVIN, S. A., GOOSSENS, H. & LAXMINARAYAN, R. 2018. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences of the United States of America,* 115**,** E3463-E3470.

KNAPP, K. M. & ENGLISH, B. K. 2001. Carbapenems. *Seminars in Pediatric Infectious Diseases,* 12**,** 175-185.

KOFTERIDIS, D. P., VALACHIS, A., DIMOPOULOU, D., MARAKI, S., CHRISTIDOU, A., MANTADAKIS, E. & SAMONIS, G. 2014. Risk factors for carbapenem-resistant Klebsiella pneumoniae infection/colonization: a case-case-control study. *Journal of Infection and Chemotherapy,* 20**,** 293-297.

KOHLENBERG, A., WEITZEL-KAGE, D., VAN DER LINDEN, P., SOHR, D., VOGELER, S., KOLA, A., HALLE, E., RUDEN, H. & WEIST, K. 2010. Outbreak of carbapenem-resistant Pseudomonas aeruginosa infection in a surgical intensive care unit. *Journal of Hospital Infection,* 74**,** 350-357.

KOHLER, P. P., VOLLING, C., GREEN, K., ULERYK, E. M., SHAH, P. S. & MCGEER, A. 2017. Carbapenem Resistance, Initial Antibiotic Therapy, and Mortality in Klebsiella pneumoniae Bacteremia: A Systematic Review and Meta-Analysis. *Infection Control and Hospital Epidemiology,* 38**,** 1319-1328.

KOLLEF, M. H. 2000. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. *Clinical Infectious Diseases,* 31 Suppl 4**,** S131-138.

KONG, H. F., HU, Z. D., LI, J., LI, Y. C., LI, J. & TIAN, B. 2016. Case-case-control study of risk factors of Carbapenem-resistant Acinetobacter baumannii infection. *Chinese Journal of Clinical Infectious Diseases,* 9**,** 224-229.

KOPTERIDES, P., KOLETSI, P. K., MICHALOPOULOS, A. & FALAGAS, M. E. 2007. Exposure to quinolones is associated with carbapenem resistance among colistin-susceptible Acinetobacter baumannii blood isolates. *International Journal of Antimicrobial Agents,* 30**,** 409-414.

KOSTYANEV, T., VILKEN, T., LAMMENS, C., TIMBERMONT, L., VAN'T VEEN, A. & GOOSSENS, H. 2019. Detection and prevalence of carbapenem-resistant Gram-negative bacteria among European laboratories in the COMBACTE network: a COMBACTE LAB-Net survey. *International Journal of Antimicrobial Agents,* 53**,** 268-274.

KOYANO, S., SAITO, R., NAGAI, R., TATSUNO, K., OKUGAWA, S., OKAMURA, N. & MORIYA, K. 2013. Molecular characterization of carbapenemase-producing clinical isolates of Enterobacteriaceae in a teaching hospital, Japan. *Journal of Medical Microbiology,* 62**,** 446-450.

KRITSOTAKIS, E. I., TSIOUTIS, C., ROUMBELAKI, M., CHRISTIDOU, A. & GIKAS, A. 2011. Antibiotic use and the risk of carbapenem-resistant extended-spectrum-{beta}-lactamase-producing Klebsiella pneumoniae infection in hospitalized patients: results of a double case-control study. *Journal of Antimicrobial Chemotherapy,* 66**,** 1383-1391.

KUMAR, A., RANDHAWA, V. S., NIRUPAM, N., RAI, Y. & SAILI, A. 2014. Risk factors for carbapenem-resistant Acinetobacter baumanii blood stream infections in a neonatal intensive care unit, Delhi, India. *Journal of Infection in Developing Countries,* 8**,** 1049-1054.

KUMARASAMY, K. K., TOLEMAN, M. A., WALSH, T. R., BAGARIA, J., BUTT, F., BALAKRISHNAN, R., CHAUDHARY, U., DOUMITH, M., GISKE, C. G., IRFAN, S., KRISHNAN, P., KUMAR, A. V., MAHARJAN, S., MUSHTAQ, S., NOORIE, T., PATERSON, D. L., PEARSON, A., PERRY, C., PIKE, R., RAO, B., RAY, U., SARMA, J. B., SHARMA, M., SHERIDAN, E., THIRUNARAYAN, M. A., TURTON, J., UPADHYAY, S., WARNER, M., WELFARE, W., LIVERMORE, D. M. & WOODFORD, N. 2010. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infectious Diseases,* 10**,** 597-602.

KWAK, Y. G., CHOI, S. H., CHOO, E. J., CHUNG, J. W., JEONG, J. Y., KIM, N. J., WOO, J. H., RYU, J. & KIM, Y. S. 2005. Risk factors for the acquisition of carbapenem-resistant Klebsiella pneumoniae among hospitalized patients. *Microbial Drug Resistance-Mechanisms Epidemiology and Disease,* 11**,** 165-169.

KWINT, H. M., VAN DER LINDEN, P. D., ROUKENS, M. M. B., NATSCH, S. & SURVEILLANCE, S. S. W. G. 2012. Intensification of antibiotic use within acute care hospitals in the Netherlands. *Journal of Antimicrobial Chemotherapy,* 67**,** 2283-2288.

LATIBEAUDIERE, R., ROSA, R., LAOWANSIRI, P., ARHEART, K., NAMIAS, N. & MUNOZ-PRICE, L. S. 2015. Surveillance cultures growing carbapenem-Resistant Acinetobacter baumannii predict the development of clinical infections: a retrospective cohort study. *Clinical Infectious Diseases,* 60**,** 415-422.

LAUTENBACH, E., SYNNESTVEDT, M., WEINER, M. G., BILKER, W. B., VO, L., SCHEIN, J. & KIM, M. 2009. Epidemiology and impact of imipenem resistance in Acinetobacter baumannii. *Infection Control and Hospital Epidemiology,* 30**,** 1186-1192.

LAUTENBACH, E., SYNNESTVEDT, M., WEINER, M. G., BILKER, W. B., VO, L., SCHEIN, J. & KIM, M. 2010. Imipenem resistance in Pseudomonas aeruginosa: emergence, epidemiology, and impact on clinical and economic outcomes. *Infection Control and Hospital Epidemiology,* 31**,** 47-53.

LAUTENBACH, E., WEINER, M. G., NACHAMKIN, I., BILKER, W. B., SHERIDAN, A. & FISHMAN, N. O. 2006. Imipenem resistance among pseudomonas aeruginosa isolates: risk factors for infection and impact of resistance on clinical and economic outcomes. *Infection Control and Hospital Epidemiology,* 27**,** 893-900.

LE HELLO, S., FALCOT, V., LACASSIN, F., MIKULSKI, M. & BAUMANN, F. 2010. Risk factors for carbapenem-resistant Acinetobacter baumannii infections at a tertiary care hospital in New Caledonia, South Pacific. *Scandinavian Journal of Infectious Diseases,* 42**,** 821-826.

LEDEBOER, N. A., LOPANSRI, B. K., DHIMAN, N., CAVAGNOLO, R., CARROLL, K. C., GRANATO, P., THOMSON, R., BUTLER-WU, S. M., BERGER, H., SAMUEL, L., PANCHOLI, P., SWYERS, L., HANSEN, G. T., TRAN, N. K., POLAGE, C. R., THOMSON, K. S., HANSON, N. D., WINEGAR, R. & BUCHAN, B. W. 2015. Identification of Gram-Negative Bacteria and Genetic Resistance Determinants from Positive Blood Culture Broths by Use of the Verigene Gram-Negative Blood Culture Multiplex Microarray-Based Molecular Assay. *Journal of Clinical Microbiology,* 53**,** 2460-2472.

LEE, G. C., LAWSON, K. A. & BURGESS, D. S. 2013a. Clinical epidemiology of carbapenem-resistant enterobacteriaceae in community hospitals: a case-case-control study. *Annals of Pharmacotherapy,* 47**,** 1115-1121.

LEE, H. J., CHOI, J. K., CHO, S. Y., KIM, S. H., PARK, S. H., CHOI, S. M., LEE, D. G., CHOI, J. H. & YOO, J. H. 2016. Carbapenem-resistant Enterobacteriaceae: Prevalence and risk factors in a single community-based hospital in Korea. *Infection and Chemotherapy,* 48**,** 166-173.

LEE, K., YUM, J. H., YONG, D., LEE, H. M., KIM, H. D., DOCQUIER, J. D., ROSSOLINI, G. M. & CHONG, Y. 2005. Novel acquired metallo-beta-lactamase gene, bla(SIM-1), in a class 1 integron from Acinetobacter baumannii clinical isolates from Korea. *Antimicrobial Agents and Chemotherapy,* 49**,** 4485-4491.

LEE, M. H., CHEN, T. L., LEE, Y. T., HUANG, L., KUO, S. C., YU, K. W., HSUEH, P. R., DOU, H. Y., SU, I. J. & FUNG, C. P. 2013b. Dissemination of multidrug-resistant Acinetobacter baumannii carrying BlaOxA-23 from hospitals in central Taiwan. *Journal of Microbiology, Immunology and Infection,* 46**,** 419-424.

LEE, S. O., KIM, N. J., CHOI, S. H., KIM, T. H., CHUNG, J. W., WOO, J. H., RYU, J. & KIM, Y. S. 2004. Factors for Acquisition of Imipenem-Resistant Acinetobacter baumannii: A Case-Control Study. *Antimicrobial Agents and Chemotherapy,* 48**,** 224-228.

LEPELLETIER, D., CADY, A., CAROFF, N., MARRAILLAC, J., REYNAUD, A., LUCET, J. C. & CORVEC, S. 2009. Imipenem-resistant Pseudomonas aeruginosa gastrointestinal carriage among hospitalized patients: risk factors and resistance mechanisms. *Diagnostic Microbiology and Infectious Disease,* 66**,** 1-6.

LEROY, O., D'ESCRIVAN, T., DEVOS, P., DUBREUIL, L., KIPNIS, E. & GEORGES, H. 2005. Hospital-acquired pneumonia in critically ill

patients: factors associated with episodes due to imipenem-resistant organisms. *Infection,* 33**,** 129-135.
LI, F. T., WANG, Z. H., ZHOU, G. H., LI, Y. W. & FENG, Y. G. 2015. Analysis of risk factors of drug resistance of Pseudomonas aeruginosa with meropenem. *Practical Pharmacy and Clinical Remedies,* 18**,** 83-85.
LI, J. J., XIA, G. L., F., Z. A., SHEN, J. Y. & ZHOU, Y. 2016. Trentment of Meropenem-resistnat Pseudomonas aeruginosa infection in ICU. *Chinese Journal of Nosocomiology,* 26**,** 2038-2040.
LI, X., XU, X., YANG, X., LUO, M., LIU, P., SU, K., QING, Y., CHEN, S., QIU, J. & LI, Y. 2017. Risk factors for infection and/or colonisation with extended-spectrum beta-lactamase-producing bacteria in the neonatal intensive care unit: a meta-analysis. *International Journal of Antimicrobial Agents,* 50**,** 622-628.
LI, X. & YE, H. 2017. Clinical and mortality risk factors in bloodstream infections with carbapenem-resistant enterobacteriaceae. *Canadian Journal of Infectious Diseases and Medical Microbiology,* 2017**,** 6212910.
LIBERATI, A., ALTMAN, D. G., TETZLAFF, J., MULROW, C., GOTZSCHE, P. C., IOANNIDIS, J. P., CLARKE, M., DEVEREAUX, P. J., KLEIJNEN, J. & MOHER, D. 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *BMJ,* 339**,** b2700.
LIEW, Y. X., KRISHNAN, P., YEO, C. L., TAN, T. Y., LEE, S. Y., LIM, W. P., LEE, W., HSU, L. Y. & S, N. A. R. 2011. Surveillance of Broad-Spectrum Antibiotic Prescription in Singaporean Hospitals: A 5-Year Longitudinal Study. *PLoS ONE,* 6**,** e28751.
LIN, K. Y., LAUDERDALE, T. L., WANG, J. T. & CHANG, S. C. 2016. Carbapenem-resistant Pseudomonas aeruginosa in Taiwan: Prevalence, risk factors, and impact on outcome of infections. *Journal of Microbiology, Immunology and Infection,* 49**,** 52-59.
LING, M. L., TEE, Y. M., TAN, S. G., AMIN, I. M., HOW, K. B., TAN, K. Y. & LEE, L. C. 2015. Risk factors for acquisition of carbapenem resistant Enterobacteriaceae in an acute tertiary care hospital in Singapore. *Antimicrobial Resistance and Infection Control,* 4**,** 26-32.
LIU, H. G., LIU, J., XING, S. D. & XU, Y. J. 2006. Multi-drug resistance of Pseudomonas aeruginosa resistant or sensitive to carbapenem and an analysis of correlated factors. *Herald of Medicine,* 25**,** 1326-1328.
LIU, J. T., CUI, X. F. & MEI, Y. N. 2011a. Drug resistance of imipenem-resistant Pseudomonas aeruginosa in ICU and the risk factors for its infections. *Jiangsu Medical Journal,* 37**,** 1646-1648.
LIU, P., ZHANG, Z. L., NI, D. N. & WU, H. J. 2011b. Factors associated with metallo-beta-lactamase-producing Pseudomonas aeruginosa. *Chinese Journal of Nosocomiology,* 21**,** 5058-5060.
LIU, S. W., CHANG, H. J., CHIA, J. H., KUO, A. J., WU, T. L. & LEE, M. H. 2012. Outcomes and characteristics of ertapenem-nonsusceptible Klebsiella pneumoniae bacteremia at a university hospital in Northern

Taiwan: a matched case-control study. *Journal of Microbiology, Immunology and Infection,* 45**,** 113-119.

LIVERMORE, D. M., WALSH, T. R., TOLEMAN, M. & WOODFORD, N. 2011. Balkan NDM-1: escape or transplant? *Lancet Infectious Diseases,* 11**,** 164.

LIVERMORE, D. M. & WOODFORD, N. 2006. The beta-lactamase threat in Enterobacteriaceae, Pseudomonas and Acinetobacter. *Trends in Microbiology,* 14**,** 413-420.

LODISE, T. P., MILLER, C., PATEL, N., GRAVES, J. & MCNUTT, L. A. 2007. Identification of patients with Pseudomonas aeruginosa respiratory tract infections at greatest risk of infection with carbapenem-resistant isolates. *Infection Control and Hospital Epidemiology,* 28**,** 959-965.

LOGAN, L. K. & WEINSTEIN, R. A. 2017. The epidemiology of carbapenem-resistant Enterobacteriaceae: the impact and evolution of a global menace. *Journal of Infectious Diseases,* 215**,** S28-S36.

LOLANS, K., RICE, T. W., MUNOZ-PRICE, L. S. & QUINN, J. P. 2006. Multicity outbreak of carbapenem-resistant Acinetobacter baumannii isolates producing the carbapenemase OXA-40. *Antimicrobial Agents and Chemotherapy,* 50**,** 2941-2945.

LOU, G. P., ZHANG, Z. Y. & ZHOU, Z. H. 2013. The analysis of Carbapenem resistant Pseudomonas aeruginosa isolate from the intensive care unit patients: risk factors for pulmonary infection. *International Journal of Laboratory Medicine,* 34**,** 570-572.

LU, J. C., CAI, S. X., GENG, S. N., TONG, W. C., MA, Z., MENG, Y. & LIU, L. Y. 2009. Risk factors and prognosis of hospital acquired pneumonia caused by Carbapenem-resistant Acinetobacter baumanni. *Chinese Journal of Respiratory and Critical Care Medicine,* 8**,** 24-27.

LUTGRING, J. D. & LIMBAGO, B. M. 2016. The Problem of Carbapenemase-Producing-Carbapenem-Resistant-Enterobacteriaceae Detection. *Journal of Clinical Microbiology,* 54**,** 529-534.

LUZZARO, F., DOCQUIER, J. D., COLINON, C., ENDIMIANI, A., LOMBARDI, G., AMICOSANTE, G., ROSSOLINI, G. M. & TONIOLO, A. 2004. Emergence in Klebsiella pneumoniae and Enterobacter cloacae clinical isolates of the VIM-4 metallo-beta-lactamase encoded by a conjugative plasmid. *Antimicrobial Agents and Chemotherapy,* 48**,** 648-650.

LV, D., WANG, L., P., C. D., MA, H. Y., SUN, S. F., CHEN, Z. B., DING, Q. L. & DENG, Z. C. 2015. Risk factors for lower respiratoty tract infections caused by imipenem-resistant Klebsiella pneumoniae. *Chinese Journal of Nosocomiology,* 25**,** 981-983.

LYNCH, J. P. 2001. Hospital-acquired pneumonia - Risk factors, microbiology, and treatment. *Chest,* 119**,** 373s-384s.

MA, M. S., WANG, D. H., SUN, X. J., LI, Z. H. & WANG, C. 2014. Risk factors for Klebsiella pneumoniae carbapenemase-producing Klebsiella pneumoniae colonization in neonates. *Zhongguo Dangdai Erke Zazhi,* 16**,** 970-974.

MAGIORAKOS, A. P., BURNS, K., BANO, J. R., BORG, M., DAIKOS, G., DUMPIS, U., LUCET, J. C., MORO, M. L., TACCONELLI, E., SIMONSEN, G. S., SZILAGYI, E., VOSS, A. & WEBER, J. T. 2017. Infection prevention and control measures and tools for the prevention of entry of carbapenem-resistant Enterobacteriaceae into healthcare settings: guidance from the European Centre for Disease Prevention and Control. *Antimicrobial Resistance and Infection Control,* 6**,** 113.

MAIRI, A., PANTEL, A., OUSALEM, F., SOTTO, A., TOUATI, A. & LAVIGNE, J. P. 2019. OXA-48-producing Enterobacterales in different ecological niches in Algeria: clonal expansion, plasmid characteristics and virulence traits. *Journal of Antimicrobial Chemotherapy,* 74**,** 1848-1855.

MALLETT, R., HAGEN-ZANKER, J., SLATER, R. & DUVENDACK, M. 2012. The benefits and challenges of using systematic reviews in international development research. *Journal of Development Effectiveness,* 4**,** 445-455.

MANDELL, L. 2009. Doripenem: a new carbapenem in the treatment of nosocomial infection. *Clinical Infectious Diseases,* 49 Suppl 1**,** S1-3.

MANENZHE, R. I., ZAR, H. J., NICOL, M. P. & KABA, M. 2015. The spread of carbapenemase-producing bacteria in Africa: a systematic review. *Journal of Antimicrobial Chemotherapy,* 70**,** 23-40.

MANTEL, N. 1966. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Reports,* 50**,** 163-170.

MANTZARLIS, K., MAKRIS, D., MANOULAKAS, E., KARVOUNIARIS, M. & ZAKYNTHINOS, E. 2013. Risk factors for the first episode of Klebsiella pneumoniae resistant to carbapenems infection in critically ill patients: a prospective study. *BioMed Research International,* 2013**,** 850547.

MARCHAIM, D., CHOPRA, T., BHARGAVA, A., BOGAN, C., DHAR, S., HAYAKAWA, K., POGUE, J. M., BHEEMREDDY, S., BLUNDEN, C., SHANGO, M., SWAN, J., LEPHART, P. R., PEREZ, F., BONOMO, R. A. & KAYE, K. S. 2012. Recent exposure to antimicrobials and carbapenem-resistant Enterobacteriaceae: the role of antimicrobial stewardship. *Infection Control and Hospital Epidemiology,* 33**,** 817-830.

MARCHAIM, D., NAVON-VENEZIA, S., SCHWABER, M. J. & CARMELI, Y. 2008. Isolation of imipenem-resistant Enterobacter species: emergence of KPC-2 carbapenemase, molecular characterization, epidemiology, and outcomes. *Antimicrobial Agents and Chemotherapy,* 52**,** 1413-1418.

MARCHENAY, P., BLASCO, G., NAVELLOU, J. C., LEROY, J., CHOLLEY, P., TALON, D., BERTRAND, X. & GBAGUIDI-HAORE, H. 2015. Acquisition of carbapenem-resistant Gram-negative bacilli in intensive care unit: predictors and molecular epidemiology. *Medecine et Maladies Infectieuses,* 45**,** 34-40.

MARQUE, S., POIREL, L., HERITIER, C., BRISSE, S., BLASCO, M. D., FILIP, R., COMAN, G., NAAS, T. & NORDMANN, P. 2005. Regional

occurrence of plasmid-mediated carbapenem-hydrolyzing oxacillinase OXA-58 in Acinetobacter spp. in Europe. *Journal of Clinical Microbiology,* 43**,** 4885-4888.

MARTIN, J., PHAN, H. T. T., FINDLAY, J., STOESSER, N., PANKHURST, L., NAVICKAITE, I., DE MAIO, N., EYRE, D. W., TOOGOOD, G., ORSI, N. M., KIRBY, A., YOUNG, N., TURTON, J. F., HILL, R. L. R., HOPKINS, K. L., WOODFORD, N., PETO, T. E. A., WALKER, A. S., CROOK, D. W. & WILCOX, M. H. 2017. Covert dissemination of carbapenemase-producing Klebsiella pneumoniae (KPC) in a successfully controlled outbreak: long- and short-read whole-genome sequencing demonstrate multiple genetic modes of transmission. *Journal of Antimicrobial Chemotherapy,* 72**,** 3025-3034.

MATASEJE, L. F., ABDESSELAM, K., VACHON, J., MITCHEL, R., BRYCE, E., ROSCOE, D., BOYD, D. A., EMBREE, J., KATZ, K., KIBSEY, P., SIMOR, A. E., TAYLOR, G., TURGEON, N., LANGLEY, J., GRAVEL, D., AMARATUNGA, K. & MULVEY, M. R. 2016. Results from the Canadian Nosocomial Infection Surveillance Program on Carbapenemase-Producing Enterobacteriaceae, 2010 to 2014. *Antimicrobial Agents and Chemotherapy,* 60**,** 6787-6794.

MAYA, J. J., RUIZ, S. J., BLANCO, V. M., GOTUZZO, E., GUZMAN-BLANCO, M., LABARCA, J., SALLES, M., QUINN, J. P. & VILLEGAS, M. V. 2013. Current status of carbapenemases in Latin America. *Expert Review of Anti-infective Therapy,* 11**,** 657-667.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY. Available: https://products.mhra.gov.uk/ [Accessed 06/02/2020].

MELETIS, G. 2016. Carbapenem resistance: overview of the problem and future perspectives. *Therapeutic Advances in Infectious Disease,* 3**,** 15-21.

MENDES, R. E., MENDOZA, M., SINGH, K. K. B., CASTANHEIRA, M., BELL, J. M., TURNIDGE, J. D., LIN, S. S. & JONES, R. N. 2013. Regional resistance surveillance program results for 12 Asia-Pacific nations (2011). *Antimicrobial Agents and Chemotherapy,* 57**,** 5721-5726.

MERADJI, S., BARGUIGUA, A., ZEROUALI, K., MAZOUZ, D., CHETTIBI, H., ELMDAGHRI, N. & TIMINOUNI, M. 2015. Epidemiology of carbapenem non-susceptible Pseudomonas aeruginosa isolates in Eastern Algeria. *Antimicrobial Resistance and Infection Control,* 4.

MERRER, J., SANTOLI, F., APPERE-DE VECCHI, C., TRAN, B., DE JONGHE, B. & OUTIN, H. 2000. "Colonization pressure" and risk of acquisition of methicillin-resistant Staphylococcus aureus in a medical intensive care unit. *Infection Control and Hospital Epidemiology,* 21**,** 718-723.

MEUNIER, D., DOUMITH, M., FINDLAY, J., MUSTAFA, N., MALLARD, K., ANSON, J., PANAGEA, S., PIKE, R., WRIGHT, L., WOODFORD, N. & HOPKINS, K. L. 2016. Carbapenem resistance mediated by blaOXA-181 in Pseudomonas aeruginosa. *Journal of Antimicrobial Chemotherapy,* 71**,** 2056-2057.

MEYER, E., SCHWAB, F., SCHROEREN-BOERSCH, B. & GASTMEIER, P. 2010. Dramatic increase of third-generation cephalosporin-resistant E. coli in German intensive care units: secular trends in antibiotic drug use and bacterial resistance, 2001 to 2008. *Critical Care,* 14**,** R113.

MICKEY, R. M. & GREENLAND, S. 1989. The Impact of Confounder Selection Criteria on Effect Estimation. *American Journal of Epidemiology,* 129**,** 125-137.

MILLER, B. M. & JOHNSON, S. W. 2016. Demographic and infection characteristics of patients with carbapenem-resistant Enterobacteriaceae in a community hospital: Development of a bedside clinical score for risk assessment. *American Journal of Infection Control,* 44**,** 134-137.

MILLS, J. P., TALATI, N. J., ALBY, K. & HAN, J. H. 2016. The Epidemiology of Carbapenem-Resistant Klebsiella pneumoniae Colonization and Infection among Long-Term Acute Care Hospital Residents. *Infection Control and Hospital Epidemiology,* 37**,** 55-60.

MINISTRY OF HEALTH NEW ZEALAND GOVERMENT. 2018. *Infection prevention and control and management of Carbapenemase-producing Enterobacteriaceae* [Online]. Ministry of Health New Zealand Goverment. Available: https://www.health.govt.nz/system/files/documents/publications/infection-prevention-control-management-carbapenemase-producing-enterobacteriaceae-dec18.pdf [Accessed 24/12/2019].

MITGANG, E. A., HARTLEY, D. M., MALCHIONE, M. D., KOCH, M. & GOODMAN, J. L. 2018. Review and mapping of carbapenem-resistant Enterobacteriaceae in Africa: Using diverse data to inform surveillance gaps. *International Journal of Antimicrobial Agents,* 52**,** 372-384.

MITTAL, G., GAIND, R., KUMAR, D., KAUSHIK, G., GUPTA, K. B., VERMA, P. K. & DEB, M. 2016. Risk factors for fecal carriage of carbapenemase producing Enterobacteriaceae among intensive care unit patients from a tertiary care center in India. *BMC Microbiology,* 16**,** 1-10.

MORRIS, J. G., SHAY, D. K., HEBDEN, J. N., MCCARTER, R. J., PERDUE, B. E., JARVIS, W., JOHNSON, J. A., DOWLING, T. C., POLISH, L. B. & SCHWALBE, R. S. 1995. Enterococci resistant to multiple antimicrobial agents, including vancomycin: establishment of endemicity in a university medical center. *Annual of Internal Medicine,* 123**,** 250-259.

MOULOUDI, E., MASSA, E., PAPADOPOULOS, S., IOSIFIDIS, E., ROILIDES, I., THEODORIDOU, T., PIPERIDOU, M., ORPHANOU, A., PASSAKIOTOU, M., IMVRIOS, G., FOUZAS, I., PAPANIKOLAOU, V. & GRITSI-GEROGIANNI, N. 2014. Bloodstream infections caused by carbapenemase-producing Klebsiella pneumoniae among intensive care unit patients after orthotopic liver transplantation: risk factors for infection and impact of resistance on outcomes. *Transplantation Proceedings,* 46**,** 3216-3218.

MOULOUDI, E., PROTONOTARIOU, E., ZAGORIANOU, A., IOSIFIDIS, E., KARAPANAGIOTOU, A., GIASNETSOVA, T., TSIOKA, A.,

ROILIDES, E., SOFIANOU, D. & GRITSI-GEROGIANNI, N. 2010. Bloodstream infections caused by metallo-beta-lactamase/Klebsiella pneumoniae carbapenemase-producing K. pneumoniae among intensive care unit patients in Greece: risk factors for infection and impact of type of resistance on outcomes. *Infection Control and Hospital Epidemiology,* 31**,** 1250-1256.

NAAS, T., CUZON, G., BABICS, A., FORTINEAU, N., BOYTCHEV, I., GAYRAL, F. & NORDMANN, P. 2010. Endoscopy-associated transmission of carbapenem-resistant Klebsiella pneumoniae producing KPC-2 beta-lactamase. *Journal of Antimicrobial Chemotherapy,* 65**,** 1305-1306.

NAAS, T., VANDEL, L., SOUGAKOFF, W., LIVERMORE, D. M. & NORDMANN, P. 1994. Cloning and sequence analysis of the gene for a carbapenem-hydrolyzing class A beta-lactamase, Sme-1, from Serratia marcescens S6. *Antimicrobial Agents and Chemotherapy,* 38**,** 1262-1270.

NABARRO, L. E. B., SHANKAR, C., PRAGASAM, A. K., MATHEW, G., JEYASEELAN, V., VEERARAGHAVAN, B. & VERGHESE, V. P. 2017. Clinical and Bacterial Risk Factors for Mortality in Children With Carbapenem-resistant Enterobacteriaceae Bloodstream Infections in India. *Pediatric Infectious Disease Journal,* 36**,** e161-e166.

NATIONAL HEALTH SERVICE DIGITAL. 2013. *OPCS Classification of Interventions and Procedures version 4.7* [Online]. National Health Service Digital. Available: https://digital.nhs.uk/data-and-information/information-standards/information-standards-and-data-collections-including-extractions/publications-and-notifications/standards-and-collections/scci0084-opcs-classification-of-interventions-and-procedures [Accessed 24/12/2019].

NATIONAL RECORDS OF SCOTLAND. 2019. *Mid-2018 population estimates Scotland* [Online]. National Records of Scotland. Available: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/population/population-estimates/mid-year-population-estimates/mid-2018 [Accessed 24/12/2019].

NAVON-VENEZIA, S., LEAVITT, A., SCHWABER, M. J., RASHEED, J. K., SRINIVASAN, A., PATEL, J. B. & CARMELI, Y. 2009. First report on a hyperepidemic clone of KPC-3-producing Klebsiella pneumoniae in Israel genetically related to a strain causing outbreaks in the United States. *Antimicrobial Agents and Chemotherapy,* 53**,** 818-820.

NG, T. K. C., LING, J. M., CHENG, A. F. B. & NORRBY, S. R. 1996. A retrospective study of clinical characteristics of acinetobacter bacteremia. *Scandinavian Journal of Infectious Diseases,* 101**,** 26-32.

NORDMANN, P. 2014. Carbapenemase-producing Enterobacteriaceae: overview of a major public health challenge. *Médecine et Maladies Infectieuses,* 44**,** 51-56.

NORDMANN, P., CUZON, G. & NAAS, T. 2009. The real threat of Klebsiella pneumoniae carbapenemase-producing bacteria. *Lancet Infectious Diseases,* 9**,** 228-236.

NORDMANN, P., DORTET, L. & POIREL, L. 2012a. Carbapenem resistance in Enterobacteriaceae: here is the storm! *Trends in Molecular Medicine,* 18**,** 263-272.

NORDMANN, P., GNIADKOWSKI, M., GISKE, C. G., POIREL, L., WOODFORD, N., MIRIAGOU, V. & CARBAPENEMASES, E. N. 2012b. Identification and screening of carbapenemase-producing Enterobacteriaceae. *Clinical Microbiology and Infection,* 18**,** 432-438.

NORDMANN, P. & POIREL, L. 2002. Emerging carbapenemases in Gram-negative aerobes. *Clinical Microbiology and Infection,* 8**,** 321-331.

NORDMANN, P. & POIREL, L. 2019. Epidemiology and Diagnostics of Carbapenem Resistance in Gram-negative Bacteria. *Clinical Infectious Diseases,* 69**,** S521-S528.

NORDMANN, P., POIREL, L. & DORTET, L. 2012c. Rapid Detection of Carbapenemase-producing Enterobacteriaceae. *Emerging Infectious Diseases,* 18**,** 1503-1507.

NORDMANN, P., POIREL, L., TOLEMAN, M. A. & WALSH, T. R. 2011. Does broad-spectrum β-lactam resistance due to NDM-1 herald the end of the antibiotic era for treatment of infections caused by Gram-negative bacteria? *Journal of Antimicrobial Chemotherapy,* 66**,** 689-692.

NOUER, S. A., NUCCI, M., DE-OLIVEIRA, M. P., PELLEGRINO, F. L. & MOREIRA, B. M. 2005. Risk factors for acquisition of multidrug-resistant Pseudomonas aeruginosa producing SPM metallo-beta-lactamase. *Antimicrobial Agents and Chemotherapy,* 49**,** 3663-3667.

NOUVENNE, A., TICINESI, A., LAURETANI, F., MAGGIO, M., LIPPI, G., GUIDA, L., MORELLI, I., RIDOLO, E., BORGHI, L. & MESCHI, T. 2014. Comorbidities and disease severity as risk factors for carbapenem-resistant Klebsiella pneumoniae colonization: report of an experience in an internal medicine unit. *PLoS ONE,* 9**,** e110001.

NSEIR, S., BLAZEJEWSKI, C., LUBRET, R., WALLET, F., COURCOL, R. & DUROCHER, A. 2011. Risk of acquiring multidrug-resistant Gram-negative bacilli from prior room occupants in the intensive care unit. *Clinical Microbiology and Infection,* 17**,** 1201-1208.

NSEIR, S., MAKRIS, D., MATHIEU, D., DUROCHER, A. & MARQUETTE, C. H. 2010. Intensive care unit-acquired infection as a side effect of sedation. *Critical Care,* 14**,** R30.

NY, P., NIEBERG, P. & WONG-BERINGER, A. 2015. Impact of carbapenem resistance on epidemiology and outcomes of nonbacteremic Klebsiella pneumoniae infections. *American Journal of Infection Control,* 43**,** 1076-1080.

ONGURU, P., ERBAY, A., BODUR, H., BARAN, G., AKINCI, E., BALABAN, N. & CEVIK, M. A. 2008. Imipenem-resistant Pseudomonas aeruginosa: risk factors for nosocomial infections. *Journal of Korean Medical Science,* 23**,** 982-987.

ORSI, G. B., BENCARDINO, A., VENA, A., CARATTOLI, A., VENDITTI, C., FALCONE, M., GIORDANO, A. & VENDITTI, M. 2013. Patient risk factors for outer membrane permeability and KPC-producing carbapenem-resistant Klebsiella pneumoniae isolation: results of a double case-control study. *Infection,* 41**,** 61-67.

ORSI, G. B., GARCIA-FERNANDEZ, A., GIORDANO, A., VENDITTI, C., BENCARDINO, A., GIANFREDA, R., FALCONE, M., CARATTOLI, A. & VENDITTI, M. 2011. Risk factors and clinical significance of ertapenem-resistant Klebsiella pneumoniae in hospitalised patients. *Journal of Hospital Infection,* 78**,** 54-58.

OTEO, J., DELGADO-IRIBARREN, A., VEGA, D., BAUTISTA, V., RODRIGUEZ, M. C., VELASCO, M., SAAVEDRA, J. M., PEREZ-VAZQUEZ, M., GARCIA-COBOS, S., MARTINEZ-MARTINEZ, L. & CAMPOS, J. 2008. Emergence of imipenem resistance in clinical Escherichia coli during therapy. *International Journal of Antimicrobial Agents,* 32**,** 534-537.

OTTER, J. A., DYAKOVA, E., BISNAUTHSING, K. N., QUEROL-RUBIERA, A., PATEL, A., AHANONU, C., AUGUET, O. T., EDGEWORTH, J. D. & GOLDENBERG, S. D. 2016. Universal hospital admission screening for carbapenemase-producing organisms in a low-prevalence setting. *Journal of Antimicrobial Chemotherapy,* 71**,** 3556-3561.

OZKURT, Z., ERTEK, M., EROL, S., ALTOPARLAK, U. & AKCAY, M. N. 2005. The risk factors for acquisition of imipenem-resistant Pseudomonas aeruginosa in the burn unit. *Burns,* 31**,** 870-873.

PAAUW, A., CASPERS, M. P. M., LEVERSTEIN-VAN HALL, M. A., SCHUREN, F. H. J., MONTIJN, R. C., VERHOEF, J. & FLUIT, A. C. 2009. Identification of resistance and virulence factors in an epidemic Enterobacter hormaechei outbreak strain. *Microbiology,* 155**,** 1478-1488.

PALEPOU, M.-F., WOODFORD, N., HOPE, R., COLMAN, M., GLOVER, J., KAUFMANN, M. E., LAFONG, C., REYNOLDS, R. & LIVERMORE, D. M. 2005. Novel class A carbapenemase, KPC-4, in an Enterobacter isolate from Scotland. *15th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID).* 2-5 April 2005. Copenhagen, Denmark: Abstract. P427.

PAN, L., ZHU, F. X., LI, S., ZHAO, X. J., DU, A. Q. & AN, Y. Z. 2016. Risk factors of Carbapenem-resistant Enterobacteriaceae infection in intensive care unit. *China Medicine,* 11**,** 1200-1203.

PANO-PARDO, J. R., LOPEZ QUINTANA, B., LAZARO PERONA, F., RUIZ CARRASCOSO, G., ROMERO-GOMEZ, M. P., LOECHES YAGUE, B., DIAZ-POLLAN, B., MARTINEZ-VIRTO, A., MINGORANCE, J., GARCIA RODRIGUEZ, J., ARRIBAS, J. R. & GOMEZ-GIL, R. 2016. Community-Onset Bloodstream and Other Infections, Caused by Carbapenemase-Producing Enterobacteriaceae: Epidemiological, Microbiological, and Clinical Features. *Open Forum Infectious Diseases,* 3**,** ofw136.

PANO PARDO, J. R., SERRANO VILLAR, S., RAMOS RAMOS, J. C. & PINTADO, V. 2014. Infections caused by carbapenemase-producing Enterobacteriaceae: risk factors, clinical features and prognosis. *Enfermedades Infecciosas y Microbiología Clínica,* 32 Suppl 4**,** 41-48.

PAPADIMITRIOU-OLIVGERIS, M., FLIGOU, F., BARTZAVALI, C., ZOTOU, A., SPYROPOULOU, A., KOUTSILEOU, K., VAMVAKOPOULOU, S., SIOULAS, N., KARAMOUZOS, V., ANASTASSIOU, E. D.,

SPILIOPOULOU, I., CHRISTOFIDOU, M. & MARANGOS, M. 2017. Carbapenemase-producing Klebsiella pneumoniae bloodstream infection in critically ill patients: risk factors and predictors of mortality. *European Journal of Clinical Microbiology and Infectious Diseases,* 36**,** 1125-1131.

PAPADIMITRIOU-OLIVGERIS, M., MARANGOS, M., CHRISTOFIDOU, M., FLIGOU, F., BARTZAVALI, C., PANTELI, E. S., VAMVAKOPOULOU, S., FILOS, K. S. & ANASTASSIOU, E. D. 2014. Risk factors for infection and predictors of mortality among patients with KPC-producing Klebsiella pneumoniae bloodstream infections in the intensive care unit. *Scandinavian Journal of Infectious Diseases,* 46**,** 642-648.

PAPADIMITRIOU-OLIVGERIS, M., MARANGOS, M., FLIGOU, F., CHRISTOFIDOU, M., BARTZAVALI, C., ANASTASSIOU, E. D. & FILOS, K. S. 2012. Risk factors for KPC-producing Klebsiella pneumoniae enteric colonization upon ICU admission. *Journal of Antimicrobial Chemotherapy,* 67**,** 2976-2981.

PAPADIMITRIOU-OLIVGERIS, M., MARANGOS, M., FLIGOU, F., CHRISTOFIDOU, M., SKLAVOU, C., VAMVAKOPOULOU, S., ANASTASSIOU, E. D. & FILOS, K. S. 2013. KPC-producing Klebsiella pneumoniae enteric colonization acquired during intensive care unit stay: the significance of risk factors for its development and its impact on mortality. *Diagnostic Microbiology and Infectious Disease,* 77**,** 169-173.

PAPP-WALLACE, K. M., ENDIMIANI, A., TARACILA, M. A. & BONOMO, R. A. 2011. Carbapenems: past, present, and future. *Antimicrobial Agents and Chemotherapy,* 55**,** 4943-4960.

PASTERAN, F., FACCONE, D., PETRONI, A., RAPOPORT, M., GALAS, M., VAZQUEZ, M. & PROCOPIO, A. 2005. Novel variant (bla(VIM-11)) of the metallo-{beta}-lactamase bla(VIM) family in a GES-1 extended-spectrum-{beta}-lactamase-producing Pseudomonas aeruginosa clinical isolate in Argentina. *Antimicrobial Agents and Chemotherapy,* 49**,** 474-475.

PATEL, G., HUPRIKAR, S., FACTOR, S. H., JENKINS, S. G. & CALFEE, D. P. 2008. Outcomes of carbapenem-resistant Klebsiella pneumoniae infection and the impact of antimicrobial and adjunctive therapies. *Infection Control and Hospital Epidemiology,* 29**,** 1099-1106.

PATEL, N., HARRINGTON, S., DIHMESS, A., WOO, B., MASOUD, R., MARTIS, P., FIORENZA, M., GRAFFUNDER, E., EVANS, A., MCNUTT, L. A. & LODISE, T. P. 2011. Clinical epidemiology of carbapenem-intermediate or -resistant Enterobacteriaceae. *Journal of Antimicrobial Chemotherapy,* 66**,** 1600-1608.

PATON, R., MILES, R. S., HOOD, J., AMYES, S. G. B., MILES, R. S. & AMYES, S. G. B. 1993. ARI 1: β-lactamase-mediated imipenem resistance in Acinetobacter baumannii. *International Journal of Antimicrobial Agents,* 2**,** 81-87.

PENA, C., GUZMAN, A., SUAREZ, C., DOMINGUEZ, M. A., TUBAU, F., PUJOL, M., GUDIOL, F. & ARIZA, J. 2007. Effects of carbapenem

exposure on the risk for digestive tract carriage of intensive care unit-endemic carbapenem-resistant Pseudomonas aeruginosa strains in critically ill patients. *Antimicrobial Agents and Chemotherapy,* 51**,** 1967-1971.

PENA, C., SUAREZ, C., GOZALO, M., MURILLAS, J., ALMIRANTE, B., POMAR, V., AGUILAR, M., GRANADOS, A., CALBO, E., RODRIGUEZ-BANO, J., RODRIGUEZ, F., TUBAU, F., MARTINEZ-MARTINEZ, L., OLIVER, A. & SPANISH NETWORK FOR RESEARCH IN INFECTIOUS DISEASES, R. 2012. Prospective multicenter study of the impact of carbapenem resistance on mortality in Pseudomonas aeruginosa bloodstream infections. *Antimicrobial Agents and Chemotherapy,* 56**,** 1265-1272.

PENG, S. H., JIN, Z. J., LUO, L. & LI, C. R. 2005. A case-control study on the risk factors of nosocomial infection caused by imipenem-resistant Pseudomonas aeruginosa. *Chung-Hua Liu Hsing Ping Hsueh Tsa Chih Chinese Journal of Epidemiology,* 26**,** 511-514.

PEREZ, F., PULTZ MJ FAU - ENDIMIANI, A., ENDIMIANI A FAU - BONOMO, R. A., BONOMO RA FAU - DONSKEY, C. J. & DONSKEY, C. J. 2011. Effect of antibiotic treatment on establishment and elimination of intestinal colonization by KPC-producing Klebsiella pneumoniae in mice. *Antimicrobial Agents and Chemotherapy,* 55**,** 2585-2589.

PETO, R. & PETO, J. 1972. Asymptotically Efficient Rank Invariant Test Procedures. *Journal of the Royal Statistical Society. Series A (General),* 135**,** 185-207.

PETRIKKOS, P., KOSMIDIS, C., PSICHOGIOU, M., TASSIOS, P., TZOUVELEKIS, L., AVLAMIS, A., STEFANOU, I., PLATSOUKA, E., PANIARA, O., XANTHAKI, A., TOUTOUZA, M., VRIONIS, E., SKOUTELIS, A., GEORGOUSI, K., BAMIA, C., PETRIKKOS, G. & DAIKOS, G. L. 2009. Prospective study of Klebsiella pneumoniae bacteremia: Risk factors and clinical significance of type VIM-1 metallo-beta-lactamases. [Greek]. *Archives of Hellenic Medicine,* 26**,** 374-383.

PITOUT, J. D. D. & LAUPLAND, K. B. 2008. Extended-spectrum beta-lactamase-producing enterobacteriaceae: an emerging public-health concern. *Lancet Infectious Diseases,* 8**,** 159-166.

PLACHOURASI, D., KARKI, T., HANSEN, S., HOPKINS, S., LYYTIKAINEN, O., MORO, M. L., RELLLY, J., ZARB, P., ZINGG, W., KINROSS, P., WEISTL, K., MONNET, D. L., SUETENS, C. & GRP, P. P. S. S. 2018. Antimicrobial use in European acute care hospitals: results from the second point prevalence survey (PPS) of healthcare-associated infections and antimicrobial use, 2016 to 2017. *Eurosurveillance,* 23**,** 15-28.

PLAYFORD, E. G., CRAIG, J. C. & IREDELL, J. R. 2007. Carbapenem-resistant Acinetobacter baumannii in intensive care unit patients: risk factors for acquisition, infection and their consequences. *Journal of Hospital Infection,* 65**,** 204-211.

POIREL, L., AL MASKARI, Z., AL RASHDI, F., BERNABEU, S. & NORDMANN, P. 2011. NDM-1-producing Klebsiella pneumoniae isolated in the Sultanate of Oman. *Journal of Antimicrobial Chemotherapy,* 66**,** 304-306.

POIREL, L., HERITIER, C., SPICQ, C. & NORDMANN, P. 2004a. In vivo acquisition of high-level resistance to imipenem in Escherichia coli. *Journal of Clinical Microbiology,* 42**,** 3831-3833.

POIREL, L., HERITIER, C., TOLUN, V. & NORDMANN, P. 2004b. Emergence of oxacillinase-mediated resistance to imipenem in Klebsiella pneumoniae. *Antimicrobial Agents and Chemotherapy,* 48**,** 15-22.

POIREL, L., LE THOMAS, I., NAAS, T., KARIM, A. & NORDMANN, P. 2000a. Biochemical sequence analyses of GES-1, a novel class A extended-spectrum beta-lactamase, and the class 1 integron In52 from Klebsiella pneumoniae. *Antimicrobial Agents and Chemotherapy,* 44**,** 622-632.

POIREL, L., MAGALHAES, M., LOPES, M. & NORDMANN, P. 2004c. Molecular analysis of metallo-beta-lactamase gene bla(SPM-1)-surrounding sequences from disseminated Pseudomonas aeruginosa isolates in Recife, Brazil. *Antimicrobial Agents and Chemotherapy,* 48**,** 1406-1409.

POIREL, L., MARQUE, S., HERITIER, C., SEGONDS, C., CHABANON, G. & NORDMANN, P. 2005. OXA-58, a novel class D {beta}-lactamase involved in resistance to carbapenems in Acinetobacter baumannii. *Antimicrobial Agents and Chemotherapy,* 49**,** 202-208.

POIREL, L., NAAS, T., NICOLAS, D., COLLET, L., BELLAIS, S., CAVALLO, J. D. & NORDMANN, P. 2000b. Characterization of VIM-2, a carbapenem-hydrolyzing metallo-beta-lactamase and its plasmid- and integron-borne gene from a Pseudomonas aeruginosa clinical isolate in France. *Antimicrobial Agents and Chemotherapy,* 44**,** 891-897.

POIREL, L., POTRON, A. & NORDMANN, P. 2012. OXA-48-like carbapenemases: the phantom menace. *Journal of Antimicrobial Chemotherapy,* 67**,** 1597-1606.

POIREL, L., WELDHAGEN, G. F., DE CHAMPS, C. & NORDMANN, P. 2002. A nosocomial outbreak of Pseudomonas aeruginosa isolates expressing the extended-spectrum beta-lactamase GES-2 in South Africa. *Journal of Antimicrobial Chemotherapy,* 49**,** 561-565.

POIREL, L., WELDHAGEN, G. F., NAAS, T., DE CHAMPS, C., DOVE, M. G. & NORDMANN, P. 2001. GES-2, a class A beta-lactamase from Pseudomonas aeruginosa with increased hydrolysis of imipenem. *Antimicrobial Agents and Chemotherapy,* 45**,** 2598-2603.

POLITO, A., PATORNO, E., COSTELLO, J. M., SALVIN, J. W., EMANI, S. M., RAJAGOPAL, S., LAUSSEN, P. C. & THIAGARAJAN, R. R. 2011. Perioperative factors associated with prolonged mechanical ventilation after complex congenital heart surgery. *Pediatric Critical Care Medicine,* 12**,** e122-126.

POOLE, K. 2001. Multidrug efflux pumps and antimicrobial resistance in Pseudomonas aeruginosa and related organisms. *Journal of Molecular Microbiology and Biotechnology,* 3**,** 255-264.

POOLE, K., GEORGE, R., DECRAENE, V., SHANKAR, K., CAWTHORNE, J., SAVAGE, N., WELFARE, W. & DODGSON, A. 2016. Active case finding for carbapenemase-producing Enterobacteriaceae in a teaching hospital: prevalence and risk factors for colonization. *Journal of Hospital Infection,* 94**,** 125-129.

POTRON, A., NORDMANN, P., LAFEUILLE, E., AL MASKARI, Z., AL RASHDI, F. & POIREL, L. 2011. Characterization of OXA-181, a carbapenem-hydrolyzing class D beta-lactamase from Klebsiella pneumoniae. *Antimicrobial Agents and Chemotherapy,* 55**,** 4896-4899.

POTRON, A., POIREL, L. & NORDMANN, P. 2014. Derepressed Transfer Properties Leading to the Efficient Spread of the Plasmid Encoding Carbapenemase OXA-48. *Antimicrobial Agents and Chemotherapy,* 58**,** 467-471.

POUCH, S. M., KUBIN, C. J., SATLIN, M. J., TSAPEPAS, D. S., LEE, J. R., DUBE, G. & PEREIRA, M. R. 2015. Epidemiology and outcomes of carbapenem-resistant Klebsiella pneumoniae bacteriuria in kidney transplant recipients. *Transplant Infectious Disease,* 17**,** 800-809.

PRASAD, N., LABAZE, G., KOPACZ, J., CHWA, S., PLATIS, D., PAN, C. X., RUSSO, D., LABOMBARDI, V. J., OSORIO, G., POLLACK, S., KREISWIRTH, B. N., CHEN, L., URBAN, C. & SEGAL-MAURER, S. 2016. Asymptomatic rectal colonization with carbapenem-resistant Enterobacteriaceae and Clostridium difficile among residents of a long-term care facility in New York City. *American Journal of Infection Control,* 44**,** 525-532.

PUBLIC HEALTH ENGLAND. 2015. *Carbapenemase-producing Enterobacteriaceae: non-acute and community toolkit* [Online]. Public Health England. Available: https://www.gov.uk/government/publications/carbapenemase-producing-enterobacteriaceae-non-acute-and-community-toolkit [Accessed 24/12/2019].

PUBLIC HEALTH ENGLAND. 2016. *UK Standards for Microbiology Investigations, Detection of bacteria with carbapenem-hydrolysing beta-lactamases (carbapenemases) methodology* [Online]. Public Health England. Available: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/554654/B_60i2.1.pdf [Accessed 24/12/2019].

PUBLIC HEALTH ENGLAND. 2018. *English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2018* [Online]. Public Health England. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/759975/ESPAUR_2018_report.pdf [Accessed 24/12/2019].

PUNPANICH, W., NITHITAMSAKUN, N., TREERATWEERAPHONG, V. & SUNTARATTIWONG, P. 2012. Risk factors for carbapenem non-

susceptibility and mortality in Acinetobacter baumannii bacteremia in children. *International Journal of Infectious Diseases,* 16**,** e811-815.
QUEENAN, A. M. & BUSH, K. 2007. Carbapenemases: the versatile beta-lactamases. *Clinical Microbiology Reviews,* 20**,** 440-458.
QUEENAN, A. M., SHANG, W., FLAMM, R. & BUSH, K. 2010. Hydrolysis and inhibition profiles of beta-lactamases from molecular classes A to D with doripenem, imipenem, and meropenem. *Antimicrobial Agents and Chemotherapy,* 54**,** 565-569.
QURESHI, Z. A., SYED, A., CLARKE, L. G., DOI, Y. & SHIELDS, R. K. 2014. Epidemiology and Clinical Outcomes of Patients with Carbapenem-Resistant Klebsiella pneumoniae Bacteriuria. *Antimicrobial Agents and Chemotherapy,* 58**,** 3100-3104.
RADICE, M., POWER, P., GUTKIND, G., FERNANDEZ, K., VAY, C., FAMIGLIETTI, A., RICOVER, N. & AYALA, J. A. 2004. First class a carbapenemase isolated from enterobacteriaceae in Argentina. *Antimicrobial Agents and Chemotherapy,* 48**,** 1068-1069.
RASMUSSEN, B. A., BUSH, K., KEENEY, D., YANG, Y., HARE, R., O'GARA, C. & MEDEIROS, A. A. 1996. Characterization of IMI-1 beta-lactamase, a class A carbapenem-hydrolyzing enzyme from Enterobacter cloacae. *Antimicrobial Agents and Chemotherapy,* 40**,** 2080-2086.
REID, S. & TIBSHIRANI, R. 2014. Regularization Paths for Conditional Logistic Regression: The clogitL1 Package. *Journal of Statistical Software,* 58**,** 12.
RHODES, N. J., WAGNER, J. L., DAVIS, S. L., BOSSO, J. A., GOFF, D. A., RYBAK, M. J., SCHEETZ, M. H. & NETWORK, M.-I. R. 2019. Trends in and Predictors of Carbapenem Consumption across North American Hospitals: Results from a Multicenter Survey by the MAD-ID Research Network. *Antimicrobial Agents and Chemotherapy,* 63**,** e00327-19.
RIEBER, H., FRONTZEK, A. & PFEIFER, Y. 2012. Emergence of metallo-beta-lactamase GIM-1 in a clinical isolate of Serratia marcescens. *Antimicrobial Agents and Chemotherapy,* 56**,** 4945-4947.
RIGHI, E., PERI, A. M., HARRIS, P. N. A., WAILAN, A. M., LIBORIO, M., LANE, S. W. & PATERSON, D. L. 2017. Global prevalence of carbapenem resistance in neutropenic patients and association with mortality and carbapenem use: Systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy,* 72**,** 668-677.
ROLINSON, G. N. 1991. Evolution of Beta-Lactamase Inhibitors. *Reviews of Infectious Diseases,* 13**,** S727-S732.
ROSA, R., ARHEART, K. L., DEPASCALE, D., CLEARY, T., KETT, D. H., NAMIAS, N., PIZANO, L., FAJARDO-AQUINO, Y. & MUNOZ-PRICE, L. S. 2014. Environmental exposure to carbapenem-resistant Acinetobacter baumannii as a risk factor for patient acquisition of A. baumannii. *Infection Control and Hospital Epidemiology,* 35**,** 430-433.
ROSSI GONCALVES, I., DANTAS, R. C. C., FERREIRA, M. L., BATISTAO, D., GONTIJO-FILHO, P. P. & RIBAS, R. M. 2017. Carbapenem-

resistant Pseudomonas aeruginosa: association with virulence genes and biofilm formation. *Brazilian Journal of Microbiology,* 48**,** 211-217.

ROSSINI, A., DI SANTO, S. G., LIBORI, M. F., TIRACCHIA, V., BALICE, M. P. & SALVIA, A. 2016. Risk factors for carbapenemase-producing Enterobacteriaceae colonization of asymptomatic carriers on admission to an Italian rehabilitation hospital. *Journal of Hospital Infection,* 92**,** 78-81.

ROUTSI, C., PRATIKAKI, M., PLATSOUKA, E., SOTIROPOULOU, C., NANAS, S., MARKAKI, V., VRETTOU, C., PANIARA, O., GIAMARELLOU, H. & ROUSSOS, C. 2010. Carbapenem-resistant versus carbapenem-susceptible Acinetobacter baumannii bacteremia in a Greek intensive care unit: risk factors, clinical features and outcomes. *Infection,* 38**,** 173-180.

ROUTSI, C., PRATIKAKI, M., PLATSOUKA, E., SOTIROPOULOU, C., PAPAS, V., PITSIOLIS, T., TSAKRIS, A., NANAS, S. & ROUSSOS, C. 2013. Risk factors for carbapenem-resistant Gram-negative bacteremia in intensive care unit patients. *Intensive Care Medicine,* 39**,** 1253-1261.

SAAVEDRA-TRUJILLO, C. H., ARIAS-LEON, G., GUALTERO-TRUJILLO, S. M., LEAL, A. L., SAAVEDRA-ROJAS, S. Y. & MURCIA, M. I. 2016. Risk factors for colonisation or infection by Acinetobacter baumannii resistant to carbapenems in adult patients hospitalised in Intensive Care Units in Bogota, Colombia. *Infection,* 20**,** 238-249.

SABBAGH, P., RIAHI, S. M., GAMBLE, H. R. & ROSTAMI, A. 2019. The global and regional prevalence, burden, and risk factors for methicillin-resistant Staphylococcus aureus colonization in HIV-infected people: A systematic review and meta-analysis. *American Journal of Infection Control,* 47**,** 323-333.

SADIKOT, R. T., BLACKWELL, T. S., CHRISTMAN, J. W. & PRINCE, A. S. 2005. Pathogen-host interactions in Pseudomonas aeruginosa pneumonia. *American Journal of Respiratory and Critical Care Medicine,* 171**,** 1209-1223.

SAEYS, Y., INZA, I. & LARRANAGA, P. 2007. A review of feature selection techniques in bioinformatics. *Bioinformatics,* 23**,** 2507-2517.

SALSANO, A., GIACOBBE, D. R., SPORTELLI, E., OLIVIERI, G. M., BREGA, C., DI BIASE, C., COPPO, E., MARCHESE, A., DEL BONO, V., VISCOLI, C. & SANTINI, F. 2016. Risk factors for infections due to carbapenem-resistant Klebsiella pneumoniae after open heart surgery. *Interactive Cardiovascular and Thoracic Surgery,* 23**,** 762-768.

SANCHEZ-ROMERO, I., ASENSIO, A., OTEO, J., MUNOZ-ALGARRA, M., ISIDORO, B., VINDEL, A., ALVAREZ-AVELLO, J., BALANDIN-MORENO, B., CUEVAS, O., FERNANDEZ-ROMERO, S., AZANEDO, L., SAEZ, D. & CAMPOS, J. 2012. Nosocomial outbreak of VIM-1-producing Klebsiella pneumoniae isolates of multilocus sequence type 15: molecular basis, clinical risk factors, and outcome. *Antimicrobial Agents and Chemotherapy,* 56**,** 420-427.

SANCHEZ, M. B. 2015. Antibiotic resistance in the opportunistic pathogen Stenotrophomonas maltophilia. *Frontiers in Microbiology,* 6**,** 658.

SATLIN, M. J., COHEN, N., MA, K. C., GEDRIMAITE, Z., SOAVE, R., ASKIN, G., CHEN, L., KREISWIRTH, B. N., WALSH, T. J. & SEO, S. K. 2016. Bacteremia due to carbapenem-resistant Enterobacteriaceae in neutropenic patients with hematologic malignancies. *Journal of Infection,* 73**,** 336-345.

SBRANA, F., MALACARNE, P., BASSETTI, M., TASCINI, C., VEGNUTI, L., DELLA SIEGA, P., RIPOLI, A., ANSALDI, F. & MENICHETTI, F. 2016. Risk factors for ventilator associated pneumonia due to carbapenemase-producing Klebsiella pneumoniae in mechanically ventilated patients with tracheal and rectal colonization. *Minerva Anestesiologica,* 82**,** 635-640.

SCHECHNER, V., KOTLOVSKY, T., TARABEIA, J., KAZMA, M., SCHWARTZ, D., NAVON-VENEZIA, S. & CARMELI, Y. 2011. Predictors of rectal carriage of carbapenem-resistant Enterobacteriaceae (CRE) among patients with known CRE carriage at their next hospital encounter. *Infection Control and Hospital Epidemiology,* 32**,** 497-503.

SCHWABER, M. J., KLARFELD-LIDJI, S., NAVON-VENEZIA, S., SCHWARTZ, D., LEAVITT, A. & CARMELI, Y. 2008. Predictors of carbapenem-resistant Klebsiella pneumoniae acquisition among hospitalized adults and effect of acquisition on mortality. *Antimicrobial Agents and Chemotherapy,* 52**,** 1028-1033.

SCOTLAND'S HEALTH ON THE WEB. 2019. *NHS Scotland Health Boards* [Online]. Scotland's Health on the Web. Available: https://www.scot.nhs.uk/organisations/ [Accessed 24/12/2019].

SCOTTISH GOVERNMENT. 2013. *Antimicrobial Resistance-CMO/SGHD(2013)14* [Online]. Scottish Government. Available: www.sehd.scot.nhs.uk/cmo/CMO(2013)14.pdf [Accessed 24/12/2019].

SCOTTISH MEDICINES CONSORTIUM. Available: https://www.scottishmedicines.org.uk/medicines-advice/ [Accessed 06/02/2020].

SCOTTISH MEDICINES CONSORTIUM. 2014. *doripenem (Doribax)* [Online]. Available: https://www.scottishmedicines.org.uk/medicines-advice/doripenem-doribax-fullsubmission-52909/ [Accessed 06/02/2020].

SEKIGUCHI, J., MORITA, K., KITAO, T., WATANABE, N., OKAZAKI, M., MIYOSHI-AKIYAMA, T., KANAMORI, M. & KIRIKAE, T. 2008. KHM-1, a novel plasmid-mediated metallo-beta-lactamase from a Citrobacter freundii clinical isolate. *Antimicrobial Agents and Chemotherapy,* 52**,** 4194-4197.

SHARAF, H. E. & GERGES, M. A. 2016. Nosocomial imipenem-resistant Acinetobacter Baumannii infections in intensive care units: Incidence and risk factors assessment. *African Journal of Clinical and Experimental Microbiology,* 17**,** 243-249.

SHENG, W. H., BADAL, R. E., HSUEH, P. R. & PROGRAM, S. 2013. Distribution of Extended-Spectrum beta-Lactamases, AmpC beta-Lactamases, and Carbapenemases among Enterobacteriaceae Isolates Causing Intra-Abdominal Infections in the Asia-Pacific Region:

Results of the Study for Monitoring Antimicrobial Resistance Trends (SMART). *Antimicrobial Agents and Chemotherapy,* 57**,** 2981-2988.

SHENG, W. H., LIAO, C. H., LAUDERDALE, T. L., KO, W. C., CHEN, Y. S., LIU, J. W., LAU, Y. J., WANG, L. H., LIU, K. S., TSAI, T. Y., LIN, S. Y., HSU, M. S., HSU, L. Y. & CHANG, S. C. 2010. A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant Acinetobacter baumannii. *International Journal of Infectious Diseases,* 14**,** e764-769.

SHILO, S., ASSOUS, M. V., LACHISH, T., KOPUIT, P., BDOLAH-ABRAM, T., YINNON, A. M. & WIENER-WELL, Y. 2013. Risk factors for bacteriuria with carbapenem-resistant Klebsiella pneumoniae and its impact on mortality: a case-control study. *Infection,* 41**,** 503-509.

SIEVERT, D. M., RICKS, P., EDWARDS, J. R., SCHNEIDER, A., PATEL, J., SRINIVASAN, A., KALLEN, A., LIMBAGO, B. & FRIDKIN, S. 2013. Antimicrobial-Resistant Pathogens Associated with Healthcare-Associated Infections Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. *Infection Control and Hospital Epidemiology,* 34**,** 1-14.

SIMKINS, J., MUGGIA, V., COHEN, H. W. & MINAMOTO, G. Y. 2014. Carbapenem-resistant Klebsiella pneumoniae infections in kidney transplant recipients: a case-control study. *Transplant Infectious Disease,* 16**,** 775-782.

SONG, J. H. & KIM, Y. S. 2019. Recurrent Clostridium difficile Infection: Risk Factors, Treatment, and Prevention. *Gut Liver,* 13**,** 16-24.

SONMEZER, M. C., ERTEM, G., ERDINC, F. S., KAYA KILIC, E., TULEK, N., ADILOGLU, A. & HATIPOGLU, C. 2016. Evaluation of Risk Factors for Antibiotic Resistance in Patients with Nosocomial Infections Caused by Pseudomonas aeruginosa. *Canadian Journal of Infectious Diseases and Medical Microbiology,* 2016 (no pagination)**,** 1321487.

SSEKATAWA, K., BYARUGABA, D. K., WAMPANDE, E. & EJOBI, F. 2018. A systematic review: the current status of carbapenem resistance in East Africa. *BMC Research Notes,* 11**,** 629.

STEYERBERG, E. W., EIJKEMANS, M. J. C., HARRELL, F. E. & HABBEMA, J. D. F. 2001. Prognostic modeling with logistic regression analysis: In search of a sensible strategy in small data sets. *Medical Decision Making,* 21**,** 45-56.

SUN, C. L., GAN, Z. H. & YAO, B. F. 2016. Analysis of drug resistance characteristics of Imipenem-resistant Pseudomonas aeruginosa and infection risk factors in Zhoushan. *China Pharmacy,* 27**,** 1061-1063.

SWAMINATHAN, M., SHARMA, S., POLIANSKY BLASH, S., PATEL, G., BANACH, D. B., PHILLIPS, M., LABOMBARDI, V., ANDERSON, K. F., KITCHEL, B., SRINIVASAN, A. & CALFEE, D. P. 2013. Prevalence and risk factors for acquisition of carbapenem-resistant Enterobacteriaceae in the setting of endemicity. *Infection Control and Hospital Epidemiology,* 34**,** 809-817.

TAKEUCHI, D., AKEDA, Y., SUGAWARA, Y., SAKAMOTO, N., YAMAMOTO, N., SHANMUGAKANI, R. K., ISHIHARA, T., SHINTANI, A., TOMONO, K. & HAMADA, S. 2018. Establishment of a dual-wavelength spectrophotometric method for analysing and detecting carbapenemase-producing Enterobacteriaceae. *Scientific Reports,* 8**,** 15689.

TAM, V. H., CHANG, K. T., LAROCCO, M. T., SCHILLING, A. N., MCCAULEY, S. K., POOLE, K. & GAREY, K. W. 2007. Prevalence, mechanisms, and risk factors of carbapenem resistance in bloodstream isolates of Pseudomonas aeruginosa. *Diagnostic Microbiology and Infectious Disease,* 58**,** 309-314.

TAMMA, P. D., GOODMAN, K. E., HARRIS, A. D., TEKLE, T., ROBERTS, A., TAIWO, A. & SIMNER, P. J. 2017a. Comparing the Outcomes of Patients With Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae Bacteremia. *Clinical Infectious Diseases,* 64**,** 257-264.

TAMMA, P. D., KAZMI, A., BERGMAN, Y., GOODMAN, K. E., EKUNSEITAN, E., AMOAH, J. & SIMNER, P. J. 2019. The Likelihood of Developing a Carbapenem-Resistant Enterobacteriaceae Infection during a Hospital Stay. *Antimicrobial Agents and Chemotherapy,* 63**,** e00757-19.

TAMMA, P. D., OPENE, B. N., GLUCK, A., CHAMBERS, K. K., CARROLL, K. C. & SIMNER, P. J. 2017b. Comparison of 11 Phenotypic Assays for Accurate Detection of Carbapenemase-Producing Enterobacteriaceae. *Journal of Clinical Microbiology,* 55**,** 1046-1055.

TENOVER, F. C., KALSI, R. K., WILLIAMS, P. P., CAREY, R. B., STOCKER, S., LONSWAY, D., RASHEED, J. K., BIDDLE, J. W., MCGOWAN, J. E., JR. & HANNA, B. 2006. Carbapenem resistance in Klebsiella pneumoniae not detected by automated susceptibility testing. *Emerging Infectious Diseases,* 12**,** 1209-1213.

TEO, J., CAI, Y., TANG, S., LEE, W., TAN, T. Y., TAN, T. T. & KWA, A. L. 2012. Risk factors, molecular epidemiology and outcomes of ertapenem-resistant, carbapenem-susceptible Enterobacteriaceae: a case-case-control study. *PLoS ONE,* 7**,** e34254.

THAKUR, S. & GRAY, G. C. 2019. The Mandate for a Global "One Health" Approach to Antimicrobial Resistance Surveillance. *American Journal of Tropical Medicine and Hygiene,* 100**,** 227-228.

THATRIMONTRICHAI, A., APISARNTHANARAK, A., CHANVITAN, P., JANJINDAMAI, W., DISSANEEVATE, S. & MANEENIL, G. 2013. Risk factors and outcomes of carbapenem-resistant Acinetobacter baumannii bacteremia in neonatal intensive care unit: a case-case-control study. *Pediatric Infectious Disease Journal,* 32**,** 140-145.

THATRIMONTRICHAI, A., TECHATO, C., DISSANEEVATE, S., JANJINDAMAI, W., MANEENIL, G., KRITSANEEPAIBOON, S. & TANAANANTARAK, P. 2016. Risk factors and outcomes of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia in the neonate: A case-case-control study. *Journal of Infection and Chemotherapy,* 22**,** 444-449.

THE EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING. 2019. *Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0.* [Online]. The European Committee on Antimicrobial Susceptibility Testing. Available: http://www.eucast.org [Accessed 24/12/2019].

THE SCOTTISH GOVERNMENT. 2010. *SGHD/CMO letter on Antimicrobial Resistance* [Online]. The Scottish Government. Available: https://www.sehd.scot.nhs.uk/cmo/CMO(2010)24.pdf [Accessed 24/12/2019].

THE SCOTTISH GOVERNMENT. 2013. *CMO/SGHD letter on Antimicrobial Resistance* [Online]. The Scottish Government. Available: http://www.sehd.scot.nhs.uk/cmo/CMO(2013)14.pdf [Accessed 24/12/2019].

THE SCOTTISH GOVERNMENT. 2015. *Healthcare Associated Infection (HAI) and Antimicrobial Resistance (AMR) Policy Requirements* [Online]. The Scottish Government. Available: https://www.sehd.scot.nhs.uk/dl/DL%282015%2919.pdf [Accessed 24/12/2019].

THE SCOTTISH GOVERNMENT. 2017. *Carbapenemase-producing Enterobacteriaceae (CPE) Policy Requirement* [Online]. The Scottish Government. Available: https://www.sehd.scot.nhs.uk/dl/DL(2017)02.pdf [Accessed 24/12/2019].

THE SCOTTISH PUBLIC HEALTH OBSERVATORY. 2017. *Sex distribution of Scotland'spopulation within 5-year age group* [Online]. The Scottish Public Health Observatory. Available: https://www.scotpho.org.uk/population-groups/gender/data/demography/ [Accessed 24/12/2019].

THE WORLD BANK. 2017. *World Bank Country Classification by Income* [Online]. The World Bank. Available: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups [Accessed 30/12/2019].

TIAN, L., TAN, R., CHEN, Y., SUN, J., LIU, J., QU, H. & WANG, X. 2016. Epidemiology of Klebsiella pneumoniae bloodstream infections in a teaching hospital: Factors related to the carbapenem resistance and patient mortality. *Antimicrobial Resistance and Infection Control,* 5**,** 48-59.

TIBSHIRANI, R. 1996. Regression shrinkage and selection via the Lasso. *Journal of the Royal Statistical Society Series B-Methodological,* 58**,** 267-288.

TISCHENDORF, J., DE AVILA, R. A. & SAFDAR, N. 2016. Risk of infection following colonization with carbapenem-resistant Enterobactericeae: A systematic review. *American Journal of Infection Control,* 44**,** 539-543.

TONER, G., RUSSELL, C. D., HAMILTON, F., TEMPLETON, K. & LAURENSON, I. F. 2019. Phenotypic and molecular detection methods for carbapenemase-producing organisms and their clinical significance at two Scottish tertiary care hospitals. *Journal of Medical Microbiology,* 68**,** 560-565.

TORNIEPORTH, N. G., ROBERTS, R. B., JOHN, J., HAFNER, A. & RILEY, L. W. 1996. Risk Factors Associated with Vancomycin-Resistant Enterococcus faecium Infection or Colonization in 145 Matched Case Patients and Control Patients. *Clinical Infectious Diseases,* 23**,** 767-772.

TORRES-GONZALEZ, P., CERVERA-HERNANDEZ, M. E., NIEMBRO-ORTEGA, M. D., LEAL-VEGA, F., CRUZ-HERVERT, L. P., GARCIA-GARCIA, L., GALINDO-FRAGA, A., MARTINEZ-GAMBOA, A., BOBADILLA-DEL VALLE, M., SIFUENTES-OSORNIO, J. & PONCE-DE-LEON, A. 2015. Factors Associated to Prevalence and Incidence of Carbapenem-Resistant Enterobacteriaceae Fecal Carriage: A Cohort Study in a Mexican Tertiary Care Hospital. *PLoS ONE,* 10**,** e0139883.

TORRES-GONZALEZ, P., ORTIZ-BRIZUELA, E., CERVERA-HERNANDEZ, M. E., BOBADILLA-DEL VALLE, M., MARTINEZ-GAMBOA, A., SIFUENTES-OSORNIO, J. & PONCE-DE-LEON, A. 2016. Associated factors and outcomes for OXA-232 Carbapenem-resistant Enterobacteriaceae infections in a tertiary care centre in Mexico City: A case-control-control study. *Diagnostic Microbiology and Infectious Disease,* 86**,** 243-248.

TRECARICHI, E. M., PAGANO, L., MARTINO, B., CANDONI, A., DI BLASI, R., NADALI, G., FIANCHI, L., DELIA, M., SICA, S., PERRIELLO, V., BUSCA, A., AVERSA, F., FANCI, R., MELILLO, L., LESSI, F., DEL PRINCIPE, M. I., CATTANEO, C. & TUMBARELLO, M. 2016. Bloodstream infections caused by Klebsiella pneumoniae in onco-hematological patients: clinical impact of carbapenem resistance in a multicentre prospective survey. *American Journal of Hematology,* 91**,** 1076-1081.

TREPANIER, P., MALLARD, K., MEUNIER, D., PIKE, R., BROWN, D., ASHBY, J. P., DONALDSON, H., AWAD-EL-KARIEM, F. M., BALAKRISHNAN, I., CUBBON, M., CHADWICK, P. R., DOUGHTON, M., DOUGHTON, R., HARDIMAN, F., HARVEY, G., HORNER, C., LEE, J., LEWIS, J., LOUGHREY, A., MANUEL, R., PARSONS, H., PERRY, J. D., VANSTONE, G., WHITE, G., SHETTY, N., COIA, J., WIUFF, C., HOPKINS, K. L. & WOODFORD, N. 2017. Carbapenemase-producing Enterobacteriaceae in the UK: a national study (EuSCAPE-UK) on prevalence, incidence, laboratory detection methods and infection control measures. *Journal of Antimicrobial Chemotherapy,* 72**,** 596-603.

TROILLET, N., CARMELI, Y., VENKATARAMAN, L., DEGIROLAMI, P. & SAMORE, M. H. 1999. Epidemiological analysis of imipenem-resistant Serratia marcescens in hospitalized patients. *Journal of Hospital Infection,* 42**,** 37-43.

TROILLET, N., SAMORE, M. H. & CARMELI, Y. 1997. Imipenem-resistant Pseudomonas aeruginosa: risk factors and antibiotic susceptibility patterns. *Clinical Infectious Diseases,* 25**,** 1094-1098.

TUMBARELLO, M., TRECARICHI, E. M., TUMIETTO, F., BONO, V. D., DE ROSA, F. G., BASSETTI, M., LOSITO, A. R., TEDESCHI, S.,

SAFFIOTI, C., CORCIONE, S., GIANNELLA, M., RAFFAELLI, F., PAGANI, N., BARTOLETTI, M., SPANU, T., MARCHESE, A., CAUDA, R., VISCOLI, C. & VIALE, P. 2014. Predictive models for identification of hospitalized patients harboring KPC-producing klebsiella pneumoniae. *Antimicrobial Agents and Chemotherapy,* 58**,** 3514-3520.

TUMBARELLO, M., VIALE, P., VISCOLI, C., TRECARICHI, E. M., TUMIETTO, F., MARCHESE, A., SPANU, T., AMBRETTI, S., GINOCCHIO, F., CRISTINI, F., LOSITO, A. R., TEDESCHI, S., CAUDA, R. & BASSETTI, M. 2012. Predictors of Mortality in Bloodstream Infections Caused by Klebsiella pneumoniae Carbapenemase-Producing K. pneumoniae: Importance of Combination Therapy. *Clinical Infectious Diseases,* 55**,** 943-950.

TUON, F. F., GORTZ, L. W. & ROCHA, J. L. 2012a. Risk factors for pan-resistant Pseudomonas aeruginosa bacteremia and the adequacy of antibiotic therapy. *Brazilian Journal of Infectious Diseases,* 16**,** 351-356.

TUON, F. F., ROCHA, J. L., TOLEDO, P., AREND, L. N., DIAS, C. H., LEITE, T. M., PENTEADO-FILHO, S. R., PILONETTO, M. & ZAVASCKI, A. P. 2012b. Risk factors for KPC-producing Klebsiella pneumoniae bacteremia. *Brazilian Journal of Infectious Diseases,* 16**,** 416-419.

TURTON, J. F., KAUFMANN, M. E., GLOVER, J., COELHO, J. M., WARNER, M., PIKE, R. & PITT, T. L. 2005. Detection and typing of integrons in epidemic strains of Acinetobacter baumannii found in the United Kingdom. *Journal of Clinical Microbiology,* 43**,** 3074-3082.

TURTON, J. F., PAYNE, Z., COWARD, A., HOPKINS, K. L., TURTON, J. A., DOUMITH, M. & WOODFORD, N. 2018. Virulence genes in isolates of Klebsiella pneumoniae from the UK during 2016, including among carbapenemase gene-positive hypervirulent K1-ST23 and 'non-hypervirulent' types ST147, ST15 and ST383. *Journal of Medical Microbiology,* 67**,** 118-128.

TZOUVELEKIS, L. S., MARKOGIANNAKIS, A., PSICHOGIOU, M., TASSIOS, P. T. & DAIKOS, G. L. 2012. Carbapenemases in Klebsiella pneumoniae and Other Enterobacteriaceae: an Evolving Crisis of Global Dimensions. *Clinical Microbiology Reviews,* 25**,** 682-707.

UK GOVERNMENT: DEPARTMENT OF HEALTH. 2000. *Comprehensive critical care: review of adult critical care services* [Online]. UK Government: Department of Health. Available: https://webarchive.nationalarchives.gov.uk/20121014090959/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4082872.pdf [Accessed 24/12/2020].

UNAL, S. & GARCIA-RODRIGUEZ, J. A. 2005. Activity of meropenem and comparators against Pseudomonas aeruginosa and Acinetobacter spp. isolated in the MYSTIC Program, 2002-2004. *Diagnostic Microbiology and Infectious Disease,* 53**,** 265-271.

VALDERRAMA, S. L., GONZALEZ, P. F., CARO, M. A., ARDILA, N., ARIZA, B., GIL, F. & ALVAREZ, C. 2016. Risk factors for hospital-acquired

bacteremia due to carbapenem-resistant Pseudomonas aeruginosa in a Colombian hospital. *Biomedica,* 36**,** 69-77.

VAN DER ZWALUW, K., DE HAAN, A., PLUISTER, G. N., BOOTSMA, H. J., DE NEELING, A. J. & SCHOULS, L. M. 2015. The carbapenem inactivation method (CIM), a simple and low-cost alternative for the Carba NP test to assess phenotypic carbapenemase activity in gram-negative rods. *PLoS ONE,* 10**,** e0123690.

VAN DUIN, D. & DOI, Y. 2017. The global epidemiology of carbapenemase-producing Enterobacteriaceae. *Virulence,* 8**,** 460-469.

VAN LOON, K., VOOR IN 'T HOLT, A. F. & VOS, M. C. 2018. A Systematic Review and Meta-analyses of the Clinical Epidemiology of Carbapenem-Resistant Enterobacteriaceae. *Antimicrobial Agents and Chemotherapy,* 62**,** e01730-17.

VARDAKAS, K. Z., MATTHAIOU, D. K., FALAGAS, M. E., ANTYPA, E., KOTELI, A. & ANTONIADOU, E. 2015. Characteristics, risk factors and outcomes of carbapenem-resistant Klebsiella pneumoniae infections in the intensive care unit. *Journal of Infection,* 70**,** 592-599.

VILLEGAS, M. V., PALLARES, C. J., ESCANDON-VARGAS, K., HERNANDEZ-GOMEZ, C., CORREA, A., ALVAREZ, C., ROSSO, F., MATTA, L., LUNA, C., ZURITA, J., MEJIA-VILLATORO, C., RODRIGUEZ-NORIEGA, E., SEAS, C., CORTESIA, M., GUZMAN-SUAREZ, A. & GUZMAN-BLANCO, M. 2016. Characterization and clinical impact of bloodstream infection caused by carbapenemase-producing enterobacteriaceae in seven Latin American countries. *PLoS ONE,* 11**,** e0154092.

VINCENT, J. L., RELLO, J., MARSHALL, J., SILVA, E., ANZUETO, A., MARTIN, C. D., MORENO, R., LIPMAN, J., GOMERSALL, C., SAKR, Y. & REINHART, K. 2009. International study of the prevalence and outcomes of infection in intensive care units. *The Journal of the American Medical Association,* 302**,** 2323-2329.

VITKAUSKIENE, A., DAMBRAUSKIENE, A., CERNIAUSKIENE, K., RIMDEIKA, R. & SAKALAUSKAS, R. 2013. Risk factors and outcomes in patients with carbapenem-resistant Acinetobacter infection. *Scandinavian Journal of Infectious Diseases,* 45**,** 213-218.

WACHINO, J., DOI, Y., YAMANE, K., SHIBATA, N., YAGI, T., KUBOTA, T., ITO, H. & ARAKAWA, Y. 2004. Nosocomial spread of ceftazidime-resistant Klebsiella pneumoniae strains producing a novel class a beta-lactamase, GES-3, in a neonatal intensive care unit in Japan. *Antimicrobial Agents and Chemotherapy,* 48**,** 1960-1967.

WACHOLDER, S., MCLAUGHLIN, J. K., SILVERMAN, D. T. & MANDEL, J. S. 1992a. Selection of Controls in Case-Control Studies .1. Principles. *American Journal of Epidemiology,* 135**,** 1019-1028.

WACHOLDER, S., SILVERMAN, D. T., MCLAUGHLIN, J. K. & MANDEL, J. S. 1992b. Selection of Controls in Case-Control Studies .2. Types of Controls. *American Journal of Epidemiology,* 135**,** 1029-1041.

WALSH, T. R. 2010. Emerging carbapenemases: a global perspective. *International Journal of Antimicrobial Agents,* 36**,** S8-S14.

WALTER, S. D. & YAO, X. 2007. Effect sizes can be calculated for studies reporting ranges for outcome variables in systematic reviews. *Journal of Clinical Epidemiology,* 60**,** 849-852.

WAN, X., WANG, W. Q., LIU, J. M. & TONG, T. J. 2014. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology,* 14**,** 135-147.

WANG, L., YANG, L. S., WANG, Q. H. & WANG, J. L. 2011. Risk factors of hospital-acquired pneumonia caused by Carbapenem-resistant Acinetobacter baumannii. *Chinese Journal of Nosocomiology,* 21**,** 2954-2956.

WANG, L. J., LI, W. P. & XU, X. L. 2014. Risk factors for Imipenem-resistant Pseudomonas aeruginosa infections in Xi'an. *Chinese Journal of Infection Control,* 13**,** 332-334, 348.

WANG, N., JIA, L. P., WANG, L., FENG, X. & WEI, K. 2016a. Analysis if prevalence and correlation factors for Carbapenem-resistant Pseudomonas aeruginosa in a hospital. *Chinese Journal of Hospital Pharmacy,* 36**,** 138-141.

WANG, Q., ZHANG, Y., YAO, X., XIAN, H., LIU, Y., LI, H., CHEN, H., WANG, X., WANG, R., ZHAO, C., CAO, B. & WANG, H. 2016b. Risk factors and clinical outcomes for carbapenem-resistant Enterobacteriaceae nosocomial infections. *European Journal of Clinical Microbiology and Infectious Diseases,* 35**,** 1679-1689.

WANG, Q. Z., ZHOU, H. & ZHOU, J. Y. 2013. Analysis of risk factors and drug resistance for hospital-acquired pneumonia caused by Imipenem-resistant Acinetobacter baumannii. *Chinese Journal of Microecology,* 25**,** 1053-1057.

WANG, X., WANG, Q., CAO, B., SUN, S., ZHANG, Y., GU, B., LI, B., LIAO, K., ZHAO, F., JIN, L., JIN, C., YANG, C., PEI, F., ZHANG, Z. & WANG, H. 2019. Retrospective Observational Study from a Chinese Network of the Impact of Combination Therapy versus Monotherapy on Mortality from Carbapenem-Resistant Enterobacteriaceae Bacteremia. *Antimicrobial Agents and Chemotherapy,* 63**,** e01511-18.

WANG, Y., FU, R., ZHENG, Y. L., WAN, Y. F. & ZHOU, L. Y. 2016c. Risk factors and mortality of patients with nosocomial Carbapenem-resistant Acinetobacter baumannii pneumonia. *Journal of Clinical Pulmonary Medicine,* 21**,** 784-788.

WANNARO, J., NAKWAN, N., PATUNGKALO, W. & CHOKEPHAIBULKIT, K. 2012. Clinical features, risk factors, and outcome of carbapenem-resistant Acinetobacter baumannii bacteremia in a Thai neonatal intensive care unit. *Asian Biomedicine,* 6**,** 473-479.

WEINER, L. M., WEBB, A. K., LIMBAGO, B., DUDECK, M. A., PATEL, J., KALLEN, A. J., EDWARDS, J. R. & SIEVERT, D. M. 2016. Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infection Control and Hospital Epidemiology,* 37**,** 1288-1301.

WEINSTEIN, R. A. & HAYDEN, M. K. 2000. Insights into the Epidemiology and Control of Infection with Vancomycin-Resistant Enterococci. *Clinical Infectious Diseases,* 31**,** 1058-1065.

WELLS, G. A., SHEA, B., O'CONNELL, D., PETERSON, J., WELCH, V., LOSOS, M. & TUGWELL, P. 2011. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses* [Online]. The Ottawa Hospital Research Institute, Ottawa, Canada. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 30/12/2019].

WIENER-WELL, Y., RUDENSKY, B., YINNON, A. M., KOPUIT, P., SCHLESINGER, Y., BROIDE, E., LACHISH, T. & RAVEH, D. 2010. Carriage rate of carbapenem-resistant Klebsiella pneumoniae in hospitalised patients during a national outbreak. *Journal of Hospital Infection,* 74**,** 344-349.

WINGARD, J. R., DICK, J., CHARACHE, P. & SARAL, R. 1986. Antibiotic-resistant bacteria in surveillance stool cultures of patients with prolonged neutropenia. *Antimicrobial Agents and Chemotherapy,* 30**,** 435-439.

WORLD HEALTH ORGANIZATION. 2014. *Antimicrobial resistance: global report on surveillance* [Online]. World Health Organization. Available: http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf [Accessed 24/12/2019].

WORLD HEALTH ORGANIZATION. 2017a. *Countries in WHO regions* [Online]. World Health Organization. Available: http://www.who.int/about/regions/en/ [Accessed 30/12/2019].

WORLD HEALTH ORGANIZATION. 2017b. *Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics* [Online]. World Health Organization. Available: http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf [Accessed 24/12/2019].

WORLD HEALTH ORGANIZATION. 2017c. *Guidelines for the Prevention and Control of Carbapenem-Resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in Health Care Facilities* [Online]. World Health Organization. Available: https://apps.who.int/iris/bitstream/handle/10665/259462/9789241550178-eng.pdf?sequence=1 [Accessed 24/12/2019].

WORLD HEALTH ORGANIZATION. 2018. *Global Antimicrobial Resistance Surveillance System (GLASS) Report* [Online]. World Health Organization. Available: https://www.who.int/docs/default-source/searo/amr/global-antimicrobial-resistance-surveillance-system-(glass)-report-early-implementation-2016-2017.pdf?sfvrsn=ea19cc4a_2 [Accessed 24/12/2019].

WU, D., CAI, J. & LIU, J. 2011. Risk factors for the acquisition of nosocomial infection with carbapenem-resistant Klebsiella pneumoniae. *Southern Medical Journal,* 104**,** 106-110.

WU, X. P., GUO, S. Q., ZHONG, M. Z., ZHENG, Q. Q. & WU, J. Z. 2016. Risk factors of Meropenem-resistant Klebsiella pneumoniae infections in preterm infants. *Chinese Journal of Nosocomiology,* 26**,** 925-927.

XIAO, T. T., YU, W., NIU, T. S., HUANG, C. & XIAO, Y. H. 2018. A retrospective, comparative analysis of risk factors and outcomes in carbapenem-susceptible and carbapenem-nonsusceptible Klebsiella pneumoniae bloodstream infections: tigecycline significantly increases the mortality. *Infection and Drug Resistance,* 11**,** 595-606.

XU, C. Y., YU, S. F., PENG, M. F., GUO, F., QIAN, J. & WEI, J. F. 2015. Risk factors for infections caused by carbapenemase-producing Klebsiella pneumoniae. *Chinese Journal of Rural Medicine and Pharmacy,* 22**,** 72-74.

XU, M., FU, Y., KONG, H., CHEN, X., CHEN, Y., LI, L. & YANG, Q. 2018. Bloodstream infections caused by Klebsiella pneumoniae: prevalence of blaKPC, virulence factors and their impacts on clinical outcome. *BMC Infectious Diseases,* 18**,** 358.

YANG, D., XIE, Z., XIN, X., XUE, W. & ZHANG, M. 2016a. A model for predicting nosocomial carbapenem-resistant Klebsiella pneumoniae infection. *Biomedical Reports,* 5**,** 501-505.

YANG, Y., WANG, J., ZHENG, Y. Y., LU, H. J. & LV, H. Y. 2016b. Risk factors and preventive measures for neurology patients infected with Carbapenem-resistant Acinetobacter baumanni. *Chinese Journal of Nosocomiology,* 26**,** 1471-1473.

YANG, Y. J., WU, P. J. & LIVERMORE, D. M. 1990. Biochemical characterization of a beta-lactamase that hydrolyzes penems and carbapenems from two Serratia marcescens isolates. *Antimicrobial Agents and Chemotherapy,* 34**,** 755-758.

YE, D., SHAN, J., HUANG, Y., LI, J., LI, C., LIU, X., HE, W., LI, Y. & MAO, P. 2015. A gloves-associated outbreak of imipenem-resistant Acinetobacter baumannii in an intensive care unit in Guangdong, China. *BMC Infectious Diseases,* 15**,** 179-187.

YE, J. J., HUANG, C. T., SHIE, S. S., HUANG, P. Y., SU, L. H., CHIU, C. H., LEU, H. S. & CHIANG, P. C. 2010. Multidrug resistant Acinetobacter baumannii: risk factors for appearance of imipenem resistant strains on patients formerly with susceptible strains. *PLoS ONE,* 5**,** e9947.

YIGIT, H., QUEENAN, A. M., ANDERSON, G. J., DOMENECH-SANCHEZ, A., BIDDLE, J. W., STEWARD, C. D., ALBERTI, S., BUSH, K. & TENOVER, F. C. 2001. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of Klebsiella pneumoniae. *Antimicrobial Agents and Chemotherapy,* 45**,** 1151-1161.

YOGEESHA BABU, K. V., NIRANJAN, H. P., VIJAYANATH, V., ANITHA, M. R., RAJU, G. M. & PATIL, R. 2011. Study of imipenem resistant Pseudomonas aeruginosa and associated predisposing risk factors in a rural tertiary care hospital. *Journal of Pure and Applied Microbiology,* 5**,** 793-800.

YONG, D., BELL, J., RITCHIE, B., PRATT, R., TOLEMAN, M. & WALSH, T. 2007. A novel subgroup Metallo-β-lactamase (MBL) AIM-1 emerges in Pseudomonas aeruginosa (PSA) from Australia. *47th Interscience*

Conference on Antimicrobial Agents and Chemotherapy. 17-20 September, 2007. Chicago, Illinois, USA: Abstract C1-593.

YONG, D., TOLEMAN, M. A., GISKE, C. G., CHO, H. S., SUNDMAN, K., LEE, K. & WALSH, T. R. 2009. Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India. *Antimicrobial Agents and Chemotherapy,* 53**,** 5046-5054.

ZARAKOLU, P., ESER, O. K., ALADAG, E., AL-ZAHRANI, I. A., DAY, K. M., ATMACA, O., BORAL, B., CAKIR, B., PERRY, J. D. & AKOVA, M. 2016. Epidemiology of carbapenem-resistant Klebsiella pneumoniae colonization: a surveillance study at a Turkish university hospital from 2009 to 2013. *Diagnostic Microbiology and Infectious Disease,* 85**,** 466-470.

ZARKOTOU, O., POURNARAS, S., TSELIOTI, P., DRAGOUMANOS, V., PITIRIGA, V., RANELLOU, K., PREKATES, A., THEMELI-DIGALAKI, K. & TSAKRIS, A. 2011. Predictors of mortality in patients with bloodstream infections caused by KPC-producing Klebsiella pneumoniae and impact of appropriate antimicrobial treatment. *Clinical Microbiology and Infection,* 17**,** 1798-1803.

ZARRILLI, R., GIANNOULI, M., TOMASONE, F., TRIASSI, M. & TSAKRIS, A. 2009. Carbapenem resistance in Acinetobacter baumannii: the molecular epidemic features of an emerging problem in health care facilities. *Journal of Infection in Developing Countries,* 3**,** 335-341.

ZAVASCKI, A. P. 2004. Assessing risk factors for acquiring antimicrobial-resistant pathogens: A time for a comparative approach. *Clinical Infectious Diseases,* 39**,** 871-872.

ZAVASCKI, A. P., BARTH, A. L., GASPARETO, P. B., GONCALVES, A. L., MORO, A. L., FERNANDES, J. F. & GOLDANI, L. Z. 2006a. Risk factors for nosocomial infections due to Pseudomonas aeruginosa producing metallo-beta-lactamase in two tertiary-care teaching hospitals. *Journal of Antimicrobial Chemotherapy,* 58**,** 882-885.

ZAVASCKI, A. P., BARTH, A. L., GONCALVES, A. L., MORO, A. L., FERNANDES, J. F., MARTINS, A. F., RAMOS, F. & GOLDANI, L. Z. 2006b. The influence of metallo-beta-lactamase production on mortality in nosocomial Pseudomonas aeruginosa infections. *Journal of Antimicrobial Chemotherapy,* 58**,** 387-392.

ZAVASCKI, A. P., CRUZ, R. P. & GOLDANI, L. Z. 2005a. Risk factors for imipenem-resistant Pseudomonas aeruginosa: a comparative analysis of two case-control studies in hospitalized patients. *Journal of Hospital Infection,* 59**,** 96-101.

ZAVASCKI, A. P., GASPARETO, P. B., MARTINS, A. F., GONCALVES, A. L. & BARTH, A. L. 2005b. Outbreak of carbapenem-resistant Pseudomonas aeruginosa producing SPM-1 metallo-{beta}-lactamase in a teaching hospital in southern Brazil. *Journal of Antimicrobial Chemotherapy,* 56**,** 1148-1151.

ZENG, X. T., LIU, H., CHEN, X. & LENG, W. D. 2012. Meta Analysis Series IV: A Quality Assessment Tool for Observational Studies. *Chinese Journal of Evidence-Based Cardiovascular Medicine,* 4**,** 297-299.

ZHANG, J. F., CHEN, B. L., XIN, X. Y., ZHAO, H. B., WANG, H. Y., SONG, H. & XU, Z. K. 2009. Carbapenem resistance mechanism and risk factors of Pseudomonas aeruginosa clinical isolates from a University Hospital in Xi'an, China. *Microbial Drug Resistance-Mechanisms Epidemiology and Disease,* 15**,** 41-45.

ZHANG, Q. L., LIU, Y. F., LIU, M. H. & WANG, X. Y. 2004. Evaluating risk factors for ICU Patients with Carbapenem-resistant Acinetobacter baumannii positive. *Nursing Journal Of Chinese People's Liberation Army,* 21**,** 26-28.

ZHANG, T. Q., DONG, L., WANG, Z. Y. & LI, H. Y. 2011. Analysis of clinical characteristics and antimicrobial resistance of carbapenem-resistant Acinetobacter baumannii infections in children. *Zhonghua Erke Zazhi,* 49**,** 545-549.

ZHANG, Y., HE, J. & XIE, Z. H. 2012. Incidence and risk factors for carbapenemases-producing gram-negative bacteria infections. *Chinese Journal of Nosocomiology,* 22**,** 4271-4273.

ZHANG, Y., WANG, Q., YIN, Y., CHEN, H., JIN, L., GU, B., XIE, L., YANG, C., MA, X., LI, H., LI, W., ZHANG, X., LIAO, K., MAN, S., WANG, S., WEN, H., LI, B., GUO, Z., TIAN, J., PEI, F., LIU, L., ZHANG, L., ZOU, C., HU, T., CAI, J., YANG, H., HUANG, J., JIA, X., HUANG, W., CAO, B. & WANG, H. 2018. Epidemiology of Carbapenem-Resistant Enterobacteriaceae Infections: Report from the China CRE Network. *Antimicrobial Agents and Chemotherapy,* 62**,** e01882-17.

ZHAO, W. H. & HU, Z. Q. 2011a. Epidemiology and genetics of VIM-type metallo-beta-lactamases in Gram-negative bacilli. *Future Microbiology,* 6**,** 317-333.

ZHAO, W. H. & HU, Z. Q. 2011b. IMP-type metallo-beta-lactamases in Gram-negative bacilli: distribution, phylogeny, and association with integrons. *Critical Reviews in Microbiology,* 37**,** 214-226.

ZHAO, Z. C., XU, X. H., LIU, M. B., WU, J., LIN, J. & LI, B. 2014. Fecal carriage of carbapenem-resistant Enterobacteriaceae in a Chinese university hospital. *American Journal of Infection Control,* 42**,** e61-64.

ZHENG, Y. L., WAN, Y. F., ZHOU, L. Y., YE, M. L., LIU, S., XU, C. Q., HE, Y. Q. & CHEN, J. H. 2013. Risk factors and mortality of patients with nosocomial carbapenem-resistant Acinetobacter baumannii pneumonia. *American Journal of Infection Control,* 41**,** e59-63.

ZILBERBERG, M. D., NATHANSON, B. H., SULHAM, K., FAN, W. & SHORR, A. F. 2017. Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis. *BMC Infectious Diseases,* 17**,** 279.

ZILBERBERG, M. D., NATHANSON, B. H., SULHAM, K., FAN, W. & SHORR, A. F. 2019. A Novel Algorithm to Analyze Epidemiology and Outcomes of Carbapenem Resistance Among Patients With Hospital-

Acquired and Ventilator-Associated Pneumonia: A Retrospective Cohort Study. *Chest,* 155**,** 1119-1130.