Measures to eradicate multidrug-resistant organism outbreaks: How much does it cost?

Journal:	*Clinical Microbiology and Infection*
Manuscript ID	CLM-15-8831.R1
Article Type:	Original Article
Date Submitted by the Author:	n/a

Complete List of Authors:	Birgand, Gabriel; Bichat-Claude Bernard Hospital, Infection control unit BOURIGAULT, Céline; CHU de Nantes, Service de Bactériologie-Hygiène hospitalière Moore, Luke; Imperial College London, Health Protection Research Unit Vella, Venanzio; Imperial College London, Health Protection Research Unit Lepelletier, Didier; CHU de Nantes, Service de Bactériologie-Hygiène hospitalière Holmes, Alison; Imperial College London, Health Protection Research Unit lucet, Jean- Christophe; GH Bichat Claude Bernard, UHLIN

Key Words:	infection control, search and isolate, glycopeptide resistant enterococci, carbapenemase-producing Enterobacteriaceae, contact precautions, meticillin resistant Staphylococcus aureus, carbapenem resistant Acinetobacter baumannii

Abstract:	Objective: To assess the economic burden of infection control measures that succeeded in eradicating multidrug resistant organisms (MDROs) in emerging epidemic contexts in hospital settings. Design: Systematic literature review Methods: Medline, Embase and Ovid databases were systematically interrogated for original English language articles detailing costs associated with strict measures to eradicate MDROs published between 1st January 1974 and 2nd November 2014. This study was conducted in accordance with the PRISMA guidelines. Results: 13 original articles were retrieved reporting data on several MDROs including; glycopeptide resistant enterococci (n=5), carbapenemase producing Enterobacteriacae (n=1), meticillin resistant Staphylococcus aureus (n=5) and carbapenem-resistant Acinetobacter baumannii (n=2). Overall, the cost of strict measures to eradicate MDROs ranged from €285 to €57,532 per positive patient. The major component of these overall costs was related to interruption of new admissions, representing from €2,466 to €47,093 per positive patient (69% of the overall cost in mean, range: 13 - 100), followed by mean laboratory costs of €628 to €5,849 (24%, range: 3.3 - 56.7), staff reinforcement €6,204 to €148,381 (22%, range: 3.3 – 52) and contact precautions €166 to €10,438 per positive patient (18%, range: 0.7 - 43.3). Conclusions: Published data on the economic burden of strict measures to

	eradicate MDRO are limited, heterogeneous, and weakened by several methodological flaws. Novel economic studies should be performed to assess the financial impact of current policies and identify the most cost-effective strategies to eradicate emerging MDROs in healthcare facilities.

Measures to eradicate multidrug-resistant organism outbreaks:
How much does it cost?

Gabriel Birgand [1,2,3]*; Celine Bourigault [4]; Luke SP Moore, h [1]; Venanzio Vella [1]; Didier Lepelletier [4]; Alison H Holmes [1] ; Jean-Christophe Lucet [2,3]

[1] Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London, Du Cane Road, London, W12 0NN. UK

[2] INSERM, IAME, UMR 1137, F-75018 Paris, France; Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France

[3] AP-HP, Hôpital Bichat – Claude Bernard, Infection Control Unit, F-75018 Paris, France

[4] Nantes Teaching Hospital, Infection Control Unit, Nantes, France

[*]**Corresponding author :**

Dr Gabriel Birgand

Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance,, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, UK Imperial College Healthcare NHS Trust, Fulham Palace Road, London W6 8RF, UK

Tel.: +44 203 313 2732; Fax:

E-mail: gbirgand@gmail.com

Abbreviated title: Costs due to multi resistant bacteria

Word count (body of text): 2505

Keywords: infection control, search and isolate, glycopeptide resistant enterococci, carbapenemase-producing Enterobacteriaceae, contact precautions, meticillin resistant *Staphylococcus aureus*, carbapenem resistant *Acinetobacter baumannii*

ABSTRACT

Objective: To assess the economic burden of infection control measures to eradicate multidrug resistant organisms (MDROs) in emerging epidemic contexts.

Design: Systematic literature review

Methods: Medline, Embase and Ovid databases were systematically interrogated for original English language articles detailing costs associated with strict measures to eradicate MDROs published between 1st January 1974 and 2nd November 2014. This study was conducted in accordance with the PRISMA guidelines.

Results: 12 original articles were retrieved reporting data on several MDROs including; glycopeptide resistant enterococci (n=5), carbapenemase producing Enterobacteriacae (n=1), meticillin resistant *Staphylococcus aureus* (n=4) and carbapenem-resistant *Acinetobacter baumannii* (n=2). The mean cost of strict measures to eradicate MDROs was €18,519 (range: €386 – €57,532) per positive patient. The major component of these overall costs was related to interruption of new admissions, representing a mean of €19,384 per positive patient (77%, range: 39.9 - 100), followed by mean laboratory costs of €1,280 (22.7%, 3.3 - 47.2), staff reinforcement €1,414 (20.9%, 8 – 52.3) and contact precautions €1,752 (18.3%, 0.7 - 53.5).

Conclusions: Published data on the economic burden of strict measures to eradicate MDRO are limited, heterogeneous, and weakened by several methodological flaws. Novel economic studies should be performed to assess the financial impact of current policies and identify the most cost-effective strategies to eradicate emerging MDROs in healthcare facilities.

INTRODUCTION

Multi-drug resistant organisms (MDROs) are increasingly prevalent causes of healthcare associated infections . Meticillin resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamase producing Enterobacteriacae (ESBLPE) and glycopeptide-resistant enterococci (GRE) have emerged and spread in hospital settings over the last several decades. In addition other MDROs including carbapenemase-producing *Enterobacteriaceae* (CPE) and carbapenem-resistant *Acinetobacter baumannii* (CRAB) represent a more recent threat [1].

In Europe some countries have focused their efforts on particular MDROs considered to be significant threats to public health according to the local epidemiology, implementing strict national "search and isolate/destroy" policies [2,3]. These strategies often assume most MDRO-positive patients are unknown asymptomatic carriers and standard precautions do not reliably halt MDRO transmission in all circumstances [2]. Thus enhanced, or 'strict' measures are sometimes needed to control the spread and eradicate MDRO at the level of the ward, the hospital, and nationally. These strategies range from the enforcement of strict contact precautions associated with cross-sectional screening of patients exposed, to a rigorous "search and isolate" policy. This latter may include cohorting of MDRO-positive/contact patients, repeated rectal sampling of contact patients, and both limiting transfer of contact patients out of the care unit (bay or ward) and avoidance of new admissions until after negative screening tests are available.

These strict recommendations are difficult to implement and require additional human and material resources. Moreover interruption of admission into, and transfer from, the involved ward leads to a decrease in hospital medical service utilization and therefore a loss of hospital income and interruption of care to patients [4]. The costs associated with these strict measures to eradicate and avoid the spread of emerging MRDOs are not known. This systematic review aims to assess the current body of scientific literature regarding the financial burden associated with strict control measures to eradicate MDRO outbreaks.

METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [5].

Search strategy

A systematic search for original articles in Medline, Embase, and Ovid databases was performed. The search covered the period from January 1, 1974 to November 2, 2014. Search terms were devised and tailored to each database (Appendix 1) covering (i) infection prevention and control, (ii) cost and economic evaluations and (iii) MDRO outbreaks. In addition, the reference lists for all selected full-text articles (below) and related reviews were scanned to derive any further relevant manuscripts.

Study selection

Outbreak situations from any type of ward were considered. All studies that evaluated the cost and economic burden of strict infection control measures ("search and isolate" or "search and destroy" strategies) to eradicate MDROs (including MRSA, ESBLPE, CPE, GRE, CRAB) were included. Consideration was given to both descriptive studies with costings, and economic evaluations. Studies that contained no original data and those that evaluated interventions to decrease prevalence in an endemic context were excluded [6–10].

Quality criteria

The Drummond checklist was used to evaluate the quality of economic evaluations [11]. For descriptive studies including exclusively costings, the Drummond Checklist was modified to 9 items, excluding items required only for economic analyses: 2 items on study design, 3 on data collection, 4 on analysis and interpretation of results. For each study evaluated, a total methodological score was derived by attributing one point for each item present.

Data collection process

Title and abstract evaluation was undertaken for all papers arising from the literature search, with subsequent full text analysis and quality assessment of those studies fulfilling the inclusion/exclusion criteria. Two authors (GB and CB) independently reviewed the titles and abstracts, and disagreements were resolved by a third person (VV). A data extraction form was developed and validated on 10 randomly selected articles. Data from the included studies were recorded by two reviewers (GB and CB) then subjected to further critical appraisal during a narrative synthesis. In order to compare the costs in different countries and at varying points in time, all cost estimates were adjusted for inflation using the Consumer Price Index [12] and converted into 2015 Euros. Statistical analyses were performed using Epidata 3.1 and Stata® release 10.0 (Stata Corp LP, College Station, TX).

RESULTS

Study selection

Electronic and subsequent manual searches identified 2406 articles, of which 142 were selected based on title; among these, 127 were excluded based on the abstract, leaving 15 articles, of which two were irretrievable online (Figure 1). Two further articles were identified by manually searching the reference lists. Of these 15 articles, one was in an endemic situation, one was unrelated to costs and one did not provide original data, leaving 12 studies for analysis. The marked heterogeneity in the study objectives and designs precluded a meta-analysis.

Study characteristics

The 12 included studies described outbreaks of GRE (n=5), MRSA (n=4), CPE (n=1) and CRAB (n=2) and were conducted in a range of countries from Europe (n=8) and the USA (n=2). Most studies were located in a single hospital (11/12; with one study being undertaken in three centers), with the number of beds reported in 9/12 studies, varying from 254 to 2100. The number of wards affected was reported in 10/12 studies and varied from one to 22, involving intensive care units (ICUs) in seven studies, medical wards in five studies, one surgical ward and one long term care facility (LTCF). Outbreaks lasted from one month to eight years. Among the 12 studies, all were descriptive with costings; no study reported a formal economic evaluation. The infection control measures implemented and costs assessed for each study are described in Figure 2.

The quality criteria for the 12 observational studies are presented in Appendix 2. Overall, the mean score was 0.75/2 for study design, 1.33/3 for data collection and 2/4 for the analysis and interpretation of results. Finally, the aggregated mean score was 4.1/9.

Laboratory costs

Ten studies assessed the laboratory costs associated with the screening of suspected/contact patients or environmental samples (Figure 2). Cost estimation methods were detailed in four studies [13–17]. All studies considered consumables and technician time, yet only three included nurse time for obtaining swabs [13–15]. One study differentiated costs by negative and positive results [14]. The calculated cost per screening culture varied by organism; for GRE from €3.7 to €55.8,[13,18] for CPE €44.2,[19] for MRSA from €11.5 to €21.5,[15,17] and for the one study estimating the cost of environmental surveillance of CRAB, a cost of €26.1 per surface swabbed was cited [20]. Three studies on GRE included molecular typing [13,18,21]. Finally, one study gave an overall cost including laboratory, contact precautions, decolonization and staff costs [16].

The overall cost from laboratory screening for the MDRO outbreaks varied from €3,141 to €7.05 million, with a mean cost of €1,954 (range: €628 – €5,732) per positive patient and €35 (range: €3.7-€122) per screening sample. The laboratory activity represented on average 22.5% (range: 3.3 - 56.7) of the overall cost of infection control measures (Table 2).

Costs of contact precautions

Nine studies assessed costs related to contact precautions. Five studies detailed the elements included in the costing, of which two also included the method of estimation [13–15,18,22]. Among these five studies, the overall cost included the use of gloves (n=5) and gowns (n=5), procedures of disinfection (n=4), consumable material or material destruction (n=2), waste elimination (n=1), alcohol hand rub (n=1) and personal care caddies (n=1). Overall, the mean cost was €2,148 (range: €166 - €10,438) per positive patient. Costs or contact precautions represented, on average, 15.9% (range: 0.7 - 43.3) of the total cost of infection control measures.

Costs associated with additional staff

Seven studies assessed extra costs from staffing during the MDRO outbreaks. Among these costs included: additional nursing personnel for cohorting (n=4) [13,15,19,21], laboratory staff/ administrative support and contracting cleaners (n=1) [23], and the absence of personnel during MRSA personnel screening and decolonization (n=1) [16]. One study reported that the control of a GRE outbreak lasting 40 days required 1663 extra hours of nursing staff for 16 positive cases [19]. Overall, the mean additional staff costs was €55,641 per outbreak (range: €6,204 - €148,381) and €1,414 (range: €477 – €4,086) per positive patient when only considering situations with cohorting. On average, the proportion of the total cost attributable to additional staffing during MDRO outbreaks was 22.4% (range: 3.3 – 52).

Costs associated to the decrease in hospital service use

Eight studies assessed the loss of income for wards due to the implementation of infection control measures. Among these, six described costs due to the suspension of transfers/admissions [15,18–22]. Three methods were described to determine these costs; (i) comparison of activity during the outbreak period to that of the preceding year (n=2) [19,21], (ii) multiplication of the number of days beds were unavailable by the average daily activity estimated in the concerned unit during another period (n=3) [15,20,22], or (iii) multiplication of the number of admissions lost during the outbreak (or during a comparable period in the preceding year) by a cost per admission (n=1) [18].

The overall mean costs due to ward closure was €446,597 per outbreak (range: €38,026 – €1,402,452), equating to €21,497 per positive patient (€884 - €47,093), or €10,509 per day of outbreak (€422 – €38,670).

One study estimated the loss of bed occupancy due to contact isolation in single rooms to be 93 patients isolated for a total of 2631 days, at a loss per bed-day of between €441 and €735 (according to hospital ward type) [24]. Finally, one study evaluated costs linked to patient isolation pending screening results for MRSA. This loss was estimated at 20,424 bed-days with a unit cost of €569 per bed-day equating to a cost of €34,404 per positive case and €76 per screened patient [17].

Costs associated with the loss of hospital activity represented a mean of 76.9% (range: 39 - 100) of the overall cost of infection control measures.

Other types of costs

Four other studies reported additional types of costs: antimicrobials for decolonization (n=2),[13,16] installation of electronic taps, dispensers for disinfectants, and printing stationary (n=1),[23] and changes to healthcare professional education (n=1) [13].

Overall, the mean cost of strict measures to eradicate MDROs during outbreaks was €19,144 (range: €386 – €57,532) per positive patient. After stratification according to the type of MDRO, mean costs per positive patient were €9,277 for GRE, €13,995 for MRSA, €38,597 for CPE and €44,385 for CRAB. Analysis of cost by ward type demonstrated the mean cost per outbreak case to be €23,379 in ICU, €18,957 in mixed ICU and medical ward outbreaks, €11,021 for surgical/medical wards and €1,329 in LTCF.

DISCUSSION

Some European countries are at the gate of a post-antimicrobial era [1]. Strict infection control strategies applied by several European countries to control such spread, appears to be effective to fight emerging MDROs [1,3]. However these strategies can be costly, difficult to implement, and require increased human/laboratory resources and occasionally warrant interruption of admissions.

The 12 studies identified in this systematic review were heterogeneous, using different methods, settings, and including various types of costs. Analysis of aggregated data from across these different contexts, MDROs, wards, hospital, countries using different methods therefore offers a more robust range of costs for interventions to terminate MDRO outbreaks. From this, potential options to minimize the financial burden associated with "search and isolate" strategies can be constructed. Of particular note, the loss of income due to the interruption of transfer/admissions represents the main cost of strategies to control MDRO spread (mean €21,497 (€884 - €47,093) per positive patient; €11,255 (€422 – €38,670) per day of outbreak), whereas mean costs due to additional human resources were dramatically lower. These results raise the question of whether dedicated areas for managing MDRO outbreak patients might better enable continuity of care for service provision as a whole, bringing appreciable cost-savings. The early identification of patients suspected of being colonized with an MDRO, combined with rapid implementation of contact precautions, is probably the cornerstone of a cost-saving strategy. This may facilitate rapid interruption of cross-transmission, thereby avoiding the major categories of expenses observed in this review. In keeping with this strategy, many countries have issued guidelines in order to promptly identify, screen, and implement strict contact precautions for patients recently hospitalized in a foreign country [2,25].

The estimation of costs related to infection control measures is challenging. The loss of income described in studies in this review was frequently assessed by comparing the activity of the affected ward during the outbreak to a previous period. This retrospective method provides only a crude estimate. The solution, prospective collection of lost patient-bed days/admissions during an MDRO outbreak, would provide more detailed data but would need to be considered in the context of a realistic rate of ward occupancy. The cost per bed-day is another important parameter often approximated, frequently through dividing total hospital stay cost by the number of patient-days. However, this method does not give exact costs at the patient level. All these methods make results deeply dependent on the local context (activity, reimbursement system etc.) which limits generalizability.

The unit costs of screening and contact precautions were also highly variable across the included studies. Laboratory costs vary according to the type of organism, the technique (culture vs PCR), the result (addition of bacterial identification and susceptibility testing for positive cultures) and the use of molecular typing. Few studies distinguished between consumable costs for strain identification, susceptibility tests and PCR, often giving an overall cost for microbiological analysis.

The heterogeneity of costs arising from contact precautions can be explained by the variety of included components: the personal protective equipment on the basis of a number of visits per patient, cleaning or alcohol hand rub, and other materials needed to implement or facilitate the contact isolation. Some studies described implementing standard precautions, while others reported more specific facets of contact precautions.

This review underlines several gaps in understanding the economic impact of MDRO outbreaks. First, data were not available from any robust economic evaluations. Explicit economic studies in this area are urgently needed, specifically cost-effectiveness analyses to establish both the financial and medical impact of interventions to control MDROs. Secondly, among the studies included, the methods used demonstrated marked heterogeneity, often including a restricted panel of costs. Three types of indirect costs were poorly considered: (i) time spent by infection control teams in organizing preventive measures, education and participation in meetings; (ii) costs linked to delays in transfer of colonized patients to downstream care facilities; and (iii) the impact of contact isolation on the quality and safety of patient care. These measures can induce reluctance among downstream units to accept admission of MDRO-positive patients with a mean excess length of stay estimated at 23.7-days and a mean cost of €6,381 [26]. Finally, using relative rather than crude descriptions of costs might facilitate the interpretation of results and comparison of results between outbreaks.

In conclusion, costs associated with strict measures to control MDRO outbreaks are highly variable across outbreak organism and location, but in all cases an outbreak-associated decrease in hospital service use is the major financial driver. Formal economic studies must be performed to evaluate current policies and identify optimal strategies to eradicate emerging MDROs in healthcare facilities.

Acknowledgments:

Financial support: The research was partially funded by the National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Healthcare Associated Infection and Antimicrobial Resistance at Imperial College London in partnership with Public Health England (PHE), and the NIHR Imperial Patient Safety Translational Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England. The authors also acknowledge the UK Clinical Research Collaboration (UKCRC) Centre for Infection Prevention and Management, Imperial College Healthcare NHS Trust, and the NIHR Imperial Biomedical Research Centre (BRC).

Conflicts of interest: AHH and LSPM have previously consulted for bioMérieux. All other others declare no conflict of interest.

References

[1] European Center for Disease Prevention And Control. Antimicrobial resistance interactive database (EARS-Net). HttpwwwecdceuropaeuenhealthtopicsantimicrobialresistancedatabasePagesdatabaseaspx 2012 n.d.

[2] Haut Conseil de la Santé Publique. Prévention de la transmission croisée des Bactéries Hautement Résistantes aux antibiotiques émergentes (BHRe). http://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=372 2013.

[3] Kluytmans-Vandenbergh MFQ, Kluytmans J a. JW, Voss A. Dutch guideline for preventing nosocomial transmission of highly resistant microorganisms (HRMO). Infection 2005;33:309–13. doi:10.1007/s15010-005-5079-z.

[4] Birgand G, Ruimy R, Schwarzinger M, Lolom I, Bendjelloul G, Houhou N, et al. Rapid detection of glycopeptide-resistant enterococci: impact on decision-making and costs. Antimicrob Resist Infect Control 2013;2:30. doi:10.1186/2047-2994-2-30.

[5] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100. doi:10.1371/journal.pmed.1000100.

[6] Wassenberg MWM, de Wit GA, van Hout BA, Bonten MJM. Quantifying cost-effectiveness of controlling nosocomial spread of antibiotic-resistant bacteria: the case of MRSA. PloS One 2010;5:e11562. doi:10.1371/journal.pone.0011562.

[7] Young LS, Sabel AL, Price CS. Epidemiologic, clinical, and economic evaluation of an outbreak of clonal multidrug-resistant Acinetobacter baumannii infection in a surgical intensive care unit. Infect Control Hosp Epidemiol 2007;28:1247–54. doi:10.1086/521660.

[8] Danchivijitr S, Chokloikaew S, Chantrasakul C, Trakoolsomboon S. An outbreak of methicillin-resistant Staphylococcus aureus (M.R.S.A.) in a burn unit. J Med Assoc Thail Chotmaihet Thangphaet 1995;78 Suppl 1:S11–4.

[9] Coast J, Smith RD. Antimicrobial resistance: cost and containment. Expert Rev Anti Infect Ther 2003;1:241–51.

[10] Taylor J, Stevenson G. Nursing implications of a vancomycin resistant enterococcus outbreak in a renal unit. EDTNAERCA J Engl Ed 1999;25:42–4.

[11] Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996;313:275–83.

[12] Eurostat (2014) HICP - inflation rate n.d.

[13] Armstrong-Evans M, Litt M, McArthur M, Willey B, Cann D, Liska S, et al. Control of transmission of vancomycin-resistant Enterococcus faecium in a long-term-care facility. Infect CONTROL Hosp Epidemiol 1999;20:312–7.

[14] Karchmer T, Durbin L, Simonton B, Farr B. Cost-effectiveness of active surveillance cultures and contact/droplet precautions for control of methicillin-resistant Staphylococcus aureus. J Hosp Infect 2002;51:126–32. doi:10.1053/jhin.2002.1200.

[15] Kanerva M, Blom M, Tuominen U, Kolho E, Anttila V-J, Vaara M, et al. Costs of an outbreak of meticillin-resistant Staphylococcus aureus. J Hosp Infect 2007;66:22–8. doi:10.1016/j.jhin.2007.02.014.

[16] Rao N, Jacobs S, Joyce L. Cost-effective eradication of an outbreak of methicillin-resistant Staphylococcus aureus in a community teaching hospital. Infect Control Hosp Epidemiol 1988;9:255–60.

[17] Van der Zee A, Hendriks WDH, Roorda L, Ossewaarde JM, Buitenwerf J. Review of a major epidemic of methicillin-resistant Staphylococcus aureus: the costs of screening

and consequences of outbreak management. Am J Infect Control 2013;41:204–9. doi:10.1016/j.ajic.2012.02.033.

[18] Ridwan B, Mascini E, van Der Reijden N, Verhoef J, Bonten M. What action should be taken to prevent spread of vancomycin resistant enterococci in European hospitals? BMJ 2002;324:666–8.

[19] Daroukh A, Delaunay C, Bigot S, Ceci JM, Siddhoun N, Bukreyeva I, et al. Characteristics and costs of carbapenemase-producing enterobacteria carriers (2012/2013). Med Mal Infect 2014. doi:10.1016/j.medmal.2014.06.004.

[20] Ayraud-Thévenot S, Huart C, Mimoz O, Taouqi M, Laland C, Bousseau A, et al. Control of multi-drug-resistant Acinetobacter baumannii outbreaks in an intensive care unit: feasibility and economic impact of rapid unit closure. J Hosp Infect 2012;82:290–2. doi:10.1016/j.jhin.2012.08.016.

[21] Escaut L, Bouam S, Frank-Soltysiak M, Rudant E, Saliba F, Kassis N, et al. Eradication of an outbreak of vancomycin-resistant Enterococcus (VRE): the cost of a failure in the systematic screening. Antimicrob Resist Infect Control 2013;2:18. doi:10.1186/2047-2994-2-18.

[22] Garlantezec R, Bourigault C, Boles J-M, Prat G, Baron R, Tonnelier J-M, et al. Investigation and management of an imipenem-resistant oxa-23 Acinetobacter baumannii outbreak in an intensive care unit. Med Mal Infect 2011;41:430–6. doi:10.1016/j.medmal.2011.01.013.

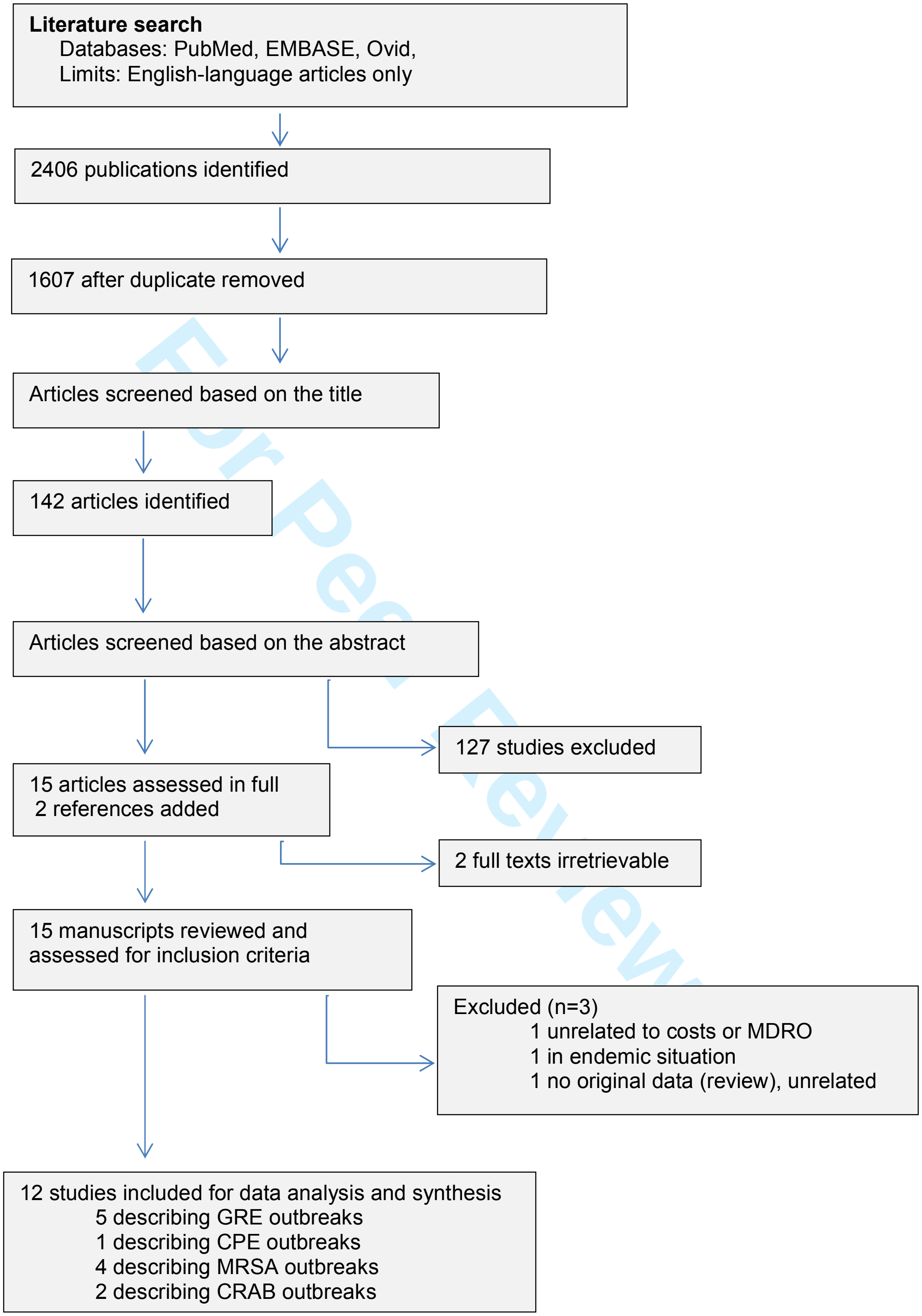
[23] Christiansen K, Tibbett P, Beresford W, Pearman J, Lee R, Coombs G, et al. Eradication of a large outbreak of a single strain of vanB vancomycin-resistant Enterococcus faecium at a major Australian teaching hospital. Infect CONTROL Hosp Epidemiol 2004;25:384–90. doi:10.1086/502410.

[24] Sagel U, Schulte B, Heeg P, Borgmann S. Vancomycin-resistant enterococci outbreak, Germany, and calculation of outbreak start. Emerg Infect Dis 2008;14:317–9. doi:10.3201/eid1402.070752.

[25] ECDC. Carbapenemase-producing bacteria in Europe. Interim results from the European survey on carbapenemase-producing Enterobacteriaceae (EuSCAPE) project 2013. HttpwwwecdceuropaeuenpublicationsPublicationsantimicrobial-Resist-Carbapenemase-Prod-Bact-Eur 2013.

[26] Birgand G, Schwarzinger M, Perozziello A, Lolom I, Pelat C, Armand-Lefevre L, et al. Prolonged hospital stay, an adverse effect of strict national policy for controlling the spread of highly resistant microorganisms. Infect Control Hosp Epidemiol 2014;35:1427–9. doi:10.1086/678425.

Figure 1. Flowchart of the search strategy



Abbreviations: MDRO, multidrug resistant organisms; GRE, glycopeptide resistant enterococci; CPE, carbapenemase producing *Enterobacteriacae*; MRSA, meticillin resistant *Staphylococcus aureus*; CRAB, carbapenemase resistant *Acinetobacter baumannii*

Figure 2. Description of infection control measures used and cost estimated in included studies.

References	23	14	25	19	20	22	17	16	18	15	24	21
Infection control measures												
Contact precautions	■	■	■	■	■	■	■	■	■	■	■	■
Screening	■	■		■	■	■	■	■	■	■	■	■
Environment culture	■	■										■
Cohorting	■	■		■	■	■		■		■	■	■
Ward closure					■	■					■	■
Cleaning	■	■									■	■
Decolonisation		■			■		■					
Others (training, meetings...)	■	■			■							
Costs												
Contact precautions	■	■		■	■		■	■		■	■	■
Laboratory cost	■	■		■	■	■	■	■	■	■		■
Loss of activity			■	■	■	■		■	■		■	■
Staff reinforcement	■	■			■	■	■	■	■			
Opportiny cost		■						■				
Others (training, meetings...)	■	■			■		■				■	

Footnote: Descriptors of infection control measures or costs from each study are represented by a green box.

Table 1. Summary of studies meeting inclusion/exclusion criteria and included in the review with crude costs

Ref.	Outbreak duration	Cases/ suspects	Ward/N	Costs					
				Laboratory	Contact Precautions	Loss of income	Staff	Others	Overall
Glycopeptide resistant *enterococci* (GRE)									
23	9 months	169/196 58	ICU, M/23	Drug, diagnostic supplies: €326,707 PCR equipment: €77,178	Cleaning and clothing consumables: €380,662	-	Cleaners and other staff: €693,801 Nursing, lab and administrative staff: €704,823	€520,820 printing, stationary and other consumables	€2,703,993
14	Unclear	5/849	LTCF/1	Swabs, lab processing & typing: €3,141	Disposable: €645 Cleaning: €93 Reusable gowns: €38 Personal caddie: €55	-	Healthcare aide, housekeeping: €2,592	Formal education: €82	€6,646

25	1 month	48/NR	NR	-	-	2631 days, cost per isolation: €1,160,108– €1,933,513	-	-	€1,160,108 – €1,933,513
19	3 months	43	Nephrology, ICU/6	1543 culture: €23,638 Mol typ: €12,504	Gloves: €1,815; Gowns: €5,361; Disinfection: €13,874	37 admissions and 11 in ICU: €38,026	-	-	€97,806
20	6 weeks	13/294	M/3	Screening, typing: €16,408	Gowns, gloves, single use material, AHR, disinfection: €15,771	33 admissions lost: €120,326	Overtime + interim: €6,204	Antibiotics: €27,275	€185,984
Carbapenemase producing *Enterobacteriaceae* (CPE)									
22	1 & 2 months	16/463	ICU,M,S/ 4 &	716 screening: €31,665	-	Admission stopped 1 to 5 times,	1663 extra hours: €65,385	-	€617,553

			ICU,M,S/4			€520,503			
Meticillin resistant *Staphylococcus aureus* (MRSA)									
17	14 months	25/NR	ICU/2	Culturette, lab material, 200 personnel Sc (10 pos) and 26 Env	Isolation supplies	-	Additional staffing during personnel decolonization	Decolonisation	€9,644
16	12 months	257/1240	S,M/NR	Sc: €320,842	20424 days of contact isolation: €116,559	112 days lost: €1,402,452	Extra working hours: €148,381	-	€1,988,234
18	8 years	1230/5268	NR/3 Hosp.	Pts cult: €2,910,476 Pts PCR: €351,1967 Staff cult: €532,251 Staff PCR: €95,104	-	Isolation costs with culture: €34,363,277 With PCR: €7,831,397	Absence cult: €3,084,400 Absence PCR: €1,173,579	-	Cult: €40,890,404 PCR: €12,612,04

									7
15	10.5 months	18/587	NICU/1	Neg cult: €44,234 Pos cult: €321	Glove, paper gown, mask, 691 Pts day of isolation: €33,958-€67,905	-	-	-	€78,514 - €110,847
Carbapenem resistant *Acinetobacter baumannii* (CRAB)									
24	1 month	5/NR	ICU/1	-	Waste elimination & cleaning: €13,048 Drug and non-cleanable destruction: €39,144	Ward closure: €235,467	-	-	€287,659
21	Unclear	Episode 1: 20/230 Episode	SICU/1	Ep1: 230 Sc, €8,474; 500 Env, €13,052 Ep2: 34 Sc, €1,252; 200 Env, €5,221	Ep1: €5,187 Ep2: €853	Ep1: 560 days, €586,727 Ep2: 220 days, €222,676	-	-	Ep1: €613,440 Ep2: €230,002

2: 7/34

Abbreviations: Ref, reference; Des, descriptive study; ICU, intensive care unit; M, medical wards; S, surgical wards; NICU, neonatal intensive care unit; SICU, surgical intensive care unit; LTCF. Long term care facility; NR, not reported; Hosp, hospital; Sc, patient screening; Env, environment screening

Table 2. Quality analysis of included studies against the Drummond criteria.

Ref.	Study design			Data collection				Analysis and interpretation of results					
	Research question stated	View-point of analysis clearly stated	Sub-total/ 2	Quantities of resources reported separately from unit costs	Methods for the estimation of both quantities and prices given	Currency and price data are recorded	Sub-total /3	Outcomes presented aggregated and disaggreg-ated	Conclusions follow from the data reported	Limit-ations are addressed	The answer to the study question is given	Sub-total /4	Total /9
23	No	No	0/2	No	No	Yes	1/3	Yes	No	No	No	1/4	2/9
14	Not clear	No	0/2	No	No	Yes	1/3	No	No	No	Not clear	0/4	1/9
25	No	Yes	1/2	No	Not clear	No	0/3	Yes	Yes	No	No	2/4	3/9
19	No	No	0/2	No	No	No	0/3	Yes	No	No	Not clear	1/4	1/9
20	Yes	Yes	2/2	No	Yes	No	1/3	Yes	Yes	No	Yes	3/4	6/9
22	No	Yes	1/2	Yes	No	Yes	2/3	Yes	Yes	No	No	2/4	5/9
17	Not clear	No	0/2	No	No	Yes	1/3	Yes	Yes	No	Not clear	2/4	3/9
16	Yes	Yes	2/2	Yes	Yes	Yes	3/3	Yes	Yes	No	Yes	3/4	8/9
18	Yes	Yes	2/2	Yes	Yes	No	2/3	Yes	Yes	No	Yes	3/4	7/9
15	Yes	No	1/2	Yes	Yes	No	2/3	Yes	Yes	No	Yes	3/4	6/9
24	No	No	0/2	No	Yes	Yes	2/3	No	No	Yes	No	1/4	3/9
21	Not clear	No	0/2	Yes	No	No	1/3	Yes	Yes	Yes	No	3/4	4/9

Table 3. Description of relative costs; per positive patient, per screening, and per day of outbreak.

Euros	Costs per positive patient		Costs per screening		Costs per day of outbreak		Proportional contribution to total costs
	Average (median)	Min - Max	Average (median)	Min - Max	Average (median)	Min - Max	
Overall	19144 (13390)	386- 57532	-	-	10285 (5522)	23 - 38670	-
Mean 'all-organism' laboratory costs	1954 (1262)	628 - 5732	35 (21.5)	3.7-121.7	866 (646)	164 - 2414	22.5% (3.3-56.7)
GRE	1280 (1051)	628 - 2390	25.9 (22)	3.7-55.8	754 (401)	364-1495.9	27% (8.8-47.3)
MRSA	3151 (2475)	1248 - 5732	15.2 (12.7)	11.5-21.5	1151 (891)	148 - 2414	29% (16-57)
CPE	1979	-	44.2	-	1055	-	5.1%
CRAB	1400	-	36.8	-	164	-	3.3%
Contact precautions	2148 (881)	166 - 10438	18.4 (15.3)	1-53.6	605 (323)	35.3 - 1739	15.9% (0.7-43.3)
Staff reinforcement	2899 (2019)	477 - 8276	34 (15.5)	3.1 - 91.3	1977 (1296)	137 - 5180	22% (3.3 – 51.7)
Decrease in hospital service use	21497 (21226)	884 - 47093	733 (251)	24.6 - 3066	11255 (6291)	422 - 38670	76.9% (38.9 – 100)

Appendix 1

Medline search algorithm

The following search algorithm was developed to search the database using Boolean operators and the asterisk symbol (*) as for wildcard truncation:

Medline search 2 November 2014 GRE: 142 references

("Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Hospital Costs"[Mesh] OR "Models, Economic"[Mesh] OR "Infection Control/economics*"[Mesh] OR "Patient Isolation/economics"[Mesh] OR "Cross Infection/economics*"[Mesh] OR "Length of Stay/economics"[Mesh] OR "Length of Stay*"[Mesh]) AND ("Gram-Positive Bacterial Infections/economics"[Mesh] OR "Microbiological Techniques/economics*"[Mesh] OR "Vancomycin Resistance*"Mesh] OR "Enterococcus*"[Mesh])

Medline search 2 November 2014 CPE: 126 references

("Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Hospital Costs"[Mesh] OR "Models, Economic"[Mesh] OR "Infection Control/economics*"[Mesh] OR "Patient Isolation/economics"[Mesh] OR "Cross Infection/economics*"[Mesh] OR "Length of Stay/economics"[Mesh] OR "Length of Stay*"[Mesh]) AND ("Gram-Negative Bacterial Infections/economics"[Mesh] OR "Carbapenem Resistance*"Mesh] OR "Carbapenemase*" OR "Highly drug resistant organisms*" OR "OXA*" OR "NDM*" OR "VIM*" OR "KPC*" OR "GES*" OR "IMP*")

Medline search 2 November 2014 MRSA: 652 references

("Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Hospital Costs"[Mesh] OR "Models, Economic"[Mesh] OR "Infection Control/economics*"[Mesh] OR "Patient Isolation/economics"[Mesh] OR "Cross Infection/economics*"[Mesh] OR "Length of Stay/economics"[Mesh] OR "Length of Stay*"[Mesh]) AND ("Gram-Positive Bacterial Infections/prevention & control*"[Mesh] OR “Gram-Positive Bacterial Infections/transmission” [Mesh] OR “MRSA” OR "Methicillin-Resistant Staphylococcus aureus"[Mesh])

Medline search 2 November 2014 ESBLPE: 154 references

("Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Hospital Costs"[Mesh] OR "Models, Economic"[Mesh] OR "Infection Control/economics*"[Mesh] OR "Patient Isolation/economics"[Mesh] OR "Cross Infection/economics*"[Mesh] OR "Length of Stay/economics"[Mesh] OR "Length of Stay*"[Mesh]) AND ("Gram-Negative Bacterial Infections/prevention & control*"[Mesh] OR “Gram-Negative Bacterial Infections/transmission” [Mesh] OR “esbl” OR “extended spectrum betalactamase”)

Medline search 2 November 2014 CRAB: 175 references

("Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Hospital Costs"[Mesh] OR "Models, Economic"[Mesh] OR "Infection Control/economics*"[Mesh] OR "Patient Isolation/economics"[Mesh] OR "Cross Infection/economics*"[Mesh] OR "Length of Stay/economics"[Mesh] OR "Length of Stay*"[Mesh]) AND ("Gram-Negative Bacterial Infections/prevention & control*"[Mesh] OR “Gram-Negative Bacterial Infections/transmission” [Mesh] OR “Acinetobacter Infections/prevention &

control" [Mesh] OR "Acinetobacter baumannii" OR "Acinetobacter baumannii/isolation and purification"[Mesh])

Embase and Ovid search algorithm

(Cost-Benefit Analysis or Costs or Cost Analysis or Hospital Costs or Models, Economic) and (Infection Control or Patient Isolation or Cross infection or Length of stay) and (Gram-Positive Bacterial Infections or Microbiological Techniques or Vancomycin Resistance or Enterococcus or Gram-Negative Bacterial Infections or Carbapenem Resistance or Carbapenemase or Highly drug resistant organisms or OXA or NDM or VIM or KPC or GES or IMP or esbl OR (extended spectrum betalactamase) or (Methicillin-Resistant Staphylococcus aureus) or mrsa or (acinetobacter baumannii))

Appendix 2. List of excluded studies and reasons for exclusion

Author	Journal	Year	Category of article	Reason for exclusion
Wassemberg [7]	Plos one	2010	Major article	Endemic situation
Young [8]	Inf Cont Hosp Epidemiol	2007	Major article	Not related to costs
Danchivijitr [9]	J Med Assoc Thai.	1995	Major article	Irretrievable
Coast [10]	Expert Rev Anti Infect Ther.	2003	Review	No original data, not related to infection control during outbreak
Taylor [11]	EDTNA ERCA J.	1999	Major article	Irretrievable

Measures to eradicate multidrug-resistant organism outbreaks:

How much does it cost?

Gabriel Birgand [1,2,3]*; Luke SP Moore [1]; Celine Bourigault [4]; Venanzio Vella [1]; Didier Lepelletier [4]; Alison H Holmes [1] **;** Jean-Christophe Lucet [2,3]

[1] Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London, Du Cane Road, London, W12 0NN. UK

[2] INSERM, IAME, UMR 1137, F-75018 Paris, France; Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France

[3] AP-HP, Hôpital Bichat – Claude Bernard, Infection Control Unit, F-75018 Paris, France

[4] Nantes Teaching Hospital, Infection Control Unit, Nantes, France

***Corresponding author :**

Dr Gabriel Birgand

Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance,, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, UK Imperial College Healthcare NHS Trust, Fulham Palace Road, London W6 8RF, UK

Tel.: +44 203 313 2732; Fax:

E-mail: gbirgand@gmail.com

Abbreviated title: Costs due to multi resistant bacteria

Word count (body of text): 30569

Keywords: infection control, search and isolate, glycopeptide resistant enterococci, carbapenemase-producing Enterobacteriaceae, contact precautions, meticillin resistant *Staphylococcus aureus*, carbapenem resistant *Acinetobacter baumannii*

ABSTRACT

Objective: To assess the economic burden of infection control measures that succeeded in eradicating multidrug resistant organisms (MDROs) in emerging epidemic contexts in hospital settings.

Design: Systematic literature review

Methods: Medline, Embase and Ovid databases were systematically interrogated for original English language articles detailing costs associated with strict measures to eradicate MDROs published between 1st January 1974 and 2nd November 2014. This study was conducted in accordance with the PRISMA guidelines.

Results: 13 original articles were retrieved reporting data on several MDROs including; glycopeptide resistant enterococci (n=5), carbapenemase producing Enterobacteriacae (n=1), meticillin resistant *Staphylococcus aureus* (n=5) and carbapenem-resistant *Acinetobacter baumannii* (n=2). Overall, the cost of strict measures to eradicate MDROs ranged from €285 to €57,532 per positive patient. The major component of these overall costs was related to interruption of new admissions, representing from €2,466 to €47,093 per positive patient (69% of the overall cost in mean, range: 13 - 100), followed by mean laboratory costs of €628 to €5,849 (24%, range: 3.3 - 56.7), staff reinforcement €6,204 to €148,381 (22%, range: 3.3 – 52) and contact precautions €166 to €10,438 per positive patient (18%, range: 0.7 - 43.3).

Conclusions: Published data on the economic burden of strict measures to eradicate MDRO are limited, heterogeneous, and weakened by several methodological flaws. Novel economic studies should be performed to assess the financial impact of current policies and identify the most cost-effective strategies to eradicate emerging MDROs in healthcare facilities.

INTRODUCTION

Multi-drug resistant organisms (MDROs) are increasingly prevalent causes of healthcare associated infections. Meticillin resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamase producing Enterobacteriacae (ESBLPE) and glycopeptide-resistant enterococci (GRE) have emerged and spread in hospital settings over the last several decades. In addition other MDROs including carbapenemase-producing *Enterobacteriaceae* (CPE) and carbapenem-resistant *Acinetobacter baumannii* (CRAB) represent a more recent threat [1].

In Europe some countries have focused their efforts on particular MDROs considered to be significant threats to public health according to the local epidemiology, implementing strict national "search and isolate/destroy" policies [2,3]. These strategies have demonstrated their efficiency in preventing the spread of transmissible organisms, eradicate them from hospital settings and avoid the endemic situation [4]. These strategies often assume most MDRO-positive patients are unknown asymptomatic carriers and standard precautions do not reliably halt MDRO transmission in all circumstances [2]. Thus enhanced, or 'strict' measures are sometimes needed to control the spread and eradicate MDRO at the level of the ward, the hospital, and nationally. These strategies range from the enforcement of strict contact precautions associated with cross-sectional screening of patients exposed, to a rigorous "search and isolate" policy. This latter may include cohorting of MDRO-positive/contact patients, repeated rectal sampling of contact patients, and both limiting transfer of contact patients out of the care unit (bay or ward) and avoidance of new admissions until after negative screening tests are available.

These strict recommendations are difficult to implement and require additional human and material resources. Moreover interruption of admission into, and transfer from, the involved ward leads to a decrease in hospital medical service utilization and therefore a loss of hospital income and interruption of care to patients [5]. The costs associated with these strict measures to eradicate and avoid the spread of emerging MRDOs are not known. This systematic review aims to assess the current body of scientific literature regarding the financial burden associated with strict control measures that succeeded in eradicating MDRO outbreaks and prevented progression to endemic situations.

METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [6].

Search strategy

A systematic search for original articles in Medline, Embase, and Ovid databases was performed. The search covered the period from January 1, 1974 to November 2, 2014. Search terms were devised and tailored to each database (Appendix 1) covering (i) infection prevention and control, (ii) cost and economic evaluations and (iii) MDRO outbreaks. In addition, the reference lists for all selected full-text articles (below) and related reviews were scanned to derive any further relevant manuscripts.

Study selection

Emerging outbreak situations from any type of ward were considered. An emerging outbreak was defined as the identification of several cases (at least 2) of a same MDRO with the same resistance pattern in a same period of time and area, in hospitals never affected before. Studies could include several epidemic episodes. All studies that evaluated the cost or economic burden of strict infection control measures (“search and isolate” or “search and destroy” strategies) to eradicate MDROs (including MRSA, ESBLPE, CPE, GRE, CRAB) were included. Consideration was given to both descriptive studies with costings, and economic evaluations. Studies that contained no original data and those that evaluated interventions to decrease prevalence in an endemic context were excluded [7–11].

Quality criteria

The Drummond checklist was used to evaluate the quality of economic evaluations [12]. For descriptive studies including exclusively costings, the Drummond Checklist was modified to 9 items, excluding items required only for economic analyses: 2 items on study design, 3 on data collection, 4 on analysis and interpretation of results. For each study evaluated, a total methodological score was derived by attributing one point for each item present.

Data collection process

Title and abstract evaluation was undertaken for all papers arising from the literature search, with subsequent full text analysis and quality assessment of those studies fulfilling the inclusion/exclusion criteria. Two authors (GB and CB) independently reviewed the titles and abstracts, and disagreements were resolved by a third person (VV). A data extraction form was developed and validated on 10 randomly selected articles. Data from the included studies were recorded by two reviewers (GB and CB) then subjected to further critical appraisal during a narrative synthesis. In order to compare the costs in different countries and at varying points in time, all cost estimates were adjusted for inflation using the Consumer Price Index [13] and converted into 2015 Euros.

We aimed to extract the costs of the intervention, this include the total sum of all costs, but also the individual components including for personnel (nursing, physician, laboratory and infection control staff), materials (laboratory, contact precaution supplies, antibiotics etc…) and the loss of income attributable to the implementation of the strategy. In addition, where possible, we extracted data on the components of the infection control intervention.

Costs were expressed per positive case and the proportional contribution of laboratory, contact precautions, staff and activity components to the total cost calculated for each study and in mean for all studies. Since cost values were not normally distributed and highly heterogeneous, no formal meta-analysis was performed. We summaries the results with ranges (minimum – maximum). Studies were excluded from the analysis when cost values were aggregated or insufficiently detailed.

Statistical analyses were performed using Epidata 3.1 and Stata® release 10.0 (Stata Corp LP, College Station, TX).

RESULTS

Study selection

Electronic and subsequent manual searches identified 2406 articles, of which 400 were selected based on title; among these, 364 were excluded based on the abstract, leaving

36 articles, of which two were irretrievable online (Figure 1). Two further articles were identified by manually searching the reference lists. Of these 36 articles, four were in an endemic situation, five were unrelated to costs, 13 did not provide original data and one was unable to be interpreted leaving 13 studies for analysis [14–26].

Study characteristics

The 13 included studies described outbreaks of GRE (n=5), MRSA (n=5), CPE (n=1) and CRAB (n=2) and were conducted in a range of countries from Europe (n=8) and the USA (n=3). All studies were located in a single hospital, with the number of beds reported in 12/13 studies, varying from 254 to 2100. The number of wards affected was reported in 11/13 studies and varied from one to 22, involving intensive care units (ICUs) in eight studies, medical wards in six studies, two surgical wards and one long term care facility (LTCF). Outbreaks lasted from one to 43 months. Among the 13 studies, 12 were descriptive with costings and one reported a formal economic evaluation. The infection control measures implemented and costs assessed for each study are described in Figure 2.

The quality criteria for the 13 studies are presented in Appendix 2. For descriptive studies, the mean score was 0.7/2 for study design, 1.2/3 for data collection and 2/4 for the analysis and interpretation of results. Finally, the aggregated mean score was 3.9/9. The cost-effectiveness study obtained a score of 24 after analysis of the full 35 Drummond checklist items.

Laboratory costs

Twelve studies assessed the laboratory costs associated with the screening of suspected/contact patients or environmental samples (Figure 2). Cost estimation methods were detailed in four studies [15,20–22]. All studies considered consumables and technician time, yet only three included nurse time for obtaining swabs [15,21,22]. One study differentiated costs by negative and positive results [22]. The calculated cost per screening culture varied by organism; for GRE from €3.7 to €55.8,[15,17] for CPE €44.2,[19] for MRSA from €11.5 to €21,[21,23] and for the one study estimating the cost of environmental surveillance of CRAB, a cost of €26.1 per surface swabbed was cited [26]. Three studies on GRE included molecular typing [15,17,18]. Finally, one study gave an overall cost including laboratory, contact precautions, decolonization and staff costs [20].

The Table 3 describes results of relative costs per positive patient and proportional contribution to total taken by the four main categories of cost excluding two studies [20,24] with aggregated and undetailed data. The overall cost from laboratory screening for the MDRO outbreaks varied from €3,141 to €684,362 per outbreak, with a cost per positive patient ranging from €628 to €5,849 and €3.7 to €122 per screening sample. The laboratory activity represented on average 24% (range: 3.3 - 56.7) of the overall cost of infection control measures.

Costs of contact precautions

Eleven studies assessed costs related to contact precautions. Six studies detailed the elements included in the costing, of which two also included the method of estimation [15,17,21,22,24,25]. Among these six studies, the overall cost included the use of gloves (n=6) and gowns (n=6), procedures of disinfection (n=4), consumable material or material destruction (n=2), waste elimination (n=1), alcohol hand rub (n=1) and personal care caddies (n=1), laundering for reusable material (n=1). Overall, cost ranged from €166 to €10,438 per positive patient. Costs or contact precautions represented, on average, 18% (range: 0.7 - 43) of the total cost of infection control measures.

Costs associated with additional staff

Seven studies assessed extra costs from staffing during the MDRO outbreaks. Among these costs included: additional nursing personnel for cohorting (n=4) [15,18,19,21], laboratory staff/ administrative support and contracting cleaners (n=1) [14], additional infection control staff [23] and the absence of personnel during MRSA personnel screening and decolonization (n=1) [20]. One study reported that the control of a GRE outbreak lasting 40 days required 1663 extra hours of nursing staff for 16 positive cases [19]. Overall, the additional staff costs ranged from €6,204 to €148,381 per outbreak and from €477 – €4,086 per positive patient when only considering situations with cohorting. On average, the proportion of the total cost attributable to additional staffing during MDRO outbreaks was 22.4% (range: 3.3 – 52).

Costs associated to the decrease in hospital service use

Eight studies assessed the loss of income for wards due to the implementation of infection control measures. Among these, six described methods to assess costs due to the suspension of transfers/admissions [17–19,21,25,26]. Three methods were described to determine these costs; (i) comparison of activity during the outbreak period to that of the preceding year (n=2) [18,19], (ii) multiplication of the number of days beds were unavailable by the average daily activity estimated in the concerned unit during another period (n=3) [21,25,26], or (iii) multiplication of the number of admissions lost during the outbreak (or during a comparable period in the preceding year) by a cost per admission (n=1) [17].

The overall costs due to ward closure ranged from €38,026 to €1,402,452 per outbreak, equating from €2,466 to €47,093 per positive patient, or from €481 to €17,350 per day of outbreak.

One study estimated the loss of bed occupancy due to contact isolation in single rooms to be 93 patients isolated for a total of 2631 days, at a loss per bed-day of between €441 and €735 (according to hospital ward type) [16]. Costs associated with the loss of hospital activity represented a mean of 68.6% (range: 13 - 100) of the overall cost of infection control measures.

Other types of costs

Four other studies reported additional types of costs: antimicrobials for decolonization (n=2) or treatment (n=1),[15,20,23] installation of electronic taps, dispensers for disinfectants, and printing stationary (n=1),[14] and changes to healthcare professional education (n=1) [15].

Analysis by subgroups was performed to avoid the large heterogeneity of results obtained in the overall population. Analysis of the cost by ward type demonstrated the cost per positive patient varied from: €4,352 to €57,532 in ICU, €2,275 to 38,597in mixed ICU and medical ward outbreaks, €7,736 to 19,387 for surgical/medical wards and €1,329 in LTCF. After stratification for those studies which employed the same five strategies (contact isolation, screening, cohorting patients, cohorting staff, and ward closure; adopted in five studies) the cost per positive patient ranged from €14,306 to €57,532. In ICU, the cost of adopting these five strategies ranged from€42,172 to €57,532 per positive patient, and from €14,306 to €38,597 in medical/surgical wards. The proportional contribution to total costs from each contributory category did not significantly differ between subpopulations.

The cost-effectiveness study concluded that an aggressive strategy of search and isolate, demonstrated cost saving where the number of new cases exceeded four per month, and if the strategy was followed for more than 24 months [23].

DISCUSSION

Some European countries are at the gate of a post-antimicrobial era [1]. Strict infection control strategies applied by several European countries to control such spread, appears to be effective to fight emerging MDROs [1,3]. However these strategies can be costly, difficult to implement, and require increased human/laboratory resources and occasionally warrant interruption of admissions.

The 13 studies identified in this systematic review were heterogeneous, using different methods, settings, and including various types of costs. Analysis of aggregated data from across these different contexts, MDROs, wards, hospital, countries using different methods therefore offers a more robust range of costs for interventions to terminate MDRO outbreaks. From this, potential options to minimize the financial burden associated with "search and isolate" strategies can be constructed. Of particular note, the loss of income due to the interruption of transfer/admissions represents the main cost of strategies to control MDRO spread (from €38,026 to €1,402,452 per outbreak, €2,466 to €47,093 per positive patient, and €481 to €17,350 per day of outbreak), whereas mean costs due to additional human resources were dramatically lower. These results raise the question of whether dedicated areas for managing MDRO outbreak patients might better enable continuity of care for service provision as a whole, bringing appreciable cost-savings. The early identification of patients suspected of being colonized with an MDRO, combined with rapid implementation of contact precautions, is probably the cornerstone of a cost-saving strategy. This may facilitate rapid interruption of cross-transmission, thereby avoiding the major categories of expenses observed in this review. In keeping with this strategy, many countries have issued guidelines in order to promptly identify, screen, and implement strict contact precautions for patients recently hospitalized in a foreign country [2,27].

The estimation of costs related to infection control measures is challenging. The loss of income described in studies in this review was frequently assessed by comparing the activity of the affected ward during the outbreak to a previous period. This retrospective method provides only a crude estimate. The solution, prospective collection of lost patient-bed days/admissions during an MDRO outbreak, would provide more detailed data but would need to be considered in the context of a realistic rate of ward occupancy. The cost per bed-day is another important parameter often approximated, frequently through dividing total hospital stay cost by the number of patient-days. However, this method does not give exact costs at the patient level. All these methods make results deeply dependent on the local context (activity, reimbursement system etc.) which limits generalizability.

The unit costs of screening and contact precautions were also highly variable across the included studies. Laboratory costs vary according to the type of organism, the technique (culture vs PCR), the result (addition of bacterial identification and susceptibility testing for positive cultures) and the use of molecular typing. Few studies distinguished between consumable costs for strain identification, susceptibility tests and PCR, often giving an overall cost for microbiological analysis.

The heterogeneity of costs arising from contact precautions can be explained by the variety of included components: the personal protective equipment on the basis of a number of visits per patient, cleaning or alcohol hand rub, and other materials needed to implement or facilitate the contact isolation. Some studies described implementing standard precautions, while others reported more specific facets of contact precautions.

A previous study reviewed economic studies of strategies to control the spread of endemic MRSA in hospital settings [28]. This article concluded in a large economic benefit (savings seven times higher than costs particularly in long-term strategies) with infection control measures to prevent MRSA transmission in low or high endemicity hospitals. The findings from our systemic review compliment those of Farbman et al, with our data now providing the costs of strategies in emerging outbreak situations, and includes data on including various types of MDROs.

This review underlines several gaps in our understanding of the economic impact of MDRO outbreaks. First, only one study provided a full economic evaluation of a long term strategy of search and isolate. More explicit economic studies in this area are urgently needed, specifically cost-effectiveness analyses to establish both the financial and medical impact of interventions to control MDROs. Several countries have implemented national aggressive strategies to control the spread of GRE, CPE or CRAB. Facing expensive measures, the recurrent question of the financial impact of such strategies is asked. A cost-effectiveness analysis comparing different strategies of infection control based on decision analytical modelling with an effectiveness represented by the number of MDRO colonization of infection (robust in term of diagnosis) averted and the prevention of resistance extension by the increased use of broad spectrum antibiotics. As the antimicrobial resistance is a global issue with interconnection between hospitals, the modelling can only be view at the global scale. However, the economic burden at the hospital level would also be useful for a better understanding and appropriation of results.

Second, among the studies included, the methods used demonstrated marked heterogeneity, often including a restricted panel of costs. Some studies described multifaceted approaches with macro-costing and cumulative costs complicating the synthesis of results. This large heterogeneity precluded a meta-analysis. Our subgroup analysis limited to just those studies who adopted a uniform approach to their infection control strategy did however help to clarify the interpretation of results. Third, three types of indirect costs were poorly considered: (i) time spent by infection control teams in organizing preventive measures, education and participation in meetings; (ii) costs linked to delays in transfer of colonized patients to downstream care facilities; and (iii) the impact of contact isolation on the quality and safety of patient care. These measures can induce reluctance among downstream units to accept admission of MDRO-positive patients with a mean excess length of stay estimated at 23.7-days and a mean cost of €6,381 [29]. Finally, using relative rather than crude descriptions of costs might facilitate the interpretation of results and comparison of results between outbreaks.

In conclusion, costs associated with strict measures to control MDRO outbreaks are highly variable across outbreak organism and location, but in all cases an outbreak-associated decrease in hospital service use is the major financial driver. Formal economic studies must be performed to evaluate current policies and identify optimal strategies to eradicate emerging MDROs in healthcare facilities.

Acknowledgments:

Financial support: The research was partially funded by the National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Healthcare Associated Infection and Antimicrobial Resistance at Imperial College London in partnership with Public Health England (PHE), and the NIHR Imperial Patient Safety Translational Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England. The authors also acknowledge the UK Clinical Research Collaboration (UKCRC) Centre for Infection Prevention and Management, Imperial College Healthcare NHS Trust, and the NIHR Imperial Biomedical Research Centre (BRC).

Conflicts of interest: AHH and LSPM have previously consulted for bioMérieux. All other others declare no conflict of interest.

References

[1] European Center for Disease Prevention And Control. Antimicrobial resistance interactive database (EARS-Net). HttpwwwecdceuropaeuenhealthtopicsantimicrobialresistancedatabasePagesdatabaseaspx 2012 n.d.

[2] Haut Conseil de la Santé Publique. Prévention de la transmission croisée des Bactéries Hautement Résistantes aux antibiotiques émergentes (BHRe). http://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=372 2013.

[3] Kluytmans-Vandenbergh MFQ, Kluytmans J a. JW, Voss A. Dutch guideline for preventing nosocomial transmission of highly resistant microorganisms (HRMO). Infection 2005;33:309–13. doi:10.1007/s15010-005-5079-z.

[4] Fournier S, Brun-Buisson C, Jarlier V. Twenty years of antimicrobial resistance control programme in a regional multi hospital institution, with focus on emerging bacteria (VRE and CPE). Antimicrob Resist Infect Control 2012;1:9. doi:10.1186/2047-2994-1-9.

[5] Birgand G, Ruimy R, Schwarzinger M, Lolom I, Bendjelloul G, Houhou N, et al. Rapid detection of glycopeptide-resistant enterococci: impact on decision-making and costs. Antimicrob Resist Infect Control 2013;2:30. doi:10.1186/2047-2994-2-30.

[6] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100. doi:10.1371/journal.pmed.1000100.

[7] Wassenberg MWM, de Wit GA, van Hout BA, Bonten MJM. Quantifying cost-effectiveness of controlling nosocomial spread of antibiotic-resistant bacteria: the case of MRSA. PloS One 2010;5:e11562. doi:10.1371/journal.pone.0011562.

[8] Young LS, Sabel AL, Price CS. Epidemiologic, clinical, and economic evaluation of an outbreak of clonal multidrug-resistant Acinetobacter baumannii infection in a surgical intensive care unit. Infect Control Hosp Epidemiol 2007;28:1247–54. doi:10.1086/521660.

[9] Danchivijitr S, Chokloikaew S, Chantrasakul C, Trakoolsomboon S. An outbreak of methicillin-resistant Staphylococcus aureus (M.R.S.A.) in a burn unit. J Med Assoc Thail Chotmaihet Thangphaet 1995;78 Suppl 1:S11–4.

[10] Coast J, Smith RD. Antimicrobial resistance: cost and containment. Expert Rev Anti Infect Ther 2003;1:241–51.

[11] Taylor J, Stevenson G. Nursing implications of a vancomycin resistant enterococcus outbreak in a renal unit. EDTNAERCA J Engl Ed 1999;25:42–4.

[12] Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996;313:275–83.

[13] Eurostat (2014) HICP - inflation rate n.d.

[14] Christiansen K, Tibbett P, Beresford W, Pearman J, Lee R, Coombs G, et al. Eradication of a large outbreak of a single strain of vanB vancomycin-resistant Enterococcus faecium at a major Australian teaching hospital. Infect CONTROL Hosp Epidemiol 2004;25:384–90. doi:10.1086/502410.

[15] Armstrong-Evans M, Litt M, McArthur M, Willey B, Cann D, Liska S, et al. Control of transmission of vancomycin-resistant Enterococcus faecium in a long-term-care facility. Infect CONTROL Hosp Epidemiol 1999;20:312–7.

[16] Sagel U, Schulte B, Heeg P, Borgmann S. Vancomycin-resistant enterococci outbreak, Germany, and calculation of outbreak start. Emerg Infect Dis 2008;14:317–9. doi:10.3201/eid1402.070752.

[17] Ridwan B, Mascini E, van Der Reijden N, Verhoef J, Bonten M. What action should be taken to prevent spread of vancomycin resistant enterococci in European hospitals? BMJ 2002;324:666–8.

[18] Escaut L, Bouam S, Frank-Soltysiak M, Rudant E, Saliba F, Kassis N, et al. Eradication of an outbreak of vancomycin-resistant Enterococcus (VRE): the cost of a failure in the systematic screening. Antimicrob Resist Infect Control 2013;2:18. doi:10.1186/2047-2994-2-18.

[19] Daroukh A, Delaunay C, Bigot S, Ceci JM, Siddhoun N, Bukreyeva I, et al. Characteristics and costs of carbapenemase-producing enterobacteria carriers (2012/2013). Med Mal Infect 2014. doi:10.1016/j.medmal.2014.06.004.

[20] Rao N, Jacobs S, Joyce L. Cost-effective eradication of an outbreak of methicillin-resistant Staphylococcus aureus in a community teaching hospital. Infect Control Hosp Epidemiol 1988;9:255–60.

[21] Kanerva M, Blom M, Tuominen U, Kolho E, Anttila V-J, Vaara M, et al. Costs of an outbreak of meticillin-resistant Staphylococcus aureus. J Hosp Infect 2007;66:22–8. doi:10.1016/j.jhin.2007.02.014.

[22] Karchmer T, Durbin L, Simonton B, Farr B. Cost-effectiveness of active surveillance cultures and contact/droplet precautions for control of methicillin-resistant Staphylococcus aureus. J Hosp Infect 2002;51:126–32. doi:10.1053/jhin.2002.1200.

[23] Björholt I, Haglind E. Cost-savings achieved by eradication of epidemic methicillin-resistant Staphylococcus aureus (EMRSA)-16 from a large teaching hospital. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol 2004;23:688–95. doi:10.1007/s10096-004-1198-1.

[24] Walsh TJ, Vlahov D, Hansen SL, Sonnenberg E, Khabbaz R, Gadacz T, et al. Prospective microbiologic surveillance in control of nosocomial methicillin-resistant Staphylococcus aureus. Infect Control IC 1987;8:7–14.

[25] Garlantezec R, Bourigault C, Boles J-M, Prat G, Baron R, Tonnelier J-M, et al. Investigation and management of an imipenem-resistant oxa-23 Acinetobacter baumannii outbreak in an intensive care unit. Med Mal Infect 2011;41:430–6. doi:10.1016/j.medmal.2011.01.013.

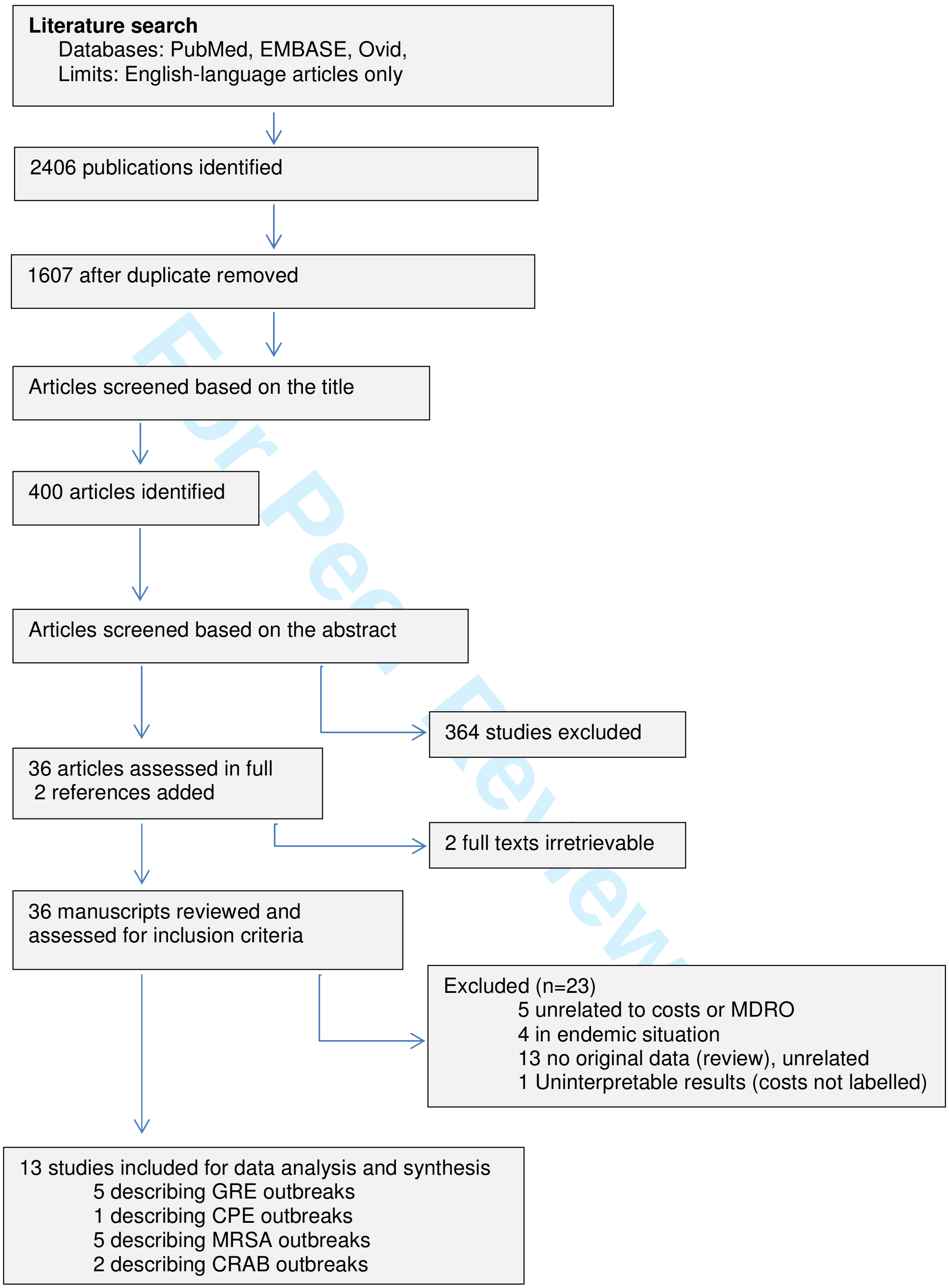
[26] Ayraud-Thévenot S, Huart C, Mimoz O, Taouqi M, Laland C, Bousseau A, et al. Control of multi-drug-resistant Acinetobacter baumannii outbreaks in an intensive care unit: feasibility and economic impact of rapid unit closure. J Hosp Infect 2012;82:290–2. doi:10.1016/j.jhin.2012.08.016.

[27] ECDC. Carbapenemase-producing bacteria in Europe. Interim results from the European survey on carbapenemase-producing Enterobacteriaceae (EuSCAPE) project 2013. HttpwwwecdceuropaeuenpublicationsPublicationsantimicrobial-Resist-Carbapenemase-Prod-Bact-Eur 2013.

[28] Farbman L, Avni T, Rubinovitch B, Leibovici L, Paul M. Cost-benefit of infection control interventions targeting methicillin-resistant Staphylococcus aureus in hospitals: systematic review. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2013;19:E582–93. doi:10.1111/1469-0691.12280.

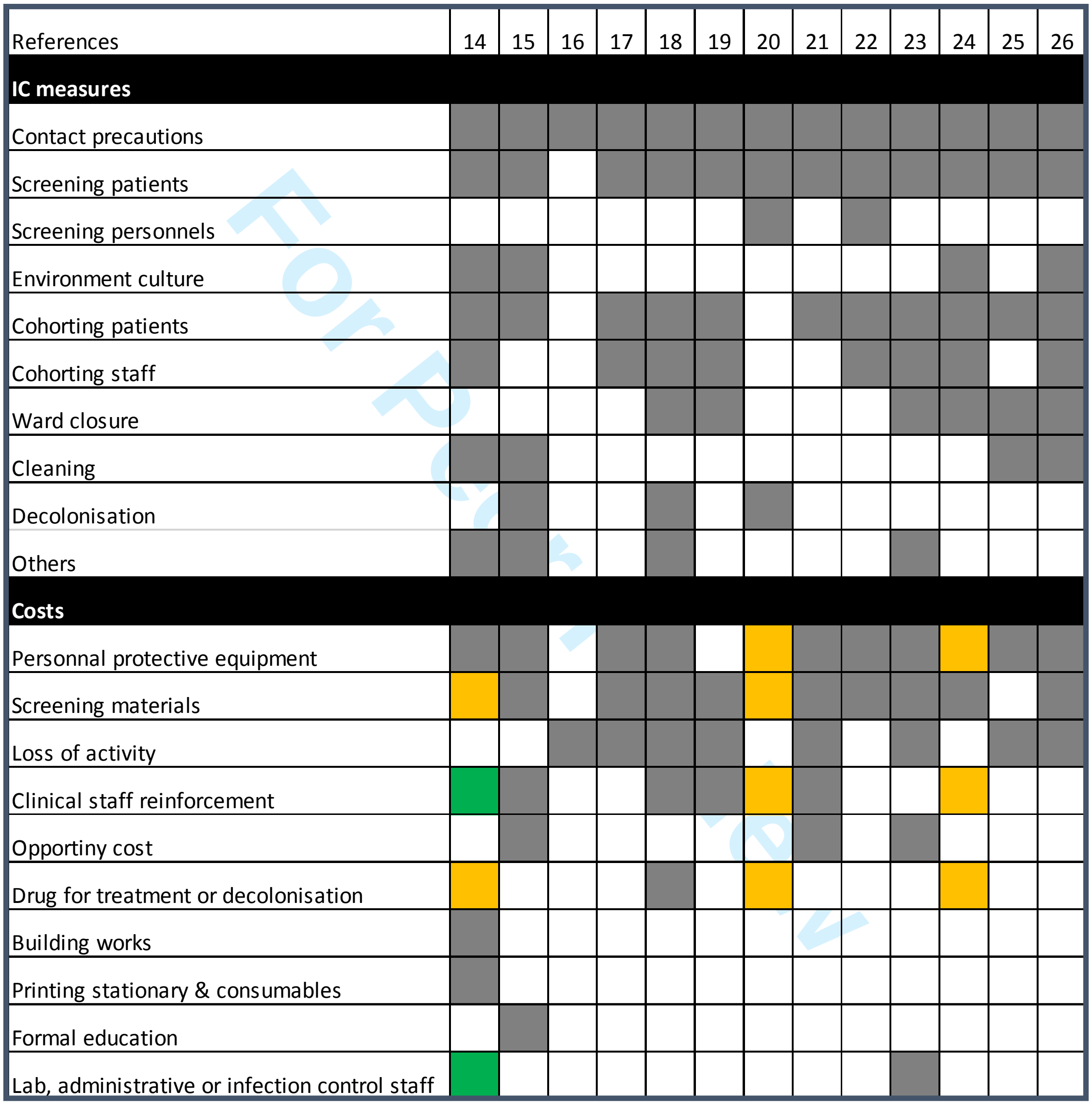
[29] Birgand G, Schwarzinger M, Perozziello A, Lolom I, Pelat C, Armand-Lefevre L, et al. Prolonged hospital stay, an adverse effect of strict national policy for controlling the spread of highly resistant microorganisms. Infect Control Hosp Epidemiol 2014;35:1427–9. doi:10.1086/678425.

Figure 1. Flowchart of the search strategy



Abbreviations: MDRO, multidrug resistant organisms; GRE, glycopeptide resistant enterococci; CPE, carbapenemase producing *Enterobacteriacae*; MRSA, meticillin resistant *Staphylococcus aureus*; CRAB, carbapenemase resistant *Acinetobacter baumannii*

Figure 2. Description of infection control measures used and cost estimated in included studies. Categories of costs given aggregated in study results were represented by boxes filled with a same colour. (e.g. all costs were given aggregated in the reference 20)



Footnote: Descriptors of infection control measures or costs from each study are represented by a green box.

Table 1. Summary of studies meeting inclusion/exclusion criteria and included in the review with crude costs

Ref.	Outbreak duration	Cases/ Suspected cases [a]	Type/Number of Wards affected	Costs					
				Laboratory	Personnal protective equipment and cleaning	Loss of income due to ward closure	Clinical and non-clinical Staff	Others	Overall
Glycopeptide resistant *enterococci* (GRE)									
14	9 months	169/19658	ICU, M (n=23 wards)	Screening & drug use: €326,707 [b] PCR equipment: €77,178	Cleaning and clothing consumables: €380,662 [b]	-	Cleaners: €693,801 Nursing, lab and administrative staff: €704,823	Printing, stationary and other consumables: €520,820	€2,703,993
15	Unclear	5/849	LTCF (n=1 wards)	Screening & typing: €3,141	Clothing consumables: €645 Cleaning: €93 Reusable gowns: €38 Personal caddie: €55	-	Assistant nurses & Cleaners: €2,592	Formal education: €82	€6,646
16	1 month	48/NR	NR	-	-	Cost for 2631 days	-	-	€1,160,108–

						of isolation: €1,160,108–€1,933,513			€1,933,513
17	3 months	43/NR	M, ICU (n=6 wards)	Screening (n=1543): €23,638 Typing: €12,504	Gloves: €1,815; Gowns: €5,361; Cleaning: €13,874	Loss of 37 admissions in nephrology and 11 in ICU: €38,026	-	-	€97,806
18	6 weeks	13/294	M (n=3 wards)	Screening & typing: €16,408	Gowns, gloves, single use material, AHR, disinfection: €15,771	33 admissions lost: €120,326	Nursing staff: €6,204	Antibiotics: €27,275	€185,984
Carbapenemase producing *Enterobacteriaceae* (CPE)									
19	Episode 1: 1 month; Episode 2: 2 months	Episode 1: n=6 Episode 2: n=10 /463	Episode 1: ICU,M,S (n=4 wards) Episode 2: ICU,M,S	Screening (n=716): €31,665	-	Cost for ward closure:€520,503	Cost for 1663 hours of nursing staff: €65,385	-	€617,553

			(n=4 wards)						
Meticillin resistant *Staphylococcus aureus* (MRSA)									
20	14 months	25/NR	ICU (n=2 wards)	Screening of personnel (n=200) & 26 Environment samples	Isolation supplies	-	Additional staffing during personnel decolonization	Drug for decolonisation	€9,644 [b]
21	12 months	257/1240	S,M	Screening: €320,842	Isolation supplies for 20424 days: €116,559	Loss of 112 days of hospitalisation due to ward closure: €1,402,452	Working hours due to MRSA (clinical and non-clinical): €148,381	-	€1,988,234
22	10.5 months	18/587	NICU (n=1 wards)	Negative screening: €44,234 Positive screening: €321	Isolation supplies for 691 patients days: €33,958- €67,905	-	-	-	€78,514 - €110,847
23	20 months	117/NR		Screenings (n= 26148): €684,362	Isolation supplies for 2,188 patients days: €871,582; & 37	Closure of 2 surgical wards: €288,576	Recruitment of 1 infection control doctor and 3 nurses:	-	€2,268,309

					Outpatients visits: €5,973		€417,816		
24	43 months	158 with 3 clusters of 10, 10 &12 cases	ICU/S/M	Screenings (n=1528) €7,199	Gloves, masks, gowns & laundry	-	Nursing staff	Vancomycin use	€45,098 [b,c]
Carbapenem resistant *Acinetobacter baumannii* (CRAB)									
25	1 month	5/NR	ICU (n=1 wards)	-	Cleaning: €13,048 Destruction of supplies: €39,144	Ward closure: €235,467	-	-	€287,659
26	Unclear	Episode 1: 20/230 Episode 2: 7/34	SICU (n=1 wards)	Episode 1: screening (n=230): €8,474; Environment samples (n=500): €13,052 Episode 2: screening (n=34): €1,252;	Isolation supplies: Episode 1: €5,187 Episode 2: €853	Ward closure: Episode 1: 560 days, €586,727 Episode 2: 220 days, €222,676	-	-	Episode 1: €613,440 Episode 2: €230,002

Environment samples

(n=200): €5,221

Abbreviations: Ref, reference; Des, descriptive study; ICU, intensive care unit; M, medical wards; S, surgical wards; NICU, neonatal intensive care unit; SICU, surgical intensive care unit; LTCF. Long term care facility; NR, not reported; AHR, alcohol hands rub

Legends:

[a] A suspect case was defined as a patient at risk of carrying the MDRO and screened according to these criteria

[b] Cumulative data for different types of costs. No detailed costs available in the article

[c] Costs for 2 epidemic episodes were detailed excluding laboratory costs: the first with €31,180 and the second with €13,917

Table 2. Quality analysis of included studies against the Drummond criteria.

Ref.	Study design			Data collection				Analysis and interpretation of results					
	Research question stated	View-point of analysis clearly stated	Sub-total/ 2	Quantities of resources reported separately from unit costs	Methods for the estimation of both quantities and prices given	Currency and price data are recorded	Sub-total /3	Outcomes presented aggregated and disaggreg-ated	Conclusions follow from the data reported	Limit-ations are addressed	The answer to the study question is given	Sub-total /4	Total /9
14	No	No	0/2	No	No	Yes	1/3	Yes	No	No	No	1/4	2/9
15	Not clear	No	0/2	No	No	Yes	1/3	No	No	No	Not clear	0/4	1/9
16	No	Yes	1/2	No	Not clear	No	0/3	Yes	Yes	No	No	2/4	3/9
17	No	No	0/2	No	No	No	0/3	Yes	No	No	Not clear	1/4	1/9
18	Yes	Yes	2/2	No	Yes	No	1/3	Yes	Yes	No	Yes	3/4	6/9
19	No	Yes	1/2	Yes	No	Yes	2/3	Yes	Yes	No	No	2/4	5/9
20	Not clear	No	0/2	No	No	Yes	1/3	Yes	Yes	No	Not clear	2/4	3/9
21	Yes	Yes	2/2	Yes	Yes	Yes	3/3	Yes	Yes	No	Yes	3/4	8/9
22	Yes	No	1/2	Yes	Yes	No	2/3	Yes	Yes	No	Yes	3/4	6/9
23	Yes	No	1/2	No	Yes	No	1/3	Yes	Yes	Yes	Partially	3/4	5/9
25	No	No	0/2	No	Yes	Yes	2/3	No	No	Yes	No	1/4	3/9
26	Not clear	No	0/2	Yes	No	No	1/3	Yes	Yes	Yes	No	3/4	4/9

The full Drummond checklist was used to assess the cost-effectiveness study which obtain a score of 24/35 [24].

Table 3. Overall and subpopulation description of relative costs per positive patient and proportional contribution to total taken by the four main categories of cost.

Euros	Costs per positive patient	Proportional contribution to total costs			
		Laboratory costs	Contact precautions	Staff reinforcement	Decrease in hospital service use
	Min - Max	Mean % (Min-Max) [a]	Mean % (Min-Max) [a]	Mean % (Min-Max) [a]	Mean % (Min-Max) [a]
Overall (n=11) [b]	1329- 57532	24 (3.3 – 57)	18 (0.7 – 43)	22 (3.3 – 52)	69 (13 [c] – 100%)
Type of wards affected					
ICU (n=3) (R1, 80, 34)	4352 - 57532	30 (3.3 – 57)	21 (0.7 – 43)	NA	89 (82 – 96)
ICU + Medical or Surgical wards (n=3) (5, 140, 25)	2275 - 38597	19 (5 – 37)	19 (14 – 24)	31 (11 – 52)	62 (39 – 84)
Medical/Surgical wards (n=3) (R4, 53, R91)	7736 - 19387	18 (9 – 30)	18 (6-39)	5 (3.3 – 7.5)	49 (13 [c] - 70)
LTCF (n=1) (35)	1329	47.3	12	39	NA
Infection control strategy					
Contact isolation + screening + cohorting patients + cohorting staff + ward closure (n=5) (R4, 25, R91, 80, 34)	14306 - 57532	12 (3.3 – 30)	16 (0.7 – 39)	7 (3.3 – 11)	68 (13[c] – 96)

Other strategies (n=6) (35, 137, 53, 5, 140, R1)	1329 - 16000	34 (15 – 57)	20 (6 – 43)	33 (7 – 52)	70 (39 – 100)

[a] Mean of the proportional contribution to total costs for the 11 studies.

[b] Two studies [20, 24] were excluded from the analysis due to aggregated data and low level of informations on costs estimated.

[c] The minimal value is an outlier study assessing cost of a long term screening strategy and including three shorter periods of outbreak with the implementation of strict measures.

Appendix 1

Medline search algorithm

The following search algorithm was developed to search the database using Boolean operators and the asterisk symbol (*) as for wildcard truncation:

Medline search 2 November 2014 GRE: 142 references

("Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Hospital Costs"[Mesh] OR "Models, Economic"[Mesh] OR "Infection Control/economics*"[Mesh] OR "Patient Isolation/economics"[Mesh] OR "Cross Infection/economics*"[Mesh] OR "Length of Stay/economics"[Mesh] OR "Length of Stay*"[Mesh]) AND ("Gram-Positive Bacterial Infections/economics"[Mesh] OR "Microbiological Techniques/economics*"[Mesh] OR "Vancomycin Resistance*"Mesh] OR "Enterococcus*"[Mesh])

Medline search 2 November 2014 CPE: 126 references

("Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Hospital Costs"[Mesh] OR "Models, Economic"[Mesh] OR "Infection Control/economics*"[Mesh] OR "Patient Isolation/economics"[Mesh] OR "Cross Infection/economics*"[Mesh] OR "Length of Stay/economics"[Mesh] OR "Length of Stay*"[Mesh]) AND ("Gram-Negative Bacterial Infections/economics"[Mesh] OR "Carbapenem Resistance*"Mesh] OR "Carbapenemase*" OR "Highly drug resistant organisms*" OR "OXA*" OR "NDM*" OR "VIM*" OR "KPC*" OR "GES*" OR "IMP*")

Medline search 2 November 2014 MRSA: 652 references

("Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Hospital Costs"[Mesh] OR "Models, Economic"[Mesh] OR "Infection Control/economics*"[Mesh] OR "Patient Isolation/economics"[Mesh] OR "Cross Infection/economics*"[Mesh] OR "Length of Stay/economics"[Mesh] OR "Length of Stay*"[Mesh]) AND ("Gram-Positive Bacterial Infections/prevention & control*"[Mesh] OR “Gram-Positive Bacterial Infections/transmission” [Mesh] OR “MRSA” OR "Methicillin-Resistant Staphylococcus aureus"[Mesh])

Medline search 2 November 2014 ESBLPE: 154 references

("Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Hospital Costs"[Mesh] OR "Models, Economic"[Mesh] OR "Infection Control/economics*"[Mesh] OR "Patient Isolation/economics"[Mesh] OR "Cross Infection/economics*"[Mesh] OR "Length of Stay/economics"[Mesh] OR "Length of Stay*"[Mesh]) AND ("Gram-Negative Bacterial Infections/prevention & control*"[Mesh] OR “Gram-Negative Bacterial Infections/transmission” [Mesh] OR “esbl” OR “extended spectrum betalactamase”)

Medline search 2 November 2014 CRAB: 175 references

("Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Hospital Costs"[Mesh] OR "Models, Economic"[Mesh] OR "Infection Control/economics*"[Mesh] OR "Patient Isolation/economics"[Mesh] OR "Cross Infection/economics*"[Mesh] OR "Length of Stay/economics"[Mesh] OR "Length of Stay*"[Mesh]) AND ("Gram-Negative Bacterial Infections/prevention & control*"[Mesh] OR “Gram-Negative Bacterial Infections/transmission” [Mesh] OR “Acinetobacter Infections/prevention &

control" [Mesh] OR "Acinetobacter baumannii" OR "Acinetobacter baumannii/isolation and purification"[Mesh])

Embase and Ovid search algorithm

(Cost-Benefit Analysis or Costs or Cost Analysis or Hospital Costs or Models, Economic) and (Infection Control or Patient Isolation or Cross infection or Length of stay) and (Gram-Positive Bacterial Infections or Microbiological Techniques or Vancomycin Resistance or Enterococcus or Gram-Negative Bacterial Infections or Carbapenem Resistance or Carbapenemase or Highly drug resistant organisms or OXA or NDM or VIM or KPC or GES or IMP or esbl OR (extended spectrum betalactamase) or (Methicillin-Resistant Staphylococcus aureus) or mrsa or (acinetobacter baumannii))

Appendix 2. List of excluded studies and reasons for exclusion

Author	Journal	Year	Category of article	Reason for exclusion
Wassemberg	Plos one	2010	Major article	Endemic situation
Young	Inf Cont Hosp Epidemiol	2007	Major article	Not related to costs
Danchivijitr	J Med Assoc Thai.	1995	Major article	Irretrievable
Coast	Expert Rev Anti Infect Ther.	2003	Review	No original data, not related to infection control during outbreak
Taylor	EDTNA ERCA J.	1999	Major article	Irretrievable
Gregory	Pediatrics	2009	Major article	Endemic
Huttner	Antimicrob Resist Infect Control.	2013	Review	No original data, not related to costs

French	Adv Drug Deliv Rev.	2005	Review	No original data
Trick	J Am Geriatr Soc.	2004	Major article	Endemic situation
Forward	Infect Control Hosp Epidemiol.	1997	Major article	Not related to costs
Lee	Clin Microbiol Infect.	2011	Major article	Not related to measure to eradicate MDROs
Schultz	Infect Control Hosp Epidemiol.	2009	Major article	Not related to measure to eradicate MDROs
Lautenbach	Infect Control Hosp Epidemiol.	2009	Major article	Not related to measure to eradicate MDROs
Khoury	Infect Control Hosp Epidemiol.	2005	Major article	No costs
Pike	Arch Phys Med Rehabil.	2002	Major article	Not related to measure to eradicate MDROs
Cimolai	Can J Microbiol.	2010	Review	No original data

Regev-Yochay	Emerg Infect Dis.	2005	Major article	No costs
Nixon	J Bone Joint Surg Br	2006	Major article	Not related to measure to eradicate MDROs
Goetghebeur	Can J Infect Dis Med Microbiol	2007	Review	No original data
Raka	Braz J Infect Dis.	2009	Major article	No costs
Koeleman	J Hosp Infect.	1997	Major article	No costs
Wassenberg	Clin Microbiol Infect.	2011	Major article	Not related to measure to eradicate MDROs
Millar	J Hosp Infect.	2014	Review	No original data
Weddle	Am J Infect Control.	2012	Major article	Not related to measure to eradicate MDROs
Snyder	Journal of Burn Care & Rehab	1993	Major article	Uninterpretable data