Title page

Article title

Optimising carbapenem use through a national quality improvement programme

Author names and affiliations

Siân E Robson[1], Alison Cockburn[1], Jacqueline Sneddon[1], Abdulrhman Mohana[3], Marion Bennie[3,4], Alexander B Mullen[3], William Malcolm[5], Jennifer Armstrong[4], Andrea Patton[1], Ronald Andrew Seaton[1,6]

1. Scottish Antimicrobial Prescribing Group, Healthcare Improvement Scotland, Delta House, 50 West Nile St, Glasgow, G1 2NP.
2. Regional Infectious Diseases Unit, Western General Hospital, Crewe Road, Edinburgh, EH4-2XU.
3. Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE.
4. Public Health and Intelligence, National Services Scotland, Gyle Square, 1 South Gyle Crescent, Edinburgh EH12 9EB.
5. Health Protection Scotland, National Services Scotland, Meridian Court, 5 Cadogan St, Glasgow G2 6QE.
6. Infectious diseases unit, Queen Elizabeth University Hospital, 1345 Govan Road, Glasgow, G51 4TF

Corresponding author contact details (phone, fax and email)

Dr Jacqueline Sneddon, phone +44141 227 3258, email jacqueline.sneddon@nhs.net.

Short running title

Carbapenems Quality Improvement Programme

Synopsis (250 words)

Background

Concern about increasing carbapenem and piperacillin/tazobactam use led the Scottish Antimicrobial Prescribing Group (SAPG) to develop national guidance on optimal use of these agents, and to implement a quality improvement programme to assess the impact of guidance on practice.

Objectives

To evaluate how SAPG guidance had been implemented by health boards, assess how this translated into clinical practice, and investigate clinicians' views and behaviours about prescribing carbapenems and alternative agents.

Methods

Local implementation of SAPG guidance was assessed using an online survey. A bespoke Point Prevalence Survey was used to evaluate prescribing. Clinicians' experience of using carbapenems and alternatives was examined through semi-structured interviews. National prescribing data were analysed to assess the impact of the programme.

Results

There were greater local restrictions for carbapenems than for piperacillin/tazobactam. Laboratory result suppression was inconsistent between boards and carbapenem sparing antibiotics were not widely available**.** Compliance with local guidelines was good for meropenem but lower for piperacillin/tazobactam. Indication for use was well documented but review/stop dates were poorly documented for both antibiotics. Decisions to prescribe a carbapenem were influenced by local guidelines and specialist advice. Many clinicians lacked confidence to de-escalate treatment. Use of both antibiotics decreased during the course of the programme.

Conclusions

A multi-faceted quality improvement programme was used to gather intelligence, promote behaviour change and focus interventions on use of carbapenems and piperacillin/tazobactam. Use

of these antimicrobials decreased during the programme; a trend not seen in Europe outwith the UK. The programme could be generalised to other antimicrobials.

Introduction

Multi-drug resistant Gram negative bacteria (MDRGNB) are an escalating global problem[1] and in Europe, increases in carbapenem use[2] have been associated with increases in MDRGNB.[3] In 2015 no European country showed a significant decrease in carbapenem use and use of piperacillin/tazobactam increased compared with 2014 data.[4] Globally, carbapenem use is also increasing[5] as is the incidence of carbapenem resistant Gram negative bacteria.[6,7] Carbapenems and piperacillin/tazobactam have been designated as critically important antibiotics by the World Health Organisation since 2005[8] and in 2013, the Department of Health in England recommended protecting carbapenems and anti-pseudomonal agents to preserve their efficacy.[9]

In Scotland, reported incidence of resistant Gram negative organisms including bacteria producing extended spectrum beta-lactamase (ESBL) were stable between 2009 and 2012, [10] although small numbers of carbapenemase-producing organisms (CPO) were increasing year on year. Piperacillin/tazobactam and carbapenem use was relatively low in Scottish hospitals in 2012: 1.9% and 1.3% respectively of total antibiotic use (defined daily dose/100 admissions), but use of both antibiotics had increased between 2009 and 2014 (51.1% and 23.1% respective increases).[10]

In Scotland the National Health Service comprises 14 regional health boards providing hospital and community services, plus one national hospital. The national antimicrobial stewardship programme is led by the Scottish Antimicrobial Prescribing Group (SAPG), an NHS organisation hosted by Healthcare Improvement Scotland, and delivered by health board Antimicrobial Management Teams (AMTs). With the increasing threat from MDRGNB and CPO and increased use of carbapenems and piperacillin/tazobactam in Scotland, in October 2013 SAPG produced and disseminated guidance related to MDRGNB infections to AMTs (Supplementary Information). The guidance emphasised optimising use of carbapenems and piperacillin/tazobactam and considering use of carbapenem sparing antibiotics (CSA) e.g. aztreonam, temocillin, fosfomycin and pivmecillinam. The intention was

for AMTs to integrate this national guidance within local policies and education programmes. This project aimed to evaluate local implementation of the national guidance and to investigate its impact on clinical practice.

Materials and methods

Study design

The programme was overseen by a multi-professional steering group. There were three elements: a national implementation survey of health boards' prescribing guidance and laboratory reporting practice; a bespoke Point Prevalence Survey (PPS) of carbapenems and piperacillin/tazobactam to assess their use in clinical practice; and qualitative interviews in selected boards to explore clinicians' attitudes, strategies and barriers to the use of these antibiotics and CSAs. Study outputs were regularly shared with SAPG members and AMTs. An interrupted time-series (ITS) analysis of antibiotic use was used to determine the impact of data sharing and clinician awareness of the programme.

Survey

A Survey Monkey© online tool (Supplementary Information) consisting of 49 questions was developed to seek feedback on: adoption of the SAPG MDRGNB guidance; implementation strategies; education; current local recommendations for use of carbapenems, piperacillin/tazobactam and CSAs; and local microbiology laboratory policy and practice for Gram negative isolates. In May 2015, a link to the survey was sent to AMTs (n=15) asking them to submit one response per board. Responses were compared to assess variation in clinical use and diagnostic microbiology laboratory practice across boards.

National Point prevalence survey (PPS)

A bespoke PPS focusing on meropenem (the predominant carbapenem in NHS Scotland) and piperacillin/tazobactam was undertaken in all acute Scottish hospitals (n=32) using the National Antimicrobial Stewardship Point Prevalence System (NAS-PPS) database and paper data collection forms for ward information and patient information (Supplementary Information). PPS data coding was based on the European Society for Antimicrobial Consumption dataset (Supplementary Information) and staff were trained through online webinar sessions.

The PPS was conducted during a 4-week period in September to October 2015. Information was collected on every prescription of a carbapenem or piperacillin/tazobactam for treatment of infection on the day of the survey. Prescriptions for antibiotic prophylaxis administered in the 24 hours prior to the survey were also included although neither antibiotic is recommended for use as prophylaxis.

Following completion of data entry, boards could analyse their own data and results were extracted by SAPG to produce summary reports for each board and a national report.

Semi-structured interviews

A semi-structured interview was developed to explore factors influencing prescribing of meropenem and CSAs. The interview (Supplementary Information) consisted of five questions about prescribing, monitoring, reviewing and de-escalating meropenem; five about factors encouraging or limiting the prescription of CSAs; and an opportunity to make any other comments. Four health boards were selected based on either their good practice in use of carbapenems or use of CSAs as identified through the survey and PPS. AMTs within each board identified a representative sample of clinicians from various specialities and grades (Supplementary Information) and each clinician was sent an invitation letter and study information. Twenty nine one-to-one interviews were conducted by author AM between June and November 2016. Interviews were audio recorded, transcribed verbatim and anonymised. A thematic analysis was conducted in NVivo 11 by author AM and was validated by author SR, followed by the two researchers reaching a consensus on thematic coding.

Sharing of project data

Summary reports on each phase of the programme were shared via SAPG meetings, and with AMTs via email and presentations at SAPG national network events.

Interrupted time-series analysis

Data on carbapenems and piperacillin/tazobactam use between January 2012 and December 2016, as defined daily doses (DDDs), were obtained from the Hospital Medicines Utilisation Database (HMUD): a national database of medicines supply. Population estimates were obtained from National Records of Scotland (NRS) and data were reported in DDDs per 100,000 population. The time-series was split into three segments to estimate the level and trend changes in the two segments that follow each intervention compared to the preceding segment (Figure 4). Segment one was 21 months (January 2012 to September 2013) followed by the introduction of the SAPG Guidance in October 2013 (Intervention one). Segment two was 19 months (October 2013 to April 2015). Intervention 2 was the quality improvement phase which included the AMT survey in May 2015, the bespoke Point Prevalence Survey in October 2015, the sharing of reports with boards in January 2016 and the AMT event in March 2016. Segment three was 23 months (May 2015 to December 2016). A segmented regression analysis of interrupted time-series data was used to examine intervention effects[11], using lag terms to adjust models for autocorrelation present in the residual terms and using heteroskedastic robust standard errors when residual terms were not homoscedastic. Intervention effect sizes are the estimated absolute and relative changes, with 95% confidence intervals[12]. The absolute change is the difference between the modelled estimate at the specified post-intervention point and the modelled estimate assuming the pre-intervention trend continued. The relative change is the absolute change as a percentage of the modelled estimate at the specified post-intervention time point. Absolute and relative effects are calculated at one

month, six months and 18 months after each intervention. All analyses were carried out in SAS (Statistical Analysis Software [13]).

Ethics

Caldicott Guardian approval for use of prescribing information was obtained locally within each health board. Clinicians involved in the interviews gave written informed consent. Formal ethical review and approval were not required because the project was a service evaluation. The project was conducted in accordance with the Declaration of Helsinki and national and institutional standards.

Results

National Survey

All 15 health boards responded to the survey and the key results are reported below. Meropenem was reported to be subject to prescribing restrictions in 13 (87%) boards, but piperacillin/tazobactam was only restricted in seven boards (47%) (Figure 1). The most common mechanism for authorisation was through an infection specialist (microbiologist or infectious diseases physician) following a restricted antibiotics policy. These policies are not effectively monitored in many boards; however, one small board uses a highly effective coding system which also controls access to stock. Access to meropenem is mostly limited by having a 24 hour supply available via an emergency cupboard or located on specific wards. Meropenem sensitivity reporting was automatically suppressed by laboratories in 9 (60%) of the 15 boards but piperacillin/tazobactam only in 5 boards (33%) (Figure 1).

The four most commonly reported approved indications for meropenem were as second line treatment of febrile neutropenia (80% of boards), severe sepsis unresponsive to piperacillin/tazobactam (53%), infections with *Pseudomonas spp.* or resistant Gram-negative organism colonisation in cystic fibrosis patients (40%) and exacerbation of bronchiectasis (33%). The

following CSAs were formulary approved for use on specialist advice: fosfomycin oral (87% of boards), pivmecillinam (73%), temocillin (67%), fosfomycin intravenous (IV) (60%), aztreonam (53%). Health boards either updated local guidelines based on the SAPG MDRGNB guidance recommendations or reviewed their local guidelines and found them to be in-line with the SAPG guidance. Many boards also informed clinicians about the guidance during medical education sessions or electronically. Training on prescribing of carbapenems and piperacillin/tazobactam is integrated into routine training in most boards, mainly targeted to junior and middle grade medical staff and pharmacists.

National Point prevalence survey

PPS data were submitted by all 15 health boards but data from 2 small island health boards were excluded from the analysis due to delays in receiving the data. A total of 12,478 patients were sampled in 32 hospitals; all patients prescribed the study antibiotics on the day of the survey were included. Data were not collected on the total number of antibiotics prescribed or on whether the study antibiotics were prescribed as monotherapy or in combination with other antibiotics. There were 466 prescriptions included: 129 of meropenem and 337 of piperacillin/tazobactam and patient demographics are shown in Figure 2A. The majority of prescriptions were for patients over 50 years (70% of meropenem and 84% of piperacillin/tazobactam) and around 60% of prescriptions were for four or more days. Figure 2B shows the number of prescriptions by specialty. The most common diagnoses for meropenem use were pneumonia, intra-abdominal sepsis, febrile neutropenia or clinical sepsis, which accounted for 66% of all prescriptions. For piperacillin/tazobactam, 70% of prescriptions were for pneumonia, intra-abdominal sepsis, febrile neutropenia or bacteraemia. The source of infection was most often community acquired (CAI) defined as present or starting within 48 hours of admission; 58% of meropenem and 53% of piperacillin/tazobactam. The prevalence of CAI was similar to that observed in the national PPS of HAI and antimicrobial prescribing in 2016.[14]

The reason for the antibiotic prescription was documented in 97% of meropenem prescriptions and 88% of piperacillin/tazobactam prescriptions. Compliance with local policy was 88% for meropenem and 70% for piperacillin/tazobactam. Documentation of a review or stop date for antibiotic prescriptions was 31% for both drugs (Figure 3).

To confirm that use of meropenem and piperacillin/tazobactam on the day of the PPS was typical, data were compared with the previous year's annual use of the drugs in each health board, measured in defined daily doses (in Supplementary Information).

Semi-structured interviews

The main themes arising from the thematic analysis of interview data were grouped into three topic areas: initiation of a prescription, continuation of a prescription and areas for improvement. Key findings included: clinicians rely on specialists' (Microbiologist/Infectious Disease) advice on initiation (which would be expected given their restricted status) but also relied on specialist advice on continuation/de-escalation which may indicate a lack of confidence amongst clinical teams; acknowledgement of overuse of very broad spectrum agents; a need for tools to facilitate review, de-escalation and intravenous to oral switch therapy (IVOST) to support clinicians; lack of awareness and confidence amongst clinicians in using CSAs unless within local guidelines or on microbiology reports or recommendation (Table 1).

Interrupted time series

Monthly carbapenem and piperacillin/ tazobactam DDDs per 100,000 population were plotted over the entire study period (Figure 4). Before Intervention one carbapenems were increasing by 1 DDD per 100,000 population each month (p=0.006) from a baseline of 128.7 DDDs per 100,000 population. Intervention one was associated with an immediate decrease of 21.3 DDDs per 100,000 population (p=0.001) and a change in trend of 0.58 DDDs per 100,000 population (p=0.28). Intervention two was associated with an immediate reduction of 12.3 DDDs per 100,000 population

(p=0.05) and a change in trend of 2.3 DDDs per 100,000 population (p<0.001). Before intervention one piperacillin/tazobactam was increasing by 1.4DDDs per 100,000 population each month (p<0.001) from a baseline of 188.8 DDDs per 100,000 population. Intervention one was associated with an immediate increase of 14.9DDDs per 100,000 population (p=0.02) and a change in trend of -1.5 DDDs per 100,000 population (p=0.002). Intervention two was associated with an immediate decrease of 17.6 DDDs per 100,000 population and a change in trend of -1.6 DDDs per 100,000 population (p=0.002).

Segmented regression analysis showed that six months following the release of SAPG Guidance in October 2013 there was an 11.4% decrease (95% CI 19.0 to3.9) in carbapenems and a 2.5% increase (95% CI -3.2 to 8.2) in piperacillin/tazobactam. By April 2015 the intervention effect was diminishing for carbapenem use with a smaller reduction of 6.5% (95% CI -18.4 to 5.5) while piperacillin/tazobactam use showed a decrease of 5.2% (95% CI -12.9 to 2.4).

Six months after the start of the quality improvement work (Intervention two) there was a reduction in carbapenem use of 15.5% (95% CI 8.3 to 22.6) which further decreased to a 28.5% reduction (95% CI 19.3 to 37.7) by November 2016. Piperacillin/tazobactam use continued to decrease after intervention two so that by November 2016 there was a 20.4% decrease (95% CI 12.7 to 28.1).

Discussion

The survey showed that the SAPG MDRGNB guidance was implemented in most boards. Meropenem is more often subject to prescribing restrictions than piperacillin/tazobactam and authorisation for use is typically through an infection specialist. There is inconsistency in the approach of microbiology laboratories towards antimicrobial stewardship nationally and the suppression and release of antimicrobials occurs via a variety of mechanisms. There is scope and an appetite amongst laboratory clinicians and scientists for standardisation, which is being progressed via collaboration of SAPG with the Scottish Microbiology and Virology Network. Most boards only use carbapenem sparing antibiotics (CSAs) for specific indications on specialist advice and only two

boards have embraced their use through inclusion in local antibiotic guidance. Barriers to use of CSAs are additional costs compared with generic meropenem and issues with stock shortages. Older CSAs have a limited evidence base and further studies are required to demonstrate efficacy in the current resistance landscape[15]. However, new agents are coming to market e.g. ceftolozane/tazobactam and may offer another alternative to carbapenems.

SAPG utilises periodic on-line surveys of AMTs to obtain feedback on implementation of national stewardship initiatives, barriers to implementation and suggestions for future improvement work. This provides an essential evaluation element to the stewardship programme and also informs future planning. The survey on the use of carbapenems and piperacillin/tazobactam was the fourth AMT survey and focused on implementation of national guidance which was subsequently reviewed and updated in 2016[16] to reflect the findings of this work and additional evidence from the literature. A multi-pronged approach to hospital stewardship is highlighted in the recent Cochrane review[17] so it is encouraging that our survey confirmed that implementation of local guidance was supported by education for key clinical staff. Extension of stewardship training beyond junior and middle grade doctors to include consultants may be helpful to ensure leadership for stewardship and drive behaviour change. Antimicrobial pharmacists are also a key source of specialist advice for clinical teams in Scotland and training for nursing staff is also important with their evolving role in stewardship.[18]

Additional to the reported results, the survey confirmed that most boards monitor consumption of carbapenems and piperacillin/tazobactam quarterly as recommended in national surveillance guidance.[19] Consumption reports are shared at AMT meetings and, in many boards, with Infection Prevention and Control Committees, supporting an integrated approach to stewardship. Awareness of consumption trends is crucial to improving prescribing practice and to assessing the impact of interventions.[20]

The survey described the local processes to support appropriate use of carbapenems and piperacillin/tazobactam but from a stewardship perspective it is important to understand how this translates into prescribing practice which was the key aim of the PPS. National PPS are used throughout Europe[21] to evaluate the prevalence of Healthcare Associated Infection and antimicrobial prescribing and have provided SAPG with quantitative and qualitative data to inform on areas for improvement.[14]

In the bespoke PPS, the lack of good documentation for piperacillin/tazobactam use may reflect its place as the 'go to' antibiotic for severe infection. The recent worldwide shortage of piperacillin/tazobactam has gone some way to changing this, with national agreement via SAPG in May 2017 to reserve piperacillin/tazobactam for treatment of suspected neutropenic sepsis and as directed by infection specialists for other specific infections. Further analysis of the PPS data showed that carbapenem use was below 2% of all antibiotics in all boards and less than 1% in many. Piperacillin/tazobactam use varied from 1% to over 6% possibly reflecting different controls over use rather than clinical justification. Another key finding from the PPS was that over half of patients had received antibiotics for over 72 hours and about one third of these patients had no documented review or stop date recorded in their medical notes. These findings are informing SAPG work on antibiotic review to support clinical teams through education and quality improvement tools to optimise prescribing practice.

The interviews with clinicians suggest that many prescribers are not confident in reviewing intravenous antimicrobial therapy in patients with severe infection where oral switch options may be unclear and there is a perceived need for additional input from infection specialists. Although carbapenems and to some extent piperacillin/tazobactam are often prescribed following advice from microbiology, there is a perception that there is a relative lack of follow-up discussion between the clinical team and microbiology. In addition, variance in the suppression or release of full microbiology reports can lead to patients remaining on the original treatment despite clinical

improvement and lack of positive microbiology. This can be addressed through Antimicrobial Ward Rounds[22] but these are unlikely to capture all patients prescribed these agents in a timely manner. Therefore there appears to be a learning need to upskill prescribers as well as developing systems to more easily identify prescription of these antibiotics to facilitate review. Evidence from the interviews clearly identified that there was a need for a whole system approach which includes the organisational systems and local policies (the environment), improved communication within the multidisciplinary team (the clinicians) and better availability and use of CSAs (the medicines). We acknowledge that selection bias is a limitation of this phase of the programme since we involved clinicians in only 4 of the 15 health boards selected based on local good practice. However they represented boards of varying size, a mix of teaching hospitals and district generals and urban and rural populations.

During the course of this two-year improvement programme, national use of carbapenems and piperacillin/tazobactam have decreased although there is some variation between boards in terms of reduced consumption. Some of this change can be attributed to the various elements of the programme as illustrated by the interrupted time series analysis. The impact on consumption may be a Hawthorn effect, but measurement and in-depth study of organisational systems coupled with continuous feedback of findings through multiple forums appears to be supportive in reducing use. During the last 2 years use of CSAs has increased in some health boards, particularly aztreonam and temocillin, and reassuringly there has been no upward trend in use of 3rd generation cephalosporins or fluoroquinolones in Scottish hospitals (data not shown).

SAPG had previously completed a quality improvement programme for gentamicin and vancomycin[23] and this work on carbapenems used a similar approach. Such programmes utilise several methods to gain intelligence about clinical practice and target areas for improvement. SAPG has an extremely well engaged network of local AMTs which support our work, facilitating a

resource-light approach. The study findings are continuing to shape the direction of SAPG quality improvement initiatives, including:

- Highlighting the need to feature CSAs in local guidelines and ensure availability of stock.
- Working with microbiology colleagues to develop a standardised approach to antimicrobial susceptibility testing and reporting.
- Encouraging boards to develop local systems to identify initiation of a carbapenem to enable a formal review process by the attending clinical team and/or infection specialists.
- Developing a national standard and supporting toolkit for review of IV antibiotic therapy.

This work demonstrates how a multi-faceted quality improvement programme can be used to gather intelligence, promote behaviour change and focus interventions to optimise use of very broad spectrum antibiotics. Recent national trends in use of these antibiotics continue to show a downward trend and rates are significantly lower than in other UK nations[24]. Comparison with other European countries[4] suggests Scotland is 'bucking the trend' of stable or increasing rates of carbapenem and piperacillin/tazobactam use. We consider this three-part improvement project will be of interest to stewardship colleagues as it can be applied to other antimicrobials to investigate and inform safe and effective clinical practice.

Acknowledgements

The Carbapenems Steering Group members not already cited as authors: Ms Ysobel Gourlay, Dr David Griffith, Mrs Heather Kennedy, Mrs Susan Roberts, and Mr Alan Timmins. Dr Becky Wilson of the Scottish Microbiology and Virology Network for analysing survey results relevant to Microbiologists. Dr Emma Corcoran for her assistance in the thematic analysis of interview data. Interim data from the AMT survey and PPS have been submitted as abstracts to the Federation of Infection Societies conferences in 2015 and 2016 and to ECCMID 2016, accepted for presentation as posters.

Funding

This work was carried out as part of the work programme of the Scottish Antimicrobial Prescribing Group which is funded by Scottish Government. The work was supported by additional funding from Scottish Government for an Antimicrobial Pharmacist (Project Manager – Alison Cockburn) from June 2015 – March 2016. The work was also supported by a post-graduate pharmacist (Abdulrhman Mohana) undertaking a PhD funded by the government of Saudi Arabia represented by the Saudi Arabian Cultural Bureau in London.

Transparency declarations

Siân E Robson has nothing to declare.

Alison Cockburn has nothing to declare.

Abdulrhman Mohana has nothing to declare.

Marion Bennie has nothing to declare.

Alexander B Mullen has nothing to declare.

William Malcolm has nothing to declare.

Jacqueline Sneddon has nothing to declare.

Ronald Andrew Seaton has nothing to declare.

Andrea Patton has nothing to declare

Jennifer Armstrong has nothing to declare

References

1. O'Neill J, Tackling Drug-Resistant Infections Globally: final report and recommendations, May 2016. https://amr-review.org/
2. Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report, January 2015, European Food Safety Agency. https://www.efsa.europa.eu/en/efsajournal/pub/4006

3. Antimicrobial resistance surveillance in Europe 2015, European Centre for Disease Prevention and Control. https://ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2015?ID=1637&List=4f55ad51-4aed-4d32-b960-af70113dbb90
4. Summary of the latest data on antibiotic consumption in EU: 2016, European Centre for Disease Prevention and Control. https://ecdc.europa.eu/en/publications-data/summary-latest-data-antibiotic-consumption-eu-2016
5. Van Boeckel TP, Gandra S, Ashok A *et al*. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *The Lancet Infectious Diseases* 2014; **14**: 742-50.
6. Canton R, Akova M, Carmeli Y *et al*. Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. *Clin Microbiol Infect* 2012; **18**: 413-31.
7. Levy Hara G, Gould I, Endimiani A *et al*. Detection, treatment, and prevention of carbapenemase-producing Enterobacteriaceae: recommendations from an International Working Group. *J Chemother* 2013; **25**: 129-40.
8. World Health Organisation. Critically Important Antimicrobials for Human Medicine, 5th Revision 2016: Ranking of antimicrobial agents for risk management of antimicrobial resistance due to non-human use. Geneva, Switzerland, 2016.
9. (ARHAI) ACoARaHAI. 4th Annual Report, February 2012 - March 2013. 2013.
10. National Services Scotland. Report on Antimicrobial Use and Resistance in Humans in 2012. 2014. http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Publications/2014-01-28/2014-01-28-SAPG-2012-Report.pdf
11. Wagner AK, Soumerai SB, Zhang F *et al*. Segmented regression analysis of interrupted time series studies in medication use research, *J Clin Pharm Ther.* 2002; 27:299-309

12. Zhang F, Wagner AK, Soumerai SB *et al*. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *J Clin Epid.* 2009; 62: 143-148
13. Statistical Analysis Software SAS Institute Inc. SAS OnlineDoc, Version 9.4 Cary NC: 2005
14. Health Protection Scotland, National Point Prevalence Survey of Healthcare Associated Infection and Antimicrobial Prescribing 2016, 2017. http://www.hps.scot.nhs.uk/haiic/amr/resourcedetail.aspx?id=3236
15. Wilson APR, Sparing Carbapenem Usage. *Journal of Antimicrobial Chemotherapy*, Volume 72, Issue 9, 1 September 2017, Pages 2410–2417.
16. Scottish Antimicrobial Prescribing Group. Position paper on optimising antimicrobial prescribing in possible or suspected infections due to multi-drug resistant Gram negative bacteria, April 2016
17. Davey P, Marwick CA, Scott CL *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database of Systematic Reviews 2017, Issue 2.*
18. Edwards R, Drumright LN, Kiernan M *et al*. Covering more Territory to Fight Resistance: considering nurses' role in antimicrobial stewardship, *J Infect Prev.* 2011 January; 12(1): 6–10.
19. Local surveillance of antimicrobial use, Scottish Antimicrobial Prescribing Group, 2015. http://www.scottishmedicines.org.uk/files/sapg1/Local_surveillance_framework_for_antimicrobial_use_2015.pdf
20. De With K, Allerberger F, Amann S *et al*. Strategies to enhance rational use of antibiotics in hospital: a guideline by the German Society for Infectious Diseases. Infection. 2016; 44: 395–439.
21. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals – protocol version 5.3, European Centre for Disease

Prevention and Control, 2016. https://ecdc.europa.eu/en/publications-data/point-prevalence-survey-healthcare-associated-infections-and-antimicrobial-use-3

22. National Institute for Health and Care Excellence Guideline (NG15), Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use, 2015. https://www.nice.org.uk/guidance/ng15/resources/antimicrobial-stewardship-systems-and-processes-for-effective-antimicrobial-medicine-use-pdf-1837273110469

23. Newham R, Thomson AH, Semple Y *et al.* Barriers to the safe and effective use of intravenous gentamicin and vancomycin in Scottish hospitals and strategies for quality improvement. *Eur J Hosp Pharm* 2015;22:32-37

24. Health Protection Scotland, Scottish One Health Antimicrobial Use and Antimicrobial Resistance Report 2016, 2017. http://www.hps.scot.nhs.uk/resourcedocument.aspx?id=625

Supplementary data

Supplementary data is available on request; the SAPG guidance on MDRGNB 2013, the AMT survey questionnaire, PPS forms, PPS codes, PPS versus average prescribing rates, clinician interview schedule, characteristics of interview participants.

Figure 1. NHS board responses to survey questions on meropenem and piperacillin/tazobactam use

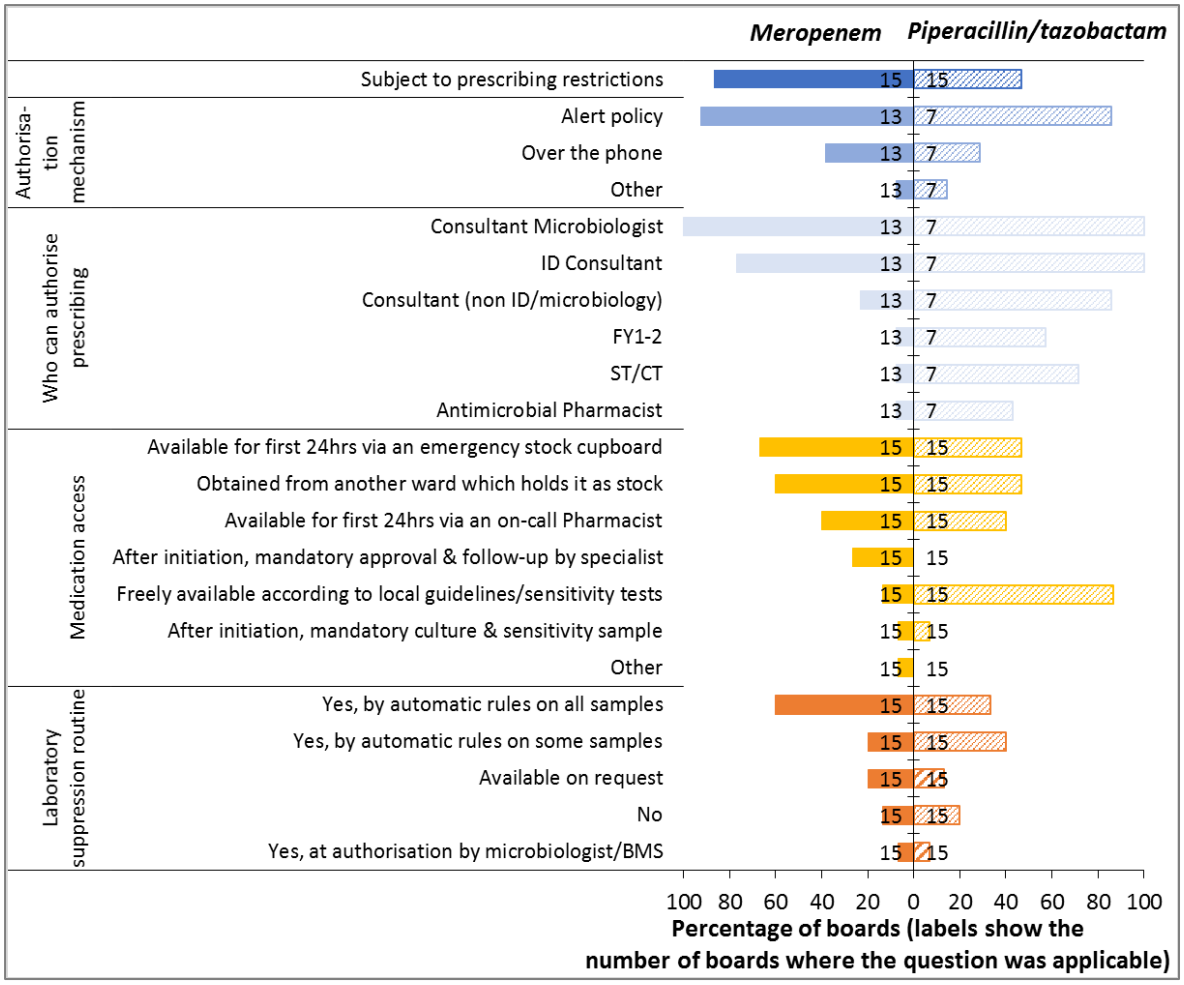


Figure 2. Summary of data from Point Prevalence Survey of meropenem and piperacillin/tazobactam use.

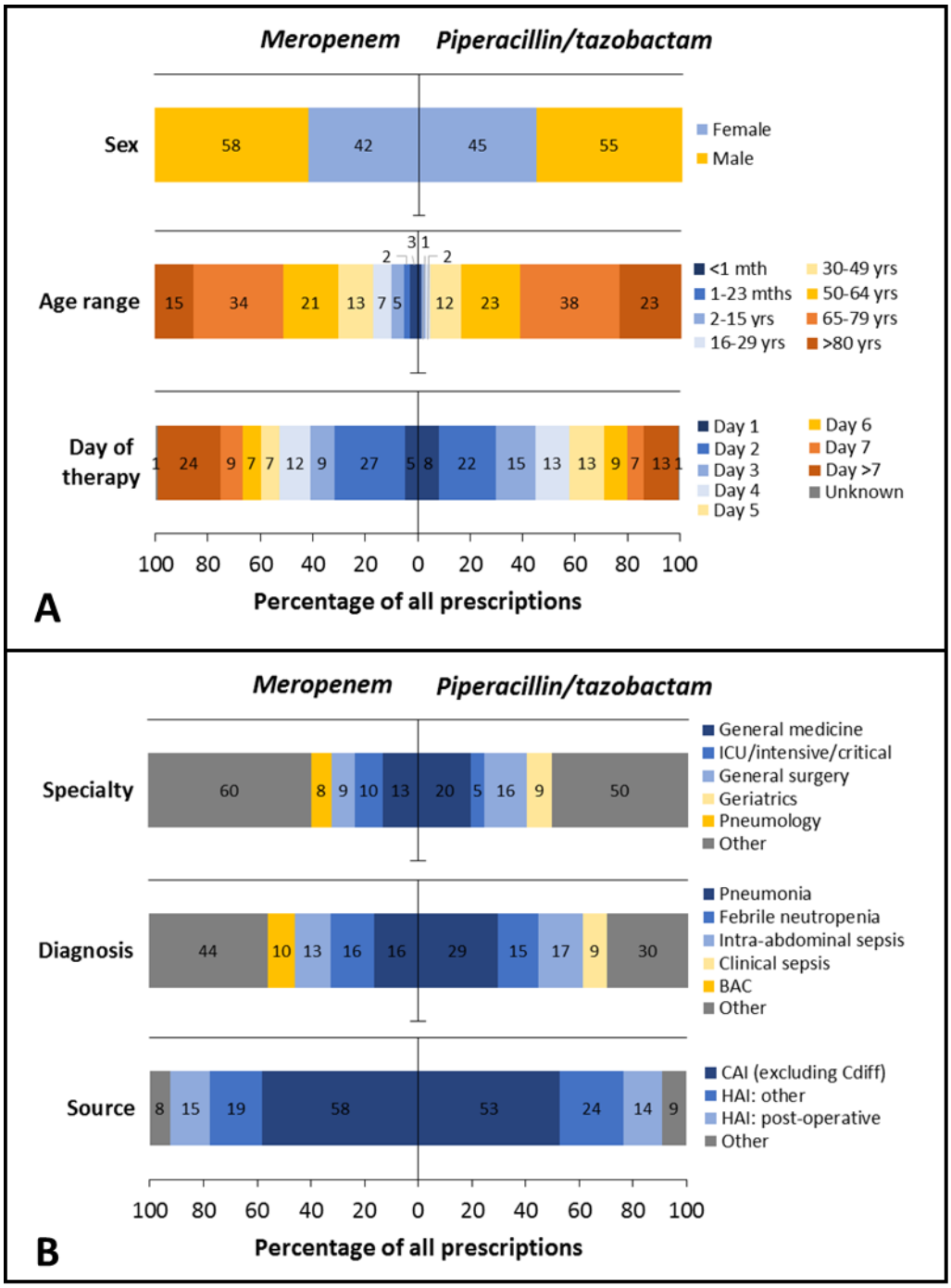
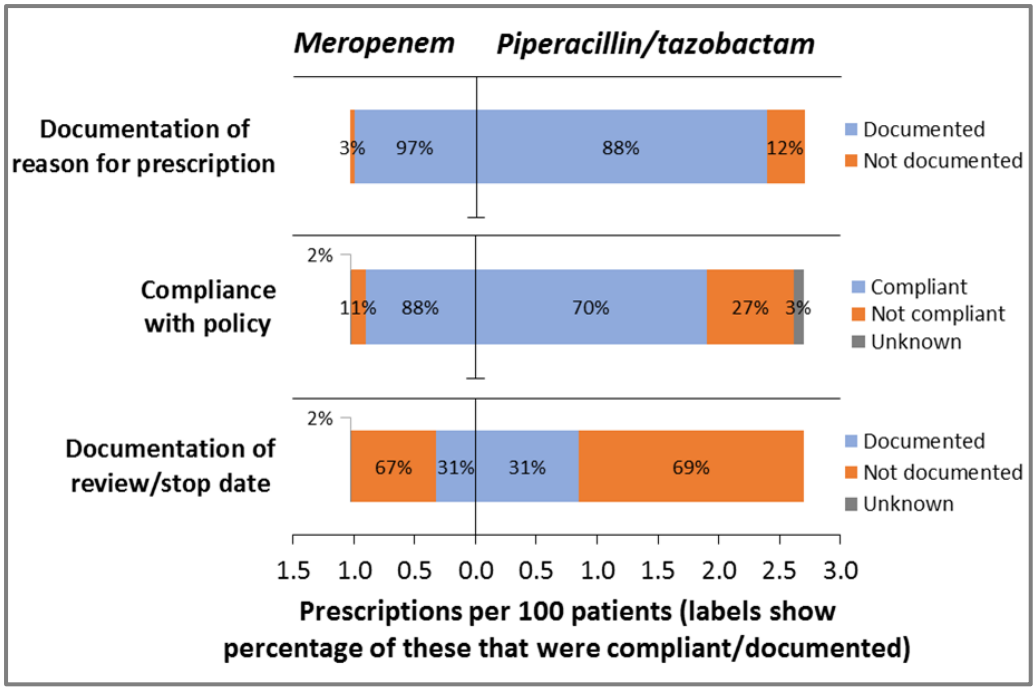


Figure 3. PPS data for quality measures of meropenem and piperacillin/tazobactam use



481

482

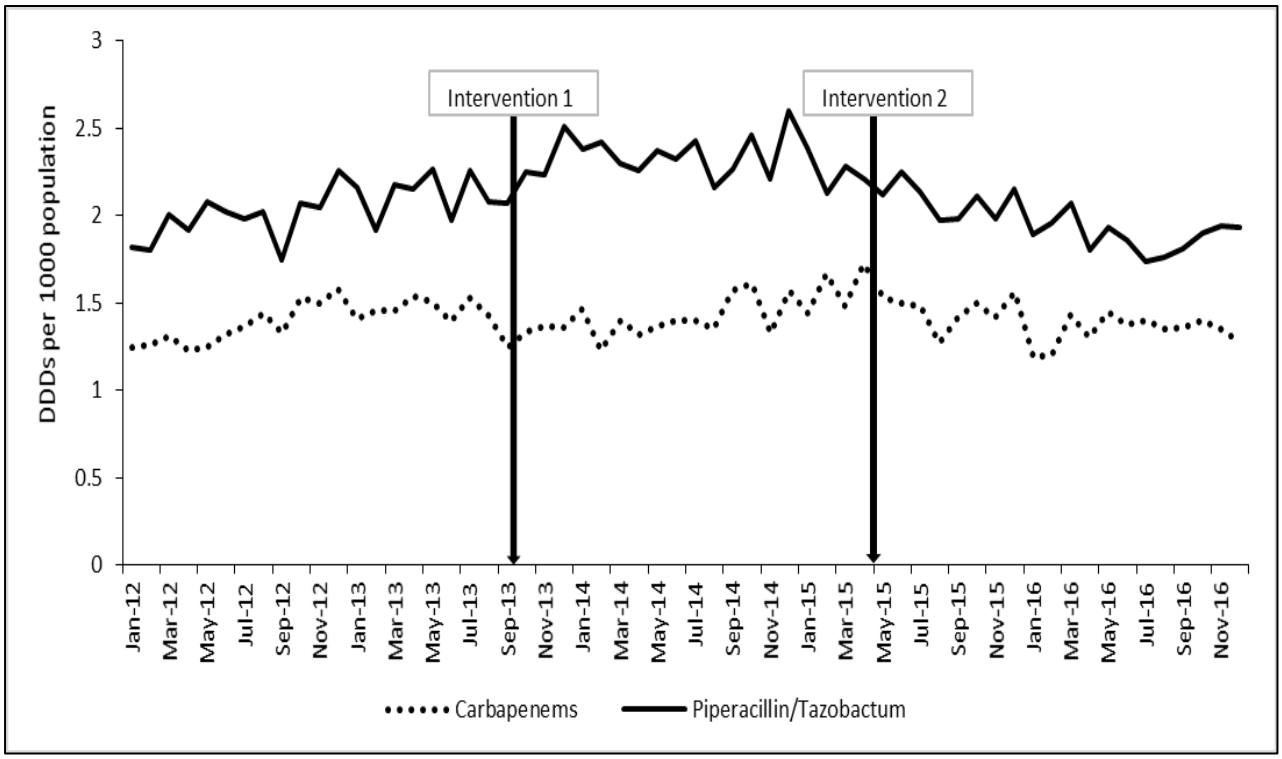
483

484

485 Figure 4. NHS Scotland: Carbapenem and Piperacillin-tazobactam use (defined daily doses) from Jan

486 2012 to March 2017

487



488

489 Intervention One: SAPG guidance on multi-drug resistant gram-negative bacteria (October 2013)

490 Intervention Two: Quality Improvement (AMT Survey (May 2015), bespoke point prevalence survey

491 (October 2015), reports shared with boards (January 2016) and AMT event (March 2016))

492 Table 1. Thematic analysis of clinician interviews about meropenem and carbapenem sparing agents

493 (CSAs) (n-21)

Topic	Themes
Initiation phase	Factors influencing prescribing of meropenem and CSAs: • Local guidelines and policies • Prescribers seeking advice or laboratory results • Patient-related factors • Carbapenem-sparing agent prescribing levers
Continuation phase	Factors influencing review of meropenem and CSA prescriptions: • Formal review policy and guidance • Duration documentation • De-escalation guide • Microbiology evidence and reports
Areas for improvement	Factors to target identified by clinicians: • Better communication with specialists and within clinical teams • Review prescribing practice in high usage wards • Piperacillin/tazobactam overuse • Audit and feedback to prescribers on their use

494

495 Figure 1. NHS board responses to survey questions on meropenem and piperacillin/tazobactam use

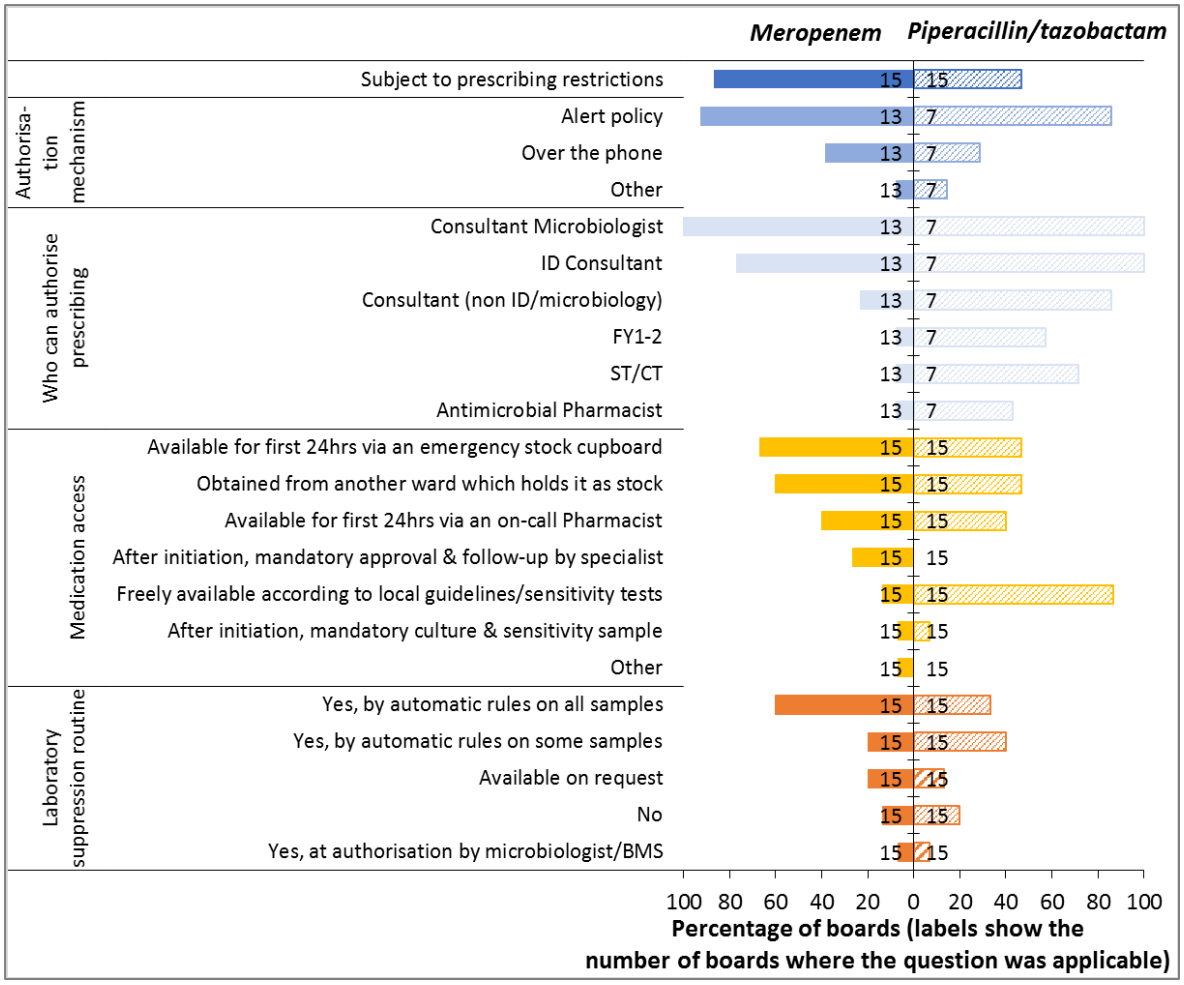


Figure 2. Summary of data from Point Prevalence Survey of meropenem and piperacillin/tazobactam use.

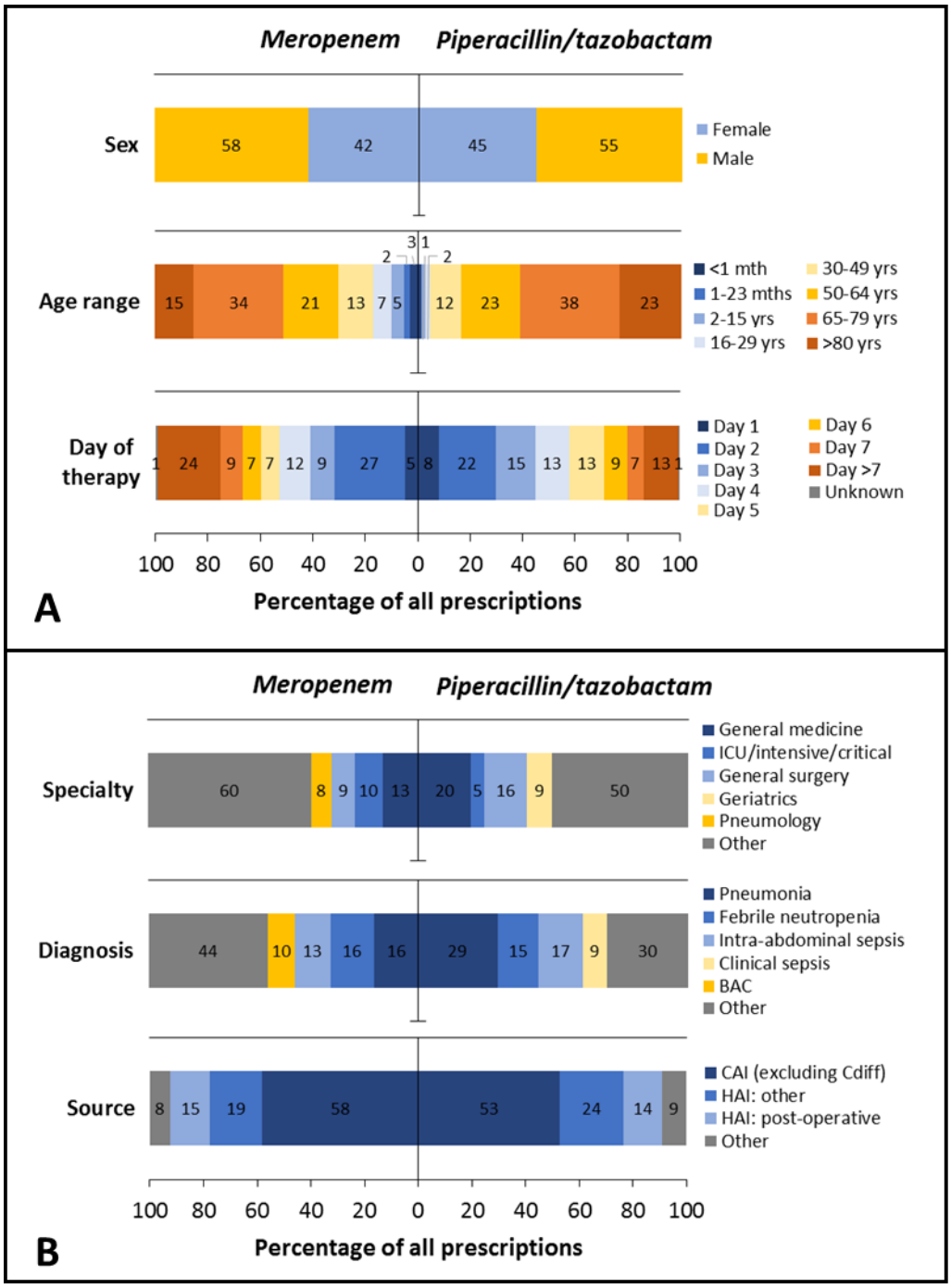
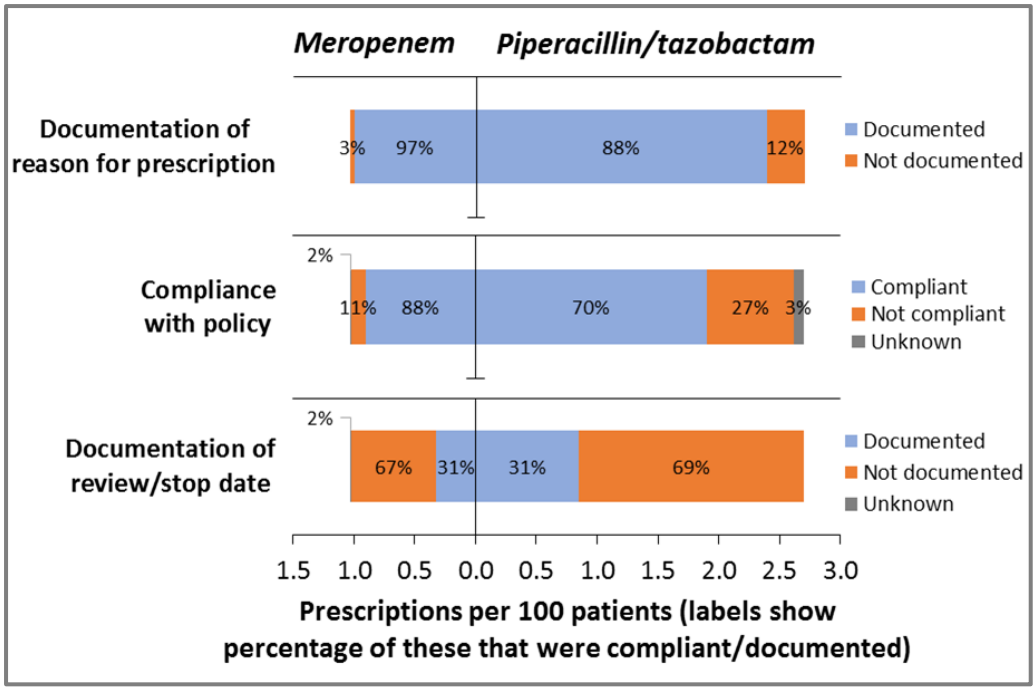


Figure 3. PPS data for quality measures of meropenem and piperacillin/tazobactam use



515

516

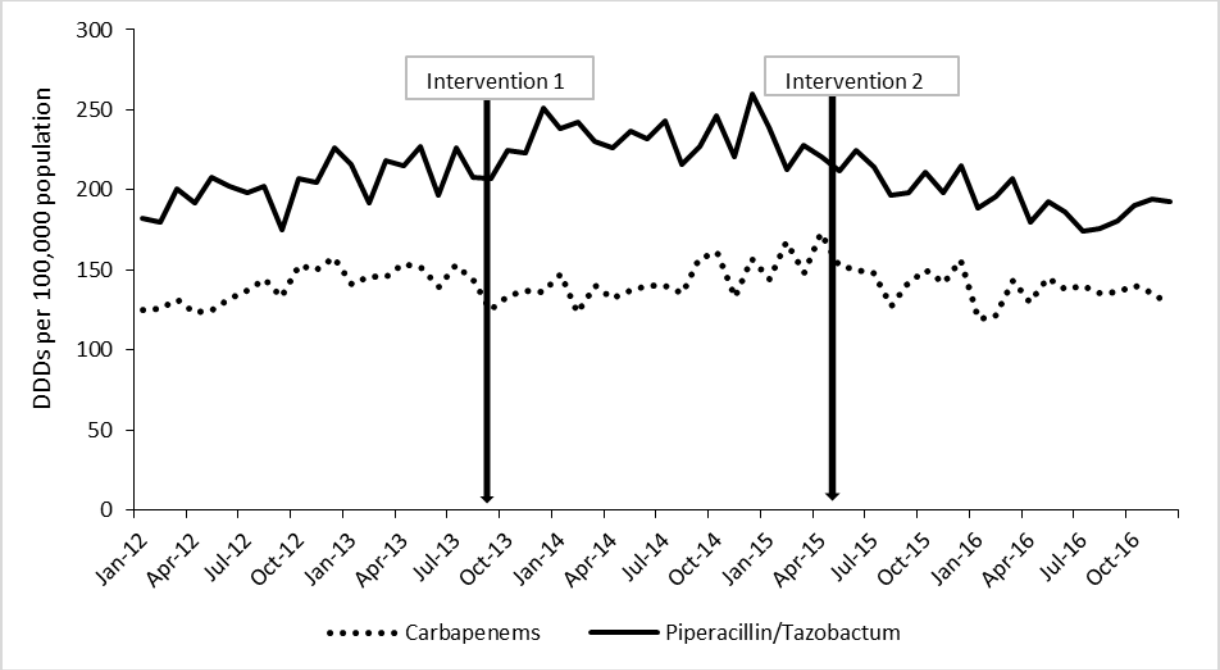
517

518

519 Figure 4. NHS Scotland: Carbapenem and Piperacillin-tazobactam use (defined daily doses) from Jan

520 2012 to December 2016

521



522

523 Intervention One: SAPG guidance on multi-drug resistant gram-negative bacteria (October 2013)

524 Intervention Two: Quality Improvement (AMT Survey (May 2015), bespoke point prevalence survey

525 (October 2015), reports shared with boards (January 2016) and AMT event (March 2016))

526 Table 1. Thematic analysis of clinician interviews about meropenem and carbapenem sparing agents

527 (CSAs) (n-21)

Topic	Themes
Initiation phase	Factors influencing prescribing of meropenem and CSAs: • Local guidelines and policies • Prescribers seeking advice or laboratory results • Patient-related factors • Carbapenem-sparing agent prescribing levers
Continuation phase	Factors influencing review of meropenem and CSA prescriptions: • Formal review policy and guidance • Duration documentation • De-escalation guide • Microbiology evidence and reports
Areas for improvement	Factors to target identified by clinicians: • Better communication with specialists and within clinical teams • Review prescribing practice in high usage wards • Piperacillin/tazobactam overuse • Audit and feedback to prescribers on their use

528

529