4 *Tackling antimicrobial resistance in the hospital sector*

RASMUS LEISTNER, INGE GYSSENS

Introduction

Antibiotic use is a major driving force behind antimicrobial resistance (AMR). Inappropriate use and poor infection prevention and control (IPC) are fuelling the increased resistance. The importance of AMR within the hospital sector is considerable because of the high volumes of antimicrobial substances used by relatively small populations.

Surveillance programmes are a crucial component of antibiotic stewardship for benchmarking antibiotic consumption and detecting possible outbreaks of resistance. Notification of outbreaks with resistant bacteria can also improve the effectiveness of EU early warning systems. In Europe, the European Centre for Disease Prevention and Control (ECDC) runs two surveillance systems, one on antibiotic consumption (European Surveillance of Antimicrobial Consumption Network (ESAC-Net)) and one on antibiotic resistance (European Antimicrobial Resistance Surveillance Network (EARS-Net)). EARS-Net is the largest publicly funded AMR surveillance system in Europe and was established in 1998 by the European Commission (Gagliotti et al., 2011). Its data are based on routine laboratory data from many participating European countries (de Kraker & van de Sande-Bruinsma, 2007). The laboratories report the results from microbiological diagnostics and susceptibility testing of blood cultures and cerebrospinal fluid. Because the data are collected and analysed continuously over time, it can reveal potential trends in AMR across Europe. However, this microbiological surveillance is limited as it lacks epidemiological, clinical, or outcome data (Tacconelli et al., 2017).

Reliable estimates of excess morbidity, mortality, and the costs of AMR must be put into perspective against other causes. Apart from malaria, tuberculosis, gonorrhoea, and HIV, most of the disease burden attributable to AMR is caused by health care-associated infections (HAIs) due to opportunistic bacteria. In the Burden of Resistance and Disease in European Nations (BURDEN) project, de Kraker et al. estimated the impact on AMR of the two most frequent causes of bloodstream

https://doi.org/10.1017/9781108864121.005 Published online by Cambridge University Press

infections (BSIs) worldwide – *Staphylococcus aureus* and *Escherichia coli* – in 13 European hospitals (de Kraker et al., 2011a; de Kraker et al., 2011b). These data were extrapolated to 31 countries that participated in the European Antibiotic Resistance Surveillance System (EARSS). It was estimated that in 2007 over 8 000 deaths and €62 million in excess costs were associated with BSIs caused by methicillin-resistant *S. aureus* (MRSA) and *E. coli* resistant to third-generation cephalosporins (G3REC) in the European Region. For G3REC and MRSA BSIs in the high-income Organisation for Economic Co-operation and Development (OECD) countries, the estimated mortality of 1.5 per 100 000 is comparable with rates for HIV/AIDS (1.5 per 100 000) or tuberculosis (1.0 per 100 000). The authors conclude that mortality attributed to AMR is high, but not excessive when compared to other conditions. The prolongation of hospital stays imposes a considerable burden on health care systems (de Kraker et al., 2011c).

The stakeholders of relevance to AMR in hospitals are the prescribing doctors, pharmacists, nurses, infection control practitioners, managers and members of the hospital board. Leadership support is critical to the success of antibiotic stewardship programmes (Fridkin & Srinivasan, 2014). All stakeholders need to make efforts to implement appropriate antibiotic management and infection prevention to curb AMR and its spread.

This chapter reviews the two main pillars of good practice for mitigation and control of AMR: infection prevention and control and antibiotic stewardship (ABS). To illustrate certain concepts, the analysis focuses on OECD countries as case examples.

Infection control

Approximately 6% of European patients develop a HAI (ECDC, 2013). Lower respiratory tract infections, urinary tract infections (UTIs), surgical site infections, and bloodstream infections account for 75% of HAIs. A number of pathogens have tested positive for resistance to clinically important antibiotic substances. For example, 41% of *S. aureus* are methicillin-resistant and 33% of Enterobacteriaceae are third-generation cephalosporin-resistant. Medically effective measures, which are also cost-effective, are necessary to reduce the number of HAIs and prevent resistance from spreading within hospitals.

Infection prevention and control should be organized centrally at the hospital level using a dedicated team of nurses and physicians, microbiological support, and data analysis support (Zingg et al., 2015). National guidelines, along with continuous education and training, provide up to date standards of care for prevention and control of HAIs throughout hospitals. Both interventions have been associated with lower HAI infection rates following implementation. More positive attitudes are generally found among nurses in paediatric intensive-care units (ICUs) than among physicians in adult ICUs. The uptake of such measures by health care professionals is most successful if they are part of a multimodal intervention, simulation-based training, or hands-on training workshops.

Infection prevention measures can be horizontal or vertical. Horizontal measures are general measures affecting an entire institution; for example, the implementation of a multimodal approach to improved hand hygiene (Pittet et al., 2000). Vertical measures tackle specific problems, such as a policy to reduce central venous catheter-associated bloodstream infections (Huang et al., 2013). In addition to both horizontal and vertical measures, it has been further shown that participation in a prospective surveillance system, regular feedback, and networking can lead to an impressive decline in HAI rates (Zingg et al., 2015). This success has been seen with the German KISS, the Dutch PREZIES, and the French ReAct surveillance systems.

Infection control measures

Several measures have been used to reduce the prevalence of HAIs and antibiotic-resistant bacteria (ARBs) in hospitals:

- *Standard and contact precautions*: Standard precautions are applied in hospitals in order to prevent basic infection. This includes hand hygiene policies and the use of personal protective equipment. Contact precautions are used in addition to standard precautions, comprising measures aimed at the discontinuation of pathogen-specific transmission pathways. These measures can include gowning, gloving, wearing a mask, and using patient-dedicated non-critical care equipment (e.g. stethoscopes) (Tacconelli et al., 2014).
- *Isolation or single-room care*: If a patient is infected or colonized with the targeted pathogen, the patient can be transferred to a single room or into a cohort isolation together with patients colonized by the same pathogen. An alert code for patients previously colonized with ARB following single-room isolation has proven to be an effective strategy in preventing further spread of ARBs. This pre-emptive isolation remains active until the current colonization status of the patient has been verified. However, in the context of increasing

colonization rates, there is an ongoing discussion on whether or not contact precautions are both effective and cost-effective, especially concerning Gram-negative bacteria (Tschudin-Sutter et al., 2017).

- *Active screening cultures*: Since many ARBs spread within the community, the number of patients with undetected colonization status can be highly dependent on the pathogen, setting, and country (Harris et al., 2004). In order to prevent hospital-wide spread of ARBs, active screening for colonization followed by strict contact precautions are recommended (Weintrob et al., 2010). For Gram-negative pathogens, the combination of screening the perirectal and groin areas results in the detection of 95% of carriers. For MRSA, the combination of screening throat and groin areas detects approximately 90% of carriers (Marshall & Spelman, 2007). This evidence indicates the need for active screening procedures as a prevention strategy since the majority of patients that enter the hospital test positive for ARBs.
- *Environmental cleaning (EC)*: Cleaning of particular surfaces near infected or colonized patients has been shown to be fundamental in HAI prevention and control (Barker, Alagoz & Safdar, 2017; Dancer, 2011). However, the pathogens on dry hospital surfaces vary in their resilience to EC. Strong evidence for EC effectiveness has been demonstrated by the control of outbreaks of *Acinetobacter baumannii* (Tankovic et al., 1994). Other examples of EC strategies have been used for *Pseudomonas aeruginosa*, which is spread via various pathways but most typically originates in biofilms in sinks (Salm et al., 2016). However, there is minimal evidence proving the effectiveness of EC in preventing HAIs in an endemic setting. EC is primarily used in a bundled approach and it is therefore difficult to assess its effectiveness as a single measure (Tacconelli et al., 2014).
- *Universal decolonization*: This strategy is used for reducing the rates of HAIs. It has shown to be successful in preventing bloodstream infections, such as extended spectrum beta-lactamase-positive Enterobacteriaceae (Huang et al., 2013). In this approach, all patients, regardless of their colonization status, receive a daily chlorhexidine bath and mupirocin nasal ointment. Apart from this, there are no other promising regimens for long-term eradication of Gram-negative gut pathogens (Tacconelli et al., 2014).

Cost–effectiveness of infection control measures to prevent HAIs

A 2007 study evaluated the complex relationship between the rate of HAIs and the cost–effectiveness of preventive measures (Halton & Graves, 2007). The study model presupposed the effectiveness of the prevention measure under evaluation. The findings demonstrated that infections due to ARBs led to a prolonged length of hospital stay, associated with increased costs for additional diagnostics, therapeutic interventions, and the additional number of hospital bed days. These effects derive from both patient complications and blocking of beds to prevent further patient contact and infection. These costs have a greater impact on hospitals that operate on a diagnosis-related group (DRG)-based system since prospective remuneration on admission is not typically covered by insurance companies. In order to assess the cost–effectiveness of a prevention measure, the excess costs of the HAI under consideration and the necessary investment to prevent the infection need to be known (Figure 4.1).

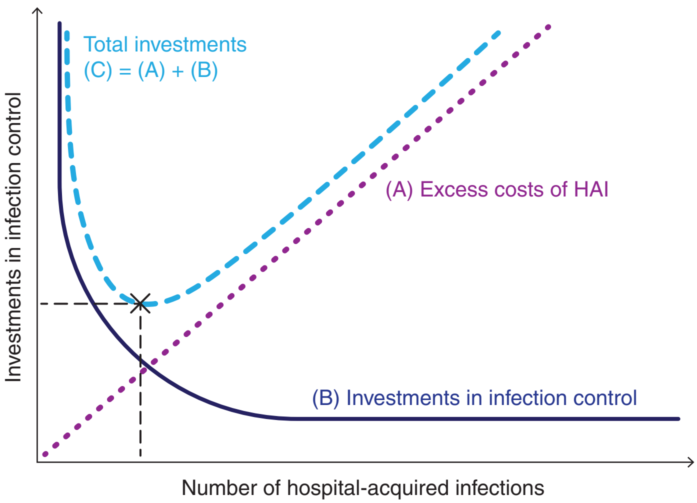

Figure 4.1 Relationship between the number of hospital-acquired infections and investments in infection control

Notes: HAI: hospital-acquired infection.

Line A (dotted) represents the costs of hospital infections, which is also the savings that would result from prevention. Line B (solid line) summarizes the relationship between the cost and the effectiveness of infection control strategies. Line C (dashes) is the sum of lines A and B for every incidence rate of hospital infections, representing the total cost of infection control strategies for HAIs. The point "X" represents the incidence of infection that minimizes total cost, which indicates a rational objective for decision-makers.

Source: Graves, Plowman & Roberts, 2001.

Robust data on the excess costs associated with HAIs are scarce. Currently, there is one meta-analysis that has estimated the excess costs of HAIs in the USA between 1986 and 2013 (Zimlichman et al., 2013). This study found that the additional costs range from approximately $900 (catheter-related UTI) to $46 000 (central line-associated bloodstream infection due to MRSA) (Table 4.1). These data should be interpreted cautiously as it represents the costs in only one national health care system. However, since most OECD countries use DRG-based payment systems, and in the absence of more reliable data, these figures can serve as orientation (OECD, 2014).

The most expensive aspects of a DRG-based hospital payment system are blocked beds and prolonged stays due to complications from HAIs. Beds are blocked in a multi-bed room in order to isolate an infected patient, leading to the non-availability of the remaining beds and reduced occupancy rates. Together, both infection control strategies account for approximately 80% of excess costs related to AMR (Conterno et al., 2007; Hübner et al., 2014). Although HAIs are commonly associated with additional diagnostics and treatment, the main driver of excess financial costs is the daily cost of hospital beds (Shepard et al., 2013).

Table 4.1 *Costs and length of stay in days by health care-associated infection type*

Health care-associated infection type	Cost ($)	LOS (days)
Surgical site infections	20 785	11.2
MRSA	42 300	23.0
Central line-associated bloodstream infections	45 814	6.9–10.4
MRSA	58 614	15.7
Catheter-associated UTIs	896	not relevant
Ventilator-associated pneumonia	40 144	8.4–13.1
Clostridium difficile infections	11 285	3.3

Notes: Data are reported as means.

LOS: Length of stay; UTI: urinary tract infection.

Source: Zimlichman et al., 2013.

https://doi.org/10.1017/9781108864121.005 Published online by Cambridge University Press

Interventions to prevent cross transmission

Similar to other bacteria, ARBs are transmitted within the hospital predominantly via patient contact with the hands of their caregivers (Longtin et al., 2011; Pittet et al., 2000; Pittet et al., 2006; Tacconelli et al., 2014). Patients who are infected or colonized with ARBs carry billions of colony-forming units per millilitre of stool or sputum. Hand hygiene involves cleaning hands with an alcohol-based hand rub to prevent the spread of bacteria. Health care workers who do not rigorously do this can carry hundreds of thousands of colony-forming units on their hands, which can then be transmitted to other patients. In the case of ARBs, this leaves the affected patients prone to diminished treatment options if exogenous infection occurs (Sax et al., 2007). Although this mode of pathogenesis is well-known and accepted in the medical world, compliance with hand hygiene policies by health care workers in hospitals is often as low as 40% (Longtin et al., 2011). In order to facilitate the promotion of good hand hygiene in hospitals, the WHO developed an educational tool consisting of five indications of when hands should be disinfected: before patient contact, before an aseptic task, after exposure to bodily fluids, after patient contact, and after contact with patient surroundings (Sax et al., 2007). However, to improve compliance, multimodal strategies or intervention bundles should be used as they are found to be more successful (Damschroder et al., 2009). Most importantly, a positive organizational culture is connected to low HAI rates and stabilizing high levels of hand hygiene compliance. Although difficult to assess, the success of this type of culture seems to be associated with the existence of role models who engage in hand hygiene and infection prevention.

From the late 1980s to early 2000s, health care systems in many industrialized countries have been restructured with the goal of decreasing hospital costs and increasing productivity (Clements et al., 2008). This most often leads to shorter hospital stays per patient, enhanced patient throughput and hospital capacity. At the same time, AMR has been on the rise for MRSA, extended spectrum beta-lactamases (ESBL), vancomycin-resistant enterococci, and carbapenem-resistant Enterobacteriaceae (ECDC, 2010; Gagliotti et al., 2011; Gastmeier et al., 2014; de Kraker & van de Sande-Bruinsma, 2007). This has created a vicious cycle characterized by overcrowding and understaffing that

https://doi.org/10.1017/9781108864121.005 Published online by Cambridge University Press

works against high levels of hand hygiene compliance. This eventually led to increased HAI rates, hospital costs, and more cost pressure (Clements et al., 2008). Although many countries have acknowledged this as a problematic situation, few have taken action or initiated measures to relieve the pressure (Kaier, Mutters & Frank, 2012).

Surveillance systems of HAIs

In many industrialized countries, HAIs are benchmarked to allow for comparison across different hospitals (Haustein et al., 2011; Tacconelli et al., 2017). This has the potential to identify best practices, improve standards of care, and stabilize the performance of the health services offered. A useful comparison of outcome indicators requires consistent definitions, surveillance methods, and standardized rates. These rates must also be risk-adjusted for differences across the patient population and types of medical procedures. In Europe, there are several national surveillance systems for HAIs and a centralized surveillance system for ARBs – EARS-Net. In 2011–2012 and in 2016–2017, the ECDC also carried out two Europe-wide point prevalence surveys (PPS) of HAIs and antimicrobial use in acute hospitals (ECDC, 2013; 2016).

Surveillance definitions for HAIs are somewhat complex and can lead to disagreement among the clinicians responsible; for example, with ventilator-associated pneumonia and surgical site infection. Surveillance systems should therefore be the responsibility of professionals trained in HAI surveillance (Gastmeier et al., 2006). Continuous surveillance systems that assess primarily for infection incidence are time-consuming and often cost-effective only for larger institutions. By contrast, measuring infection prevalence with cross-sectional surveys (e.g. PPS) is less resource-intensive (Haustein et al., 2011; Tacconelli et al., 2017).

However, this system is more applicable for assessing the overall burden of HAIs than for benchmarking between hospitals. The use of HAI indicators for benchmarking in the different national surveillance systems is well established, yet there are substantial differences with respect to the indicators, methods, and reporting techniques. An example of a successfully functioning national surveillance system is the German KISS system (Krankenhaus-Infektions-Surveillance-System). Based on the US national nosocomial infections surveillance system model, this voluntary and confidential system has been in operation since 1997 (Gastmeier et al., 2008). Currently, approximately two thirds of all

German hospitals participate in KISS (Schröder et al., 2015; Leistner et al., 2013). This system provides several small surveillance modules for various risk groups (e.g. ICU patients, surgical patients), ARBs, and *C. difficile*, and the use of an alcohol-based hand rub.

ECDC collects laboratory-based data for AMR using the European Antimicrobial Resistance Surveillance Network (EARS-Net). Although all existing national and international surveillance systems can provide comprehensive information on AMR and HAIs, the results are usually published years after the data are collected (Tacconelli et al., 2017). This diminishes their utility for clinical, institutional, and regulatory decision-making. Further, the delay may result in misalignment of targeted resources and research priorities since information will not be up to date at the time of policy development.

Measures for outbreak control

Outbreaks of HAIs pose major challenges for hospital management and the infection control department of an affected institution. Although outbreaks typically affect only one department or ward, they are often publicly perceived as a malfunction of the entire hospital. In order to control current and future outbreaks, such events should be rigorously investigated. Infection and microbiological diagnoses should be recorded and analysed continuously. This can act as an early warning system. Such systems can be based on microbiology data from the laboratory, surveillance data, or clinical data. The delay between a possible outbreak and its detection depends on the type of system used. In order to ensure cost–effectiveness of the system, it should be adapted to the individual hospital based on a risk assessment by an infection control or hospital epidemiology expert.

The results of the analysis should then be communicated to all affected players since this information presents an excellent training opportunity. In the case of an outbreak, an alert signal is provided by the surveillance system. The outbreak alert can result from clusters of:

- the same pathogen (e.g. ARBs in different microbiological specimens) (Salm et al., 2016);
- the same types of infection (e.g. central venous catheter-associated bloodstream infections due to different pathogens) (Price et al., 2002);

- a combination of both (e.g. surgical site infections with *Candida albicans*) (Pertowski et al., 1995).

An alert signal initiates outbreak investigation. This should be focused on epidemiological and microbiological data in order to identify the likelihood of an outbreak. The first evidence that can indicate a potential outbreak is the comparison of baseline and epidemic rates (Barker, Alagoz & Safdar, 2017). At this early stage, it is necessary to create a line list that aggregates relevant information on all potentially affected patients with epidemiological data. Microbiological sampling of pathogens from infection, environment, and patient colonization can then be used for further investigation (Lippmann et al., 2014). This should be conducted in a timely fashion since most microbiological laboratories dispose of their samples after 7 to 14 days. Some infection control departments store pathogens of interest in order to allow for retrospective analysis (Salm et al., 2016). These samples can then be investigated to verify their genetic relatedness using pulsed-field gel electrophoresis or whole genome sequencing (Kampmeier et al., 2017; Sax et al., 2015; Snitkin et al., 2012; Welinder-Olsson et al., 2004). The most cost-effective epidemiological approach is a case–control study, which has the potential to yield information that either reinforces suspected risk factors or leads to undiscovered connections between cases (Moolenaar et al., 2000; Salm et al., 2016).

Outbreak control measures should be directed at the pathogen, the suspected routes of transmission, and its epidemiology within the institution. An orientation on likely transmission pathways and possible control activities can be found in the Centers for Disease Control and Prevention's (CDC) *Guidelines for isolation precautions: preventing transmission of infectious agents in healthcare settings* (Siegel et al., 2007). At the outset of an outbreak, the pathogenesis is often unknown. Given this, control measures are often conducted using a broad, horizontal approach. Therefore, it is imperative for contact to be made with the key clinical players (e.g. physicians, nurses, and department chiefs) as well as to raise awareness in all affected departments (Moolenaar et al., 2000). All players should be informed of the outbreak's course to improve compliance with control measures and ensure that the outbreak serves as a learning opportunity for prevention of future outbreaks under similar conditions.

Antibiotic stewardship

ABS is defined within the goals of an antibiotic stewardship programme (ASP): to optimize clinical outcomes while minimizing unintended consequences of antibiotic use, including toxicity, the selection of opportunistic pathogens and the emergence of AMR (Dellit et al., 2007). ABS can be considered as the major tool to achieve responsible antibiotic use in hospitals. The Driving Reinvestment in Research and Development and Responsible Antibiotic Use (DRIVE-AB) project has defined responsible antibiotic use through a RAND-modified Delphi method, identifying 22 key elements (Monnier et al., 2017). Together with this definition, a set of 51 inpatient quality indicators and 12 inpatient quantity metrics was developed using a similar systematic and stepwise method combining evidence from literature and stakeholder opinion. A quality indicator reflects the degree to which antibiotic use is correct or appropriate. In contrast, a quantity metric reflects the volume or the costs of antibiotic use. The DRIVE-AB process led to multidisciplinary international consensus on generic quality indicators that can be used globally to assess the quality of antibiotic use in hospitals. The final set of 12 quantity metrics includes Defined Daily Dose (DDD) per 1 000 patient days and Days of Therapy per 1 000 patient days. It is recommended that antibiotic use should be preferably expressed in at least two metrics simultaneously (Stanić Benić et al., 2018). The inpatient quality indicators are very generic and, as with the metrics, should be refined in order to ensure applicability and measurability across different health care settings.

Taxonomy of ABS interventions

There have been several systematic reviews on interventions to change the prescribing behaviour of professionals in hospitals (Davey et al., 2005; 2013; 2017). Davey et al. performed a critical appraisal using the Cochrane Effective Practice and Organisation of Care Group (EPOC) taxonomy (Davey et al., 2017). They appraised all interventions relevant to improving antibiotic prescribing categorized as persuasive, restrictive, or structural. The EPOC definitions of the interventions and examples of the intervention components are given in Table 4.2.

https://doi.org/10.1017/9781108864121.005 Published online by Cambridge University Press

Table 4.2. *EPOC definitions of the interventions and intervention components*

Intervention function	Definition	Intervention components
Education	Increasing knowledge or understanding	Educational meetings; Dissemination of educational materials; Educational outreach
Persuasion	Using communication to induce positive or negative feelings or to stimulate action	Educational outreach by academic detailing or review and recommend change
Restriction	Using rules to reduce the opportunity to engage in the target behaviour (or increase the target behaviour by reducing the opportunity to engage in competing behaviours)	Restrictive
Environmental restructuring	Changing the physical context	Reminders (physical) such as posters, pocket-size or credit card-size summaries or on laboratory test reports; Structural (e.g. new laboratory tests or rapid reporting of results)
Enablement	Increasing means/reducing barriers to increase capability or opportunity	Audit and feedback; Decision support through computerized systems or through circumstantial reminders that were triggered by actions or events related to the targeted behaviour; Educational outreach by review and recommend change

Note: EPOC: Effective Practice and Organisation of Care Group.

Source: Davey et al., 2017.

https://doi.org/10.1017/9781108864121.005 Published online by Cambridge University Press

Evidence on effectiveness of ABS interventions

In their most recent Cochrane review, Davey et al. (2017) concluded that there is high-certainty evidence that interventions are effective in increasing compliance with antibiotic policy and reducing duration of antibiotic treatment. Lower use of antibiotics probably does not increase mortality but does reduce length of stay. Enablement (i.e. increasing means/reducing barriers to increase capability or opportunity) consistently increased the effect of interventions, including those with a restrictive component. Although feedback to health care professionals further increased the effect of an intervention, it was used in only a minority of enabling interventions. Interventions were successful in safely reducing unnecessary antibiotic use in hospitals despite the fact that the majority did not use the most effective behaviour change techniques (Davey et al., 2017).

Schuts et al. (2016a) performed a systematic review and meta-analysis of the evidence on selected ABS objectives, evaluating for the effect of 14 ABS objectives on four predefined patient outcomes: clinical outcome, adverse events, costs, and bacterial resistance rates. The ABS objectives consisted of a mixture of 11 consensus-derived quality indicators of antibiotic use and three additional objectives from the 2007 Infectious Diseases Society of America guidelines on ABS (van den Bosch et al., 2015; Dellit et al., 2007). They identified 145 unique studies with data on nine out of the 14 stewardship objectives. Objective characteristics are summarized in Table 4.3. Overall, the quality of evidence was generally low and heterogeneity between studies was mostly moderate to high. For the objectives empirical therapy according to guidelines, de-escalation of therapy, switch from intravenous to oral treatment, therapeutic drug monitoring, using a list of restricted antibiotics, and bedside consultation, the overall evidence showed significant benefits for one or more of the four outcomes. Guideline-adherent empirical therapy was associated with a 35% relative risk reduction of mortality (RRR) and de-escalation with a RRR of 56% (Schuts et al., 2016a). Evidence of effects was less clear for adjusting therapy according to renal function, discontinuing therapy based on lack of clinical or microbiological evidence of infection, and having a local antibiotic guide. Schuts et al. concluded that for several ABS objectives there is abundant, but low quality, evidence on clinical outcomes, adverse events, costs, and resistance rates in hospitals (Schuts et al., 2016a).

Table 4.3. *Antimicrobial stewardship objectives (145 studies), type of study design and reported outcomes*

Antimicrobial stewardship objective	Number of studies in qualitative synthesis	Type of study design	Outcome data
Empirical therapy according to guidelines	40	All Observational	Mortality Treatment failure LOS Costs
Blood cultures	0	N/A	N/A
Cultures from sites of infection	0	N/A	N/A
De-escalation of therapy[a]	25	1 RCT 24 Observational	Mortality LOS ICU LOS Costs
Adjustment of therapy to renal function	5	All Observational	Mortality ICU LOS Adverse effects Costs
Switch from IV to oral therapy	18	13 RCTs 5 Observational	Mortality Cure or resolution LOS Costs
Documented antibiotic plan	0	N/A	N/A
Therapeutic drug monitoring	16	9 Observational 7 RCTs	Mortality LOS Nephrotoxicity Costs
Discontinuation of antibiotic therapy if infection not confirmed	3	2 RCTs 1 Observational	Mortality ICU LOS Costs
Presence of a local antibiotic guide	1	1 Observational multicentre	Mortality

https://doi.org/10.1017/9781108864121.005 Published online by Cambridge University Press

Antimicrobial stewardship objective	**Number of studies in qualitative synthesis**	**Type of study design**	**Outcome data**
Local guide in agreement with national guidelines	0	N/A	N/A
List of restricted antibiotics	30	29 Observational 1 RCT	Mortality LOS ICU LOS Nosocomial infection rates Costs Resistance rates
Bedside consultation	7	7 Observational	Mortality LOS Costs
Assessment of patients' adherence	0	N/A	N/A

Notes: [a]From a broad-spectrum to narrower-spectrum antibiotic.

LOS: Length of stay; N/A: Not applicable; RCT: Randomized controlled trial; ICU: intensive care unit; IV: intravenous.

Source: Adapted from Schuts et al., 2016a.

Methodology of ABS interventional studies

This section provides an overview of the methodology used when testing for the effectiveness of antibiotic stewardship programmes. Studies have found overall positive effects but the methodology has not been clearly assessed for external validity or generalization to other populations.

In a narrative review, de Kraker et al. (2017) evaluated for the differences between various study designs in their ability to provide a framework for assessing the quality of evidence for ABS interventions. Relevant literature was identified using a database search of Cochrane and PubMed. The authors found that random time effects and bias can jeopardize the validity of causal inference in ABS research. The most important risks include simultaneously implemented strategies

https://doi.org/10.1017/9781108864121.005 Published online by Cambridge University Press

and regression to the mean. Inclusion of homogeneous intervention and control arms, through randomization of the intervention, can limit these risks. However, contamination, that is spill over from the intervention to the control arm, can play an important role for ABS. Therefore, it is recommended that randomization is conducted at the cluster rather than the individual-level. However, it can be challenging to identify enough representative clusters and implementation of a cluster-randomized control trial can be costly. Controlled interrupted time series design has a high validity as well, and is easier to implement, although time-varying confounding should be considered. To detect any unintended consequences, it is crucial to include multiple process, clinical outcome, microbiological and financial measures (de Kraker et al., 2017).

A recent study reviewed published systematic reviews retrieved from Medline to study the evidence base of antibiotic use recommendations and behavioural change interventions (Hulscher & Prins, 2017). It found that most current studies used designs prone to confounding by indication, where participants with less complex or less severe illness may be more likely to have received appropriate antibiotic treatment, which will confound the association between appropriate use and the outcomes tested. Much could be learnt from behavioural sciences. The literature demonstrated that the quality of evidence is low for the positive effects of appropriate antibiotic use in hospital patients. In addition, it found that all types of behavioural change intervention might work. Although effects were positive overall, there were large differences in improvement between studies that tested similar change interventions. Confirming findings elsewhere, the research showed a clear need for studies that use an appropriate study design, i.e. both randomized and controlled, to test for the effectiveness of appropriate antibiotic use in achieving meaningful outcomes (Davey et al., 2017; de Kraker et al., 2017).

ABS guidelines

With growing evidence on the benefit of particular prescription practices, national and international health agencies have issued and regularly updated guidance to address AMR by encouraging appropriate use of antibiotics. In 2014, the CDC recommended that all acute care hospitals in the United States implement ASPs (Fridkin & Srinivasan,

https://doi.org/10.1017/9781108864121.005 Published online by Cambridge University Press

2014). Importantly, the CDC recommends a commitment to stronger leadership to enable dedication of the necessary human, financial, and information technology resources to ASPs. In 2015, the WHO published its *Global action plan on antibiotic resistance* which urges all countries to optimize the use of antibiotic agents (World Health Organization, 2015). In 2016, the Infectious Diseases Society of America issued new antibiotic stewardship guidelines which focused on practical advice for implementing ASPs (Barlam et al., 2016). These replace former, outdated guidelines and focus on specific strategies that are thought to be more beneficial to ensure that the ASP will be effective and sustainable. They recommend that ASPs should tailor interventions based on local issues, resources, and expertise. To ensure this, the guidelines recommend that the ASP is led by physicians and pharmacists and rely on the expertise of infectious diseases specialists. Most recently, ECDC has issued Proposals for EU guidelines on the prudent use of antibiotics in humans in 2017 (European Commission, 2017). Many other EU Member States have issued national guidelines for antibiotic use and ASPs in response to EU-wide calls for action.

Some best ABS practices

National surveillance data on AMR show higher antibiotic use and higher resistance levels in the south and east of Europe compared to the north and west. The Netherlands is an example from the latter, with low consumption and AMR, and a long tradition of antibiotic policies in hospitals. By contrast, national data from Italy show a high antibiotic consumption (ESAC-Net). However, individual hospitals in Italy have started with ASPs focusing on local issues. Box 4.1 shows a selection of exemplary local good antibiotic stewardship practices.

Box 4.1 Two examples of local good antimicrobial stewardship practices

University hospital Modena, Italy

Italy is among the highest consumers of antibiotics and the highest antibiotic resistance rates have been reported (ECDC, 2017). The Clinic of Infectious Diseases, Azienda Ospedaliero-Universitaria, Policlinico di Modena started to expand its antibiotic stewardship

https://doi.org/10.1017/9781108864121.005 Published online by Cambridge University Press

Box 4.1 (cont.)

initiative in 2014. The multidisciplinary team reports to the antibiotic and infection prevention committee, which has a mandate from the Board of Directors. Bedini et al. (2016) describe the results of their infectious diseases (ID) consultations in a population of liver cirrhosis patients, with an in-hospital infection rate of more than 30%, mainly caused by Gram-negative microorganisms. Twice a week an ID specialist performed a face-to-face case by case audit with immediate feedback with the gastroenterologist, using (local) guidelines, available diagnostics and the expertise and experience of both physicians. A consensus-based agreement would be reached with the gastroenterologist. Antibiotic consumption and clinical outcome during the first year of the programme were compared with the previous year. The programme resulted in a decrease of antibiotic consumption from 110 to 78 DDD/100 patient days. The greatest impact was observed on carbapenems and quinolones, whose consumption fell by more than 50% without impacting length of stay or in-hospital mortality (Bedini et al., 2016).

National AMR strategy in the Netherlands

The Netherlands has been at the forefront of antibiotic stewardship for more than four decades. The Dutch national Working Party on Antibiotic Policy (SWAB) is funded by the government to conduct antimicrobial surveillance, monitor antibiotic use, and to develop guidelines. In 2006, SWAB developed an online national antimicrobial guide (SWAB-ID) for the prophylaxis and treatment of infectious diseases in hospitals. This concept of an online national antimicrobial guide with local, customizable versions is unique. Use of a local version of this national antimicrobial guide significantly increased both the comprehensiveness and guideline compliance of local antimicrobial policies, and the recommendations were often fed back to the national evidence-based guidelines (Schuts et al., 2016b).

Antibiotic stewardship teams (A-teams), recommended by the Dutch Health Care Inspectorate and the Minister of Health, have been established in every hospital as of 2014. Recent activities include implementing the local antibiotic guide and an observational

https://doi.org/10.1017/9781108864121.005 Published online by Cambridge University Press

Box 4.1 (cont.)

pilot study on A-team activities among five Dutch hospitals. The study was conducted to establish a national antibiotic stewardship registry. An assessment was made of the monitoring and documentation of 14 validated stewardship objectives by the A-teams. All A-teams monitored the performance of bedside consultations in *S. aureus* bacteraemia and the prescription of restricted antibiotics. Four fifths of the A-teams could report data on documentation and report on the use of restricted antibiotics. Lack of time and the absence of an electronic medical record system were the main barriers to documentation and reporting (Berrevoets et al., 2017).

Cost–effectiveness of interventions

Governments have limited financial resources. Interventions that are both effective and cost-saving are necessary to reduce the high cost burden of AMR on public health and health system functioning.

A study reviewed the literature on cost–effectiveness of ABS programmes in hospital settings of OECD countries up to June 2014 (Coulter et al., 2015). The type of ABS strategy and the clinical and cost outcomes were evaluated in 36 studies on adult patients. The main ABS strategy implemented was prospective audit with intervention and feedback, followed by the use of rapid diagnostic technology, e.g. rapid polymerase chain reaction (PCR)-based methods or matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF), for the treatment of bloodstream infections. All but one of the 36 studies reported that ABS resulted in a reduction in pharmacy expenditure. Among 27 studies measuring changes to health outcomes specifically, either no change was reported after the ASP or the additional benefits achieved from these outcomes were not quantified. Only two studies performed a full cost–effectiveness analysis (CEA) (Brown & Paladino, 2010; Scheetz et al., 2009). Both CEAs used a decision-tree model from the hospital perspective and did not evaluate societal costs. Both studies found the interventions to be cost-effective. The earlier study used a model comparing costs and outcomes of bacteraemic patients receiving standard treatment with or without an ASP team consultation (structural intervention). Effectiveness was estimated as quality-adjusted life-years (QALYs) over the lifetime of patients. Incremental cost–effectiveness ratios were calculated to estimate the cost per QALY gained. The later study found that the implementation of rapid testing resulted in improved outcomes for patients. They used data from the literature both from the EU and the USA to inform the model. Rapid PCR testing for MRSA reduced mortality rates while being less costly than empirical therapy in the EU and the USA, even when factoring in a wide range of MRSA prevalence rates and PCR test costs. ABS programmes frequently resulted in a reduction in pharmacy costs. However, there was a lack of consistency in the reported cost outcomes making it difficult to compare the results of the included interventions (Coulter et al., 2015).

The most recent study on the cost–effectiveness and cost–benefits of ASPs summarized the literature from 2000 to 2007 (Naylor et al., 2017). In addition to the CEAs discussed above, it included a CEA that used a Markov model for analysing a bundled ABS strategy (persuasive intervention) conducted in a hospital in Brazil (Okumara et al., 2016). Overall, it concluded that the cost–effectiveness evidence for ABS is severely limited and remains inadequate for investment decision-making. Robust health economics research is needed to enhance the generalizability and usability of cost–effectiveness results.

Conclusions

There are huge challenges in the implementation of infection control and antibiotic stewardship strategies. Increasing levels of antibiotic-resistant pathogens from HAIs indicate the urgent need for early warning systems based on real-time international surveillance. Due to various technological and political barriers, current surveillance systems for HAIs are operating separately on a national level or are laboratory-based with limited clinical and molecular biological data input. Mostly due to technological hurdles, there is a significant delay between data input, analysis, and the report. This diminishes the potential benefits from implementing surveillance programmes, such as monitoring of therapy guidelines, antibiotic formularies, antibiotic stewardship programmes, public health interventions and infection control policies. Following implementation, studies on excess costs of HAIs and ARB-related infections are needed in order to estimate the financial scope of hospital infection control measures and their cost–effectiveness. However, studies on this subject are scarce and often not representative of conditions in diverse settings. As health-care costs are related to the economic circumstances of the particular healthcare system, the comparability between countries is limited.

Any behavioural change intervention in ABS may work in a certain setting for a period of time. However, the evidence on the effectiveness of specific interventions is of rather low quality. The literature shows a clear need for the application of appropriate study designs in a randomized and controlled fashion in order to test the effectiveness of appropriate antibiotic use in achieving meaningful outcomes. The objective would be to identify a set of key interventions with proven effectiveness with results that can be replicated in other settings. Most current studies have used designs prone to confounding by indication. There are many good examples of local practices that could be scaled up to the national level, using insights from the behavioural sciences to select interventions that might work best in a chosen setting. However, a major cause of antibiotic misuse is the insufficient knowledge of prescribing that is rooted in the education system. A suggested approach is to advance the start of education on principles of prudent prescribing towards the undergraduate phase of the medical, pharmacist and nursing curriculum (Pulcini & Gyssens, 2013). It is expected that optimizing the behaviour of professionals requires less effort when attitudes towards prescribing have not yet been shaped or established.

Recommendations

The following recommendations can be made:

- Regarding AMR and HAI surveillance, intensified international collaboration is needed in order to overcome existing barriers to high-quality surveillance.
- Robust data from national surveys are needed to provide useful and comprehensive information to decision-makers in local hospitals.
- To increase the success of educational ABS interventions, education of all professionals should start at the undergraduate level and include medical students, pharmacists and nurses.
- Other stakeholders should be involved to promote responsible antibiotic use in hospitals.

Future directions for research

Although there is a large amount of published literature on interventions to curb AMR in hospitals, some of the relevant outcomes relating to patient health such as patient safety or economics have been neglected. In addition, intervention studies should have more robust designs.

Future research should focus on:

- Targeting treatment and assessing other measures of patient safety, assessing different stewardship interventions, and exploring the barriers and facilitators to implementation. More research is required on unintended consequences of restrictive interventions.
- Robust study designs such as cluster-randomized controlled trials, or interrupted time series including a control arm. A detailed process evaluation should be provided to adequately inform implementation of successful ABS strategies.
- High-quality health economics research on ABS with an appropriate health-economic methodological choice to enhance the generalizability and applicability of cost–effectiveness results.

References

Baker AW, Lewis SS, Alexander BD et al. (2017). Two-phase hospital associated outbreak of Mycobacterium abscessus: investigation and mitigation. Clin Infect Dis. 64(7):902–911.

Barker AK, Alagoz O, Safdar N (2017). Interventions to reduce the incidence of hospital-onset Clostridium difficile infection: An agent-based modeling approach to evaluate clinical effectiveness in adult acute care hospitals. Clin Infect Dis. 66(8):1192–1203.

Barlam TF, Cosgrove SE, Abbo LM et al. (2016). Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 62(10):e51–77.

Bedini A, De Maria N, Del Buono M et al. (2016). Antimicrobial stewardship in a Gastroenterology Department: Impact on antimicrobial consumption, antimicrobial resistance and clinical outcome. Dig Liver Dis. 48(10):1142–1147.

Berrevoets MA, Ten Oever J, Sprong T et al. (2017). Monitoring, documenting and reporting the quality of antibiotic use in the Netherlands: a pilot study to establish a national antimicrobial stewardship registry. BMC Infect Dis. 17(1):565.

https://doi.org/10.1017/9781108864121.005 Published online by Cambridge University Press

Brown J, Paladino JA (2010). Impact of rapid methicillin-resistant Staphylococcus aureus polymerase chain reaction testing on mortality and cost effectiveness in hospitalized patients with bacteraemia: a decision model. Pharmacoeconom. 28(7):567–575.

Clements A, Halton K, Graves N et al. (2008). Overcrowding and understaffing in modern health-care systems: key determinants in methicillin-resistant Staphylococcus aureus transmission. Lancet Infect Dis. 8(7):427–434.

Conterno LO, Shymanski J, Ramotar K et al. (2007). Impact and cost of infection control measures to reduce nosocomial transmission of extended-spectrum β-lactamase-producing organisms in a nonoutbreak setting. J Hosp Infect. 65(4):354–360.

Coulter S, Merollini K, Roberts JA et al. (2015). The need for costeffectiveness analyses of antimicrobial stewardship programmes: A structured review. Int J Antimicrob Agents. 46(2):140–149.

Damschroder LJ, Banaszak-Holl J, Kowalski CP et al. (2009). The role of the champion in infection prevention: results from a multisite qualitative study. Qual Saf Health Care. 18(6):434–440.

Dancer SJ (2011). Hospital cleaning in the 21st century. Eur J Clin Microbiol Infect Dis. 30(12):1473–1481.

Davey P, Marwick CA, Scott CL et al. (2005). Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 4:CD003543.

Davey P, Brown E, Charani E et al. (2013). Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 4:CD003543.

Davey P, Brown E, Fenelon L et al. (2017). Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2:CD003543.

de Kraker M (2007). Trends in antimicrobial resistance in Europe: update of EARSS results. Euro Surveill. 12(3):E070315.3.

de Kraker ME, van de Sande-Bruinsma N (2007). Trends in antimicrobial resistance in Europe: update of EARSS results. Euro Surveill. 12(11):3156.

de Kraker ME, Wolkewitz M, Davey PG et al. (2011a). Burden of antibiotic resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to Escherichia coli resistant to third-generation cephalosporins. J Antimicrob Chemother. 66(2):398–407.

de Kraker ME, Wolkewitz M, Davey PG et al. (2011b). Clinical impact of antibiotic resistance in European hospitals: excess mortality and length of hospital stay related to methicillin-resistant Staphylococcus aureus bloodstream infections. Antimicrob Agents Chemother. 55(4):1598–1605.

de Kraker ME, Abbas M, Huttner B et al. (2017). Good epidemiological practice: a narrative review of appropriate scientific methods to evaluate the impact of antimicrobial stewardship interventions. Clin Microbiol Infect. 23(11):819–825.

de Kraker ME, Davey PG, Grundmann H et al. (2011c). Mortality and hospital stay associated with resistant Staphylococcus aureus and Escherichia coli bacteremia: Estimating the burden of antibiotic resistance in Europe. PLoS Med. 8(10):e1001104.

Dellit TH, Owens RC, McGowan JE Jr et al. (2007). Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 44(2):159–177.

European Centre for Disease Prevention and Control (ECDC) (2010). Antibiotic resistance 2010: global attention on carbapenemase-producing bacteria. Stockholm: European Centre for Disease Prevention and Control. (http://www.eurosurveillance.org/docserver/fulltext/ eurosurveillance/15/46/art19719-en.pdf?expires=1511794526&id=id&accname=guest&checksum=797316D1C4E88391081819C8A61E9267, accessed 06 September 2018).

European Centre for Disease Prevention and Control (ECDC) (2013). Point prevalence survey of healthcare-associated infections and antibiotic use in European acute care hospitals, 2011–2012. Stockholm: European Centre for Disease Prevention and Control. (https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/ healthcare-associated-infections-antimicrobial-use-PPS.pdf, accessed 06 September 2018).

European Centre for Disease Prevention and Control (ECDC) (2016). Technical Document: Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals Protocol version 5.3 2016–2017. Stockholm: European Centre for Disease Prevention and Control. (https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/PPS-HAI-antimicrobial-use-EU-acute-care-hospitals-V5-3.pdf, accessed 06 September 2018).

European Centre for Disease Prevention and Control (ECDC) (2017). Antimicrobial resistance surveillance in Europe 2016. Stockholm: European Centre for Disease Prevention and Control. (https://ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillanceeurope-2016, accessed 06 September 2018).

European Commission (2017). EU Guidelines for prudent use of antimicrobials in human health. Brussels: European Commission. (https://ec.europa.eu/

health/amr/sites/amr/files/amr_guidelines_prudent_use_en.pdf, accessed 06 September 2018).

Fridkin SK, Srinivasan A (2014). Implementing a strategy for monitoring inpatient antimicrobial use among hospitals in the United States. Clin Infect Dis. 58(3):401–406.

Gagliotti C, Balode A, Baquero F et al. (2011). Escherichia coli and Staphylococcus aureus: bad news and good news from the European Antibiotic Resistance Surveillance Network (EARS-Net, formerly EARSS), 2002 to 2009. Euro Surveill. 16(11):19819.

Gastmeier P, Geffers C, Brandt C et al. (2006). Effectiveness of a nationwide nosocomial infection surveillance system for reducing nosocomial infections. J Hosp Infect. 64(1):16–22.

Gastmeier P, Sohr D, Schwab F et al. (2008). Ten years of KISS: the most important requirements for success. J Hosp Infect. 70:11–16.

Gastmeier P, Schröder C, Behnke M et al. (2014). Dramatic increase in vancomycin-resistant enterococci in Germany. J Antimicrob Chemother. 69(6):1660–1664.

Graves N, Plowman R, Roberts JA (2001). The epic project: developing national evidence-based guidelines for preventing healthcare associated infections. J Hosp Infect. 48(4):320–321.

Halton K, Graves N (2007). Economic evaluation and catheter-related bloodstream infections. Emerg Infect Dis. 13(6):815–823.

Harris AD, Nemoy L, Johnson JA et al. (2004). Co-carriage rates of vancomycin-resistant Enterococcus and extended-spectrum betalactamase-producing bacteria among a cohort of intensive care unit patients: implications for an active surveillance program. Infect Control Hosp Epidemiol. 25(2):105–108.

Haustein T, Gastmeier P, Holmes A et al. (2011). Use of benchmarking and public reporting for infection control in four high-income countries. Lancet Infect Dis. 11(6):471–481.

Huang SS, Septimus E, Kleinman K et al. (2013). Targeted versus universal decolonization to prevent ICU infection. N Engl J Med. 368(24):2255–2265.

Hübner C, Hübner NO, Hopert K et al. (2014). Analysis of MRSA-attributed costs of hospitalized patients in Germany. Eur J Clin Microbiol Infect Dis. 33(10):1817–1822.

Hulscher ME, Prins JM (2017). Antibiotic stewardship: does it work in hospital practice? A review of the evidence base. Clin Microbiol Infect. 23(11):799–805.

Kaier K, Mutters N, Frank U (2012). Bed occupancy rates and hospital-acquired infections – should beds be kept empty? Clin Microbiol Infect. 18(10):941–945.

https://doi.org/10.1017/9781108864121.005 Published online by Cambridge University Press

Kampmeier S, Knaack D, Kossow A et al. (2017). Weekly screening supports terminating nosocomial transmissions of vancomycin-resistant enterococci on an oncologic ward – a retrospective analysis. Antimicrob Resist Infect Contr. 16(1):48.

Leistner R, Piening B, Gastmeier P et al. (2013). Nosocomial infections in very low birthweight infants in Germany: current data from the National Surveillance System NEO-KISS. Klinische Padiatrie. 225(2):75–80.

Lippmann N, Lübbert C, Kaiser T et al. (2014). Clinical epidemiology of Klebsiella pneumoniae carbapenemases. Lancet Infect Dis. 14(4):271–272.

Longtin Y, Sax H, Allegranzi B et al. (2011). Videos in clinical medicine: Hand hygiene. N Engl J Med. 364(13):e24.

Marshall C, Spelman D (2007). Is throat screening necessary to detect methicillin-resistant Staphylococcus aureus colonization in patients upon admission to an intensive care unit? J Clin Microbiol. 45(11):3855.

Monnier AA, Eisenstein BI, Hulscher ME et al. (2018). Towards a global definition of responsible antibiotic use: results of an international multidisciplinary consensus procedure. J Antimicrob Chemother. 73(6):3–16.

Moolenaar RL, Crutcher JM, San Joaquin VH et al. (2000). A prolonged outbreak of Pseudomonas aeruginosa in a neonatal intensive care unit: did staff fingernails play a role in disease transmission? Infect Control Hosp Epidemiol. 21(2):80–85.

Naylor NR, Zhu N, Hulscher M et al. (2017). Is antibiotic stewardship cost-effective? A narrative review of the evidence. Clin Microbiol Infect. 23(11):806–811.

OECD (2014). Paying providers for healthcare. Paris: Organisation for Economic Co-operation and Development. (http://www.oecd.org/els/health-systems/paying-providers.htm, accessed 06 September 2018).

Okumara LM, Riveros BS, Gomes-da-Silva MM et al. (2016). A cost–effectiveness analysis of two different antibiotic stewardship programs. Brazil J Infect Dis. 20(3):255–261.

Pertowski CA, Baron RC, Lasker BA et al. (1995). Nosocomial outbreak of Candida albicans sternal wound infections following cardiac surgery traced to a scrub nurse. J Infect Dis. 172(3):817–822.

Pittet D, Hugonnet S, Harbarth S et al. (2000). Effectiveness of a hospitalwide programme to improve compliance with hand hygiene. Lancet. 356(9238):1307–1312.

Pittet D, Allegranzi B, Sax H et al. (2006). Evidence-based model for hand transmission during patient care and the role of improved practices. Lancet Infect Dis. 6(10):641–652.

Price CS, Hacek D, Noskin GA et al. (2002). An outbreak of bloodstream infections in an outpatient hemodialysis center. Infect Control Hosp Epidemiol. 23(12):725–729.

Pulcini C, Gyssens IC (2013). How to educate prescribers in antimicrobial stewardship practices. Virulence. 4(2):192–202.

Salm F, Deja M, Gastmeier P et al. (2016). Prolonged outbreak of clonal MDR Pseudomonas aeruginosa on an intensive care unit: contaminated sinks and contamination of ultra-filtrate bags as possible route of transmission? Antibiot Resist Infect Cont.5:53.

Sax H, Allegranzi B, Uçkay I et al. (2007). "My five moments for hand hygiene": a user-centred design approach to understand, train, monitor and report hand hygiene. J Hosp Infect. 67(1):9–21.

Sax H, Bloemberg G, Hasse B et al. (2015). Prolonged outbreak of Mycobacterium chimaera infection after open-chest heart surgery. Clin Infect Dis. 61(1):67–75.

Scheetz MH, Bolon MK, Postelnick M et al. (2009). Cost-effectiveness analysis of an antibiotic stewardship team on bloodstream infections: a probabilistic analysis. J Antimicrob Chemother. 63(4):816–825.

Schröder C, Schwab F, Behnke M et al. (2015). Epidemiology of healthcare associated infections in Germany: Nearly 20 years of surveillance. Int J Med Microbiol. 305(7):799–806.

Schuts EC, Hulscher MEJL, Mouton JW et al. (2016a). Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 16(7):847–856.

Schuts EC, van den Bosch CM, Gyssens IC et al. (2016b). Adoption of a national antimicrobial guide (SWAB-ID) in the Netherlands. Eur J Clin Pharmacol. 72(2):249–252.

Shepard J, Ward W, Milstone A et al. (2013). Financial impact of surgical site infections on hospitals: the hospital management perspective. JAMA Surgery. 148(10):907–914.

Siegel JD, Rhinehart E, Jackson M et al. (2007). Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings. Atlanta: US Centers for Disease Control and Prevention. (https://www.cdc.gov/infectioncontrol/pdf/guidelines/isolation-guidelines.pdf, accessed 06 September 2018).

Snitkin ES, Zelazny AM, Thomas PJ et al. (2012). Tracking a hospital outbreak of carbapenem-resistant Klebsiella pneumoniae with whole-genome sequencing. Sci Transl Med. 4(148):148ra116.

Stanić Benić M, Milanic R, Monnier AA et al. (2018). Metrics for quantifying antibiotic use in the hospital setting: results from a systematic review and international multidisciplinary consensus procedure. J Antimicrob Chemother. 73(6):50–58.

Tacconelli E, Cataldo MA, Dancer SJ et al. (2014). ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect. 20 Suppl(1):1–55.

Tacconelli E, Sifakis F, Harbarth S et al. (2017). Surveillance for control of antibiotic resistance. Lancet Infect Dis. 18(3):99–106.

Tankovic J, Legrand P, De Gatines G et al. (1994). Characterization of a hospital outbreak of imipenem-resistant Acinetobacter baumannii by phenotypic and genotypic typing methods. J Clin Microbiol. 32(11):2677–2681.

Tschudin-Sutter S, Lucet JC, Mutters NT et al. (2017). Contact precautions for preventing nosocomial transmission of extended-spectrum beta lactamase-producing Escherichia coli: A point/counterpoint review. Clin Infect Dis. 65(2):342–347.

van den Bosch CM, Geerlings SE, Natsch S et al. (2015). Quality indicators to measure appropriate antibiotic use in hospitalized adults. Clin Infect Dis. 60(2):281–291.

Weintrob AC, Roediger MP, Barber M et al. (2010). Natural history of colonization with gram-negative multidrug-resistant organisms among hospitalized patients. Infect Control Hosp Epidemiol. 31(4):330–337.

Welinder-Olsson C, Stenqvist K, Badenfors M et al. (2004). EHEC outbreak among staff at a children's hospital – use of PCR for verocytotoxin detection and PFGE for epidemiological investigation. Epidemiol Infect. 132(1):43–49.

World Health Organization (2015). Global action plan on antibiotic resistance. Geneva: World Health Organization. (http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf, accessed 06 September 2018).

Zimlichman E, Henderson D, Tamir O et al. (2013). Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med. 173(22):2039–2046.

Zingg W, Holmes A, Dettenkofer M et al. (2015). Hospital organisation, management, and structure for prevention of health-care-associated infection: a systematic review and expert consensus. Lancet Infect Dis. 15(2):212–224.