WHAT IS RESPONSIBLE ANTIBIOTIC USE?

A search for a multi-stakeholder definition, quality indicators, barriers and facilitators

Annelie A. Monnier

For reasons of consistency within this thesis, some terms have been standardised throughout the text. As a consequence, the text may differ in this respect from the articles that have been published.

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Contents

1

General introduction

Antibiotics: etymology and historical perspective

The term *antibiotic* comes from the combination of the greek prefix *anti* (against) and the greek word *biōtikos* (fit for life, lively).[1] *Antibiotic* is derived from the words *antibiosis* and *antibiotique*, two concepts coined by Paul Vuillemin in 1889, referring to the biological interaction between two or more microorganisms that is detrimental to at least one of them.[2] The noun *antibiotic* was introduced in 1942 by Selman Waksman to describe chemical substances produced by microorganisms that have antagonistic effects on the growth of other microorganisms.[3]

The birth of the *antibiotic era* is typically associated with the serendipitous discovery of *penicillin* by Alexander Fleming 1928[4] and its subsequent large scale production in the 1940's in the US to treat soldiers during World War II.[5] However, the discovery of one natural (pyocyanase) and two synthetic antibiotics (**Box 1**) (prontosil and salvarsan) preceded that of penicillin.[6] Interestingly, antibacterial properties of natural substances have been used –unknowingly– by ancient civilisations across the world including honey, mouldy bread and clay.[5, 7, 8] Many antibiotics are produced by micro-organisms living in soil and other natural environments.[9, 10]

Antibiotics: *one-of-a-kind* drugs

Antibiotics are a special type of drugs. Five features that together illustrate their singularity are addressed below:

- First, antibiotics are unique as they are the only drugs that do not primarily target the patient's biology. Instead, antibiotics impact the biology of microorganisms, both pathogens and commensals, carried by the patient. The pyramid of infectious diseases (**Figure 1**) illustrates the many interactions between the drug, the bacteria and the patient. Inherent to this interplay is the potential for the development of resistance by the organisms resulting in antibiotics' loss of effectiveness; also referred to as the antibiotic paradox.[11] In contrast, one of the oldest human drugs, aspirin -an analgesic targeting the biology of the patient - is as effective today as it was the first time it was used.[12]
- Second, their introduction in health care, alongside improvements in hygiene and the introduction of vaccines, turned previously deadly diseases (e.g., cholera, typhoid) into manageable health problems thereby decreasing infection-related morbidity and mortality.[13, 14]
- Third, they are the most commonly prescribed antimicrobial drugs (**Box 1**) and widely used across all medical disciplines of human medicine: from primary care to oncology, from dentistry to surgery. Furthermore, antibiotics play an important role in basic care across different populations from maternal and child health to

elderly care. As such they constitute the cornerstone of basic healthcare.[15] Even in the case of a pandemic, we would be extremely dependant on antibiotics to cure secondary infections (e.g., pneumonia).[16]

- Fourth, effective antibiotics constitute the hidden backbone of modern medicine. Indeed, antibiotics are key to the development and progress of medical techniques as well as the clinical success of most surgical procedures, cancer treatments, surgical implants and organ transplants.[17]
- Finally, antibiotic use is not limited to human medicine but extends to a wide range of non-human medical uses including, e.g., veterinary health, animal husbandry, aquaculture, horticulture, bee-keeping and antifouling paints.[18]

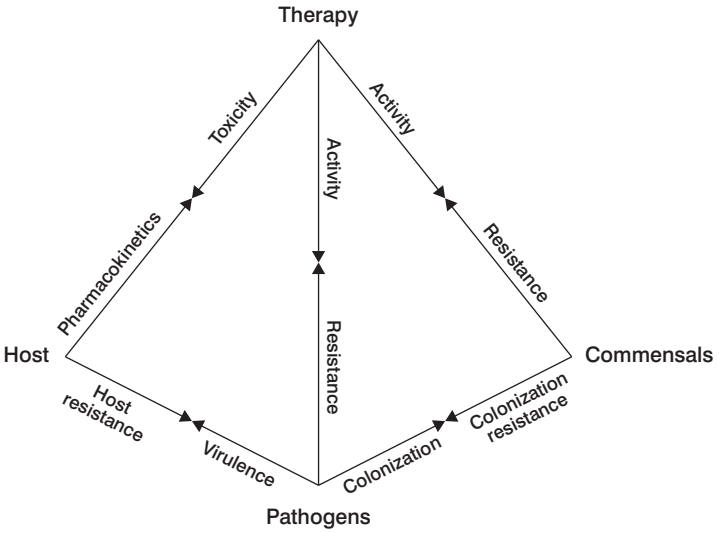

Figure 1: The pyramid of infectious diseases.[19] The arrows in the pyramid illustrate the multiple interactions between the patient, the drug, the pathogen(s) and the colonising microflora or microbiome.

Antibiotic resistance: a continuously evolving public health threat

The medical community witnessed the prompt development of penicillin-resistant bacterial strains (*S. aureus)* following the introduction of penicillin into clinical practice in the 1940s.[20] Awareness of the risk for the development of antibiotic resistance (ABR), i.e., the ability of a bacterium to resist the action of an antibiotic (**Box 1**), dates back to the cautionary statements of Fleming in 1945.[21] About two decades later, the

introduction of methicillin into clinical practice yielded methicillin resistant *S. aureus* (MRSA) strains resistant to different beta-lactam antibiotics including penicillins, cephalosporins, and carbapenems.[22] Resistance to nearly all antibiotic classes introduced in clinical use emerged over the following decades (e.g., cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, macrolides, glycopeptides).[23, 24] Bacteria are skilled in evolving and adjusting to their environment and have subsequently developed several resistance mechanisms to shield themselves from the harmful effects of antibiotics.[25] Some bacterial strains (mainly gram-negatives such as *Enterobacteriaceae)* successfully became resistant to several antibiotic classes; these organisms are classified as multi-resistant, extensively drug-resistant or pandrug-resistant.[26] The continuous development and spread of new resistance mechanisms by bacteria will eventually lead to truly untreatable infections thereby highlighting antibiotic resistance as a growing threat to global public health.[27, 28]

Antibiotic resistance: a societal problem

Consequences of antibiotic resistance (or more broadly antimicrobial resistance, **Box 1**) on patient care typically translate to higher morbidity and mortality rates, complications, prolonged hospitalisation and extended sick leave as well as higher treatment costs.[29] In Europe, the annual human burden of antibiotic resistance, recently estimated at about 33000 attributable deaths and about 875000 attributable disability-adjusted life-years (DALYs), is increasing.[30] More than 60 percent of the burden of ABR is due to healthcare-associated infections (HAIs) and the burden is highest among the very young (< 1 year) and the elderly (≥ 65 years).[30] Furthermore, about 40 percent of the burden of antibiotic resistance is caused by infections from bacteria resistant to the so called last-resort antibiotics (i.e., only to be tried after all other antibiotic options have failed to cure the infection) such as carbapenems and colistin.[30]

While the antibiotic resistance patterns in Europe display wide variations depending on the bacterial species, antibiotic class and geographical region; it represents a serious threat to public health with important societal ramifications.[31, 32] Although measuring the precise economic impact remains challenging, it is undeniable that ABR has serious financial consequences.[33-35] In Europe, healthcare costs and productivity losses associated with ABR are estimated at 1.5 billion euros per year.[15] Furthermore, the enormous flow of humans, animals and food products as a direct consequence of globalisation provides a plethora of chances for the spread of resistant bacteria beyond country and region borders.[17, 36] Consequently, today, bacteria and resistance genes travel faster and further than ever before, thereby affecting all individuals and populations across the globe.[32, 37, 38]

ABR is a complex phenomenon and despite individual stakeholders recognising the urgency of the problem, its complexity, perhaps aggravated by its invisibility for the general public, causes it to become no one's responsibility.[17] Scientists have previously described the need for the recognition of antibiotics as a non-renewable resource and a common good with paramount value to society.[17] The latter shift presents similarities with the way our society increasingly recognises the importance of preserving our environment and its natural resources. From all this, it can be concluded that ABR and its consequences affect many aspects of society.

Antibiotic use: an important driver of resistance

The development of antibiotic resistance is a natural phenomenon when bacteria are exposed to antibiotics following the Darwinian principle of *survival of the fittest*. Indeed, under the selective pressure of antibiotics, susceptible bacteria are killed or inhibited, while bacteria that are naturally resistant or that have acquired resistance features have better odds at survival and proliferation.[39, 40] Therefore, any use of antibiotics contributes to the emergence and dissemination of resistance to some degree. Antibiotic use is also correlated with (long-term) colonisation with resistant bacteria.[41-43] While colonisation with resistant bacteria does not necessarily cause harm to the human host, it increases the risk for invasive infections with these resistant bacteria,[44] further transmission to other individuals in society as well as transmission of resistance mechanisms to other, more pathogenic, bacteria species.[23] Implications of antibiotic use, through its contribution to the development of resistance, are the loss in effectiveness of currently available antibiotics which results in a limited antibiotic arsenal for future patients. Consequently, today's use of antibiotics has important implications on public health both now and the future.[17]

Solutions to the ABR threat?

Potential solutions to address the growing threat of resistance include developing new antibiotics and limiting the use of antibiotics through infection prevention and control measures as well as through antibiotic stewardship.

New antibiotics

In order to face the growing antibiotic resistance threat there is an urgent need for the development of new antibiotics. However, there has been a strong decline in therapeutic output from the antibiotic research and development (R&D) pipeline. In addition, the number of pharmaceutical companies actively developing antibiotics

has been declining over the past few decades, with only a few of the largest companies remaining active.[45] This has led to an *innovation gap* or *discovery void* with no new antibiotic class launched between 1962 and 2000.[46] There are several reasons for the dry pipeline in antibiotic R&D. From the scientific research perspective, the low-hanging fruits have been picked; new breakthroughs are difficult and expensive.[46] The greater challenge probably lies in the lack of financial incentives for the pharmaceutical sector.[47] Indeed, traditionally, in order to recover R&D costs and ensure financial returns, pharmaceutical companies aim to maximise the sales potential, and thus the consumption, of their products. However, in the case of new antibiotics, the sales-based model conflicts with the need for limiting their consumption in order to preserve their efficacy. Initiatives to improve the development pipeline for new antibiotics have been proposed,[48, 49] and some have been implemented including, e.g., the New Drugs for Bad Bugs (ND4BB) programme in Europe and the Generating Antibiotic Incentives Now (GAIN) Act in the United-States. However, it remains unclear whether these initiatives alone will suffice to revitalise the antibiotic pipeline.

Infection prevention and control

At the level of the health care facility, infection prevention and control measures are key in reducing the number of infections and thereby limiting the use of antibiotics. Indeed more than half of the HAIs are considered preventable.[50] In addition, infection prevention and control measures (e.g., hand hygiene; sterilisation and decontamination of medical devices) limit the spread of antibiotic resistance within health care facilities.[51] Infection prevention and control measures fall outside the scope of this thesis.

Antibiotic stewardship

A third approach which aims to preserve the effectiveness of antibiotics at the level of the health care facility is to focus on limiting antibiotic use to specific clinical indications. This is the core aim of antibiotic stewardship (ABS) (or more broadly antimicrobial stewarship, **Box 1**) activities, previously referred to as *antibiotic policies*. Indeed, the goal of antibiotic stewardship is most commonly defined as to 'optimise clinical outcomes while minimising unintended consequences of antibiotic use, including toxicity, the selection of pathogenic organisms (such as *Clostridium difficile*), and the emergence of resistance' (**Box 1**). While this definition by the Infectious Diseases Society of America (IDSA)[52] is probably the best known, additional definitions of stewardship have been introduced by others.[53-55] Antibiotic stewardship programmes have been shown to be effective in hospitals.[52, 56]

Good quality clinical practice is typically achieved though the development and implementation of (evidence-based) clinical guidelines.[57] Clinical guidelines are

'systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances'.[58] Ultimately, compliance to infectious disease treatment guidelines in everyday practice should decrease unwanted variation in practice and increase effectiveness of antibiotic treatment by preventing under-, over- and misuse of antibiotics.[59] In other words, infectious disease treatment guidelines should provide guidance on responsible antibiotic use. At the international level, such guidance is provided, among others, by the Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases (ESCMID). Antibiotic guidelines are also developed at a national level, e.g., by the Dutch Working Party on Antibiotic Policy (SWAB) in the Netherlands, the Belgian Antibiotic Policy Coordination Committee (BAPCOC) in Belgium and the British Society for Antimicrobial Chemotherapy (BSAC) in the United-Kingdom.

Responsible antibiotic use

Responsible antibiotic use: a multi-sectoral approach

There is increasing awareness of the need for engagement and actions from stakeholders across different sectors in order to address the problem of ABR.[60-62] The most obvious sector concerned by ABR is the medical community as it includes the prescribers of antibiotics who are confronted with the burden of ABR in daily practice while diagnosing and managing increasingly difficult-to-treat infections. However, the societal impact of ABR stretches far beyond the medical discipline. In addition, more involvement from public health organisations, policy makers, governments and the general public should be helpful to address the ever-expanding societal problem of ABR. Furthermore, engagement of stakeholders at the level of the antibiotic producers and regulatory agencies is desirable. It is expected that including the perspectives of many involved stakeholders might contribute to the optimal climate necessary for progress towards solutions. In this thesis, we aim to include the perspective of a wide range of stakeholders in the exploration of what *responsible antibiotic use* entails.

Responsible antibiotic use: we are not there yet

Responsible antibiotic use is key to slowing down the emergence of ABR. Antibiotic consumption is increasing worldwide.[27, 63] Despite efforts to improve the quality of antibiotic use (through the development and implementation of clinical guidelines) antibiotic use remains frequently inappropriate in daily practice, both in outpatient and inpatient health care settings.[64, 65] Up to 40-50% of all antibiotic prescriptions are estimated to be unnecessary or suboptimal.[65-67] As all antibiotic use contributes to

the development of resistance, inappropriate antibiotic use is an important improvement target to limit the development of resistance.[68-72] There is important methodological variability in the evaluation of the appropriateness or quality of antibiotic prescriptions.[65, 73-75] In addition, volumes of antibiotic use vary significantly across countries[76] which may reflect variation in appropriate use. Altogether this highlights the need for standardised measurements for an adequate evaluation of the quality of antibiotic use.

Responsible antibiotic use: how to define and measure it?

Definitions of rational or responsible use of medicine(s) have been proposed previously:

- Medicine use is rational (appropriate, proper, correct) when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community. Irrational (inappropriate, improper, incorrect) use of medicines is when one or more of these conditions are not met.[77]
- Responsible use of medicines implies that the activities, capabilities and existing resources of health system stakeholders are aligned to ensure patients receive the right medicines at the right time, use them appropriately, and benefit from them.[78]

However, these definitions are not tailored to antibiotics and might not fully take into account their unique features (as discussed above). Up to 2014, there was no general international and cross-disciplinary agreement on what exactly defines *responsible antibiotic use* due to the absence of common terminology and definitions. In this thesis, we aim to reach consensus on the definition of *responsible antibiotic use*, based on concepts from literature and taking into account the perspectives of different stakeholders and experts. The definition of responsible antibiotic use should be relevant regardless of geographic, socio-economic, healthcare or population setting.

Measuring (in)appropriateness of healthcare is typically done using quality indicators (QIs), defined as 'measurable elements of practice performance for which there is evidence or consensus that they can be used to assess the quality, and hence change in the quality, of care provided'.[79] QIs are typically categorised according to the Donabedian model into (i) structure indicators reflecting organisational aspects of healthcare, (ii) process indicators describing the care delivered to patients and (iii) outcome indicators specifying the effects of the care given to patients.[80] QIs for antibiotic use are valuable tools for antibiotic stewardship programmes as they can help identify improvement targets and evaluate the effectiveness of antibiotic stewardship improvement interventions.

QIs to assess the quality of antibiotics in the hospital setting have been developed previously for different types of infections including respiratory tract infections,[81]

urinary tract infections,[82] and sepsis.[83] So far, the development of quality indicators has mainly involved the medical community. In this thesis, we aim to develop a set of generic quality indicators relevant for assessing the quality of antibiotic use in the inpatient setting based on scientific evidence and taking into account the perspectives of different stakeholders and experts.

Little is known, however, about the perspective of hospital patients on responsible antibiotic use. Up to 2014, patients were usually not engaged in ABS stewardship efforts even though shared decision making and patient engagement can positively influence health-related behaviours and health outcomes.[84-86] An elucidation of patients' views on responsible antibiotic use is expected to yield valuable insights to guide the development of quality improvement projects to optimise patient care and quality of antibiotic use (i.e., antibiotic stewardship activities). In this thesis, we explore the perspective of hospital patients on responsible antibiotic use using qualitative research methods (i.e., semi-structured interviews and focus groups).

Responsible antibiotic use: barriers and facilitators?

The identification of bottlenecks and levers from the perspective of a broad range of involved stakeholders is key to steer the focus of research and policy efforts towards solutions for ABR. So far, barriers to and facilitators of responsible antibiotic use (factors that might prevent or enable responsible use; also referred to as determinants) at the health care facility level have been extensively studied among antibiotic prescribers, i.e., the medical community.[87, 88] Important factors known to impact antibiotic prescribing include physicians' attitudes (e.g., complacency or fear), patient-related factors (e.g., signs and symptoms) and healthcare system-related factors (e.g., time pressure).[67, 88] An overall conclusion of studies into determinants of antibiotic prescribing among physicians reveals that antibiotic prescribing is a complex process influenced by many factors affecting all actors involved (e.g., physicians, other healthcare providers, healthcare systems, patients and the general public); and that these factors are closely intertwined.[88] In addition, stakeholders and experts involved in the process of drug development, drug regulation and dispensing (but outside the medical and patient communities) are increasingly expected to get involved and work towards solutions. These *third-party* stakeholders include, inter alia, governments, drug regulatory agencies and professionals working in antibiotic R&D. However, up to 2014, there was only little literature addressing barriers and facilitators from the perspective of a broad range of third-party stakeholders. In this thesis, we explore barriers to and facilitators of responsible antibiotic use among *third-party* stakeholders using qualitative research methods.

Responsible antibiotic use: the example of *Staphylococcus aureus* bacteraemia

In this thesis, an example of infectious disease was sought to illustrate the consequences of ABR on the availability of antibiotic treatment options as well as to steer reflections on priorities for antibiotic R&D and responsible antibiotic use strategies. *Staphylococcus aureus* bacteraemia (SAB) was chosen as an example. *Staphylococcus aureus*, both a human commensal and an opportunistic pathogen, is a frequent cause of bacteraemia in industrialised nations.[89, 90] The mortality associated with SAB, estimated at 20-25 %, is considerable,[89, 91] and is expected to expand further with the aging of the population. Furthermore, the great aptitude of *S. aureus* for becoming resistant (e.g., MRSA) to antibiotics poses challenges for the clinical management of *S. aureus* infections. A case study on SAB was performed through 'detailed, in-depth data collection involving multiple sources of information'[92] including a review of currently available antibiotics, treatment guidelines and recent output of the antibiotic R&D.

The DRIVE-AB project

The research conducted in this thesis is part of the DRIVE-AB (Driving Re-InVEstment in R&D and responsible AntiBiotic use) project which was launched in 2014.[93] DRIVE-AB was a public-private consortium funded by the EU Innovative Medicines Initiative's (IMI) New Drugs 4 Bad Bugs (ND4BB) with support from the European Federation of Pharmaceutical Industries and Associations (EFPIA) partners. The multidisciplinary and multi-stakeholder DRIVE-AB consortium brought together 23 partners including pharmaceutical companies, academic institutions, and public health organisations spread over 12 countries. DRIVE-AB was tasked *(i)* to define what constitutes responsible antibiotic use and *(ii)* to develop new economic models to promote antibiotic innovation.[47] This thesis is embedded in the work performed for the first task.

Research questions and thesis outline

The aim of this thesis is to explore responsible antibiotic use. A search for a global definition, quality indicators, barriers and facilitators was conducted involving a wide range of stakeholders. The thesis addresses antibiotics (**Box 1**) and focuses on human medicine.

The following research questions are addressed:

- *What is responsible antibiotic use?* **Chapter 2** describes an international and multidisciplinary consensus procedure towards a global definition of responsible antibiotic use.
- *What quality indicators are relevant to assess responsible use in the inpatient setting?* **Chapter 3** presents a multidisciplinary international consensus procedure on quality indicators for responsible antibiotic use in the inpatient setting.
- *What are views on responsible antibiotic use from the patient's perspective?* **Chapter 4** describes a qualitative exploration of views and experiences of hospital patients regarding responsible antibiotic use.
- *What are barriers to and facilitators of responsible antibiotic use according to third party- stakeholders?* **Chapter 5** provides a qualitative elucidation of barriers to and facilitators of responsible use from the perspective of international multidisciplinary *third-party* stakeholders (i.e., those involved with antibiotics but outside of the medical practice and patient communities).
- *What are antibiotic R&D priorities and responsible use strategies for a major infectious disease threat?* **Chapter 6** presents a case study illustrating these issues based on the example of *S. aureus* bacteraemia.

Finally, in **Chapter 7** (General Discussion), the main findings presented across the various chapters of this thesis are summarised and discussed.

Box 1 Definitions and terminology.

Antimicrobial	An agent that kills or inhibits the growth of living microorganisms regardless of its source. Antimicrobials include amongst others: • Antibiotics or antibacterials (active against bacterial infections) • Antimycobacterials (which are antibacterials specifically active against the tuberculosis bacteria and other mycobacterial infections) • Antivirals (active against viral infections) • Antifungals (active against fungal infections) • Antiparasitic drugs (active against infections due to parasites).[94]
Antibacterial	An agent that kills (i.e., bactericidal) or inhibits the growth (i.e., bacteriostatic) of living bacteria regardless of its source (natural, semi-synthetic or synthetic).
Antibiotic	A substance produced by living organisms that kills (i.e., bactericidal) or inhibits the growth (i.e., bacteriostatic) of other microorganisms. Strictly speaking, antibiotics do not include substances produced (semi-) synthetically. However for simplicity, synthetic and semi-synthetic variants are usually included under the term antibiotics.[3, 95]
Antimicrobial resistance (AMR)	The ability of a microorganism (e.g., bacterium, virus, fungus or a parasite) to resist the action of an antimicrobial agent.[94]
Antibiotic resistance (ABR)	The ability of a bacterium to resist to the action of an antibiotic.[94] This thesis focuses on antibiotics rather than antimicrobials therefore the term ABR is used instead of AMR.
Antimicrobial Stewardship (AMS)	The goal of AMS is to optimise clinical outcomes while minimising unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as *Clostridium difficile*) and the emergence of resistance.[52]
Antibiotic stewardship (ABS)	Antimicrobial stewardship limited to antibiotics. This thesis focusses on antibiotics rather than antimicrobials therefore the term ABS is used instead of AMS.

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2

Towards a global definition of responsible antibiotic use: results of an international and multidisciplinary consensus procedure

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Abstract

Aim This study aimed to identify key elements for a global definition of responsible antibiotic use based on diverse stakeholder input.

Methods A three-step RAND-modified Delphi method was applied. First, a systematic review of antibiotic stewardship literature and relevant organisation web sites identified definitions and synonyms of responsible use. Identified elements of definitions were presented by questionnaire to a multidisciplinary international stakeholder panel for appraisal of their relevance. Finally, questionnaire results were discussed in a consensus meeting.

Results The systematic review and the web site search identified 17 synonyms (e.g., appropriate, correct) and 22 potential elements to include in a definition of responsible use. Elements were grouped into patient-level (e.g., Indication, Documentation) or societal-level elements (e.g., Education, Future Effectiveness). Forty-eight stakeholders with diverse backgrounds (medical community, public health, patients, antibiotic research and development (R&D), regulators, governments) from 18 countries across all continents participated in the questionnaire. Based on relevance scores, 21 elements were retained, 9 were rephrased and 1 was added. Together, the 22 elements and associated best-practice descriptions comprise an exhaustive list of elements to be considered when defining responsible use.

Conclusion Combination of concepts from the literature and stakeholder opinion led to an international multidisciplinary consensus on a global definition of responsible antibiotic use. The widely diverging perspectives of stakeholders providing input should ensure the comprehensiveness and relevance of the definition for both individual patients and society. An aspirational goal would be to address all elements.

Introduction

The human impact of antibiotic resistance is increasing worldwide with more and more antibiotics losing their power to cure infections. At the same time, the pipelines for new antibiotics are running dry.[1, 2] A steep growth of initiatives aiming at improving antibiotic use and tackling resistance indicate that the *tipping point* [3] on this major global health threat may have been reached. Examples of such international initiatives include the WHO's Global Action Plan on Antimicrobial Resistance and the Transatlantic Taskforce on Antimicrobial Resistance.[4, 5] Altogether, these initiatives contributed to a worldwide call to address resistance, making the agenda of the United Nations General Assembly as a major global health priority in September 2016.[6]

While all use of antibiotic drugs contributes to the development of resistance, major forces driving the increasing resistance include inappropriate infection prevention and inappropriate use.[1, 7] Inappropriate use is also known to drive increased costs of care, morbidity and mortality.[8-10] In order to define inappropriate use, a clear understanding of what appropriate, correct or responsible use entails is crucial. The definition of rational use of drugs, as per the WHO, states that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community.[11] More recently, the WHO introduced the concept of responsible use of medicines implying that the activities, capabilities and existing resources of health system stakeholders should be aligned to ensure patients receive the right medicines at the right time, use them appropriately, and benefit from them.[12]

However, antibiotics are one-of-a-kind drugs as they are the only drugs that do not directly and exclusively affect the patient. Indeed, antibiotics target the biology of microorganisms, both pathogens and commensals, carried by the patient, which can also be shared with a larger human or animal community. Antibiotic therapy should therefore consider factors related to these microorganisms and the societal ramifications of antibiotic use in addition to patient and drug related characteristics. The *pyramid of infectious diseases* illustrates the many interplays between the bug, the drug and the patient.[13] These interactions are the basis of the complexity of antibiotic prescription and use, but are not explicitly addressed in the WHO definition of rational drug use.

Activities aiming at reducing the undesired consequences of inappropriate use have been undertaken since the early seventies.[14] In the mid-1990s, the term 'stewardship' was introduced, describing a collection of strategies, policies, guidelines or tools that could improve antimicrobial prescribing with the aim of decreasing antibiotic resistance and use.[15, 16] Stewardship addresses *how* improved antibiotic use should be achieved. A definition of responsible antibiotic use would provide clear goals of *what* should be improved and should thereby steer stewardship activities.

While the medical community, including the antibiotic prescribers, are crucial in assessing responsible antibiotic use, they are not the only stakeholders concerned by the global antibiotic resistance health threat. Great expectations are arising for public health organisations, developers and producers of antibiotics to help solve the issue. Increased political attention is leading to the involvement of policy makers and governments. It is therefore important that all these different cross-disciplinary perspectives should be accounted for in any attempt to define responsible antibiotic use. This study was conducted within the Driving Re-InVEstment in R&D and responsible AntiBiotic use (DRIVE-AB) project focusing on human antibiotic use.[17, 18] The aim of this study was to develop a consensus-driven definition of responsible antibiotic use considering different perspectives including those of the medical community, public health, patients, antibiotic developers, regulators and governments. The definition should account for diverse socioeconomic settings thereby ensuring a global scope.

Materials and methods

A three-step RAND modified Delphi method[18, 19] was applied to reach consensus on a global definition of responsible antibiotic use (**Figure 1**). The consensus procedure combined the individual opinions of four groups of stakeholders.

Step 1 – Literature and website search

A systematic review was performed in the MEDLINE database (since 1966) to identify elements of, and definitions of responsible antibiotic use and its synonyms in the scientific literature. Articles were screened in title and abstract with the following search strategy: 'antibiotic stewardship' OR 'antimicrobial stewardship' OR 'antibiotic policies' OR 'antibiotic policy'. In the context of antibiotic use, *policy* is a synonym and a predecessor of the term *stewardship,* a term coined in the mid-1990s.[15, 16] The search was performed on 25th of March 2015. Two researchers (AM and MH) independently screened papers discussing general principles of antibiotic stewardship within a random sample of 25% of the found literature. After reaching consensus on this 25% sample, one researcher (MH) continued the selection process of the remaining literature. Exclusion criteria were papers: not written in English, not discussing antibiotics, not describing general principles of antibiotic stewardship and not containing statements on responsible antibiotic use or its synonyms. Papers of which the full-text version was not accessible from one of the following libraries: Radboud University Medical Center, University of Rijeka, University of Antwerp, University of Genève, University of Leuven, University of Lorraine and Google Scholar® were also excluded. A complementary search was performed on websites of relevant (inter)national organisations and institutions active in the field of antibiotic

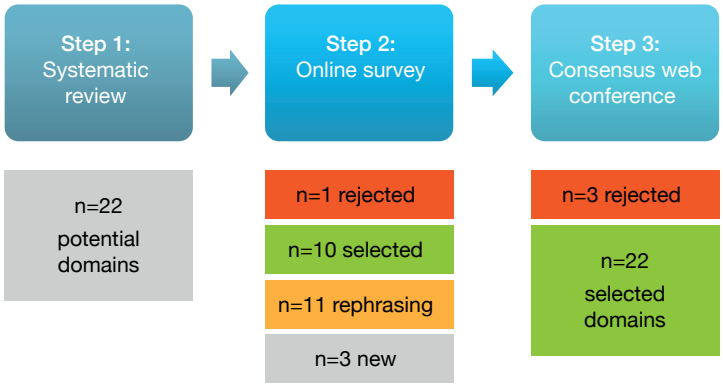

Figure 1: The number of elements of the definition of responsible use resulting from each step of the RAND-modified Delphi method.

stewardship and/or public health. Organisations, institutions and their websites were identified using lists provided in four publications on antibiotic stewardship and R&D activities.[20-23] Ultimately, an exhaustive search of references of included web pages was done. The searches were restricted to websites in English. Relevant sections of the websites were searched by one researcher (AM) using the search terms 'antibiotic' and 'use'.

The data extraction of synonyms and definitions of responsible antibiotic use was performed by one researcher (AM). For the papers included in the systematic review, the extraction process was repeated by the same researcher a month later for 10% of the references. No discrepancies were found, thus ensuring comprehensiveness of the data and intra-rater reproducibility. The data extraction from websites was performed by the same researcher twice in order to ensure the comprehensiveness of the data. The extracted data were compiled and definition components were clustered into different non-overlapping logical elements (e.g., *Microbiological Diagnostics, Indication)*, each of which appeared distinctly relevant to define responsible use. The categorisation into elements was done by one researcher (AM) and then validated by a second researcher (IG). Discrepancies were discussed until consensus was reached. For each potential element, an explanatory phrase describing the goal for responsible use was proposed by combining different phrasings extracted from the literature. The phrasing was done in consensus between three authors (AM, IG and MH). The explanatory phrases for each element were formulated to complete the sentence 'Responsible antibiotic use includes...' (e.g., 'Responsible antibiotic use includes *using microbiology diagnostic tools to provide diagnostic testing.')*. Finally, the wording of the element names and corresponding

explanatory phrases was reviewed by two native English speakers and experts in the field of antibiotic stewardship, one from the UK and one from the US. Preliminary results of the systematic review were discussed at a 'train-the-trainer event' in collaboration with the British Society for Antimicrobial Chemotherapy (BSAC) during the 26th European Congress of Clinical Microbiology and Infectious Diseases. Senior members of the European medical antibiotic stewardship community were asked for feedback.[24]

Step 2 – Online questionnaire

The consensus procedure took place from July until September 2016. Seventy-four international stakeholders were invited by e-mail to participate. Reminders were sent four and two weeks, before the closing of the questionnaire. Stakeholders were invited based either on demonstrated experience and expertise on the topic of antibiotic use and/or stewardship (e.g., relevant publications, involvement in national stewardship activities) or on different perspectives on antibiotic use (e.g., having a prominent role within a relevant organisation, institute, society or company). Stakeholders from the extended international network of academic and European Federation of Pharmaceutical Industries and Associations (EFPIA) partners of the DRIVE-AB project were solicited. Individuals amongst four different stakeholder groups, aiming at representing all parties involved with antibiotic use, were identified: medical community (n=18); public health and patients (n=18); antibiotic research and development (R&D) (n=21); payers, policy makers, governments and regulators (n=17). The invited stakeholders originated from 20 countries across all continents.

A web-based questionnaire on responsible antibiotic use was designed in Survey-Monkey®. Together with the invitation e-mail, stakeholders were sent a document providing the scientific references from the systematic review for each of the identified elements. The stakeholders were asked to appraise the relevance of each element to be included in the definition of responsible antibiotic use. The relevance was graded using a 9-point Likert scale (1=Clearly not relevant, 9=Clearly relevant). Relevance scores were calculated for each element following the RAND agreement criteria.[19] Median scores were analysed across the four stakeholder groups. If the element had a median of 8 or 9 and ≥70% of the stakeholders scored in the upper tertile (i.e., 7, 8 or 9), the element was selected. If the element had a median <8 or <70% of the stakeholders scored in the upper tertile, the element was rejected.

Stakeholders could comment on the elements as well as make suggestions for new elements. If comments referred to the clarity of the element and/or wording of its explanatory phrase, elements were labelled for discussion. Newly proposed elements that did not present any overlap with other elements were selected.

Step 3 – Consensus Meeting

The first twenty stakeholders that filled in the questionnaire were asked for their availability to take part in a consensus meeting after the summer of 2016. The aim was to have balanced numbers of participants across the four stakeholder groups. The meeting was held on 28th September 2016 using a web conferencing interface. During the meeting, the stakeholders discussed elements labelled for discussion and newly proposed elements. For the elements labelled for discussion, the researchers prepared a new wording proposal based on the comments made by the stakeholders in the questionnaire. These comments were categorised per stakeholder group and shown during the consensus meeting to expedite the discussions. Typically, modifications to the new wording proposal were made until agreement was reached. An audio recording of the meeting was made and used to make sure no relevant suggestions were missed.

Results

Step 1 – Literature and website search

The systematic literature search identified 1700 articles of which 343 were considered eligible for full-text screening. After exclusion and inclusion criteria were applied, 161 articles (9.5%) were included and data extraction was performed. The flowchart of the systematic review is shown in **Supplementary Figure S1**. The websites of 50 institutions and organisations were identified and searched for definitions. Fifteen websites (32%) were ultimately included for data extraction (**Supplementary Table S1**). The systematic review and the complementary website search led to the identification of 17 synonyms of responsible use: *adequate, appropriate, better, correct, effective, focused, improved, judicious, optimal, optimised, proper, proportionate, prudent, rational, right, safe, thoughtful* use. Furthermore, this first step led to the identification of 22 potential elements of responsible antibiotic use for appraisal by the stakeholders (**Figure 1** and **Table 1**).

Delegates from 19 EU countries attended the train-the-trainer event. During discussions at this event it was acknowledged that the balance between the elements *Patient outcome*, *Resistance* and *Future effectiveness* of the antibiotic drug implied important ethical considerations, which should be made visible. As a result, '*Ethics*: *Making the balance between Patient Outcome, Future Effectiveness and Resistance based on ethical considerations.*' was added as an aspect of importance to the definition of responsible antibiotic use as shown in the infographic (**Figure 2**) and **Table 2**.

Table 1 Results of the consensus procedure on the elements of responsible antibiotic use. Element 1-14: patient level elements; element 15-22: societal elements.

Final #	Element name	References	Result after the online survey
1	**Microbiological Diagnostics**	25-45	Labelled for rephrasing
2	**Indication**	30-34, 36, 37, 39, 41, 43-81	Labelled for rephrasing
3	**Antibacterial Activity**	25-27, 29, 30, 32, 34, 36-39, 43, 48, 50, 51, 53-55, 59, 60, 63, 64, 69, 71, 72, 74, 78, 79, 82-137	Labelled for rephrasing
4	**Antibacterial Spectrum**	25-27, 29, 31-35, 40, 42, 51, 53, 58, 60, 62, 63, 70, 71, 79, 90, 108, 112, 124, 128, 138-141	Selected
5	**Dosing, PK/PD, Interval**	Dosing 16, 25-27, 29-33, 35-38, 43, 44, 48-55, 57-60, 62-64, 69-72, 74, 79-84, 86, 87, 89-92, 94-96, 98, 100-102, 104, 105, 108-110, 113-123, 125, 127-137, 142-144 PK/PD 26, 29, 34, 35, 60, 73, 128, 139-141, 145 Interval 31, 60, 72, 80, 111	Labelled for rephrasing
6	**Duration**	16, 25-27, 29-39, 43, 44, 48-51, 53-55, 57-60, 62-64, 69-74, 76, 79-84, 86, 87, 89-92, 94-96, 98, 100-106, 109-123, 125, 127-136, 140, 141, 143, 144, 146	Labelled for rephrasing
7	**Route**	25, 27, 30, 32, 35-38, 48, 50, 52, 54, 58-60, 63, 64, 70, 71, 78, 82, 83, 86, 87, 89, 90, 94, 96, 98, 100-102, 105, 108-110, 112, 113, 117, 124, 125, 128, 129, 131-135, 137, 147	Labelled for rephrasing
8	**Timing**	33, 36, 50, 52, 55, 58, 62, 67, 71, 74, 79, 106, 108, 109, 111, 112, 127, 138, 141	Labelled for rephrasing
9	**Interactions**	29, 60, 144	Selected

Result after the consensus meeting	Element Description
Rephrased and selected	*Using high quality available microbiology laboratory facilities to provide routine diagnostic testing.* Rephrased: **Using microbiology diagnostic tools to provide diagnostic testing.**
Rephrased and selected	*Restricting antibiotic use to prevent or cure suspected or microbiologically proven bacterial infections.* Rephrased: **Using antibiotics only to prevent or cure infections for which antibiotic treatment provides a proven benefit.**
Rephrased and selected	*Rationally selecting antibiotics based on their antibacterial activity.* Rephrased: **Selecting antibiotics based on their antibacterial activity.**
-	**Selecting antibiotics based on their antibacterial spectrum (as narrow as possible).**
Rephrased and selected	*Dosing and dosing frequency of the antibiotic regimen based on clear PK/PD principles (ensuring sufficient free concentrations of antibiotic at the site of infection).* Rephrased: **Dose and dosing frequency of the antibiotic regimen based on available knowledge on PK/PD (ensuring sufficient free concentrations of antibiotic at the site of infection).**
Rephrased and selected	*Using the shortest possible duration of the antibiotic regimen.* Rephrased: **Using the shortest possible evidence-based duration of the antibiotic regimen.**
Rephrased and selected	*Selecting the proper route (parenteral or oral) based on antibiotic and patient characteristics.* Rephrased: **Selecting the proper route (e.g., parenteral or oral) based on antibiotic, severity or type of infection and patient characteristics.**
Selected	**Administering antibiotics in a timely manner.**
-	**Selecting antibiotics taking into account possible interactions with other medication(s).**

Table 1 Continued.

Final #	Element name	References	Result after the online survey
10	**Toxicity**	21, 25, 29, 32-34, 36-39, 43, 44, 46, 57, 59, 60, 67, 69-71, 78, 82, 84, 86, 91, 94, 100, 101, 103, 104, 107, 108, 110, 111, 113, 116, 118, 119, 121-123, 126, 133, 134, 136-139, 144, 145, 147-165	Selected
11	**Unintended Consequences**	21, 25, 32, 33, 37, 39, 50, 52, 53, 55, 57, 59, 60, 69, 71, 74, 76, 79, 84, 88, 95, 99, 102, 104, 108, 110-112, 117-119, 121, 123, 125, 126, 128, 129, 131, 132, 134, 136-138, 145, 148, 149, 153, 157, 158, 162, 164-174	Selected
12	**Documentation**	25, 31, 33, 73	Selected
13	**Patient Compliance**	31, 34, 44, 139	Selected
14	**Patient Outcome**	21, 25, 26, 29, 31, 32, 34, 36-38, 41, 43, 46, 50, 55-58, 61, 63, 67, 69, 71, 74, 76, 78, 82, 83, 86, 91, 92, 94, 95, 99-101, 103, 104, 107, 108, 110, 111, 113, 114, 116-119, 121-123, 125, 127-129, 131-136, 138, 139, 141, 143, 147, 149-155, 157-170, 172-184	Labelled for rephrasing
15	**Access-Availability**	41, 44, 45, 185	Selected
-	Costs	21, 25, 29, 31, 34, 36-38, 41, 44, 50, 53, 55, 69, 74, 82, 95, 97, 100, 102, 103, 111, 118, 119, 126-128, 133-135, 138-140, 143, 147-155, 160, 164-166, 173, 174, 176-178, 180, 186	Rejected
16	**Resistance**	16, 25, 26, 28, 29, 32-34, 37-39, 41, 43, 44, 46, 50, 53, 55, 57, 59, 60, 65, 67, 69, 71, 74, 76, 82, 84, 86, 88, 91, 94, 95, 97, 99, 100, 102, 105, 108, 110-112, 116-119, 121-123, 125-127, 129-136, 138, 145, 148-159, 161, 163-180, 182-185, 187, 188	Labelled for rephrasing
17	**Future Effectiveness**	25, 33, 37, 41, 46, 78, 88, 90, 105, 113, 119, 178, 185, 189-192	Selected
18	**Resistance Surveillance**	32, 34, 41, 44, 45, 70, 79, 88, 90, 108, 115, 119, 124, 174, 193, 194	Labelled for rephrasing

Result after the consensus meeting	Element Description
-	**Selecting the antibiotic with the least toxicity possible.**
-	**Selecting the antibiotic with the lowest risk of secondary infections such as *C. difficile* diarrhea.**
-	**Fully documenting the antibiotic regimen including indication in the medical record.**
-	**Ensuring patient compliance with the antibiotic prescription.**
Rephrased and selected	*Optimising outcome (reduced morbidity, mortality and length of hospital stay) following the treatment or prevention of bacterial infections.* Rephrased: **Optimising patient outcome (reduced morbidity, mortality and length of hospital stay) by treating or preventing bacterial infections.**
-	**Ensuring access and routine availability of quality antibiotics.**
-	*Using the most cost-effective antibiotic regimen.*
Selected	**Limiting the emergence of antibiotic resistance.**
-	**Conserving the effectiveness of antibiotics for the future.**
Rephrased and selected	*Using resistance surveillance data for empiric prescribing.* Rephrased: **Using local antibiotic resistance surveillance data for guidelines on empiric antibiotic prescribing.**

Table 1 Continued.

Final #	Element name	References	Result after the online survey
19	**Evidence-based Guidelines**	Evidence 31, 83, 144, 176, 194-196 Guidelines 25, 31, 33, 34, 36, 44, 50, 54, 55, 60, 76, 88, 140, 174, 193, 197, 198	Selected
20	**Expertise and Resources**	33, 44, 54, 108, 124	Selected
21	**Education**	44-46, 61, 71, 76, 78, 80, 83, 88, 108, 145, 146, 193	Labelled for rephrasing
22	**Waste Disposal**	Proposed in the online survey	-
-	Alternatives	Proposed in the online survey	-
-	Multidisciplinarity	Proposed in the online survey	-

*: rejected as an element of responsible antibiotic use but added to the figure as an additional aspect.

Step 2 – Online questionnaire

In the online questionnaire, a multidisciplinary panel of 50 stakeholders (response rate 68%) from 18 countries across all continents appraised the relevance of the 22 potential elements of responsible antibiotic use. The online questionnaire is shown in **Supplementary Figure S2**. These 50 stakeholders were distributed as follows: 13 belonged to the medical community group including professional societies, hospital pharmacists, infectious disease physicians, clinical microbiologists and a nurse; 12 to the public health and patients group including the World Health Organization, Médecins Sans Frontières, national public health institutes and ethicists; 13 to the antibiotic R&D including Small and Medium Enterprises, pharmaceutical companies and economists; and 12 payers, policy makers, governments and regulators including the European Centre for Disease Prevention and Control, the Centers for Disease Control and Prevention, the US Food and Drug Administration, European Medicines

Result after the consensus meeting	Element Description
-	*Ensuring the availability and use of local (or national) evidence-based treatment guidelines.* Rephrased: **Ensuring educational programs on antibiotic use from an early stage for the public and all relevant professionals, including trainees in health care curricula.**
-	**Using available infectious disease expertise and resources.**
Rephrased and selected	*Ensuring educational programs on antibiotic use for all relevant professionals and the public.* Rephrased: **Ensuring educational programs on antibiotic use from an early stage for the public and all relevant professionals, including trainees in health care curricula.**
Rephrased and selected	*Disposing waste antibiotics to prevent selection in the environment.* Rephrased: **Safely disposing of unused antibiotics and waste products containing antibiotics to prevent selection in the environment.**
Rejected*	*Considering alternatives for antibiotics to prevent infections (e.g., vaccines, hygiene, infection control).*
Rejected	*Stimulating collaboration between different types of health care professionals (e.g., nurses, doctors, pharmacists).*

Agency, governments and a national health insurance advisor. The answers of two stakeholders were incomplete; as a result 48 answers were used for data analysis. A detailed list of all the stakeholders and their affiliations is shown in **Supplementary Table S2**.

The results of the questionnaire are shown in **Table 1**. Based on relevance scores, 21 elements to be included in the definition of responsible use were selected and one element, '*Costs: Using the most cost-effective antibiotic regimen.*', was rejected. Comments provided by stakeholders to explain their low relevance scores for this element included, e.g., '*ceftriaxone has been a major driver of inappropriate use due to cost'*, and '*cost-efficiency is not a great criterion for being responsible*'.

Ten elements were selected without suggestions for rephrasing: *Access-Availability, Antibacterial Spectrum, Documentation, Evidence-based Guidelines, Expertise and Resources*, *Future Effectiveness, Interactions, Patient Compliance, Toxicity, Unintended Consequences.*

Among the 21 selected elements, 11 were labelled for rephrasing of the explanatory text based on comments made by stakeholders: *Antibacterial Activity, Dosing-PK/PD-Interval, Duration, Education, Indication, Microbiological Diagnostics, Patient Outcome, Route, Resistance, Resistance Surveillance* and *Timing.* Three new potential elements were suggested: *Waste Disposal, Alternatives and Multidisciplinarity.*

Step 3 – Consensus meeting

Ten stakeholders discussed the 11 elements labelled for rephrasing as well as the three newly suggested elements. The stakeholders represented all groups: medical community (n=3); public health and patients (n=3); antibiotic R&D (n=1); payers, policy makers, governments and regulators (n=3). The details of the consensus procedure including the final selection and rejection as well as the rephrasing of the elements are shown in **Table 1**. Nine elements were rephrased and two remained unchanged (*Resistance, Timing*). The newly suggested element *Waste disposal* was rephrased to '*Safely disposing of unused antibiotics and waste products containing antibiotics to prevent selection in the environment.*' and selected. The other two suggested elements (*Multidisciplinarity* and *Alternatives)* were rejected as these were not found to be defining elements of responsible antibiotic use. *'Multidisciplinarity: Stimulating collaboration between different types of health care professionals (e.g., nurses, doctors, pharmacists)'* was rejected as it was argued that the opposite, antibiotic stewardship performed without any multidisciplinary aspect, could not be considered bad clinical practice. '*Alternatives: considering alternatives for antibiotics to prevent infections (e.g., vaccines, hygiene, infection control*).' was recognised as extremely important for reducing the number of infections and thereby reducing antibiotic resistance, however, it also did not directly contribute to defining responsible use. Therefore, 'Vaccination' and 'Infection control' were added to the infographic as additional aspects of importance related to the definition of responsible antibiotic use (**Figure 2**). The final 22 elements of responsible use resulting from the Delphi procedure are shown in **Table 2** and illustrated in **Figure 2**. Fourteen elements were patient-level elements that related to aspects of responsible use of antibiotics: *Antibacterial Activity, Antibacterial Spectrum, Documentation, Dosing-PK/PD-Interval, Duration, Indication, Interactions, Microbiological Diagnostics, Patient Compliance, Patient Outcome, Route, Timing, Toxicity, Unintended Consequences.* Eight elements were considered societal-level as relating to responsible antibiotic use in a broader societal context: *Access-Availability, Education, Evidence-based Guidelines, Expertise and Resources, Future Effectiveness, Resistance, Resistance Surveillance* and *Waste Disposal.*

Table 2 The final 22 elements of the definition of responsible antibiotic use and their explanatory phrase.

Element	Explanatory phrase
Microbiological Diagnostics	Using microbiology diagnostic tools to provide diagnostic testing.
Indication	Using antibiotics only to prevent or cure infections for which antibiotic treatment provides a proven benefit.
Antibacterial Activity	Selecting antibiotics based on their antibacterial activity.
Antibacterial Spectrum	Selecting antibiotics based on their antibacterial spectrum (as narrow as possible).
Dosing, PK/PD, Interval	Dose and dosing frequency of the antibiotic regimen based on available knowledge on PK/PD (ensuring sufficient free concentrations of antibiotic at the site of infection).
Duration	Using the shortest possible evidence-based duration of the antibiotic regimen.
Route	Selecting the proper route (e.g., parenteral or oral) based on antibiotic, severity or type of infection and patient characteristics.
Timing	Administering antibiotics in a timely manner.
Interactions	Selecting antibiotics taking into account possible interactions with other medication(s).
Toxicity	Selecting the antibiotic with the least toxicity possible.
Unintended Consequences	Selecting the antibiotic with the lowest risk of secondary infections such as *C. difficile* diarrhea.
Documentation	Fully documenting the antibiotic regimen including indication in the medical record.
Patient Compliance	Ensuring patient compliance with the antibiotic prescription.
Patient Outcome	Optimising patient outcome (reduced morbidity, mortality and length of hospital stay) by treating or preventing bacterial infections.
Access-Availability	Ensuring access and routine availability of quality antibiotics.
Resistance	Limiting the emergence of antibiotic resistance.
Future Effectiveness	Conserving the effectiveness of antibiotics for the future.
Resistance Surveillance	Using local antibiotic resistance surveillance data for guidelines on empiric antibiotic prescribing.
Evidence-based Guidelines	Ensuring the availability and use of local (or national) evidence-based treatment guidelines.
Expertise and Resources	Using available infectious disease expertise and resources.
Education	Ensuring educational programs on antibiotic use from an early stage for the public and all relevant professionals, including trainees in health care curricula.
Waste Disposal	Safely disposing of unused antibiotics and waste products containing antibiotics to prevent selection in the environment.

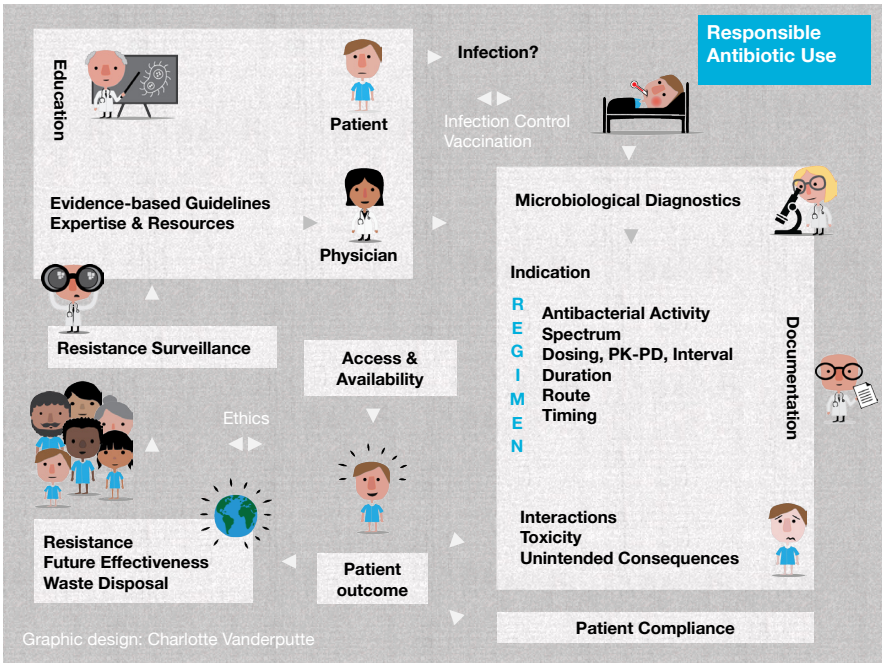

Figure 2: The final 22 elements included in the definition of responsible antibiotic use. The elements of responsible antibiotic use are shown in black characters on a white background; two additional aspects are shown in white characters. On the right: patient-level elements; on the left: societal elements.

Discussion

In this study a list of 22 key elements and their associated best-practice descriptions were developed that, taken together, need to be included in the definition of responsible antibiotic use. This exhaustive list was the result of a systematic review followed by an international and multidisciplinary consensus. Fourteen elements corresponded to patient-level and eight to societal level elements. Patient-level elements reflect individual care parameters whereas societal level elements typically affect large populations. At present, all the identified elements should be considered relevant and an aspirational goal would be to address them when using antibiotics.

Two additions, suggested during stakeholder consultations, were inserted in the infographic of responsible antibiotic use: 'Ethics' and 'Alternatives' were considered of important value without directly defining responsible use. The ethical dimensions of the balance between present and future patients have been addressed previously

by others.[199, 200] In a recent perspective on responsible use, Dyar and colleagues also highlight two relevant dimensions of 'responsible': the responsible individual practices and the societal implications of being responsible.[201] Regarding alternatives to antibiotics, the importance of infection control in parallel to stewardship activities has been highlighted by *inter alia* the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America.[21, 202] In addition, vaccines are effective against bacterial diseases and therefore reduce the need for antibiotic usage.[203]

The global scope of the definition was emphasised by considering both its comprehensiveness and its worldwide relevance. Socio-economic, cultural or care setting specific factors as well as feasibility or practical implications were not considered in this study, so that resulting elements would be relevant to any setting worldwide. The elements of responsible antibiotic use should be considered as a consensus-derived set of principles of what responsible antibiotic use should entail. From these elements, generic quality and quantity measures can be developed, for both current and newly developed antibiotic drugs in the future. Finally, the definition constitutes a valuable educational tool for use in different health care curricula, including undergraduate education.[71]

Until now, such a consensus-driven definition of responsible antibiotic use was lacking within the infectious disease and antibiotic stewardship community. The limitations of the WHO definition of rational use were previously addressed in the introduction of this manuscript. A strength of this work is the use of a systematic and stepwise method combining both concepts from literature and stakeholder opinion. An additional innovative aspect is that the perspectives of a wide range of stakeholders involved with antibiotics were accounted for. This approach contrasts, however, with previous research efforts to mainly involve medical and public health communities. Previously, scientists have called for a multi-stakeholder approach including the producers and regulators of antibiotics, without any concrete success to this date.[204, 205]

The adjective *responsible* was the terminology used in the IMI call, therefore it was a logical continuation for use in the DRIVE-AB project. In our study, seventeen synonyms of responsible antibiotic use were identified. This diversity in vocabulary is also illustrated by the fact that currently the WHO opts for *rational* and *appropriate*[7], while the ECDC uses the term *prudent*[206] and the CDC *appropriate*[207]. Per the authors, the identified synonyms should be considered as interchangeable as long as all the 22 elements are being considered.

A limitation of this work is the focus on human medicine only. As human health, animal health and the environment are closely interrelated, a One Health approach is of paramount importance. Antibiotic resistance has been recognised as the quintessential One Health issue, illustrating its principles better than any other public health threat.[208] In the global definition of responsible use, the element *Waste disposal* of human antibiotics addresses the environment. Over the last 20 years,

the importance of '*safely disposing of unused antibiotics and waste products containing antibiotics to prevent selection in the environment'* has been demonstrated by several studies reporting pollution with antibiotics in effluents of drug manufacturers, which is driving antibiotic selection pressure in the environment.[209] Another limitation is that the veterinary sector was not addressed in any of the elements of the definition. However, the principles illustrated by the human elements of responsible antibiotic use are equally pertinent for animal health. Aspects relating to the applicability or the implementation in clinical practice were not included in this definition. While this contributes to the simplicity required for the global scope, including the coverage of low-income settings, and could be considered a strength, this should also be addressed as a flaw. A methodological limitation of this study is the use of one single literature database (MEDLINE) for the systematic review. However, both the complementary website search and the opportunity given to the stakeholders to propose new elements should have ensured that no relevant element was missed. Another limitation is that the screening of the literature and websites and the data extraction process were performed by a single researcher. However, measures to address intra-rater bias included a second data extraction process for a proportion of the articles and for all the websites, and inter-rater bias was reduced by performing the screening of a proportion of the articles in duplicate. Finally, language subtleties might have been missed or might have contributed to a lack of understanding of the elements, as the researchers as well as some of the stakeholders were non-native English speakers.

In conclusion, a global list of elements key to the definition of responsible antibiotic use was developed considering the perspectives of a wide range of stakeholders involved with antibiotics. DRIVE-AB identified measures for assessing the quality and quantity of antibiotic use.[210-212] Together, these tools will be proposed as a global standard of responsible use for old and new antibiotics. Indeed, the ultimate goal of the DRIVE-AB initiative is to reconcile the long-term conservation of antibiotics through responsible use and incentives for novel antibiotic development.[213]

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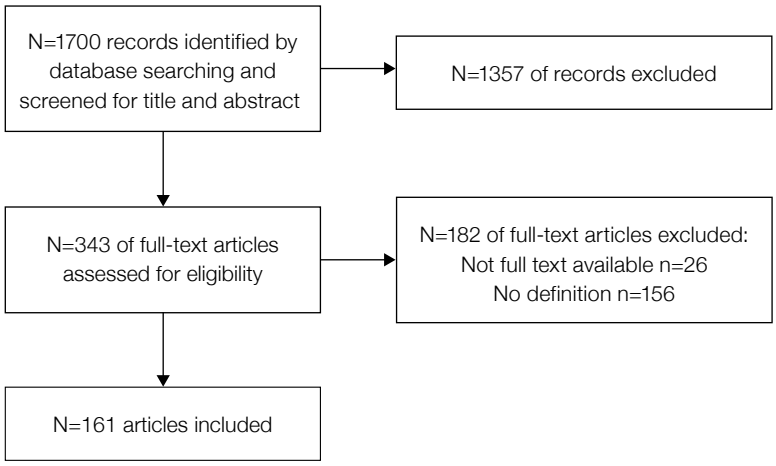
Chapter 2 - Supplementary data



Supplementary Figure S1: Flowchart of the systematic review following the PRISMA template.

Supplementary Figure S2: Online questionnaire 'Towards a definition of responsible antibiotic use'. Available at: ***https://doi.org/10.1093/jac/dky114***

Supplementary Table S1 List of included organisations, institutions or initiatives and their websites.

Organisation, institution or initiative	Website
Action of Antibiotic Resistance (React)	www.reactgroup.org
Alliance for the Prudent Use of Antibiotics	www.tufts.edu
Centers for Disease Control and Prevention (CDC)	www.cdc.gov
Community for Open Antimicrobial Drug Discovery	www.co-add.org
Department of Health UK	www.dh.gov.uk
European Centre for Disease Prevention and Control (ECDC)	www.ecdc.europa.eu
Global Antibiotic Resistance Partnership (GARP)	www.cddep.org/projects/global-antibiotic-resistance-partnership/garp-network/
Infectious Diseases Society of America (IDSA)	www.idsociety.org
Nebraska Medical Center	www.nebraskamed.com
Pew Charitable Trusts	www.pewtrusts.org
Review of Antimicrobial Resistance	www.amr-review.org
The Public Health Agency of Canada	www.phac-aspc.gc.ca
Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)	https://www.cdc.gov/drugresistance/tatfar/index.html
World Alliance Against Antibiotic Resistance (WAAAR)	www.ac2bmr.fr
World Health Organization (WHO)	www.who.int

Supplementary Table S2 List of stakeholders that participated to the consensus procedure.

Name	Position and Affiliation	Continent
Stakeholder group 1 'Medical community' n=13		
Diane Ashiru-Oredope	Pharmacist Lead for Antimicrobial Resistance and Stewardship and HCAI, Public Health England, United-Kingdom	Europe
Luis Bavestrello	Asociacion Panamericana de Infectiologia - API, Chile	South-America
Franky Buyle*	Hospital Pharmacist, Ghent University Hospital, Belgium	Europe
Barry Cookson	Medical Microbiologist, United-Kingdom	Europe
Pieter-Jan Cortoos	Clinical Pharmacist, University Hospital Brussels, Belgium	Europe
Gabriel Levy Hara	Infectious Diseases Unit, Hospital Durand, Buenos Aires, & Chair, Antimicrobial Stewardship Working Group, International Society of Chemotherapy, Argentina	South-America
Marc Mendelson*	Head, Division of Infectious Diseases & HIV Medicine, Department of Medicine, University of Cape Town, South-Africa	Africa
Blandina Theophil Mmbaga	Paediatrician, Kilimanjaro Christian Medical Centre & Director, Kilimanjaro Clinical Research Institute, Tanzania	Africa
Iruka N Okeke	Pharmaceutical and Clinical Microbiologist, Faculty of Pharmacy, University of Ibadan, Nigeria	Africa
Jesús Rodríguez-Baño	Professor of Medicine, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen Macarena, Universidad de Sevilla, Seville, Spain	Europe
Monique Rothan-Tondeur	Nurse, University Paris 13 & Assistance Publique – Hôpitaux de Paris, France	Europe
Karin Thursky*	Director NHMRC National Centre for Antimicrobial Stewardship, Royal Melbourne Hospital, Australia	Australia
Theo Verheij	Professor, Department of General Practice, Utrecht University Medical Center, the Netherlands	Europe

Supplementary Table S2 Continued.

Name	Position and Affiliation	Continent
Stakeholder group 2 'Public Health & Patients' n=12		
Sujith John Chandy*	Professor, Clinical Pharmacology, Christian Medical College, Vellore, India & Department of Public Health Sciences, Karolinska Institutet, Sweden	India & Europe
Abdul Ghafur	MD, Consultant Infectious Diseases, Chennai Declaration Group, India in the Department of Medicine at Brigham and Women's Hospital, United-States	India & North-America
David Heymann	Professor of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine; head of the Centre on Global Health Security at Chatham House, London; and chairman of Public Health England, United-Kingdom	Europe
Karianne Johansen	Senior advisor, Norwegian Public Health Institute, Norway	Europe
Rupa Kanapathipillai*	Infectious Disease Advisor, Médecins Sans Frontières, United-States	North-America
Marie Paule Kieny*	Assistant Director-General - Health Systems and Innovation, World Health Organization, Switzerland	Europe
David Kronlid	Professor of Ethics, University of Uppsala, Sweden	Europe
Cliodna McNulty	Head, Public Health England Primary Care Unit & Consultant Medical Microbiologist, UK	Europe
Enrique Perez**	Senior Advisor Foodborne Diseases and Zoonosis, Department of Communicable Diseases and Health Analysis, Pan American Health Organization, Regional office for the Americas, United-States	North-America
Babette Rump	MD, Infection Control and Public Health Ethics, National Institute for Public Health and the Environment, the Netherlands	Europe
Thomas Tängdén	MD, Action on Antibiotic Resistance - ReAct, Sweden	Europe
Visanu Thamlikitkul	MD, Professor of Medicine, Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University and member of WHO Strategic and Technical Advisory Group on Antimicrobial Resistance, Thailand	Asia

Stakeholder group 3 'Antibiotic R&D' n=13		
Claudie Charbonneau	Director, Global Health & Value, AI Team Lead, Pfizer P.I.O., France	Europe
Shiva Dustdar**	Head of Division, Innovation Finance Advisory, European Investment Bank, Luxembourg	Europe
James David Findlay	Lead Consultant, Morton Findlay Associates Limited & GSK, United-Kingdom	Europe
Jérôme Gabard	COO, Pherecydes Pharma, France	Europe
Elizabeth Hermsen	Head, Global Antimicrobial Stewardship, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, United-States	North-America
Aaron S. Kesselheim	Associate Professor of Medicine, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, United States	North-America
Charles Knirsch	Vice President, Therapeutic Vaccines Program Lead, Vaccine Clinical Research and Development, Pfizer, United-States	North-America
Marc Lemonnier	Founder and CEO, Antabio, France	Europe
Jean-Pierre Paccaud	Business development director, Drugs for Neglected Diseases initiative - DNDi, Switzerland	Europe
David Payne	Vice President and Head of the Antibacterial Discovery Performance Unit and Responsible Antibiotic Discovery, GSK, United-States	North-America
John H. Rex*	Chief Strategy Officer, CARB-X; Chief Medical Officer & Director, F2G, Ltd; Non-Executive Director & Consultant, Adenium Biotech ApS; Operating Partner & Consultant, Advent Life Sciences; Expert-in-Residence, Wellcome Trust; United-States	North-America
Gert-Jan van der Wilt	Professor of Health Technology Assessment, Radboud Center for Health Economics, Radboud University Medical Center, the Netherlands	Europe
Alexandra Waluszewski	Professor at the Department of Economic History, University of Uppsala, Sweden	Europe
Stakeholder group 4 'Payers/Policy makers/Government/Regulators' n=12		
Radu Botgros	Scientific Officer, Office of Anti-Infectives and Vaccines, European Medicines Agency, United-Kingdom	Europe
Christian Brun-Buisson	Ministerial representative for antibiotic resistance, Ministry of Social Affairs and Health, France	Europe

Supplementary Table S2 Continued.

Name	Position and Affiliation	Continent
Stakeholder group 4 'Payers/Policy makers/Government/Regulators' n=12		
John Farley	Deputy Director, Office of Antimicrobial Products, US Food and Drug Administration - FDA, United-States	North America
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Legend: * These stakeholders have participated to the consensus meeting; ** Incomplete answers.

3

Quality indicators for responsible antibiotic use in the inpatient setting: a systematic review followed by an international multi-disciplinary consensus procedure

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Abstract

Aim This study aimed to develop generic quality indicators (QIs) for responsible antibiotic use in the inpatient setting.

Methods A RAND-modified Delphi method was applied. First, QIs were identified by a systematic review. A complementary search was performed on web sites of relevant organisations. Duplicates were removed and disease and patient-specific QIs were combined into generic indicators. The relevance of these QIs was appraised by a multidisciplinary international stakeholder panel through two questionnaires and an in-between consensus meeting.

Results The systematic review retrieved 70 potential generic QIs. The QIs were appraised by 25 international stakeholders with diverse backgrounds (medical community, public health, patients, antibiotic research and development, regulators, governments). Ultimately, 51 QIs were selected in consensus. QIs with the highest relevance score included: (i) an antibiotic plan should be documented in the medical record at the start of the antibiotic treatment; (ii) the results of bacteriological susceptibility testing should be documented in the medical record; (iii) the local guidelines should correspond to the national guidelines but should be adapted based on local resistance patterns; (iv) an antibiotic stewardship programme should be in place at the healthcare facility; and (v) allergy status should be taken into account when antibiotics are prescribed.

Conclusion This systematic and stepwise method combining evidence from literature and stakeholder opinion led to multidisciplinary international consensus on generic inpatient QIs that can be used globally to assess the quality of antibiotic use.

Introduction

The loss of effectiveness of many antibiotics as a consequence of the emergence of antibiotic resistance has evolved to become a major threat to global public health. Unfortunately, this phenomenon coincides with a dry pipeline in antibiotic research and development (R&D).[1] Repercussions on patient care include increased mortality and limited effective therapy options for multidrug resistant and hospital-acquired infections.[2] In addition, treatment failure caused by antibiotic resistance has considerable financial consequences through, e.g., prolonged hospital stay or more expensive antibiotic therapy.[2]

While all antibiotic use drives the emergence and dissemination of resistance to some degree, a major aggravating force is the inappropriate use of antibiotics.[3] Therefore, reducing both overall antibiotic consumption and inappropriate use became a strategy to slow the pace of the emergence of resistant bacteria.[4-6] This strategy, commonly referred to as antibiotic stewardship, aims to measure and to improve antibiotic use.[7] In order to be successful, antibiotic stewardship programs (ASP) should comprise distinct tools for measuring both the quantity and quality of antibiotic use.

Measuring (in)appropriateness of health care is typically done using quality indicators (QIs) defined as 'measurable elements of practice performance for which there is evidence or consensus that they can be used to assess the quality, and hence change the quality of care provided'.[8] QIs of appropriate antibiotic use are valuable tools for ASPs as they guide the selection of improvement targets as well as help establish the effectiveness of improvement interventions.[9]

The Driving Reinvestment in Research and Development and Responsible Antibiotic Use (DRIVE-AB) research consortium proposes the following definitions to distinguish between the assessment of quality and quantity of antibiotic use. A quality indicator reflects the degree in which antibiotic use is correct or appropriate while, in contrast, a quantity metric reflects the volume or the costs of antibiotic use.[10] Therefore, the quality indicator has a value on its own while the quantity metric only gains value when comparisons are made between, e.g., wards, hospitals or countries.

The DRIVE-AB project aims at reaching consensus on a standard for 'responsible antibiotic use', including quality indicators, between a large variety of stakeholders involved in antibiotic use: from prescribers through producers and regulators to patients. Indeed, the large scale of societal implications of the loss of antibiotic effectiveness as a result of resistance development requires combined cross-disciplinary efforts throughout the whole society.

The aim of this study was to develop generic quality indicators for the inpatient setting taking into account different perspectives including the medical community, public health, patients, developers and producers (antibiotic R&D), regulators and governments.

Altogether, the quality indicators should serve as guiding principles for antibiotic use in the inpatient setting across diverse socioeconomic settings.

Materials and methods

A four-step RAND modified Delphi method,[11, 12, 13] an iterative process of rating and soliciting expert input with multiple opportunities for feedback, was applied to develop generic QIs for antibiotic use in the inpatient setting. The consensus procedure combined the individual opinions of four groups of stakeholders. All the stakeholders consented to participate in the study and were aware that their answers would be used for research. The consensus procedure took place from mid-August 2015 till the end of January 2016.

Step 1 – Literature and website search

A systematic review was performed in the MEDLINE database (since 1966) to identify papers describing inpatient quality indicators for antibiotic use. An inpatient was defined as a patient who is admitted to a hospital or health care facility for treatment. A health care facility was defined as any location where health care is provided, ranging from small clinics to hospitals. The search was performed on 5th of February 2015. The search strategy is detailed in **Figure S1** (Supplementary data). The aim was to identify QIs for antibiotic use that were either evidence-based (literature review, evidence-based guidelines) or consensus based (formal and validated consensus, like Delphi). Papers were included when written in English, on the use of systemically administered antibiotics drugs and when describing QIs for antibiotic use in the inpatient setting. Papers on the use of anti-viral, anti-fungal, anti-parasitic, anti-tuberculosis drugs were excluded. Papers were also excluded when describing quality indicators for rare or orphan diseases, as reported by Orphanet.[14] Finally, papers of which the full-text version was not accessible from one of the following libraries were also excluded: French National Institute of Health and Medical Research (INSERM), Radboud University Medical Center, University of Rijeka, University of Antwerp, University of Geneva, University of Leuven and University of Lorraine and Google Scholar®.

Two researchers (AM and IG) independently examined all titles and abstracts to select papers describing QIs for the inpatient setting using the Distiller® software (Evidence partners, Ottawa, Canada). Any disagreement on inclusion or exclusion of studies was resolved through discussion with a third author (MH). If no abstract was available or information was lacking for eligibility assessment, papers were selected for full text screening. The exclusion of papers based on full text screening was performed by one author (AM) and validated by a senior researcher (IG).

A complementary search was performed on English websites of relevant (inter) national organisations and institutions active in the field of antibiotic stewardship, quality improvement and/or public health. Relevant websites were selected in consensus by the authors, all working in the field of infectious diseases and/or antibiotic stewardship. Relevant sections of the websites were searched by one reviewer (AM) using the search terms 'indicator' and/or 'antibiotic/antimicrobial'.
The data extraction of QIs of antibiotic use was performed by one researcher (AM) using a standardised form. For the papers identified by the systematic review, the extraction process was repeated by the same researcher a second time for 10% of the references. Similarly, the data extraction from websites was performed by the same researcher twice. The extracted QIs were then clustered into different non-overlapping logical themes based on the elements of the definition of responsible use.[15] When a QI could be allocated to more than one theme, the predominant theme was chosen in consensus between two authors (AM and IG). Duplicates were removed. Overlapping QIs were then aggregated, and when applicable, disease and patient specific QIs were made more generic. Generic was defined as general and applicable to a large group of patients, not specific to any particular disease, country region or inpatient care setting.[16] When needed, QIs were rephrased as a recommendation. The clustering, aggregation and rephrasing steps were undertaken in consensus between four authors (AM, IG, JS and MH).

Step 2 – First questionnaire

International stakeholders were invited by e-mail to participate. Stakeholders were invited based either on demonstrated experience and expertise on the topic of antibiotic use and/or stewardship, or on different perspectives on antibiotic use. Invited stakeholders originated from various countries across all continents. Stakeholders among the extended international network of academic and European Federation of Pharmaceutical Industries and Associations (EFPIA) partners of the DRIVE-AB project were solicited. Fifty-two stakeholders amongst four different groups, aiming at representing all parties involved with antibiotic use, were invited: medical community (n=15); public health and patients (n=12); antibiotic R&D (n=14); payers, policy makers, governments and regulators (n=11).
A digital web-based questionnaire, with the potential inpatient QIs identified by the literature and websites searches, was designed using SurveyMonkey® (Palo Alto, California, USA). Together with the invitation e-mail, stakeholders received a document providing the scientific references for each of the identified QIs. The stakeholders were asked to appraise the relevance of each indicator for assessing the quality of antibiotic use. The 70 potential QIs were categorised and presented to the stakeholders. The assessment of the relevance was done using a 9-point Likert scale (1=Clearly not relevant, 9=Clearly relevant). Stakeholders could also select the

'cannot assess' answer. Median scores were analysed across the four stakeholder groups. Relevance scores were interpreted as described elsewhere.[17, 18] If the QI had a median of 8 or 9 and if there was agreement between the stakeholders, the QI was selected. If the QI had a median of 8 or 9 in combination with stakeholder disagreement, the QI was labelled for discussion. If the QI had a median <8, the QI was rejected. Agreement and disagreement were defined as ≥70% and <70% of the scores being in the upper tertile (score 7-9), respectively.[17, 18] Stakeholders could comment on each indicator as well as propose new QIs. Newly proposed QIs that did not present any overlap with other QIs were selected for discussion in the consensus meeting.

Step 3 – Consensus Meeting

Stakeholders that participated in the first questionnaire were asked to take part in a face-to-face consensus meeting on 29th September 2015. In addition, stakeholders from outside Europe could participate through a web conferencing interface. The aim was to reach a balanced number of stakeholders across the four groups. Before the meeting, participants received a personal feedback report with the results of the first questionnaire including their own relevance scores together with the group scores. For the QIs labelled for discussion, the comments made by the stakeholders in the first online questionnaire were shown to expedite the discussion. During the meeting, the stakeholders discussed QIs labelled for discussion and newly proposed QIs. Discussed QIs could either be selected, rejected or rephrased. For the latter, modifications would typically be made to the new wording proposal until agreement was reached between all participating stakeholders. An audio recording of the meeting was made and used to make sure no relevant suggestions or comments were missed during the meeting.

Step 4 – Second questionnaire

A second web-based questionnaire including all selected and rephrased QIs was sent to all participating stakeholders together with a personal feedback report (providing the results of the previous two steps of the consensus procedure). Stakeholders were asked to appraise the QIs by answering the question 'Do you agree with this indicator?' with 'yes' or 'no'. Stakeholders could select the 'cannot assess' answer and provide comments. Indicators were selected if >70% of the stakeholders agreed.[18]

The quality indicators were finally categorised in (i) structure indicators reflecting organisational aspects of health care, (ii) process indicators describing the care delivered to patients and (iii) outcome indicators specifying the effects of the care given to patients according to the Donabedian model.[19]

Results

Figure 1 shows the results of the selection process of the inpatient QIs after the different steps of the RAND modified Delphi method.

Step 1 – Literature and website search

The systematic literature search identified 620 articles of which 272 (43.8%) were considered eligible for full-text screening. After exclusion and inclusion criteria were applied, 139 articles (22%) were included and data extraction was performed. The flowchart of the systematic review is shown in **Figure S2** (Supplementary data). The websites of 26 institutions or organisations were searched for QIs. Eight websites (31%) were ultimately included for data extraction (**Table S1** available, Supplementary data). The systematic review and the complementary website search led to the identification of 518 QIs of antibiotic use in the inpatient setting. The website search identified 62 QIs. Systematic aggregation and rephrasing into 'generic' indicators resulted in a set of 70 QIs for appraisal by the multidisciplinary stakeholder panel (**Figure 1**). To illustrate the aggregation and rephrasing process an example is shown. The identified QIs '*Blood cultures performed in the emergency department prior to initial antibiotic received in hospital*', '*Proportion of Community Acquired Pneumonia (CAP) patients who have blood cultures drawn and proportion whose initial blood cultures are performed prior to the administration or the first hospital dose of antibiotics'*, '*Blood sample taken before start of antibiotic*s' and '*Before starting systemic antibiotic therapy, at least 2 sets of blood cultures should be taken*' led to the generic QI '*QI-31:Two sets of blood cultures should be taken before antibiotic administration when*

bacteraemia is suspected'. The 70 potential QIs were categorised into 20 themes: Access-Availability, Antibacterial Activity, Antibacterial Spectrum, Documentation, Dosing-PK/PD-Interval, Duration, Education, Expertise and Resources, Evidence-Based Guidelines, Indication, Interactions, Microbiological Diagnostics, Patient Outcome, Prescribing, Resistance Surveillance, Route, Surgical Prophylaxis, Therapeutic Drug Monitoring, Timing and Toxicity.

Step 2 – First online questionnaire

In the online questionnaire, a multidisciplinary panel of 25 stakeholders (response rate 48%) from 15 countries across four continents (n=15 from Europe, n=5 from North America, n=4 from Asia and n=1 from Australia) appraised the relevance of the potential QIs for assessing the quality of antibiotic use. The online questionnaire is shown in **Figure S3** (Supplementary data).

The 25 stakeholders were distributed as follows: n=10 (response rate 67%) belonged to the medical community group including board members of national and European

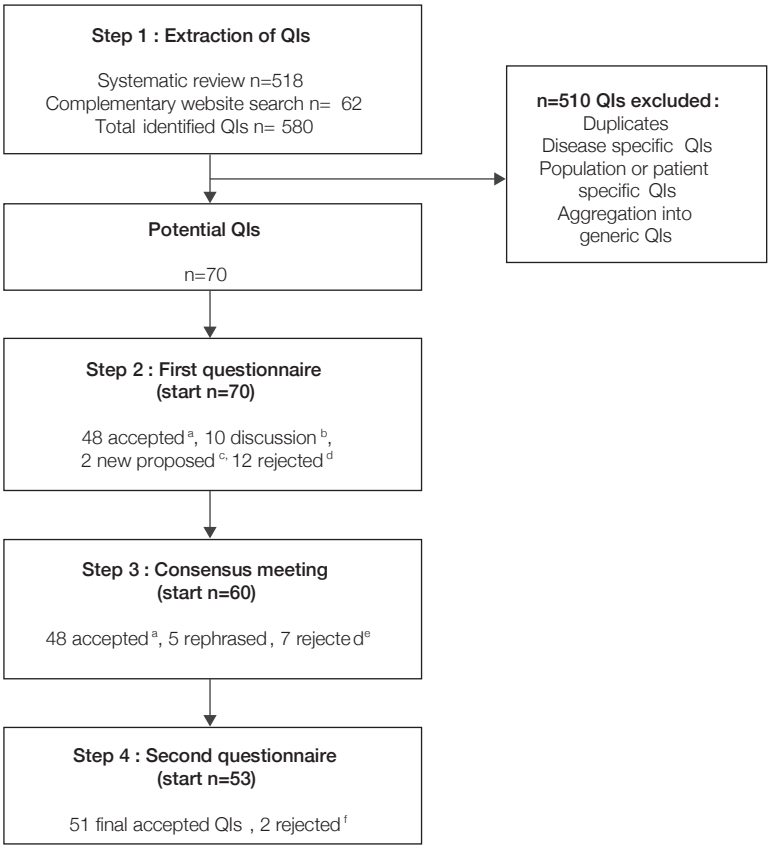

Figure 1: The results after each step of the RAND –modified Delphi method.
a. Accepted: the potential QI was selected for the next round because of an overall median score or at least 8, without disagreement. Disagreement was defined as the case in which less than 70% of the scores were in the upper tertile (scores 7, 8 or 9). **b.** Discussion: the QI had a median score of at least 8 with disagreement. **c.** Added: the indicator was proposed by one of the experts in the first survey. **d.** Rejected: Median score lower than 8. **e.** Rejected: in consensus between n=14 stakeholders. **f.** Rejected: Agreement score <70 %.

professional societies, hospital pharmacists and infectious disease physicians; n=3 (response rate 25%) to the public health and patients group including the World Health Organization, the Chennai Declaration Group and the Swedish public health institute; n=7 (response rate 50%) to the antibiotic R&D including small and medium enterprises, large pharmaceutical companies and (health) economists; and n=5

(response rate 46%) to the payers, policy makers, governments and regulators including the European Medicines Agency, the Centers for Disease Control and Prevention, governments, a health technology assessment institute and a national health insurance advisor. A detailed list of all the stakeholders and their affiliations is shown in **Table S2** (Supplementary data).

Based on relevance scores, 48 QIS were selected, 12 QIs were rejected and 10 QIs were labelled for discussion **(Figure 1**). Remarkably, the 12 rejected QIs included the two QIs relating to the theme *Indication.* Two new potential QIs were suggested by the stakeholders. Inpatient QIs with the highest relevance (median score of 9 and agreement score ≥96 %) score included: *QI-8 An antibiotic plan should be documented in the medical record at the start of the antibiotic treatment; QI-10 The results of bacteriological sensitivities should be documented in the medical record; QI-23 The local guidelines should correspond to the national guidelines but should be adapted based on local resistance patterns; QI-26 An antibiotic stewardship programme should be in place at the health care facility; QI-47 Allergy status should be taken into account when antibiotics are prescribed.* An overview of the results of the first online questionnaire is shown in **Table 1**.

Step 3- Consensus meeting

Fourteen stakeholders discussed the QIs for which there was disagreement as well as the newly suggested QIs. The stakeholders represented all groups: medical community (n=4); public health and patients (n=1); antibiotic R&D (n=6); payers, policy makers, governments and regulators (n=3). Of the 10 QIs labelled for discussion, three were rephrased and seven were rejected. The two newly suggested indicators were rephrased. The details of consensus procedure including the selection and rejection as well as the rephrasing of the QIs are shown in **Figure 1** and **Table 1**.

Step 4 – Second questionnaire

Twenty-two stakeholders answered the second questionnaire (response rate 88%). Based on agreement scores, out of the 53 potential QIs, 51 QIs were selected and two QIs were rejected (**Figure 1**). The final selected 51 inpatient QIs included 36 (71%) process, 13 (25%) structure and 2 (4%) outcome indicators and have received a final numbering in **Table 1**. The 51 inpatient QIs were classified into 19 themes of responsible antibiotic use (**Table 1**).

Table 1 Results of the consensus procedure on inpatient Quality Indicators (QIs) of antibiotic use.

Quality Indicators per theme	Type	First Questionnaire			Consensus Meeting	Second Questionnaire		Final selection
		Median	% in higher tertile	Conclusion		Agreement score (%)	Conclusion	
Access-Availability								
1. Antibiotics from the antibiotic formulary should not be out of stock at the health care facility.	Structure	9	84	Selected	-	86	Selected	QI-1
2. Prescribed antibiotics should actually be administered to the patients.	Process	9	84	Selected	-	100	Selected	QI-2
Antibacterial Activity								
3. The prescribed antibiotic should be active against all the likely causative pathogens.	Process	9	80	Selected	-	80	Selected	QI-3
4. Antibiotic empirical therapy should be considered appropriate if the bacteria identified are susceptible to at least one of the antibiotics administered.	Process	7.5	52	Rejected				
Antibacterial Spectrum								
5. The microbiological laboratory should report **individual** selective **susceptibility reports (or** antibiograms*) adapted to local guidelines.	Structure	9	68	Discussion	Rephrased	95	Selected	QI-4
6. Broad-spectrum empirical antibiotic therapy should be changed to pathogen-directed therapy as soon as culture results become available.	Process	9	84	Selected	-	96	Selected	QI-5
7. The choice of antibiotic treatment should be reviewed and modified based on clinical response.	Process	9	88	Selected	-	96	Selected	QI-6

8. Antibiotics should be continued in the ICU until assessed within 48 hours (before considering de-escalation).	Process	7	44	Rejected				
9. Antibiotics for empirical therapy should be reviewed after the third day of treatment **or when microbiological results become available.**	Process	Newly suggested QI			Rephrased	100	Selected	QI-7
Documentation								
10. An antibiotic plan should be documented in the medical record at the start of the antibiotic treatment. (Antibiotic plan includes: indication, name, doses, duration, route, and interval of administration).	Process	9	96	Selected	-	100	Selected	QI-8
11. Clinical and laboratory sepsis parameters should be documented in the medical records when prescribing antibiotics.	Process	9	80	Selected	-	86	Selected	QI-9
12. The results of bacteriological sensitivities should be documented in the medical records.	Process	9	96	Selected	-	95	Selected	QI-10
Dosing, PK/PD, Interval								
13. Dosing and dosing interval of antibiotics should be prescribed according to guidelines.	Process	8	80	Selected	-	96	Selected	QI-11
14. Dosing and dosing interval of renally eliminated antibiotics should be adapted to the patient's renal function.	Process	9	92	Selected	-	100	Selected	QI-12
15. Dosing of antibiotics should be adapted to the patient's BMI (Body Mass Index).	Process	8	64	Discussion	Rejected			
16. Dosing of antibiotics should be adapted to the patient's age.	Process	7	52	Rejected				

Table 1 Continued.

Quality Indicators per theme	Type	First Questionnaire			Consensus Meeting	Second Questionnaire		Final selection
		Median	% in higher tertile	Conclusion		Agreement score (%)	Conclusion	
Dosing, PK/PD, Interval								
17. The dosage regimen of antibiotics with an increased risk of toxicity (such as vancomycin or gentamicin) should be managed according to guidelines.	Process	9	92	Selected	-	86	Selected	QI-13
Duration								
18. Duration of antibiotic therapy should be compliant with guidelines.	Process	8	80	Selected	-	86	Selected	QI-14
19. Antibiotic therapy should be discontinued based on the lack of clinical evidence of infection.	Process	9	92	Selected	-	100	Selected	QI-15
20. Antibiotic therapy should be discontinued based on the lack of microbiological evidence of infection.	Process	5	28	Rejected	-	-	-	-
21. Antibiotic therapy should be discontinued on completion of the documented antibiotic course.	Process	8	72	Selected	-	95	Selected	QI-16
22. Stopping antibiotic therapy should always be considered after three consecutive days of defervescence.	Process	5	28	Rejected				
Education								
23. Educational sessions about local practice guidelines should be organised for ~~antibiotic stewardship teams and~~ medical staff and should have a predetermined attendance target.	Structure	8	68	Discussion	Rephrased	90	Selected	QI-17

Evidence-based Guidelines								
24. Antibiotics should be prescribed according to local practice guidelines.	Process	8	76	Selected	-	100	Selected	QI-18
25. Antibiotics should be prescribed according to national practice guidelines.	Process	8	80	Selected	-	68	Rejected	
26. Antibiotics should be prescribed according to national guidelines when no local guidelines are available.	Process	8	84	Selected	-	100	Selected	QI-19
27. Antibiotic prescriptions that deviate from guidelines should be justified.	Process	9	76	Selected	-	96	Selected	QI-20
28. A local antibiotic guideline should be present at the health care facility.	Structure	9	92	Selected	-	96	Selected	QI-21
29. An evaluation whether an update should be ~~done~~ considered for the local antibiotic guideline ~~every three years~~ **once a year.**	Structure	8	68	Discussion	Rephrased	96	Selected	QI-22
30. The local guidelines should correspond to the national guideline but should be adapted based on local resistance patterns.	Structure	9	100	Selected	-	96	Selected	QI-23
Expertise and Resources								
31. An antibiotic formulary should be available and updated continuously at the health care facility.	Structure	9	76	Selected	-	96	Selected	QI-24
32. An approval system should be in place for prescriptions of restricted antibiotics at the health care facility.	Structure	9	84	Selected	-	96	Selected	QI-25
33. A computerised decision support system based on local guidelines should be available at the health care facility.	Structure	7	60	Rejected				
34. An antibiotic stewardship programme (antibiotic prescribing control programme and/or antibiotic prescribing policy) should be in place at the health care facility.	Structure	9	100	Selected	-	100	Selected	QI-26

Table 1 Continued.

Quality Indicators per theme	Type	First Questionnaire			Consensus Meeting	Second Questionnaire		Final selection
		Median	% in higher tertile	Conclusion		Agreement score (%)	Conclusion	
Expertise and Resources								
35. Antibiotic prescribing should be compliant with recommendations from infectious disease and/or microbiology specialist(s).	Process	8	80	Selected	-	76	Selected	QI-27
36. Audits of antibiotic use by the antibiotic stewardship team should be performed regularly at the health care facility.	Structure	9	92	Selected	-	96	Selected	QI-28
37. A multidisciplinary antibiotic stewardship team appointed by the health care facility management should have meetings at least twice a year and make a report with objectives and selected performance indicators.	Structure	8	80	Selected	-	91	Selected	QI-29
38. Patients with *S. aureus* bacteraemia should be seen by ~~an infection disease specialist~~ **a physician trained in infectious diseases.**	Process	Newly suggested QI			Rephrased	68	Rejected	
Indication								
39. Antibiotics should be used only for strict indications.	Process	7.5	64	Rejected				
40. A clinical scoring system should be used to determine if there is an indication for antibiotic use.	Process	5	28	Rejected				

Interactions								
41. Identified interactions between antibiotic regimen and concurrent medications should be documented in the medical record with a recommended management plan to deal with the interaction.	Process	9	88	Selected	-	91	Selected	QI-30
Microbiological Diagnostics								
42. Two sets of blood cultures should be taken before antibiotic administration when bacteraemia is suspected.	Process	9	76	Selected	-	95	Selected	QI-31
43. Specimens for culture from suspected sites of infection should be collected before antibiotic administration.	Process	9	88	Selected	-	95	Selected	QI-32
44. Microbiological investigations should be performed according to guidelines.	Process	9	84	Selected	-	96	Selected	QI-33
Patient Outcome								
45. Clinical outcomes of patients receiving antibiotics should be monitored at the health care facility.	Outcome	8	80	Selected	-	86	Selected	QI-34
46. Bacterial outcomes of patients receiving antibiotics should be monitored at the health care facility.	Outcome	7.5	64	Rejected				
47. Resistance outcomes of patients receiving antibiotics should be monitored at the health care facility.	Outcome	8	64	Discussion	Rejected			
48. Rates of nosocomial *Clostridium difficile* should be monitored at the health care facility.	Outcome	9	80	Selected	-	100	Selected	QI-35
Prescribing								
49. Antibiotics should be prescribed by generic name.	Process	7	52	Rejected				

Table 1 Continued.

Quality Indicators per theme	Type	First Questionnaire			Consensus Meeting	Second Questionnaire		Final selection
		Median	% in higher tertile	Conclusion		Agreement score (%)	Conclusion	
Route								
50. The route of administration of antibiotics should be compliant with guidelines.	Process	9	84	Selected	-	96	Selected	QI-36
51. Antibiotic therapy in adult patients with sepsis should be started intravenously.	Process	9	76	Selected	-	84	Selected	QI-37
52. Switching from intravenous to oral antibiotic(s) should be performed according to guidelines.	Process	9	80	Selected	-	91	Selected	QI-38
53. Switching from intravenous to oral antibiotic(s) should be done within 48–72 hours based on the clinical condition and when oral treatment is adequate.	Process	8	72	Selected	-	76	Selected	QI-39
Resistance Surveillance								
54. Surveillance of antibiotic use and resistance should be performed at least once per year at the health care facility.	Structure	9	92	Selected	-	100	Selected	QI-40
Surgical Prophylaxis								
55. Prophylactic antibiotics should be available in the operating room and pre-operative admission units.	Structure	9	68	Discussion	Rejected			
56. Postoperative prophylactic antibiotics should be discontinued within 24 hours after wound closure.	Process	8	56	Discussion	Rejected			
57. Prophylactic antibiotics should be added to a preoperative checklist.	Structure	9	76	Selected	-	100	Selected	QI-41

58. A preoperative pause (time-out) should be implemented before administering antibiotic prophylaxis.	Process	7	32	Rejected				
59. Prophylactic antibiotics should be redosed intra-operatively for surgeries longer than 3-4 hours or significant blood loss (≥1500mL).	Process	8.5	60	Discussion	Rejected			
Therapeutic Drug Monitoring (TDM)								
60. Therapeutic Drug Monitoring should be performed for antibiotics with a narrow therapeutic spectrum and an increased risk of toxicity (like gentamicin and vancomycin) according to guidelines.	Process	9	88	Selected	-	86	Selected	QI-42
61. At least 75% of Therapeutic Drug Monitoring levels of antibiotics should be within the desired reference range.	Process	8	44	Discussion	Rejected			
62. If antibiotic Therapeutic Drug Monitoring levels are not in the reference range, doses should be adjusted appropriately after the results become available.	Process	9	76	Selected	-	91	Selected	QI-43
63. Therapeutic Drug Monitoring levels of antibiotics should be documented in the medical records.	Process	9	88	Selected	-	100	Selected	QI-44
Timing								
64. Timeliness of administration of antibiotic therapy and prophylaxis should be compliant with guidelines.	Process	9	92	Selected	-	100	Selected	QI-45
65. Antibiotic therapy should be started as soon as possible upon admission to the health care facility.	Process	5.5	32	Rejected				
Toxicity								
66. Duration of administration of intravenous antibiotics should be compliant with guidelines.	Process	8	76	Selected	-	86	Selected	QI-46

Table 1 Continued.

Quality Indicators per theme	Type	First Questionnaire			Consensus Meeting	Second Questionnaire		Final selection
		Median	% in higher tertile	Conclusion		Agreement score (%)	Conclusion	
Toxicity								
67. Allergy status should be taken into account when antibiotics are prescribed.	Process	9	96	Selected	-	100	Selected	QI-47
68. Allergy status (including nature and severity) of the patient should be documented in the medical records when antibiotics are prescribed.	Process	9	92	Selected	-	100	Selected	QI-48
69. Patients with a history of anaphylaxis after penicillin therapy should be prescribed an alternative drug class.	Process	9	88	Selected	-	100	Selected	QI-49
70. Medical staff should be educated regarding cross-allergy with cephalosporins in patients with penicillin allergy.	Process	9	92	Selected	-	95	Selected	QI-50
71. Antibiotics should be changed in case of adverse reaction.	Process	8.5	68	Discussion	Rejected			
72. Contraindications should be taken into account when prescribing antibiotics.	Process	9	88	Selected	-	96	Selected	QI-51

The references are shown in **Table S3** (Supplementary data).

-: not discussed; QI: Inpatient Quality Indicator; PK/PD: pharmacokinetic/pharmacodynamic.

** A selective susceptibility report (or antibiogram) is a report of a selection of antibiotic sensitivities, based on bacteriological activity, broadness of spectrum or toxicity.*

Discussion

This international and multidisciplinary consensus procedure led to the development of 51 generic quality indicators for antibiotic use in the inpatient setting. These QIs are intended to be universally applicable, regardless of infectious disease type, geographical or socioeconomic setting. Moreover, the broad background range of the stakeholders that selected them is expected to lead to a widespread support of the QIs. Most of the inpatient QIs were classified as process, about a third as structure and only two as outcome indicators according to the Donabedian model. Altogether, the QIs covered a wide range of 19 different themes of responsible inpatient antibiotic use of which the majority overlaps with the elements of the definition of responsible use.[15] During the consensus procedure, the two QIs relating to the theme 'Indication' were rejected by the stakeholder panel. This is surprising as 'Using antibiotics for the correct indication' is one of the main recommendations for prudent use by ECDC.[20] This also contrasts with the selection of the element 'Indication' phrased as 'Using antibiotics only to prevent or cure infections for which antibiotic treatment provides a proven benefit' for the global definition of responsible use by a similar international multidisciplinary panel.[15] However, the stakeholders of the present study might have considered the requirement of a correct clinical indication for the use of antibiotics being covered by six QIs in the theme 'Evidence based guidelines (QI-18 to QI-22), e.g., QI-18 'Antibiotics should be prescribed according to local practice guidelines'. In addition, several other QIs relate to the use of guidelines (e.g., QI-11, QI-14, QI-33, QI-37). Indeed, compliance with local hospital guidelines is a universal measure of health care quality.

Other researchers have developed generic (i.e., non-disease specific) inpatient process quality indicators for antibiotic use. The QIs developed in this study overlap with all eleven QIs identified by Van den Bosch and colleagues using a similar methodology with a European expert panel in which all the main medical specialties involved in antibiotic treatment were represented.[21] However, the panel did not include (inter)national professional clinical societies nor stakeholders from outside the medical community. In another initiative, the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), experts from the EU and the US identified 17 core indicators and 16 optional indicators for inpatient antibiotic use addressing the organisation of ASPs.[22] While the Van den Bosch study aimed at developing a concise set of non-disease specific QIs, the list of TATFAR indicators resulted from comparisons between antibiotic stewardship programs in EU and US hospitals. All these quality indicators should be seen as complementary output of international and cross-disciplinary efforts to improve antibiotic use.

A strength of this work is the use of a Rand-modified Delphi method combining both concepts from international literature and international stakeholder opinions.

This standardised method has been used previously for the identification of QIs of antibiotic use in the inpatient setting.[18, 23, 24] To our knowledge this is the first time that the perspectives of such a broad range of stakeholders involved with antibiotics were accounted for in the development of the QIs. The four stakeholder groups represented all parties involved with antibiotics from molecule to prescribed drug. The diversity in background and geography (15 countries across four continents) of the stakeholders emphasises the potential for global acceptance of our consensus. The use of a broad definition for the inpatient setting should ensure that QIs are relevant for a large range of health care facilities including, e.g., acute care hospitals and long term care facilities.

Methodological limitations of this study include the use of one single literature database (MEDLINE) for the systematic review. Both the complementary website search and the opportunity given to the stakeholders to propose new QIs should have ensured that no relevant QI was missed. Another limitation is the lack of grading of the evidence for the quality indicators by the authors. Instead, stakeholders were provided with the original references for each of the QIs, offering the opportunity to assess the scientific evidence by themselves. Also, there was low participation of stakeholders of the 'Public Health & Patients' group compared with the three other groups. Explanations could include the perceived lack of knowledge for assessing QIs for the inpatient setting as public health typically focuses on community care. The relevance scores for the QIs were not analysed for each individual stakeholder group separately as the aim of the study was to identify QIs taking into account different perspectives. Therefore, the data analysis was performed across the four stakeholder groups. Finally, even though the scope of the study was global, an English language restriction was applied to the literature and website searches. We may have missed important papers in other languages. However, English is nowadays considered a major global vehicle in the scientific literature that is directed to a global audience.

Aspects relating to the applicability of the QIs in clinical practice were not assessed in the consensus procedure. However, this may rather have contributed to the simplicity of the QIs, required for a global scope, including coverage of low-income settings. Certainly, before these indicators can be used in daily medical practice, their applicability should be tested in the prevailing health care setting including clinimetric properties relating to feasibility, validity, and reliability.[23-25]

How can the generic inpatient quality indicators reported in this study be used? So far, the QIs have contributed to the 'Proposals for EU guidelines for the prudent use of antimicrobials in human medicine' written by the European Centre for Disease Prevention and Control.[20] Furthermore, educational materials derived from this study, e.g., a podcast of a train the trainer event organised in collaboration with the British Society for Antimicrobial Chemotherapy (BSAC) with delegates from 19 EU countries,

are made available for use in ASPs and health care curricula.[26] In the future, the QIs, being one of the components of the DRIVE-AB standard of responsible antibiotic use, are expected to further guide (inter)national health policies.

In conclusion, the 51 generic QIs cover a broad scale of themes for responsible inpatient antibiotic use. They can be used globally to guide the use of both current and newly developed antibiotics in the future.

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Chapter 3 - Supplementary data

Concept 1 Antibiotics:

Anti-infective agents [MeSH][a] OR
Antibiotic prophylaxis [MeSH] OR
Antibiotic* [tiab][b] OR
Antiinfective* [tiab] OR
Anti infective* [tiab] OR
Antimicrobial* [tiab] OR
Anti microbial* [tiab] OR
Antibacterial* [tiab] OR
Anti bacterial* [tiab]

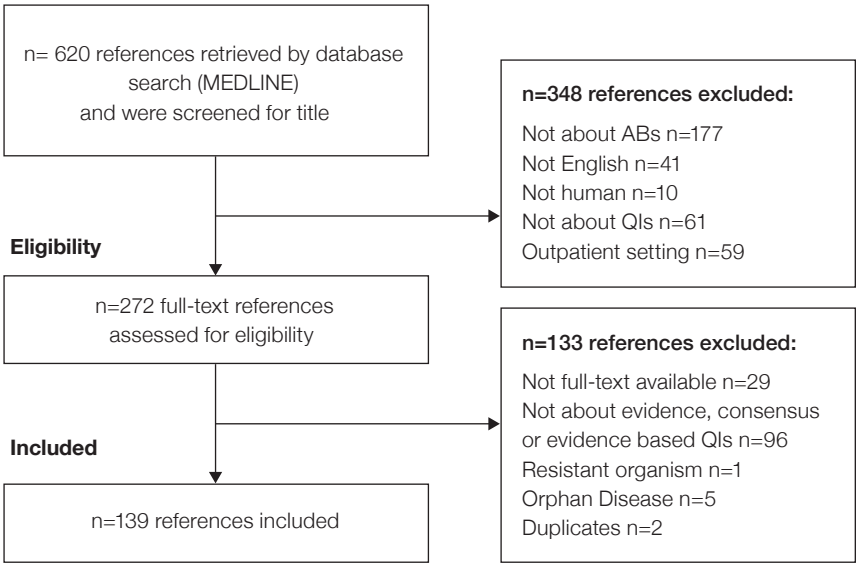
AND

Concept 2 Quality Indicators:

quality indicators, health care [MeSH] OR
quality indicator [tiab] OR
quality indicators [tiab] OR
quality measure [tiab] OR
quality measures [tiab] OR
quality metric [tiab] OR
quality metrics [tiab] OR
quality criteria [tiab] OR
qualitative measure [tiab] OR
qualitative measures [tiab] OR
quality improvement [ti][c]

Supplementary Figure S1: Search strategy of the systematic review.

Legend: [a] : Medical Subject Headings; [b] : title/abstract; [c] : title.



Supplementary Figure S2: Flowchart of the systematic review following the PRISMA template.

Legend: AB: antibiotic; QI: Quality Indicator

Supplementary Figure S3: Online questionnaire on 'Inpatient Quality Indicators'. Available at: *https://doi.org/10.1093/jac/dky116*

Supplementary Table S1 List of screened organisations, institutions or initiatives and their websites.

	Name of the organisation, institution or initiative (website)	Included for data extraction
1	Agency for Healthcare Research & Quality (www.ahrq.gov/)	✓
2	Alliance for the Prudent Use of Antibiotics (APUA) (www.apua.org/)	
3	Australian Government Department of Health (www.health.gov.au/)	✓
4	Canadian Centre for Health and Safety in Agriculture (www.cchsa-ccssma.usask.ca/)	
5	Centers for Disease Control and Prevention (CDC) (www.cdc.gov/)	✓
6	European Centre for Disease Control and Prevention (ECDC) (www.ecdc.europa.eu/)	✓
7	European Medicines Agency (EMA) (www.ema.europa.eu/)	
8	European Society of Clinical Microbiology and Infectious Diseases (ESCMID) (https://www.escmid.org/)	
9	Infectious Disease Society of America (IDSA) (www.idsociety.org/)	
10	Institute for Applied Quality Improvement and Research in Health Care GmbH (AQUA) (www.aqua-institut.de/en/home/)	
11	Institute for Healthcare improvement (IHI) (www.ihi.org/)	✓
12	International Network for the Rational Use of Drugs (INRUD) (https://www.msh.org/journal-tags/inrud-iaa-international-network-for-the-rational-use-of-drugs-initiative-on-arv)	✓
13	International Society of Chemotherapy Infection and Cancer (ISC) (www.ischemo.org/)	
14	International Society of Infectious Diseases (www.isid.org/)	
15	National Institute for Health and Care Excellence (https://www.nice.org.uk/)	✓
16	National Quality Measures Clearinghouse (https://www.qualitymeasures.ahrq.gov/)	
17	NHS institute for innovation and improvement (www.institute.nhs.uk/)	
18	Public Health Agency of Canada (www.publichealth.gc.ca/)	
19	RAND Corporation (www.rand.org/)	
20	ReAct group (www.reactgroup.org)	
21	Swedish Strategic Programme against Antibiotic Resistance (Strama) (www.strama.se)	
22	The Center for Disease Dynamics, Economics & Policy (CDDEP) (www.cddep.org/)	

Supplementary Table S1 Continued.

	Name of the organisation, institution or initiative (website)	Included for data extraction
23	The Global Antibiotic Resistance Partnership (GARP) (www.cddep.org/garp/home)	
24	Transatlantic Task Force on Antimicrobial Resistance (TATFAR) (http://www.cdc.gov/drugresistance/tatfar/)	
25	US Food and Drug Administration (www.fda.gov/)	
26	World Health Organization (WHO) (www.who.int/)	✓

Supplementary Table S2 List of the international stakeholders that participated in the different steps of the RAND-modified Delphi method.

Stakeholders per group: title, function, (department) and institute/organisation	Country	First Questionnaire QM: n=23 QI: n=25	Consensus meeting n=14	Second questionnaire for final assessment n=22
Stakeholder group 1: Medical community				
-Medical specialists and Clinical Pharmacists				
Michael Borg, MD, Associate Professor, Department of Pathology, University of Malta	Malta	✓		✓
Franky Buyle, PharmD, Hospital Pharmacist, Ghent University Hospital	Belgium	✓		✓
Catherine Dumartin, PharmD, Bordeaux Population Health Center & University Hospital Center Bordeaux	France	✓		✓
Lindsay Grayson, MD, Professor of Medicine, University of Melbourne	Australia	✓		
Philip Howard, PharmD, Professor of Hospital Pharmacy, University of Leeds	United-Kingdom	✓		✓
Mical Paul*, MD, Professor of Infectious Diseases, Rambam Health Care Campus	Israel	✓		✓
Jesús Rodríguez-Baño, MD, Professor of Medicine, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen Macarena, Universidad de Sevilla	Spain	✓		✓
Richard Drew**, PharmD, Associate Professor in Medicine, Duke University	United-States		✓	
Heiman Wertheim**, Director, Oxford University Clinical Research Unit *Presently*: Professor of Medical Microbiology, Radboudumc	Vietnam The Netherlands		✓	
-Professional societies				
Bojana Beović, MD, Professor of infectious diseases, University Medical Centre Ljubljana & Faculty of Medicine, University of Ljubljana and chair of ESCMID Study Group for Antibiotic Policies - ESGAP	Slovenia	✓	✓	✓
Garyfallia Poulakou, MD, Athens University School of Medicine & Hellenic Society for Chemotherapy	Greece	✓	✓	✓
Christian Rabaud, MD, Professor of infectious diseases & chair of Societé de Pathologie Infectieuse de Langue Française - SPILF	France	✓		✓

Stakeholder group 2: Public Health & Patients				
Abdul Ghafur, MD, Consultant in infectious diseases and clinical microbiology, Apollo Hospitals & coordinator Chennai Declaration	India	✓		✓
Cecilia Stålsby Lundborg, Professor, Department of Public Health Sciences, Karolinska Institutet	Sweden	✓		✓
Visanu Thamlikitkul, MD, Professor of Medicine, Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, and member of WHO Strategic and Technical Advisory Group on Antimicrobial Resistance	Thailand	✓		✓
Thomas Tängdén**, MD, Assistant Professor in infectious diseases, Uppsala University and Medical Director, Action on Antibiotic Resistance - ReAct	Sweden		✓	
Stakeholder group 3: Antibiotic R&D				
Ad Antonisse, Director Economic Affairs, Astra Zeneca	The Netherlands	✓		✓
Elizabeth Hermsen, PharmD, MBA, Head Global Antimicrobial Stewardship, Merck	United-States	✓	✓	✓
Mike Kenston, MBA, chief commercial officer, Melinta Therapeutics	United-States	✓		
Aaron S. Kesselheim, Associate Professor of Medicine, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School	United-States	✓	✓	✓
Charles Knirsch, MD, Vice President, Clinical Research and Development Pfizer Inc., Pfizer	United-States	✓	✓	✓
Ramanan Laxminarayan, Professor, Department of Management Sciences, University of Strathclyde & Director Center for Disease Dynamics, Economics and Policy - CDDEP	United-Kingdom United-States India	✓		✓
Alexandra Waluszewski, Professor, Department of Economic History, University of Uppsala	Sweden	✓		✓
Harpal Dhillon**, Country Medical Lead & Chair of Royal Pharmaceutical Society's AMR Expert Advisory Group, Merck Sharp & Dohme Limited	United-Kingdom		✓	
David Findlay**, Lead Consultant, Morton Findlay Associates Limited & GSK	United-Kingdom		✓	

Supplementary Table S2 Continued.

Stakeholders per group: title, function, (department) and institute/organisation	Country	First Questionnaire QM: n=23 QI: n=25	Consensus meeting n=14	Second questionnaire for final assessment n=22
Stakeholder group 3: Antibiotic R&D				
John H. Rex**, MD, Senior Vice President & Chief Strategy Officer, Infection Business Unit, AstraZeneca *Presently:* Chief Medical Officer & Director, F2G, Ltd; Chief Strategy Officer, CARB-X; Non-Executive Director & Consultant, Adenium Biotech ApS; Operating Partner & Consultant, Advent Life Sciences; and Expert-in-Residence, Wellcome Trust	United-States		✓	
Stakeholder group 4: Payers, Policy makers, Government, Regulators				
Marco Cavaleri, PhD, Head, Anti-infectives and Vaccines, European Medecines Agency	United-Kingdom	✓		✓
Patrick Lacor*, MD, INAMI/RIZIV National health insurance advisor & clinical infectiologist, University Hospital Brussels	Belgium	✓		✓
Arjun Srinivasan, MD, Associate Director for Healthcare Associated Infection Prevention Programs, Centers for Disease Control and prevention - CDC	United-States	✓	✓	✓
Claudia Wild, PhD, Director, Ludwig Boltzmann Institute for Health Technology Assessment	Austria	✓		✓
Sally Wellsteed, Team Leader Antimicrobial Resistance, Department of Health, on behalf of Dame Sally Davies	United-Kingdom	✓		✓
Lauri Hicks**, DO, Medical Epidemiologist & Medical Director, Get Smart: Know When Antibiotics Work Program, Centers for Disease Control and prevention - CDC	United-States		✓	
Diamantis Plachouras**, MD, Expert Antimicrobial Resistance and Healthcare-associated Infections, European Centre for Disease Prevention and Control - ECDC	Sweden		✓	

Legend: MD: Doctor of Medicine; PharmD: Doctor of Pharmacy; QI: Quality Indicator; QM: Quality Metric. * Only participation to the inpatient quality indicators section of the first questionnaire. ** These stakeholders participated in the consensus procedure on quality indicators of antibiotic use in the outpatient setting that was performed in parallel to our study by Le Maréchal et al.[1] and Versporten et al.[2]. They were provided with the results of the first survey and took part in the consensus meeting.

Supplementary Table S3 Results of the systematic review on inpatient Quality Indicators (QIs) of antibiotic use.

Quality Indicators per theme	References	Final numbering
Access- Availability		
1. Antibiotics from the antibiotic formulary should not be out of stock at the health care facility.	3	QI-1
2. Prescribed antibiotics should actually be administered to the patients.	3-8	QI-2
Antibacterial Activity		
3. The prescribed antibiotic should be active against all the likely causative pathogens.	9-12	QI-3
4. Antibiotic empirical therapy should be considered appropriate if the bacteria identified are susceptible to at least one of the antibiotics administered.	6, 13, 14	Rejected
Antibiotic Spectrum		
5. The microbiological laboratory should report **individual** selective **susceptibility reports (or** antibiograms***)** adapted to local guidelines.	15	QI-4
6. Broad-spectrum empirical antibiotic therapy should be changed to pathogen-directed therapy as soon as culture results become available.	16-31	QI-5
7. The choice of antibiotic treatment should be reviewed and modified based on clinical response.	24	QI-6
8. Antibiotics should be continued in the ICU until assessed within 48 hours (before considering deescalation).	32	
9. Antibiotics for empirical therapy should be reviewed after the third day of treatment **or when microbiological results become available.**	Newly suggested QI	QI-7
Documentation		
10. An antibiotic plan should be documented in the medical record at the start of the antibiotic treatment. (Antibiotic plan includes: indication, name, doses, duration, route, and interval of administration).	8, 16, 22, 24, 28, 30, 33-39	QI-8
11. Clinical and laboratory sepsis parameters should be documented in the medical records when prescribing antibiotics.	16	QI-9

Supplementary Table S3 Continued.

Quality Indicators per theme	References	Final numbering
Documentation		
12. The results of bacteriological sensitivities should be documented in the medical records.	24	QI-10
13. Dosing and dosing interval of antibiotics should be prescribed according to guidelines.	4, 8, 13, 15, 24, 25, 30, 39-43	QI-11
14. Dosing and dosing interval of renally eliminated antibiotics should be adapted to the patient's renal function.	4, 15, 17, 18, 20, 21, 28, 29, 39	QI-12
15. Dosing of antibiotics should be adapted to the patient's BMI (Body Mass Index).	4, 39-41, 44	Rejected
16. Dosing of antibiotics should be adapted to the patient's age.	39	Rejected
17. The dosage regimen of antibiotics with an increased risk of toxicity (such as vancomycin or gentamicin) should be managed according to guidelines.	45	QI-13
Duration		
18. Duration of antibiotic therapy should be compliant with guidelines.	5, 7, 13, 37, 39, 41, 46, 47	QI-14
19. Antibiotic therapy should be discontinued based on the lack of clinical evidence of infection.	28	QI-15
20. Antibiotic therapy should be discontinued based on the lack of microbiological evidence of infection.	28	Rejected
21. Antibiotic therapy should be discontinued on completion of the documented antibiotic course.	24	QI-16
22. Stopping antibiotic therapy should always be considered after three consecutive days of defervescence.	17, 18, 20, 29	Rejected
Education		
23. Educational sessions about local practice guidelines should be organised for ~~antibiotic stewardship teams and~~ medical staff and should have a predetermined attendance target.	15, 16, 48	QI-17
Evidence-based Guidelines		
24. Antibiotics should be prescribed according to local practice guidelines.	3, 5, 7-9, 13, 15, 16, 20, 22-25, 28, 31, 35, 37, 39-41, 43, 46, 49-90	QI-18
25. Antibiotics should be prescribed according to national practice guidelines.	17, 18, 21, 22, 26, 27, 29, 91-95	Rejected
26. Antibiotics should be prescribed according to national guidelines when no local guidelines are available.	28	QI-19
27. Antibiotic prescriptions that deviate from guidelines should be justified.	38	QI-20

28. A local antibiotic guideline should be present at the health care facility.	3, 8, 15, 28, 44	QI-21
29. An evaluation whether an update should be considered for the local antibiotic guideline should be done ~~every three years~~ **once a year.**	28	QI-22
30. The local guidelines should correspond to the national guideline but should be adapted based on local resistance patterns.	27, 28	QI-23
Expertise and Resources		
31. An antibiotic formulary should be available and updated continuously at the health care facility.	3, 15	QI-24
32. An approval system should be in place for prescriptions of restricted antibiotics at the health care facility.	3, 15	QI-25
33. A computerised decision support system based on local guidelines should be available at the health care facility.	15	Rejected
34. An antibiotic stewardship programme (antibiotic prescribing control programme and/or antibiotic prescribing policy) should be in place at the health care facility.	15, 96	QI-26
35. Antibiotic prescribing should be compliant with recommendations from infectious disease and/or microbiology specialist(s).	38, 39, 77	QI-27
36. Audits of antibiotic use by the antibiotic stewardship team should be performed regularly at the health care facility.	15, 96, 97	QI-28
37. A multidisciplinary antibiotic stewardship team appointed by the health care facility management should have meetings at least twice a year and make a report with objectives and selected performance indicators.	15	QI-29
38. Patients with *S. aureus* bacteraemia should be seen by ~~an infection disease specialist~~ **a physician trained in infectious diseases.**		Rejected
Indication		
39. Antibiotics should be used only for strict indications.	7, 13, 15, 17, 21, 41, 43, 85, 98-103	Rejected
40. A clinical scoring system should be used to determine if there is an indication for antibiotic use.	31, 104	Rejected
Interactions		
41. Identified interactions between antibiotic regimen and concurrent medications should be documented in the medical record with a recommended management plan to deal with the interaction.	24, 39	QI-30

Supplementary Table S3 Continued.

Quality Indicators per theme	References	Final numbering
Microbiological Diagnostics		
42. Two sets of blood cultures should be taken before antibiotic administration when bacteraemia is suspected.	15, 17-20, 23, 25, 27-29, 32, 46, 52, 55, 56, 62, 64, 68, 74, 76, 78, 86, 91, 92, 105-111	QI-31
43. Specimens for culture from suspected sites of infection should be collected before antibiotic administration.	17-21, 23-26, 28-31, 106	QI-32
44. Microbiological investigations should be performed according to guidelines.	15, 16, 22, 31, 34, 47, 90	QI-33
Patient Outcome		
45. Clinical outcomes of patients receiving antibiotics should be monitored at the health care facility.	15	QI-34
46. Bacterial outcomes of patients receiving antibiotics should be monitored at the health care facility.	48	Rejected
47. Resistance outcomes of patients receiving antibiotics should be monitored at the health care facility.	8, 16, 30	Rejected
48. Rates of nosocomial *Clostridium difficile* should be monitored at the health care facility.	8, 15, 30	QI-35
Prescribing		
49. Antibiotics should be prescribed by generic name.	3, 8, 95	Rejected
Route		
50. The route of administration of antibiotics should be compliant with guidelines.	9, 13, 24, 39, 43, 53, 112	QI-36
51. Antibiotic therapy in adult patients with sepsis should be started intravenously.	27	QI-37
52. Switching from intravenous to oral antibiotic(s) should be performed according to guidelines.	15, 16, 20, 25, 92, 99, 113	QI-38
53. Switching from intravenous to oral antibiotic(s) should be done within 48–72 hours based on the clinical condition and when oral treatment is adequate.	17, 18, 21, 24, 26, 28, 29, 46, 51	QI-39
Resistance Surveillance		
54. Surveillance of antibiotic use and resistance should be performed at least once per year at the health care facility.	15	QI-40
Surgical Prophylaxis		
55. Prophylactic antibiotics should be available in the operating room and pre-operative admission units.	44	Rejected
56. Postoperative prophylactic antibiotics should be discontinued within 24 hours after wound closure.	6-8, 10, 15, 33, 34, 36, 37, 40, 43, 54, 57-61, 63, 66, 67, 70, 75, 79, 81, 83, 93, 98-101, 114-116	Rejected
57. Prophylactic antibiotics should be added to a preoperative checklist.	44	QI-41

58. A preoperative pause (time-out) should be implemented before administering antibiotic prophylaxis.	44	Rejected
59. Prophylactic antibiotics should be redosed intra-operatively for surgeries longer than 3-4 hours or significant blood loss (≥1500mL).	44	
Therapeutic Drug Monitoring (TDM)		
60. Therapeutic Drug Monitoring should be performed for antibiotics with a narrow therapeutic spectrum and an increased risk of toxicity (like gentamicin and vancomycin) according to guidelines.	4, 24, 28	QI-42
61. At least 75% of Therapeutic Drug Monitoring levels of antibiotics should be within the desired reference range.	4	Rejected
62. If antibiotic Therapeutic Drug Monitoring levels are not in the reference range, doses should be adjusted appropriately after the results become available.	4, 39	QI-43
63. Therapeutic Drug Monitoring levels of antibiotics should be documented in the medical records.	4, 24	QI-44
Timing		
64. Timeliness of administration of antibiotic therapy and prophylaxis should be compliant with guidelines.	5, 7, 10, 11, 13, 15, 31, 32, 39-41, 43, 44, 50, 53, 54, 57-59, 63, 66, 67, 70, 75, 79, 81, 83, 93, 98, 99, 101, 115-126	QI-45
65. Antibiotic therapy should be started as soon as possible upon admission to the health care facility.	9, 11, 17-19, 21, 25, 28, 29, 50-52, 55, 56, 62, 64, 65, 68, 71, 74, 76, 78, 91, 92, 99, 105-112, 121, 127-149	Rejected
Toxicity		
66. Duration of administration of intravenous antibiotics should be compliant with guidelines.	45	QI-46
67. Allergy status should be taken into account when antibiotics are prescribed.	13, 45, 72	QI-47
68. Allergy status (including nature and severity) of the patient should be documented in the medical records when antibiotics are prescribed.	24	QI-48
69. Patients with a history of anaphylaxis after penicillin therapy should be prescribed an alternative drug class.	24	QI-49
70. Medical staff should be educated regarding cross-allergy with cephalosporins in patients with penicillin allergy.	44	QI-50
71. Antibiotics should be changed in case of adverse reaction.	9, 11, 16	Rejected
72. Contraindications should be taken into account when prescribing antibiotics.	45	QI-51

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Views and experiences with regard to antibiotic use of hospitalised patients in five European countries: a qualitative descriptive study

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Abstract

Aim This study aimed to explore inpatients experiences and views with regard to antibiotics in five European hospitals.

Methods Qualitative study where a patient-centred framework was used to explore inpatients' experiences concerning antibiotic treatment. A purposeful sample of inpatients treated with antibiotics in five hospitals participated in interviews (all centres) and focus groups (Switzerland only).

Results A total of 31 interviews (five in Belgium, ten in Croatia, nine in France, five in the Netherlands and two in Switzerland) and three focus groups (in Switzerland, 11 participants) were performed. The median age of participants was 61 years (range 33-86 years). The following main themes emerged: (i) patients trust doctors to take the best decisions for them even though communication concerning different antibiotic-related aspects is often insufficient, (ii) patients feel that doctors do not prioritise communication due to time constraints and do not seem to adapt information based on patients' preferences, (iii) patients differ in their wish to be informed but overall want to be informed on the main aspects in an understandable way, (iv) patients often find reassurance in sharing information about their antibiotic treatment with close family, (v) professionals should explore patients' preferences to be involved or not in shared decision-making for antibiotic treatment.

Conclusion Inpatients often doubt their ability to understand medical information and trust their physicians to take the best decisions for them. Tailored strategies that inform hospitalised patients, acknowledging their concerns and preferences, may be useful to promote patient involvement and to improve communication regarding antibiotic use.

Introduction

Between one third to one half of hospitalised patients in high-income countries receive antibiotics throughout their stay.[1, 2] Patients' views and experiences with regard to such antibiotic prescribing have been extensively studied in the outpatient setting,[3] for example regarding patient expectations, patient-doctor interactions and patient satisfaction.[3-6] Little is known, however, about patient views and experiences with regard to these special 'societal' drugs in the inpatient setting.

Currently, patients are usually not engaged in antibiotic stewardship efforts[7] even though *shared decision-making* and patient engagement can positively influence health-related behaviours and health outcomes.[4, 6] This could also be applied to antibiotic care as to improve the patients' experience. Consequently, in the context of the DRIVE-AB project,[8, 9] we explored (I) inpatients' experiences concerning antibiotic treatment in the five participating hospitals and (II) domains related to *responsible* antibiotic use[10] using a patient-centred framework with the ultimate aim of understanding what defines *appropriate* care in regard to antibiotic use at the hospital from the perspective of the patient. Of note, assessing factual knowledge with regard to antibiotics and bacterial resistance was not an objective of this study.

Methods

Design

This was an international qualitative study conducted in four high-income countries (Belgium-BE, France-FR, the Netherlands-NL, Switzerland-CH) and one upper middle-income country (Croatia-HR). Four study centres (BE, FR, HR, NL) conducted individual interviews. One centre (CH) conducted focus groups and individual interviews (only if < 3 patients were available). Characteristics of the included hospitals are available in **Supplementary Table S1**. Results are presented following the COREQ criteria for reporting qualitative research.[11]

Study participants

A purposeful sample of patients to ensure diversity in terms of gender, age and type of infection was selected for the study (**Supplementary Table S2**).[12] Main inclusion criteria were: (1) being an adult patient aware of having been treated with antibiotics at the hospital (2) speaking the local language and (3) being willing to communicate personal thoughts.

Potentially eligible participants were identified by one of the researchers through contact with the treating physician. The interviewers (V.Z., A.M., G.T. and M.S.B.) were not involved in the care for the participants. Patients were recruited in medical or

surgical wards and could only participate after clinical recovery (i.e., not in the acute phase of their disease). Interviews/focus groups took place either towards the end of the hospitalisation or shortly after discharge and were held at the hospital.

Theoretical framework

A semi-structured interview guide was developed (**Supplementary Figure S1**) based on the Picker 'patient-centred care' framework.[13] Six dimensions considered relevant for acute care and hospitalised patients were used to explore patients' views and experiences with regard to their antibiotic treatment. Interview topics derived from elements of the definition of responsible antibiotic use identified by a systematic review of the literature.[10] These topics were A-indication for the administered antibiotics, B-characteristics of the regimen, C-diagnostics performed prior or during treatment, D-adverse effects and E-antibiotic resistance (ABR). For each topic the focus was on information and patients' preferences (e.g., 'did you receive this information? 'who informed you?', 'was your family informed?', 'what information do you consider important to receive?', 'were your preferences taken into account?'). The interview guide was revised after a pre-testing interview/focus group in each centre.

Participant recruitment and data collection

An information leaflet (**Supplementary Figure S2**) and the informed consent form were given in person by the interviewers to eligible patients who were then re-contacted to schedule the session. Sessions were conducted between February 2016 and June 2017. Interviews lasted around 20-30 minutes and were conducted by researchers trained in qualitative research for the purpose of this study. The focus groups lasted around 1 hour and were held by a trained moderator (3 to 5 participants). The interviewers were not involved in the care of the participants. New patients were recruited until saturation, based on data collected across all centres, was reached.[14] Due to organisational and logistical issues, interviews in Belgium were performed several months later (compared with the other centres) after saturation had already occurred but as they were planned in the original protocol they were included in the analysis. Sessions were audio recorded and transcribed either by a professional transcription service (TiptopGlobal, Thedge BV, Ospel, the Netherlands in BE, CH, FR, NL) or by the interviewer (HR).

Analysis

The methodology used for data collection and analysis (grounded theory) has been previously used in other studies.[14] Due to language issues, each interviewer coded his/her own interviews. To standardise the process the first two interviews of three centres (HR, FR, NL) were translated to English and coded in parallel in each centre (V.Z., M.S.B., G.T. and A.M). Doubts over how to categorise specific quotes were

discussed in a conference call until consensus was reached. In case of uncertainties a senior researcher (M.H.) was consulted. Once every researcher felt confident about the technique, the material was independently coded in each centre. The thematic analysis was performed by 2 researchers (V.Z. and A.M.) with the help of a senior researcher in case of uncertainties. Atlas.ti software V.7.0 (ATLAS.ti Scientific Software Development Company, GmbH, Berlin, Germany) was used to facilitate the coding process.

Ethical review

Medical ethics committees were consulted and approval was obtained.

Results

In total, 42 inpatients were included (**Supplementary Table S3**). Three focus groups (CH=total 11 participants) were carried out. Thirty-one interviews were performed (BE=5, CH=2, F=9, HR=10, NL=5). There were 25 male and 17 female participants. The median age was 62 years (range 38-86) for men and 53.5 years (range 33-80) for women. The most frequent indications for antibiotic treatment were (i) lower respiratory tract infections (12/42, 28.6%), (ii) upper urinary tract infections (6/42, 14.3%) and (iii) skin and skin structure infections (6/42, 14.3%). A total of 41/42 patients were recruited in medical wards, mainly infectious diseases (34/42; 90,9%) and were interviewed of participated in the focus groups while still at the hospital (34/42, BE = 2; CH = 8, F = 9, HR = 10, NL = 5) in their room or in a meeting room.

Examples of quotes, themes and the corresponding Picker dimension are summarised in **Table 1**. A more extensive list of the most representative quotes for each theme is presented in **Supplementary Table S4.**

Characteristics of the information received and missing information

Characteristics of the information received varied in patients' descriptions and although they all knew they received antibiotics, some were unable to explain why and most could not name the antibiotic(s), reporting they had not received this information or had forgotten the name. Most considered the most valuable information in the following order: indication, adverse effects, duration, frequency and timing of antibiotic intake. Only a few were aware and reported of diagnostic tests being performed prior to treatment. Concerning adverse events, most patients felt sure doctors checked for them during the course of antibiotic treatment even though only a few reported having been informed about them before treatment. Many patients perceived information received as short, not very detailed and sometimes reported too directly. They often felt the language used by doctors was not understandable for

Table 1 Main themes recurring in the interviews and focus groups.

Theme's category (Based on the Picker model of patient-centred care)	Main themes that emerged from interviews and focus groups	Examples of quotes
Characteristics of the information received and missing information (P1, P3)	Patients often do not receive information regarding different antibiotic-related aspects and they often need to specifically solicit this information	*'Doctors tell you the minimum. It's true that in general, you need to ask, you have to insist to receive the information'* (FR_02) 'I: *And the information you received, was that enough for you?' P: 'Well very honestly: no. So first you get the antibiotic through the drip. I have absolutely no information on this. I really don't know how it* [the antibiotic] *is called'. Then you change to tablets. Well, by chance, I have worked in healthcare and I knew these tablets'* (NL_04) *'They took a lot of blood samples but I don't know why'* (FR_08) *'Everyday they ask you questions and I assume it is to check if you had side effects'* (CH_03) '*What is normal for you, sometimes is expected to be known by the other as well'* (NL_03)
Patients preferences and expressed needs: the wish to be informed and the suggested format and content of the information (P1, P3, P4, P5)	(1) Patients differ in terms of their wish to be informed, the preferred content and format of the information	*'Everybody should decide this [=receiving information] for themselves, I think. There may be some that really want to know, but I don't feel like I need it'* (BE_02) *'Doctors don't need to explain everything in detail but I would like to know the reasoning behind the treatment and its consequences… in a simple way'* (HR_01) '*I think that if the patient understands his treatment […] this can help the healing process'* (FR_07) *'They should tell you what the reason is they give you the drug, otherwise patients are just like 'guinea pigs''* (CH_01) *'You should not talk about side effects in advance or you will scare the patient'* (FR_07) *'Yes, when they talk about blood results, a normal person cannot follow it'* (BE_04) *'I would like to be informed about what side effects to expect during the antibiotic treatment. So, I know if something happens that it is due to the antibiotic, and not become hysterical and upset because I do not know why I have this symptom* (HR_01) *'I find it important that you know what side effects occur. That is what I find the most important. So that if for example one time at night you really need to go to the toilet* [...]*, that you know what the cause is, that it is because of a side-effect of the antibiotic'* (NL_04)

	(2) Patients often feel unprepared or too sick to fully understand indications, characteristics and implications of their treatment but they want to be informed on the main aspects in an understandable way to feel empowered and reassured	'*The patient can check... we are never too vigilant, even at the hospital, for example yesterday my perfusion was not working, so I immediately told the doctor*' (FR_07) '*I don't want to know, the less I know the better*' (FR_08) *'They tell me what they want to do and how and that's enough for me, I'm not a doctor, I cannot understand much more'* (CH_02) '*I was feeling too sick to understand when I arrived at the hospital […] I only wanted to feel better'* (CH_13)
Sharing the information with family members: emotional support, alleviation of fear and physical comfort (P6)	Patients often find reassurance in sharing the information about their treatment with close family and friends	'P: *Yes. For sure. I find that for sure that more should be shared with a partner.* I: *'And what is... What would it have mattered for you? So to say, what would have been the most pleasant? That he would know it too?'* P: *'For me the thing is that I am quite forgetful, so I forget quite easily'* (NL_04) *'I could be unable to take decisions and so in that case it would be a good idea to ask my husband'* (FR_07) *'Yes, that you can tell your immediate family what it is you have. That's always nice, right' (*BE_02) *'I: And is that* [=the information] *something that you shared with people around you? P: Yes. I: Such.. Such a moment of... P: Yes, that doubt, but also with the doctors…with the nursing staff and with... with anyone that could hear it (laughs)'* (NL_05) '*If my husband knows the side effects and something happens, he is already prepared*' (NL_04) *'You exchange* [=the information] *about what you receive and why and what they are doing and so on' (*NL_02)
Perceptions and beliefs about healthcare workers, the patient's role at the hospital and the decision-making process (P1)	Patients trust the competence of the hospital staff and often 'surrender' to decisions taken by doctors	*'Doctors know their job, I trust them'* (CH_04) *'Sometimes I ask questions, sometimes I don't because I tell to myself that doctors know what they do'* (CH_02) *'Doctors know their job! They know very well what they have to prescribe to cure me'* (FR_06) *'You have no choice but to wait until they know'* (NL_05) '*I felt there was a team, I was in good hands*' (NL_05) *'They are the experts, everybody to his job'* (CH_09) *'It's the nurse who gave me the information* [about the antibiotic]' (FR_09) '*The doctor told me I had an infection that required an antibiotic, then the nurse came and I asked her the name'* (FR_02)

Table 1 Continued.

Theme's category (Based on the Picker model of patient-centred care)	Main themes that emerged from interviews and focus groups	Examples of quotes
Bottlenecks in the organisation of care at the hospital (P1, P2)	Patients feel that healthcare providers do not prioritise communication and information-sharing mainly due to time constraints and do not seem to adapt their communication technique based on patients' preferences	*'Doctors are very kind but they are always so busy that sometimes they tell you something two or three times and sometimes they don't tell you nothing at all.'* (FR_05) *'This is a big hospital, if doctors had to answer every question of every patient…it would take a lot of time'* (CH_02) '*At the hospital doctors change all the time*' (CH_05) *'Doctors never stop, my doctor was very competent,* [...] *but he was running all the time' (*FR_05*)* *'I hear nobody asking'* (NL_04) *'..there is a sort of fence, a barrier.* […] *When you are here, and they are all above you* [=in hierarchy], *then it is more complicated, I find, to communicate with them'* (NL_04)
Perceptions and beliefs about antibiotics and ABR (P3)	Patients acknowledge the potentially negative impact that antibiotic overuse and misuse can have on their health (individual perspective > societal perspective). When asked, they show to have clear ideas on possible solutions to tackle the problem	*'I'm grateful, it is thanks to them that I can speak with you now.'* (HR_03) *'All drugs, including antibiotics, well, they are not so… good for the organism. Well, I mean that they help to solve some problems, but they create others.'* (FR_08) *'Yes, well you know, if I am honest, when I need it, I take it. I will not think 'This is possibly not good for the environment, or for...' No then I need it... so... yes, I am that hypocrite as well.' (NL_05)* *'If I take too many antibiotics the body gets used to them'* (CH_01) *'My immune system is weak so I can be resistant' (*CH_04) *'Well, for sure something should be done about it, I personally think that you can't constantly be on the same antibiotic. That is something that is a 100% priority for me. That you have to switch to another'* (NL_04) *'It is important that antibiotics are not grabbed too easily'* (BE_01)

Legend: P1/P2/P3/P4/P5 and P6 refer to the 6 dimensions of the Picker model, ABR: antibiotic resistance, BE: Belgium, CH: Switzerland, FR: France, HR: Croatia, NL: the Netherlands, P: patient, I: interviewer.

the common patient and that doctors sometimes only perceive things from their perspective ('*operational blindness*', NL_03).
Many underlined the need to actively ask for information. However, they did not necessarily complain about this because of: (i) the perceived role of the patient ('*the doctor decides*', CH_02) and/or (ii) doctor's time constraints.

Patient preferences and expressed needs: the wish to be informed and the suggested format and content of the information

Patients differed in terms of their wish to be informed, the preferred content (e.g., simple messages adapted to their knowledge and skills), timing (e.g., not in the acute phase) and format (e.g., use of written leaflets to facilitate understanding) of the information. Many acknowledged the importance to tailor the information to patients' preferences and emotional preparedness.
In most cases, patients described a need to understand and control (e.g., some did not want to be passive recipients of care or wanted to check their treatment) but the idea that a better understanding of the treatment can help overcome suffering and fear was also mentioned.

Sharing the information with family members: emotional support, alleviation of fear and physical comfort

Most patients felt that sharing information with their close family could be beneficial mainly for: (i) practical reasons, (ii) physical comfort, (iii) a better perceived understanding of the information received and (iv) the possibility to exchange doubts and thoughts with somebody else. However, sharing information with family members appeared to also be the result of coincidence *('by chance somebody was visiting me*', NL_05).

Perceptions and beliefs about healthcare workers, the 'patient's role' at the hospital and the decision-making process

Often patients reported a high level of trust in the expertise of doctors in charge of their treatment and did not question their choices. Concerning involvement in the decision-making process, most patients were passive and surrendering because they trusted doctors to take the best decisions for them while few had to be 'convinced' in order to accept their treatment.
The role of nurses was cited by some as additional (sometimes unique) providers of information, a patient specifically mentioned their role ('*The nurse also needs to explain when she comes to give the antibiotic'*, HR_01).

Bottlenecks in the organisation of care at the hospital

Often patients felt that healthcare workers seemed overwhelmed with work and changed very often and this had a negative impact on time and quality dedicated to

communication. On the other hand, family doctors (some patients mentioned this while comparing hospital care to general practice care) were often perceived by patients as more accessible both because (i) often they know them better and (ii) patients do not perceive the same feeling of distance they often have with doctors at the hospital.

Perceptions and beliefs about ABR

While discussing ABR, it emerged spontaneously that only a few patients had the correct knowledge that the bacteria and not the 'body' can become resistant. This misperception often led to concerns.

Antibiotic overconsumption and misuse, including in the agricultural sector, were the most frequently reported perceived drivers of resistance. Some patients were concerned because of the possible negative impact resistance could have on themselves rather than because of its societal impact. Patients were also asked their opinion on possible solutions to ABR (**Supplementary Table S5**).

Discussion

In this international, qualitative study we have identified several interesting aspects concerning patients' views and experiences about the antibiotic treatment received during their hospitalisation. The main findings were that patients trust doctors to take the best decisions for them but overall, they feel that doctors are overwhelmed with their duties. This latter aspect has a negative impact on time and quality dedicated to communication and could explain why patients overall are not adequately informed on different aspects of their antibiotic treatment even though they overall want to be informed. Often patients are reassured when discussing their antibiotic treatment with others (e.g., close family). Patients also feel that doctors should explore differences in their needs and preferences concerning timing and content of the information. They also feel that their individual preferences to be involved, or not, in shared decision-making for antibiotic treatment should be taken into account. Concerning ABR, patients acknowledge the problem but seem to prioritise the individual perspective over the societal perspective often due to misconceptions about the true mechanisms of resistance.

Heid et al. [15] interviewed 30 hospitalised patients on perceptions of antibiotic use in a US hospital. Although they used a different theoretical framework and specifically aimed to explore patients' perceptions of the potential role for patients as engaged and active participants in antibiotic stewardship programmes, some findings were similar: the high degree of confidence in decisions taken by doctors, the minimal involvement in shared decision-making and the emphasis put on the willingness of

being involved in one's own care. Misperceptions of the mechanism of bacterial resistance and feelings of it being a *very serious* issue were also overlapping. Another study by Rawson et al. took yet another approach by exploring patients' experiences of engagement with decision-making surrounding infection management in secondary care.[16] Similarly to our results, patients did not seem to be involved in shared decision-making for antibiotic treatment and were usually *told* unilaterally by doctors they had an infection and were going to receive an antibiotic (often unnamed). In the Rawson et al. study, however, this led to a feeling of anxiety and frustration that we did not find in our interviews/focus groups, where patients felt reassured overall about their antibiotic treatment.

Our results show that, although patients' preferences differed, overall they expressed a wish to receive simple and understandable key messages about the antibiotic treatment, the indication and the potential consequences, mainly in terms of controlling the disease and of adverse events. One of the most recurrent barriers to effective communication reported was that patients often do not feel comfortable asking questions because of the perceived information asymmetry (i.e., they find hard to understand medical information because they are not educated in the field of medicine). The fact that patients often undervalue their expertise relative to doctors emerged also in the findings of a recently published systematic review on perceived barriers and facilitators to shared decision-making.[17] Many patients also acknowledged the beneficial and reassuring effect of sharing information with their families. Comparing findings in outpatient studies we found fewer expectations in terms of asking for antibiotics and in general asking for their preferences to be taken into account. Inpatients seem more prone to let doctors decide without interfering. This could be explained by the lack of confidence in their own expertise.

Our study fills an important research gap as little is known about this topic in the hospital setting. Although our data may not be generalisable to all settings, we feel that they provide an interesting qualitative perspective of patient's views and experiences regarding antibiotics in different European settings. This study has also some limitations. Although efforts were made to standardise the coding process, we cannot exclude that variations and errors occurred in the interpretation of results. Finally, possible local and cultural influences on the quality of patient-centred care were not explored in this study and comparisons of findings between the different countries was not possible with this type of qualitative research.

In conclusion, finding more effective ways to provide information about antibiotics at the hospital is an aim that should be pursued in order to improve the patient's experience with care but also to raise awareness and engage patients on the problem of resistance.

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Chapter 4 - Supplementary data

Introduction

During your last hospital stay/hospitalization, you have received antibiotics. Through this interview/focus group we aim at gaining insight into your views on and experiences with antibiotic use during your hospital stay.

First, let's discuss the antibiotic treatment you received.

1. Could you tell me why or for what reason you received antibiotics? (**Indication**)

Probing:
- Did you receive this information?
- What information did you receive about that? (if no information was provided: do you feel that you should have received information on the reason for your antibiotic treatment?)
- Who provided the information? Probing: did you receive overlapping/ contradictory information from the various professionals involved in your care? (if no information was provided: who should have provided this information?)
- Was the information provided to you? To your family? Care-taker? (if no information was provided: to whom should this information been provided to?)
- Do you feel you received enough information concerning the **necessity of the treatment**? (What information did you specifically miss? What information did you specifically appreciate?)
- Were your preferences taken into account? (if no information was provided: should have your preferences been taken into account?
- What aspects of the necessity of your antibiotic treatment do you think would have been important to discuss?

2. Could you tell me more about your antibiotic prescription? (**Regimen**)

Probing:
- Name? Type? Frequency? How long? When? Oral or IV?
- Did you receive this information?
- What information did you receive about that? (If no information was provided: do you feel that you should have received information on the regimen of your antibiotic treatment?
- Who provided the information? Probing: did you receive overlapping/ contradictory information from the various professionals involved in your care?(if no information was provided: who should have provided this information?)
- Was the information provided to you? To your family? Care-taker? (if no information was provided: to whom should this information been provided to?)

- Do you feel you received enough information concerning the **necessity of the treatment**? (What information did you specifically miss? What information did you specifically appreciate?)
- Were your preferences taken into account? (if no information was provided: should have your preferences been taken into account?)
- What aspects of the **regimen** of your antibiotic treatment do you think would have been important to discuss?

3. Performing a diagnostic test (such as blood or urine cultures) helps the doctor to determine if bacteria are causing your illness and therefore to select the appropriate antibiotic to treat you. (**Diagnostics)** Could you tell me about the diagnostic tests being performed before your treatment?

Probing:
- Did you receive this information?
- What information did you receive about that? (if no information was provided: do you feel that you should have received information on the diagnostics?)
- Who provided the information? Probing: did you receive overlapping/ contradictory information from the various professionals involved in your care? (if no information was provided: who should have provided this information?)
- Was the information provided to you? To your family? Care-taker? (if no information was provided: to whom should this information been provided to?)
- Do you feel you received enough information concerning the **necessity of the treatment**? (What information did you specifically miss? What information did you specifically appreciate?)
- Were your preferences taken into account? (if no information was provided: should have your preferences been taken into account?)
- What aspects of the **diagnostics** do you think would have been important to discuss?

4. When taking antibiotics, a patient can experience side effects or drug interaction (when an antibiotic influences the effect of another drug the patient is taking). Could you tell me if you experienced any side effects of your antibiotics? (**Side effects)**

Probing:
- Did you receive this information?
- What information did you receive about that? (if no information was provided: do you feel that you should have received information on the side effects for your antibiotic treatment?)
- Who provided the information? Probing: did you receive overlapping/ contradictory information from the various professionals involved in your care? (if no information was provided: who should have provided this information?)

- Was the information provided to you? To your family? Care-taker? (if no information was provided: to whom should this information been provided to?)
- Do you feel you received enough information concerning the **necessity of the treatment**? (What information did you specifically miss? What information did you specifically appreciate?)
- Were your preferences taken into account? (if no information was provided: should have your preferences been taken into account?)
- What aspects of the **side effects** of your antibiotic treatment do you think would have been important to discuss?

5. Antibiotic resistance refers to the bacteria becoming less susceptible or sensitive to the action of the antibiotic drug. Therefore, bacteria are not being killed by the antibiotic and the patient cannot be cured. Could you tell me what you think about antibiotic resistance? (**Resistance**)

Probing:
- Are you aware of any of your friends/colleagues been confronted with antibiotic resistance?
- What do you think should be done about this problem?
- Does this problem scare you? If not, why not?
- Are you aware of the possibilities to reduce the development of antibiotic resistance?
- How do you think that doctors/pharma/governments should tackle this problem?

Final/closing questions

Are there any other relevant issues of antibiotic use we haven't covered that you would like to mention?

Are there any questions you would like to ask me?

Supplementary Figure S1 Individual interview and focus group guide.

Supplementary Figure S2: Patient information leaflet.
Available at: *https://doi.org/10.1016/j.cmi.2018.04.030*

Supplementary Table S1 Characteristics of the participating hospitals.

Hospital	City/Country	Type of hospital	Number of beds
Jessa Hospital	Hasselt, Belgium (BE)	Teaching hospital	988
Rijeka University Hospital	Rijeka, Croatia (HR)	Academic tertiary care centre	1135
Nancy University Hospital	Nancy, France (FR)	Academic tertiary care centre	1931
Geneva University Hospitals	Geneva, Switzerland (CH)	Academic tertiary care centre	1781
Radboud University Medical Center	Nijmegen, the Netherlands (NL)	Academic tertiary care centre	953

Supplementary Table S2 Patient's inclusion and exclusion criteria.

1.1 Inclusion criteria	• Adult patients (≥18 years); • Currently or recently (< 3 months before inclusion) hospitalised in an acute-care ward of one of the participating centres; • Patients with an infection as main admission diagnosis or patients who developed a nosocomial infection requiring antibiotic treatment during their hospital stay; Eligible infections were: lower respiratory tract infections (LRTI), upper urinary tract infections (UTI), intra-abdominal infections, skin and skin structure infections, central nervous system infections and primary bloodstream infections. • Patients aware of having received a minimum of 3 days of a systemic antibiotic treatment during that hospitalisation; • Capacity to give free and informed consent; • Sufficient physical and mental condition to attend the meeting/interview; • Adequate knowledge of the local language to communicate and be understood; • Ability and willingness to communicate personal thoughts; • Availability of the transportation means to be present for focus group sessions/interviews.
1.2 Exclusion criteria	• Severe immunosuppression; • Chronic conditions requiring frequent (≥4 antibiotic courses/year) antibiotic treatment (e.g., cystic fibrosis); • Patients where the interviewer would be the patient's treating physician.

Supplementary Table S3 Patient's characteristics.

Patient number	Sex	Age	Indication for antibiotic treatment
HR01	F	41	Sinusitis
HR02	M	59	Pneumonia
HR03	F	52	Meningitis
HR04	M	67	UTI
HR05	F	64	UTI
HR06	F	74	Pneumonia
HR07	F	75	UTI
HR08	M	40	Skin and soft tissue infection
HR09	M	38	Pneumonia
HR10	M	62	Skin and soft tissue infection
FR01	M	86	UTI with septic shock
FR02	F	42	Febrile neutropenia
FR03	F	54	Endocarditis
FR04	M	40	Spondylodiscitis
FR05	M	73	Pneumonia
FR06	M	51	Skin and soft tissue infection
FR07	F	37	Pneumonia
FR08	M	65	Cholangitis with septic shock
FR09	M	69	Meningitis
CH01	F	68	Pneumonia and lung abscess
CH02	F	53	Pneumonia
CH03	F	65	Pneumonia
CH04	F	47	Pneumonia
CH05	F	80	UTI
CH06	M	61	Sepsis
CH07	M	77	Skin and soft tissue infection
CH08	M	71	Spontaneous bacterial peritonitis
CH09	M	59	Skin and soft tissue infection
CH10	M	77	Sepsis
CH11	M	76	Sepsis
CH12	M	59	Pneumonia
CH13	F	33	UTI
NL01	M	56	Sternal osteomyelitis and bacteraemia
NL02	M	81	Spondylodiscitis
NL03	M	62	Endocarditis and brain abscess
NL04	F	61	Pneumonia
NL05	F	43	Sepsis
BE01	M	44	Skin and soft tissue infection
BE02	M	53	Bone and joint infection
BE03	M	79	Skin and soft tissue infection
BE04	M	45	Pneumonia
BE05	V	64	Skin and soft tissue infection, secondary bacteraemia

Legend: BE: Belgium, CH: Switzerland, FR: France, HR: Croatia, NL: the Netherlands.

Supplementary Table S4 Themes with examples of patients' quotes.

Themes	Examples of quotes
Characteristics of the information received and missing information	*'Often explanations are very short' (FR_02)* *'I asked which kind of antibiotic I received, actually the name, but it is true that in general, they do not go further in explanations' (FR_02)* *'Sometimes they {=doctors) speak their own physician language' (BE_02)* *'Yes, that they set up cultures. But what does that mean?' (BE_02)* *'Yes, when they (=the physicians) talk about blood results, a normal person can't follow it' (BE_04)* *'There are some doctors, as I said, they 'don't use gloves' to talk to you [=about bad news]. So, some doctors try to reassure you, depending on your health condition, on your psychological condition, and so on. But there are others who don't' (FR_08)* *P: 'You receive information today, it's like this, but, it can be different tomorrow […] When somebody asks how it is going, you have this story today, and tomorrow that story. […]* *I: 'So the keeping track is a bit complicated?' P: 'No […] they (=health care professionals) cannot do anything about it, […] they (=health care professionals) cannot do anything about it, but for the outsiders it can be complicated sometimes. […] it is part of the process' (NL_03)* *'I think that, yes, they could give more information, because if you do not ask, you will not have any information' (FR_02)* *'I received more information from my family doctor than at the hospital' (CH_05)* *'They tell me what they want to do and how and that's enough for me, I'm not a doctor, I cannot understand much more' (CH_02)* *'The doctor told me, as I had fever, it was necessary to prescribe an antibiotic […] and the nurse, when she came to give it to me, she told me 'I will give you the antibiotic'. And I asked the name and that's it' (FR_02)* *'The nurse gave me the information' (FR_06_02)* *'Both (nurses and physician). They all communicate very well, look you this what you have. And that was very well explained' (BE_02)* *'Doctors, I believe [gave the information]. Well actually also nurses sometimes' (NL_03)* *'I assume they told me about it. That's what I said at the beginning, and now too, there are lots of things you don't remember' (NL_03)* *I: 'Were you informed (=about side effects)?' 'P: no, but I knew it from before' (NL_02)* *'In my case, I had all the information I needed, I was in a very good department, maybe because my case was serious but I cannot complain, I knew why I was getting antibiotics' (CH_01)* *'They did not really specify for how many days I was going to take it [the antibiotic]' (FR_02)* *I: 'Were you informed about potential side effects of the antibiotic you were taking?' P: 'No, not at all' (FR_02)* *I: Were you told about it [side effects]?' P: 'If I was told about it? Actually not that much. But I think that people (=doctors/nurses) expect you to know about it' (NL_03)* *'I don't know about specific side effects of my treatment, but every day they ask me questions, they don't say why but I think it is to check if we have problems with the treatment' (CH_03)* *'I think they may have mentioned it [about side effects] like 'It is a bit of an impact on your body'' (NL_03)* *' I was informed very well about the diagnostic tests performed when I came to the hospital and I think it is important that the patient understands it all. I am very satisfied with the information received' (HR_01)*

	'The first days they didn't even tell me I was getting an antibiotic, they didn't even know what I had' (CH_03) *'they gave me this information at discharge in the letter, […], but probably without enough explanations' (FR_03)*
Patients preferences and expressed needs: the wish to be informed and the suggested format and content of the information	*'I want to be as well informed as possible'* (NL_02) *'The more information the better, I think' (*BE_01) *'When you arrive at the hospital, you are afraid of many things but if you don't get the information you are even more scared. So for me it is better to get more details'* (CH_5) *'information is always important and communication too. So, I think that actually all patients should receive it (=information) [...]'* (BE_01) *P: 'Yes, I think it is important [information]. But I think that it... depends on the patient if he thinks it is important or not. There are also patients that do not find that important, then you don't have to... Then you don't have to make them wiser than they want'* (NL_05) *'When you are sick, you don't know if you feel the need to know, but I think some people have this need, but I didn't'* (BE_05) *'Yes, because you want to know, yes, what is best, what they are doing or can do, to, to go back to a healthy body, let's say. I find that important after all. […] So that they don't do stuff just like that, or that they know what may be the best, but yes, without sharing it. So I think it is good that they, that you get a bit informed yes'* (BE_01) *'Yes, I think it depends from patient to patient. There may be some that say 'I want to know it all', and some that do not want to know […]'* (BE_02) *'I do not always understand, I do not try to understand' (*FR_05) *'Are you interested in receiving details about the treatment?' P: 'No, because in fact I don't… I don't care so much about these things about drugs, I never look at it'* (FR_05) *'[…] I think that if the patient understands his treatment and why he has to take it, this can help the healing process, because I think that the mind is connected to the body, […], I think that this can be beneficial... On the other hand, to know all side effects… […], imagine, you have to explain to a patient all side effects, in that case you will lose him, the patient, you will lose him meaning that you will scare him, this will be a cause of anxiety, […] So, in my opinion, I would say, you don't tell all side effects. Later on, if your patient has clearly a cutaneous reaction, etc., in that case you explain […]'* (FR_07) *' I think that the patient who suffers and who knows what's going on, and who knows what needs to be done and that has received the information, even if he is not a doctor, if you like, this understanding of the mechanism of what's happening in the body, I think it can only help to overcome suffering, to follow the treatment'* (FR_07) *'I leave the responsibility to them (=doctors), is not because I receive more information that I can add something to my knowledge'* (FR_01) *'We, as patients, cannot do much about it [=the treatment]'* (FR_02 *'Nowadays we don't decide anything at the hospital. We take what they give us and that's it'* (CH_02) *'It would be good to receive the information before they give you something, they should tell you what the reason is they give you the drug, otherwise patients are just like guinea pigs and that's it!'* (CH_01) *I: 'And what information would you have liked to receive? What is for you the most important let's say?' P:' How it [=the treatment] is called? What are the side effects? That is very important. Look of the tablets that I have now, I know what side effects are. So you try to take them into account.'* (NL_04) *'[…] how heavy and how long and what it does and what it entails* [the antibiotic treatment]*'* (NL_05)

Supplementary Table S4 Continued.

Themes	Examples of quotes
Patients preferences and expressed needs: the wish to be informed and the suggested format and content of the information	*I: 'So you think the most important thing is to know how many times a day you take the antibiotic?' P: 'Yes, to be aware, so I can say: did I get it?'* (FR_07) *[…] if I get antibiotics out of the hospital, I have a prescription with the information and I can read everything I want to know, but if I am hospitalised, this information is unavailable'* (HR_01) *'I would like to be informed about what I can expect from side effects during the antibiotic treatment. So, I know if something happens that it is due to the antibiotics, and not become hysterical because I do not know why I have this symptom... If I am informed, I will not be upset if some of the described side effects occur to me'* (HR_01) *P: 'I think the information I received was enough. I know a lot about my disease and treatment. I think that you should not be given too many details, it was enough for me'* (HR_04) *'I accepted everything doctors told me because I trust them a lot. My case was very difficult and I am grateful* [...]' (HR_03) *'In any case I could not give them (=doctors) my advice, it was not possible'* (FR_09) *'I would like to know simply if the treatment is the right one'* (FR_03) *'[…] I think that an explanation using a simple language* [...] *I think that would be good'* (FR_07)
Sharing the information with family members: emotional support, alleviation of fear and physical comfort	*P: 'Of course, of course [referred to the need of sharing information with the family]. Because, I mean, I am going home tomorrow with the same antibiotics, so* [...] *if a side effect occurs, then my partner needs to be informed about it' (NL_04)* *I: 'And is that something that you shared with people around you?[=doubts about antibiotic treatment]' P: 'Yes' I: 'Such... Such a moment of... ' P: 'Yes, that doubt, but also with the doctors.... with the nursing staff and with... with anyone could hear it (laughs)' (NL_05)* *P: 'For me the thing is that I am quite forgetful, so I forget quite easily' (NL'_04)* *'When my wife is here, she understands it, she is a nurse herself. She can help me with it' (BE_02)* *'It is already difficult for us, as patients, to have some information, so if the aim is to give information also to family members, it seems to me that this gets complicated' (FR_07)* *'For me it is important that I personally receive the information' (CH_07)* *'As long as I can think clearly, I want to know myself' (NL_05)* *'You exchange what* [=the information] *you receive and why and what they are doing and so on' (NL_02)* *'I think it depends, and I think that the reason why healthcare workers decide to exclude (=not give the information to) the partner is that you never know to whom you are talking to* […]*' (FR_07)*
Perceptions and beliefs about healthcare workers, the 'patient's role' at the hospital and the decision-making process	*'In the end you also believe that they* [=doctors] *know best* [...]' (NL_05) *'That is a piece of trust I find that you also have to have in the doctors'* (NL_05) *'Well, the doctors say 'this is working'. So then it is good'* (NL_03) *'For me the priority was to recover, to feel better'* (CH_13) *'I do not know antibiotics, is the doctor who decides'* (FR_06) *'Sometimes I ask questions, sometimes I don't because I tell to myself that the doctor knows what he does'* (CH_02) *'Doctors know their job! They know very well what they have to prescribe'* (FR_06) *P: 'Yes, to speak honestly, I surrendered because I had no choice, so I had to' I: 'And what was the reason you allowed yourself to surrender?' P: 'I had no choice I think'* (NL_01)

	'I accepted everything doctors told me because I trust them a lot. My case was very difficult and I am grateful [...]' (HR_03) *'And then you are here, and they are above you (=in hierarchy) and then it is more complicated, I find, to communicate with them, to ask these kinds of things. Yes. I: Okay, are there people where the obstacle is lower? Because I suspect you are talking about the doctors, now? P: No, no, no, no, the nursing staff. I: The nursing staff too. P: Nursing staff. Yes. Yes. For sure. There are always some from the nursing staff that are being quite arrogant.* […] *I: And this is something that you think other patients have as well? P: I think so. I think so. I hear nobody asking* (NL_04) *'I don't ask anything because I'm very impressionable'* (CH_03) *'Now that I know better the doctors and the nurses in the unit I feel more comfortable in asking them questions'* (CH_05) *'They started this morning with tablets, antibiotics. And it is an antibiotic for which I had a reaction in 2008. About which I always have been saying that I am not able to handle... And that they started today anyhow, […] That I found very thrilling. But because it was given then for something very different they said 'We want to try it anyway, because it is the best antibiotic against this bug, this bacterium'. They somewhat had to convince me of this'* (NL_05) *I: 'Was there room for your preferences' P: [Patients shakes no with his head] 'I was not needing it, look the tests had to be done. Whether I liked it or not'* (NL_02) *'I think that if there are two equally effective antibiotics with different spectrum of side effects, doctors should choose the one with less side effects or ask the patient's opinion'* (HR_09) *P: 'It could be that there are different options than and so on. Pills for example instead of always walking such a line, IV. I know one is busy with this also' I: 'Do you mean mainly patient comfort, that pills are more pleasant for the patient?' P: 'Yes of course' (NL_01)*
Bottlenecks in the organisation of care at the hospital	*The problem that you see in hospitals is that people run all the time, there is a lack of staff'* (FR_05) *'This is the problem, they are very kind (= doctors), but they have so many things to do […] so sometimes they give the information two-three times and sometimes they do not tell you anything'* (FR_05) *'They are very kind, but they are also so busy that sometimes they tell you something two or three times, and sometimes they don't explain things to you'* (CH_5) *'This is a big hospital, if doctors had to answer every question of every patient... it would take a lot of time'* (CH_02) *'Sometimes I try to talk with the doctor and I don't have any information… even if they are young doctors, I need sometimes to talk with them, but you don't know with whom you are talking to'* (FR_09)
Perceptions and beliefs about bacterial resistance	*'For sure I have knowledge* [=about resistance] *because I experienced it myself […] so I know this problem, I even experienced it first-hand. That was very nasty, I can tell you'* (NL_02) *'Well, look, when you are here every two weeks, then you think you are resistant. Yes I think so'* (NL_04) *'So, my experience with resistance is direct because I have children that were often prescribed antibiotics and I think it was not appropriate […] but every doctor has his opinion and style... the fact is antibiotics are prescribed more frequently than they should be in children... I think'* (HR_09) *'And I think that we, here in the Western countries, maybe have less problems with it than somewhere far away'* (NL_05) *'That is simply bad luck. This (=talking about resistance) is a more aggressive form, but you are indeed unlucky that it happens twice in the family right* [=talking about a brother]. *Simply, pure bad luck. Nothing you can do about it'* (NL_03)

Supplementary Table S4 Continued.

Themes	Examples of quotes
Patients suggestions/solutions to improve information about antibiotics and resistance	*'In my opinion an important thing is to talk with someone with authority. A doctor, who is clear, in front of you and tells you: 'here we are, we diagnosed this and now we are going to do that'. Very simple'* (FR_09) *'The person in charge should come and say 'Sir, I am mister x, this is the treatment we will prescribe during x days, with my colleagues, mister y, w…'* (FR_09) *'I think that maybe, a bit of teaching, telling, in simple terms, simplifying the explication, not giving the scientific name'* (FR_07) *'It is important to talk with the patient because saying: 'ah, this guy comes from Africa, he can't understand' It is necessary first of all to eliminate this racial prejudice'* (FR_09) *'In my opinion for the patient, the most important is to explain, because it's still […] me I will understand nothing […] but we can understand the reasoning. And that, I would say, often when you are sick that's a bit what's missing, the doctor just says 'you have to take this,' without explaining. A patient is still a human being, who can think, even if he didn't go to medical school, and he needs to understand'* (FR_07) *'In my opinion, the patient should be informed why he needs to take antibiotics, how long it would be and eventually, which side effects he should expect and what he needs to do if side effects happen.* *[…] if I get antibiotics out of the hospital, I have a prescription with the information and I can read everything I want to know, but if I am hospitalised, this information is unavailable'* (HR_01) *'Look, I think: maybe we [=patients] should ask about it ourselves, but actually, that is not how it should be. Let me say it this way'* (NL_04) *'My opinion is that when the nurse comes in the patient's room to give an antibiotic, she should always explain what she will do and why. The fact that doctors have already given the explanation is not enough; the nurse also needs to explain when she comes to give the treatment. I don't want a lot of information, but two things -what is the name of the drug and why I should be treated with it. The nurse has to tell me these things because I am not unconscious, I know what's going on'* (HR_01) *'There are different ways of telling things, you know, if the aim is to give a very scientific, very technical explanation, you will lose the patient and scare him, in my opinion, with no purpose. On the other hand, a short, targeted explanation, with an everyday language, simple, because if you want to be simple you can be simple, this, in my opinion, this will be useful and logical in view of the treatment'* (FR_07) *'Concerning side effects I wouldn't want to know them all, only the main ones, if you know too much you get scared and you don't want to take the drug anymore even though we know it is rare and it's for our own health'* (CH) *'Concerning side effects, the less I know the better'* (HR_10) *'Yes, I think you have to inform, but you need maybe to give, when you talk about risks etc., you have to give a percentage, out of a million patients… this kind of information is not always clear'* (FR_05) *'It would be good to have a leaflet about the consequences of antibiotics'* (NL_04) *[About timing of the information]* *'Maybe also during the admission/at the start of the hospitalisation'* (BE_01) *'It would be good to receive the information before they give you something, they should tell you what the reason is they give you the drug, otherwise patients are just like guinea pigs and that's it!'* (CH_01_07) *'We see antibiotics as a normal drug and I think that's why people take them too often, they don't have this feeling of danger linked to antibiotics for example when you take too much'* (CH_06)

Quotes are identified using patients' unique identifiers (e.g., NL_01, CH_01). To link these identifiers to the patients' characteristics the reader may refer to Supplementary Table S3.

Supplementary Table S5 Patient's proposed solutions to the antibiotic resistance problem.

Stakeholders	Proposed solutions	Examples of quotes
Prescribers	Doctors should prescribe fewer antibiotics	'*Doctors should give antibiotics when it is really needed*', FR_05
	Doctors should be more often part of educational programs addressed to patients	'*So, doctors should* [...] *educate patients. It should be organised at the national level, some kind of programme of basic education for the patients, for example – not to take antibiotics for flu and viral infections. So, first education for the doctors and patients who are at the hospital and second, education of the public through public campaigns',* HR_08
	Sanctions/penalties for 'bad' prescribers should be in place	'*To sanction doctors that prescribe too many antibiotics*', FR_07
Patients	Group effort to reduce antibiotic use	'*We all should influence on this point: resistance can be acquired if you use antibiotics for too long or too often. They should not be used if it is not necessary, especially if there isn't a positive microbiological test...there are other things that should be done before giving them',* HR_06
	Patients should always follow the prescription (i.e., do not stop the antibiotic earlier, do not self-prescribe)	*'Patients should always respect the doctor's opinion on the introduction of the antibiotic treatment and should take it as prescribed',* HR_09
	There should be more educational programs	*'I think that, yes, to inform people on the topic of antibiotic resistance is important, since it is true that this is not done automatically',* FR_02
Pharma R&D, regulators, government	Efforts in developing new drugs should be reinforced	*'One should make new antibiotics in order to waive this resistance. But that won't be an easy task'* NL_02
	Doctors and pharmaceutical companies should work together towards a solution and governments should facilitate the process	I: '*Do you have any insights on how these developments (=solutions to antibiotic resistance) should happen? Should physicians rouse?'* P: *'Well I think that the pharmaceutical industry and the physicians should do that together'.* I: *'What about the government?'* P: *'As far as possible the government could act in the relation between physicians and pharmaceutical industries* [...]', NL_02
	Good antibiotics are expensive	*'*[...] *That is the reason you always get the same antibiotic. That is a fact. These are the cheapest antibiotics you can get* [...]', NL_04
	More funds for research should be made available	*'More funds should be devoted to research',* CH_07

Legend: CH: Switzerland, FR: France, HR: Croatia, NL: the Netherlands, P: patient, I: interviewer, R&D: research and development.

5

Barriers to and facilitators of responsible antibiotic use from the perspective of *third-party* stakeholders: a qualitative interview study

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Abstract

Aim The study aimed to explore barriers to and facilitators of responsible antibiotic use according to third-party stakeholders

Methods In this exploratory qualitative study, individual interviews were conducted with a convenience sample of international third-party stakeholders. An interview guide was developed based on the previously developed DRIVE-AB definition of responsible antibiotic use. Interviews were transcribed and coded in Atlas.ti software. Ultimately, thematic content analysis was performed and barriers and facilitators were extracted from the data.

Results Twelve interviews were performed and included the following perspectives: antibiotic Research & Development (R&D) (n=3), health economics (n=1), medical ethics (n=3), government (n=2), health law and bioethics (n=1), public health (n=1) and regulatory agency (n=1). Identified barriers and facilitators were grouped into seven categories: scientific (e.g., uncertainty of future medical needs), economic (e.g., financial incentives), regulatory (e.g., regulatory harmonisation), ethical (e.g., responsibility for future generations), societal (e.g., invisibility of antibacterial resistance), political (e.g., changing political environment) and medical practice challenges (e.g., alternatives for antibiotics).

Conclusion A broad spectrum of barriers to and facilitators of responsible antibiotic use was identified from the perspective of a wide range of stakeholders. We recommend considering these barriers and facilitators when drafting future antibiotic policies.

Introduction

The world is currently facing an antibiotic crisis with the rapid emergence of antibiotic resistance (ABR) endangering antibiotic effectiveness and constituting a substantial clinical and economic burden[1, 2] The United Nations declared antibiotic resistance a major global health priority in 2016.[3]

If efforts to safeguard the effectiveness of antibiotics are to be successful, perspectives of multisectoral stakeholders as advised by the World Health Organization (WHO)[4] should be considered. The first stakeholders that come to mind when considering the burdens of clinical failure or costs are the prescribers and the patients. These are, however, not the only stakeholders concerned by ABR. Great expectations are currently arising for other stakeholders, the so-called *third-party* stakeholders, involved in the processes of drug development, drug regulation and dispensing, to solve the issue. The *third-party* stakeholders include, inter alia, governments, regulatory agencies, professionals working in antibiotic R&D and medical ethics.

So far, barriers to and facilitators of responsible antibiotic use have been extensively studied among prescribers[5-7] and to a lesser extent among patients.[8] Up to now, there are no studies addressing barriers and facilitators of responsible antibiotic use among a broad range of *third-party* stakeholders.

The aim of this qualitative study was to investigate barriers to and facilitators of responsible antibiotic use from the perspective of third-party stakeholders. The scope of this study was an exploration of barriers and facilitators beyond socio-economical and geographical settings. The study builds on the work performed for the development of a definition of responsible antibiotic use by the Driving Re-InVEstment in R&D and responsible AntiBiotic use (DRIVE-AB) project.[9] The qualitative and explorative design of this study did not allow a comprehensive inventory of all potential barriers and facilitators nor comparisons between countries or regions.

Methods

This study is reported following the consolidated criteria for reporting qualitative research (COREQ).[10]

Design and study participants

In this qualitative study, we conducted semi-structured individual in-depth interviews to explore barriers to and facilitators of responsible antibiotic use. International third-party stakeholders from different sectors were invited by e-mail to participate. Stakeholders were invited based on experience and expertise on antibiotics and/or stewardship and senior positions at relevant organisations or institutions. Convenience

and snowball sampling was done within the international network of academic partners and European Federation of Pharmaceutical Industries and Associations (EFPIA) partners of the DRIVE-AB project. Solicited stakeholders originated from different continents. The sampling process, however, did not aim at reflecting all regions worldwide. The interviews took place between September 2016 and May 2017.

Data collection

Two researchers (AM and GT) trained in qualitative research methods conducted the interviews. Before participation, each stakeholder was informed on the objective of the study. Upon agreement, the participants were sent additional information on the interview topics and illustrative examples of case studies reflecting major ABR problems. Digital informed consent was obtained for all participants. The interviews were held in English, either by phone or face-to-face. An interview guide was developed based on five elements of the definition of responsible antibiotic use identified in a systematic review of the literature: *Access–Availability*, *Costs*, *Patient Outcome*, *Resistance* and *Future Effectiveness* (**Supplementary Figure S1**). These five responsible antibiotic elements were chosen for the interview because of their societal implications. Explanations about these elements are provided in **Table 1**. In addition, the stakeholders could introduce any additional topics they deemed relevant for responsible antibiotic use. Two pilot interviews were conducted with stakeholders with senior positions at a government agency and at a pharmaceutical company, representing different perspectives on antibiotic use, to refine the interview guide and interview questions.

Data analysis

All interviews were audio recorded and transcribed verbatim. Atlas.ti software V.7.0 (ATLAS.ti Scientific Software Development Company, GmbH, Germany) was used to facilitate the coding process. The first three interviews were coded by AM and JS, after which any discrepancies were discussed until consensus was reached. All other transcripts were coded by one researcher (AM). The generation of new codes was discussed in meetings between two researchers (AM and JS). Ultimately, thematic content analysis was performed and barriers and facilitators were extracted from the data. Categorisation was done by one researcher (AM) and validated by three other authors (IG, JS and MH) during research meetings.

Table 1 The five elements of responsible antibiotic use addressed in the stakeholder's interviews.

Element	Phrasing
Access-Availability	Ensuring access and routine availability of quality antibiotics.
Costs	Using the most cost-effective antibiotic regimen.
Patient outcome	Optimising outcome (reduced morbidity, mortality and length of hospital stay) following the treatment or prevention of bacterial infections.
Resistance	Limiting the emergence of antibiotic resistance.
Future effectiveness	Conserving the effectiveness of antibiotics for the future.

Results

Fourteen stakeholders agreed to participate. Interviewing was suspended after twelve in-depth interviews were conducted. Eleven were held by phone and one was conducted face-to-face. The interviews lasted 30 min to 1 hour. The following perspectives were represented: antibiotic R&D (n=3), health economics (n=1), medical ethics (n=3), government (n=2), health law and bioethics (n=1), public health (n=1) and regulatory agency (n=1).

Barriers and facilitators of responsible antibiotic use that emerged from the interviews were grouped into seven categories. Representative quotes for each reported barrier and facilitator are shown in **Table 2**. Barriers and facilitators that were health care setting or country-specific or that addressed health care access in general are shown in **Supplementary Table S1**.

Scientific challenges

Several scientific barriers to responsible antibiotic use were identified. First, an urgent need for new antibiotics and a lack of a robust and sustainable antibiotic pipeline were pointed out. An additional barrier reported by the stakeholders was the uncertainty of future medical needs. Moreover, the need for *better* drugs was emphasised (e.g., antibiotics with fewer side effects and less resistance inducing). It was said that while currently scientists are typically rewarded for publishing their results in peer-review journals, product development mainly relies on intellectual property (e.g., patents). This misalignment was reported as an underlying barrier affecting scientific progress in antibiotic R&D. Other barriers included a lack of scientific data for developing rapid diagnostics, monitoring the prevalence of resistant organisms, identifying rapid resistance-inducing antibiotics, informing medical practice guidelines and measuring the effects of antibiotic stewardship (ABS).

Table 2 Barriers to and facilitators of responsible antibiotic use per category.

Barrier or facilitator	Representative quote
Scientific challenges	
New drugs	*'We desperately need new drugs and we need better use of antibiotics but I think primarily new antibacterials.'* (antibiotic R&D) *'Fundamentally, we have to have the antibiotics to conserve. One of the biggest barriers is a lack of a robust and sustainable antibiotic pipeline. You need a pipeline because no matter how well we do with infection prevention, stewardship and ensuring responsible use of antibiotics, that general resistance will happen.'* (antibiotic R&D)
Uncertainty of future medical needs	*'You really can't predict what the needs are going to be in the future so you need basically a broadly robust pipeline, rather than a pipeline that's targeting sort of the specific needs that we have today. Because those won't be the needs we have five years from now'* (regulatory agency) *'We don't know what the next MRSA is going to be. We think carbapenem-resistant Enterobacteriaceae is the big problem, which it is, but we don't know what's coming next. We need a pipeline that is diverse and renewable so that we will be able to address the next challenge in ten or twenty years'* (government)
Better drugs	*' If you would have Panacure, an antibiotic which helps everything, which eradicates everything and has no side effects and does not cause, and does not increase resistance. You don't have to think about that, you just give a pill to every patient we suspect a bacterial infection. But anyhow, get better drugs. Less side effects, less induction of resistance and better coverage'* (medical ethics)
Reward system for scientists	*'...in science you're rewarded for publication, so, when you publish something* [...] *usually* [....] *you can't patent it afterwards… So, unless the researchers and innovators, there's an easy to access programme within the university to commercialise these discoveries, it usually doesn't go anywhere. So, there's a misalignment I think also with public funds and… motivation for scientists'* (public health)
Lack of data	*'...have more studies and more evidence to inform guidelines'* (government) *'Post-marketing surveillance for new drugs, but we could add to that the question if the drug is a rapid inducer of resistance or not and we would very much like to know that if a valuable drug is a* [...] *rapidly inducing resistance ' (medical ethics)* *'...each hospital, infection director or stewardship director, the ID doc should have a much better idea of what's going on in the hospital, what susceptible, what's resistant.'* (health law and bioethics) '*There are still scientific gaps, we still don't have the rigor of science as much as we need to show that using less antibiotics leads to less resistance. Data continues to evolve'* (government)

Economic challenges	
Financial incentives	*'...incentivizing antibacterial R&D and increasing the return on investments in antibacterial R&D* [...] *To increase the pipeline, resources are very important'* (antibiotic R&D) *'Unless we completely try to remodel the system and this will of course also have advantages outside of decreasing antibiotic resistance, but unless we reform the system that we currently have, a lot, and not just make small tweaks, we will not be able to conserve the effectiveness'* (public health) *'So there have to be incentives. So having the right incentives in place to make sure that this innovation continues'* (health economics) *'If you had this diagnostic that allowed 95% to continue with the old drug, what just happened to the new drug is you just destroyed 95% of its market…so it's the right thing to do clinically, have a great diagnostic but it's a disaster for the company trying to develop the drug'* (health law and bioethics)
New economic models	*'We have to create a situation in which it is rational for a company to invent an antibiotic that will not be used very often* [...] *because in parallel we want to conserve their effectiveness, we don't want to use them except occasionally'* (antibiotic R&D) *'...it would be necessary to delink the revenue from antibiotics from their effective consumption and create a different system of reimbursement'* (government) *'...delinkage sort of models, maybe there should be a prize or a payment completely separate from the clinic system'* (health law and bioethics) *'Maybe we should look at another model which is not 100% commercial and does not assume that 100% of the drug is owned, or the rights to the drug is owned by the drug companies'* (medical ethics)
Public funds	*'An allocated budget can be a facilitator, support from governments or from a public fund'* (health economics)
Manufacturing costs and shortages	*'...when a drug gets sufficiently cheap, the* [economic] *drivers for maintaining the supply chain go away […] In particular when you're making sterile injectables supply chains are extraordinarily difficult to maintain. They break all the time* [...] *so when the supply chain gets very thin you can pretty much guarantee that from time to time you will be out of the drug. There will be none to be bought anywhere in the world.'* (antibiotic R&D) *'...antibiotics that are now back in use because of the problem of resistance, the access to them is not uniform, there's no commercial interest in producing them'* (medical ethics)

Table 2 Continued.

Barrier or facilitator	Representative quote
Economic challenges	
Pricing	*'...a lack of access to drugs themselves., that's because they're very costly relatively to the economics of that particular environment'* (health law and bioethics) *'...it is just a major overall issue of making sure antibiotics are not priced out of range for most people. Because these are drugs that are used all across the health system'* (public health)
Conservation	*'Antibiotics are not like all drugs,* [they] *suffer from the fact that they have a relatively short half-life and when you put them in the pharmacy to store* […] *a year or two from now they're no good. You have to constantly make new material, that is expensive.'* (antibiotic R&D)
Tiered pricing*	*'A second one* [solution] *may be tiered pricing'* (antibiotic R&D)
Global purchaser	*'A global purchaser could be a solution to the affordability issue, a global fund for purchasing antibiotics and making them available to lower income countries'* (antibiotic R&D)
Global framework	*'A global stewardship and access framework put in place* [...] *if a number of countries pay say a large sum to stimulate R&D, they would then get access to this drug and be able to use it at a low cost and also use it appropriately in countries that would need it, we wouldn't have this decision by individual companies to go in and register or not'* (public health)
Low pricing	'*...very low cost encourages inappropriate use because the value of the antibiotic does not seem to exist in very low cost generic antibiotics so they are used more broadly than they should be because a very low cost means they're not particularly very valued to society and they're used much more freely than they should be.'* (antibiotic R&D) *'Part of the problem of antibiotic resistance is driven by the fact that antibiotic medicines are available in drugstores and over-the-counter for a very low cost. So, there is this tension between access and availability and overuse* […] *We want patients to have access but not to abuse and overuse them. We haven't quite figured out how to solve that, but it is a barrier.'* (government)
Cost-effectiveness	*'It's a bit meaningless to talk about cost-effective use of antibiotics today because we do not have a correct evaluation of what cost effective means in terms of antibiotic use'* (antibiotic R&D) *'...well the antibiotics don't tend to be used on a cost effectiveness basis, they tend to be used on cost comparative basis. So the true value of the antibiotic isn't necessarily recognised in the society or at the individual patient level'* (antibiotic R&D) *'...if there's a cheap generic* [comparator] *it's harder to be cost effective, even if you're more efficacious'* (health economics)

	'...a new highly innovative antibiotic has a hard time getting appropriate market share and appropriate pricing for it because it has to compete against highly effective generics' (health law and bioethics) *'...it means so many different things to different folks so cost-effective from the hospital administrator is lowest budget, cost effective to me as the patient is quickest cure, out of the hospital, no complications'* (antibiotic R&D)
Lack of data	*'... we need more extensive pharmacoeconomic studies that examine not only the cost per day of the drug that's being used but the overall cost to society for the drug cost plus the hospital and physician and caregiver associated costs.* [...] *More time and effort need to be spent doing those sort of studies'* (antibiotic R&D)
Regulatory challenges	
Clinical trial design	*'We often lack data about old antibiotics, so we don't know which effectively is the most efficacious treatment. For example, for MSSA we have some data comparing anti-Staph penicillins and vancomycin, but we lack data about newer drugs, compared with older ones. We would need more data'* (government) *'lack of control groups in real world situations'* (antibiotic R&D) *'...other physicians then in fact other regulators may feel that clinical response, assessed by the physician is an outcome that they'd like to know more about. We certainly collect that in clinical trials but it wouldn't be the primary end point'* (regulatory agency) *'the ability to return to functioning work or school is more valuable than length of stay, in my view'* (government) *'it's putting the right questionnaires in the protocol, so to assess the right patient outcomes* […] *but also maybe from the patient perspective'* (health economics) *'...so we don't know a lot about the longer term patient outcome differences between antibiotic A, B and C'* (health law and bioethics) '*I think most of the challenge with data on resistant organisms is finding the patient with the resistant organism that can be enrolled in a clinic trial that's sort of feasible and ethical. Because you usually have a patient presenting with a serious, some type of serious infection.* […] *So designing a trial where the comparator for example is acceptable in that setting becomes challenging'* (regulatory agency)
Recent progress	'*... there's a fair number of registration trials that are starting in nosocomial pneumonia which no one ever thought would occur at least five years ago and things are happening so that's exciting'* (regulatory agency)
Regulatory harmonisation**	*'... companies would need to make decisions where to submit a regulatory dossier, and there may be entire settings where they* [...] *choose not to submit a dossier. So that* [regulatory harmonisation] *would obviously impact availability in those setting.'* (regulatory agency)

Table 2 Continued.

Barrier or facilitator	Representative quote
Regulatory challenges	
Regulatory harmonisation**	*'I think regulatory harmonisation would encourage the development of new* drugs [...] *because it would mean that you wouldn't be having to have many different development programs for different regulatory approval'* (public health) '*so having harmonisation would help to have a very focused clinical program'* (health economics) *'...it should be a collective effort of different regulators, to change the system'* (government)
Licensing	*'Not licensing new antibiotics for multi-drug resistant infections for use in animals, making sure they are only licensed for use in humans'* (antibiotic R&D)
Labelling to support ABS	*'Our work product for the community is the drug label and we can provide a more limited indication sort of indicating that you should think very hard about whether you want to prescribe this drug or not. So limiting when alternatives are not available that's a pretty strong indication statement'* (regulatory agency) *'Our regulatory basis for limiting that indication, is that the data is more limited. I think what some companies are doing is they then provide more data in an attempt to have that caveat removed* […] *so then what happens stewardship is left to the practicing community with respect to that drug.'* (regulatory agency)
Ethical challenges	
Moral and financial debt	'*...we have been benefiting from the access to these very easily available antibiotics for quite a while and it has brought us great prosperity* […] *Now when you look at these African countries,* [...] *they have never had this great benefit from this huge step forward from antibiotics. But still at the same time, they are also pressured and asked to be responsible in using antibiotics'* (medical ethics) *'I would urge for acknowledging the benefits that we have already had for so many years and also reimbursing these countries, the other countries.* […] *I think we should acknowledge the fact that these antibiotics have brought us at a certain level* [...] *it's not fair to sort of say to other people you cannot get on this level because we want to now take care that we are not using all our antibiotics'* (medical ethics)
Future generations	*'Are you also balancing the needs of future generations? Do we have a responsibility for people that are not born yet for instance?* […] *that is definitely a national debate or maybe a societal debate.'* (medical ethics)
Specific populations	*'We need a more inclusive approach with regard to vulnerable populations that are most of the times excluded when it comes to testing the effectiveness of diagnostic tools and new medical regiments.* *So, that would also be part of a new policy I guess.'* (medical ethics)

	'...particularly paediatrics and particularly the neonatal intensive care unit […] I think there's a lot of scientific challenges to work on [...] evaluating drugs in children in a more timely way. [...] if you have a new drug developed it's probably going to take a minimum of five years before you get to the paediatric licensing for the product, figuring out the dosing and getting the safety studies done […] There's a lot of challenges to work on and they should be prioritised.' (government)
ABS	*'...one of the major barriers is that the stewardship program, this also implies that there has to be some ethical approach. There has to be some deliberation about how things balance to each other* […] *these protocols and these guidelines written in these regional hospitals are written by medical specialists or technical specialists.* [...] *How can technical people that have no skills in balancing ethical components actually decide what is best? They naturally choose a technical solution for this problem because they don't have access to the ethical solution.'* (medical ethics)
Access versus excess	*' ...there's a fine line and too many roadblocks you'll end up and basically having worse outcomes for patients, more deaths, you might limit your resistance but because the patient will be dead.* […] so *we have to be very careful with trying to fix all this resistance without hurting the patient at the end of the day*' (health economics)
Societal challenges	
Invisibility of ABR	*'...the problem we want to prevent is invisible. What is visible to us is a very sick patient, but what isn't visible is the spread of microbes'* (medical ethics)
Lack of awareness	*'... the lack of awareness of the problem of the increasing antimicrobial resistance which still leads to overuse and leads to a practice in which people have the tendency to look at a positive side of antibiotics with little attention to the negative side of antibiotics. That's one difficult issue which may drive overuse of antibiotics'* (medical ethics)
Lack of recognised value	*'...the true value of the antibiotic isn't necessarily recognised in the society or at the individual patient level*' (antibiotic R&D) '*so they have to look beyond the cost and then really the value basically, put a value on the unmet need.'* (health economics)
Animal health and the environment	'*...the biggest tonnage of antibiotics is given to animals, not people and we know that this* affects resistance' (government) '*...stop just releasing antibiotics into waterways and rivers'* (public health)
Societal problem of an individualistic society	*'...the collective thinking to individualism has shifted in the late 50's early 60'* […] *Now the pendulum is actually at the complete other side. The individual and autonomy, those are the biggest goods that we can perceive… Now, specifically in the context of this time era of individualism a problem arises that cannot at all be addressed from the point of view of individualism'* (medical ethics)

Table 2 Continued.

Barrier or facilitator	Representative quote
Societal challenges	
Costs of ABS	*'Where do the costs of stewardship lie? Do they lie at the individual level because then this can be a very huge barrier. Or can they put them at the level of the institute or the insurance companies or maybe nationwide'* (medical ethics)
Political challenges	
Changing political environment	*'....sometimes if there's a change in president or government or anything, the environment changes.'* (health economics)
Simplification of problems	*'...in order to make policies you have to sort of simplify these aspects and simplify the problem. That is something you can do both ways, you can either make it simple and sort of state I don't really see the problem or you can simplify it by saying this is the worst thing and we're at war with antibiotics* [...] *I think when you simplify a complicated problem that you normally don't get the solution that is actually solving this complicated issue.'* (medical ethics)
Lack of outcome expectancy	*'...the policymakers are hesitant to perform these studies because there is, they don't know what to do with the findings. So, suppose that we find a huger prevalence than is to be expected from the studies that we have now, how would we act upon that?'* (medical ethics)
Lobbying	*'...big patient advocacy groups to facilitate access'* (health economics)
Worldwide approach	*'A world-level responsibility* […] *it cannot be the endeavour of one country' (medical ethics)* *'the difficulty worldwide is of course resistance in a developing country can then easily spread elsewhere'* (antibiotic R&D)
National action plans	*'The plan now is that, globally, all countries will come up with a plan that they articulate for how they are addressing the resistance problem. Many of us believe there isn't a one-size-fits-all solution and the solution will be different in different countries.'* (government)
Citizenship	*'The responsibility lies with every person and every citizen. Certainly, we as physicians should have the ability to prescribe appropriately, but these citizens have the right to ask 'do I really need this? What are the risks if I take this medicine?' and I think that type of responsible citizenship is what is needed if we are to control this problem.'* (government)
Government	*'...the governments are very important in this capacity'* (government) *'It is mostly a political question.* [...] *I think it has very huge parallels with the way we think, the way we address our environmental problems.'* (medical ethics)
Non-political organisation	*'with the right mandate a non-political organisation that is not influenced by companies would be the answer right?'* (medical ethics)

Multi-stakeholder issue	*'I think it's a multi stakeholder issue. So I think it's public health, manufacturers. Community. Technology, a multi stakeholder issue'* (antibiotic R&D)
Individual company level	*'that it would not be up to individual companies anymore if there's access or not'* (public health)
Medical practice challenges	
Quantity of AB use	*'if I would say what would conserve effectiveness, it's going to be measures that are designed to reduce the amount of use'* (antibiotic R&D) *'the main lesson that we have to learn is be restrictive in the use of antibiotics and that's I think the best policy for the future'* (medical ethics)
Control AB use	*'I think more controlled use of existing and future antibiotics, so minimizing distribution antibiotics without a prescription'* (antibiotic R&D)
Alternatives to ABs	*'...we should focus a lot of energy on doing stuff other than antibiotics themselves: correct health care, infrastructure, correct use of infection prevention techniques. All that other stuff, use of vaccinations where they exist, inventing vaccines when they're inventible'* (antibiotic R&D) *'I think vaccines is also a big part of the future. So, kind of invest to push that field further and basically eliminating any breakouts or part of these disease from starting in the first place'* (health economics) *'infection control and it's divided into staffing, infrastructure and the classical infection control measures. Yes, infection control measures, even in relatively poor countries can be implemented. It needs some resources, good will and it can be implemented'* (medical ethics)
Diagnostics	'*another very important point is diagnostics. It is very important to have good and rapid diagnosis to treat properly an infection. A rapid diagnosis allows you to stop empiric treatment and prescribe a tailored antibiotic. But often you don't have rapid diagnosis'* (government) *'we could solve a lot of other access issues if we had* [...] *a point of care diagnostic that determines susceptibility so you could know, yes, no, new drug, old drug*' (health law and bioethics)
Incentive at clinic level	'*you don't want to have any financial incentives at the clinic'* (health law and bioethics)
Education	*'education of physicians and patients as regarded expectations in when antibiotics should be used. It's important that the patients understand the difference between an antibiotic being used appropriately in a bacterial infection and inappropriately in a viral infection'* (antibiotic R&D) *'there's always an education opportunity but education alone isn't the most effective'* (government) *'if you evaluate the awareness public campaigns, if you ask people about the effectiveness of these campaigns, they all say it's very useful but it doesn't regard me'* (medical ethics)

Table 2 Continued.

Barrier or facilitator	Representative quote
Medical practice challenges	
Cultural and behavioural change	*'when it comes to the medical specialty we all sort of live a cultural, social domain that we are doing what we are used to do.* [...] *there is a cultural change needed.* [...] *a cultural change will not be there out of itself, you have to sort of promote it, you have to help it, you have to train people to do so.* [...] *how can you sort of make this cultural paradigm shift in professionals?'* (medical ethics)

AB: antibiotic ABS: Antibiotic stewardship; ABR: antibiotic resistance; ID: infectious diseases.

* Tiered pricing: the concept of selling drugs and vaccines in developing countries at prices systematically lower than in industrialised countries.[11]

**Regulatory harmonisation: the process by which technical guidelines are developed to be uniform across participating authorities.[12]

Economic challenges

Among economic barriers, many stakeholders reported the lack of sufficient financial incentives for companies to develop new antibiotics. It was stated that the right financial incentives are crucial for innovation. This barrier was also reported to be relevant for the development of new diagnostic tools. New economic models that would delink antibiotic sales revenues from their consumption were proposed as a facilitator. The example of a model in which only partial rights of the drug are owned by the company was suggested. In addition, the provision of public funds was suggested as a mean to stimulate antibiotic R&D.

Antibiotic shortages of off-patent drugs as direct consequences of high manufacturing costs were reported as another barrier. Recent examples of shortages included several injectable antibiotics. High manufacturing costs were also reported to discourage the production of older antibiotics now back in use due to increasing ABR.

One of the most frequently mentioned barriers to access and availability of antibiotics, especially in lower income countries, was the affordability and pricing of the antibiotics. The relative short life-cycle of antibiotics was identified as a barrier to the long-term conservation of antibiotics and this was described to affect pricing. Examples of suggested facilitators for the affordability of antibiotics especially in low-income settings included tiered pricing (i.e., the concept of selling drugs and vaccines in developing countries at prices systematically lower than in industrialised countries), a global purchaser and a global stewardship and access framework. In contrast, the low pricing of generic antibiotics was considered to encourage overuse.

Several stakeholders indicated that the lack of cost-effectiveness data for antibiotics was an additional barrier. It was described that antibiotics are used on a cost-comparative basis and not routinely evaluated for cost-effectiveness criteria. Furthermore, the many perspectives to take into account when discussing cost-effectiveness were highlighted. More extensive pharmacoeconomic studies on a societal level were suggested to facilitate a better understanding of the cost aspect of antibiotic use and thereby guide improvements.

Regulatory challenges

Several regulatory barriers were addressed by the stakeholders including the design and outcomes of clinical trials. It was described that currently, a new antibiotic is approved for commercialisation if it was demonstrated to be at least as effective as an already commercialised comparator using a non-inferiority trial design. Also, it was pointed out that often data on older antibiotics and data on real world situations are lacking, making it hard to establish which treatment is actually the most effective. Moreover, stakeholders reported that this design does not allow for testing additional patient outcomes relevant to physicians and society (e.g., clinical response and time to return to work/school). It was also suggested to include the patient's perspective

as an outcome (e.g., patient questionnaires). The consideration of longer-term patient outcomes and more patient follow-up data (e.g., hospital readmissions) was advocated for. The difficulties of designing trials to test a drug against resistant organisms, i.e., identifying patients with the target resistant bacteria and setting up trials that are both ethical (patients with severe infection) and feasible (acceptable comparator for that setting) were highlighted. Nonetheless, some encouraging progress was noticed by stakeholders including recent registration trials.
In contrast, regulatory harmonisation was proposed by several stakeholders as a facilitator to improve access in low-income settings and thereby ensure equal access across the world. It was pointed out that for any regulatory reform a collective, worldwide effort of different regulatory organisations and governments is crucial.
Restricting the licensing of new antibiotics only to humans was reported a facilitator to limit the spread of ABR. Another acknowledged facilitator of responsible use was the labelling by the regulator according to ABS principles (e.g., use for limited number of indications, suggestion to consider alternative treatments).

Ethical challenges

Various ethical considerations were addressed. It was pointed out that over the past decades, the availability of effective antibiotics contributed to economic prosperity. It was described that, however, not all regions and countries of the world enjoyed equal benefits of antibiotic use. Therefore, a moral and financial debt from the countries that benefited from years of unrestricted antibiotic use (typically high-income) towards the less benefiting countries (typically low-income) was suggested. Another barrier included the balance between the needs of current patients and possible damage to future generations and how to integrate these responsibilities in current policies. Another ethical barrier mentioned was that special populations are usually excluded from research on new therapeutic and diagnostic tools. Prioritising trials for specific populations (e.g., children, the elderly) was mentioned to facilitate responsible antibiotic use. The need for new research policies that are more inclusive of vulnerable populations was highlighted. The integration of explicit ethical deliberations into ABS guidelines was recommended. Finally, both the importance and difficulty of achieving a balance between restricting access to antibiotics when there is no medical indication and ensuring access to patients needing them were emphasised.

Societal challenges

First, the invisibility of ABR, for both the general public and the health care workers was mentioned. Also, the lack of awareness of increasing resistance and the tendency to focus on the benefits of antibiotic treatments rather than on their negative consequences were cited. Other barriers were the lack of recognition of the true societal value of effective antibiotics and understanding of the high unmet need they

represent. Proposed facilitators included controlling veterinary use and controlling the release of antibiotic waste in the environment. The fact that modern society, largely focused on individuality and autonomy, is currently facing a problem affecting each and every one of us and for which no individual patient-level solution exists was considered another barrier. This aspect also triggered stakeholder reflections on the distinction between collective and individual costs to finance ABS activities.

Political challenges

The changing political environment and the tendency of politics to simplify complex problems, and the lack of outcome expectancy were mentioned as barriers in politics. Lobbying by patient advocacy groups was cited as a facilitator to increase political attention.

When discussing responsibility and key players in the endeavour towards responsible antibiotic use, the answers of experts diverged. Some agreed on the world-level responsibility as ABR spreads across the globe while others highlighted the importance of national action plans to address ABR. In addition to the role of the medical community to prescribe antibiotics appropriately, the need for responsible citizenship was highlighted. The importance of governments in the same way politics is involved with environmental problems was stressed. Another participant expressed a preference for a body strictly independent from politics and industry. ABR was reported a multi-stakeholder issue and stimulating collaboration (e.g., through multisectoral initiatives) was seen as a way towards a solution. It was stated that the responsibility for access to antibiotics should not lie at the individual pharmaceutical company-level.

Medical practice challenges

Restricting the overall amount of antibiotic use was reported a facilitator to limit the spread of ABR and conserve effectiveness and was reported as the best policy for the future. Preventing the distribution of antibiotics without prescription, considering alternatives for antibiotics (e.g., vaccination) and ensuring that ABS and infection prevention measures are in place in health care facilities were reported as facilitators. As the quotes in **Table 2** show, the lack of rapid point-of-care diagnostics was mentioned as a barrier to responsible antibiotic use. It was stated that no financial incentive for prescribing antibiotics should be in place at the health care facility. Education of both patients and the public was believed to facilitate responsible use. However, for both target groups reservations on the effectiveness of education were expressed by stakeholders. Finally, the difficulties of changing behaviour and achieving cultural change were addressed as a barrier.

Discussion

This qualitative study identified barriers to and facilitators of responsible antibiotic use from the perspective of a wide range of international third-party stakeholders. Seven categories of barriers and facilitators emerged: scientific, economic, regulatory, ethical, societal, political and medical practice challenges. While the categories of barriers were addressed separately, it should be acknowledged that they are closely intertwined and reciprocally reinforce each other. Moreover, several contrasts highlighting the complexity of responsible antibiotic use emerged across the categories. Examples include the alarming worldwide spread of ABR as opposed to its invisibility, the conflicts between ABS principles and incentives for antibiotic R&D with current economic models, and the paradox between research based on current unmet needs versus the uncertainty of future medical needs. Interestingly, little disagreement was observed overall between the stakeholders despite the background diversity. Diverging answers belonged mainly to the category of political challenges and addressed the topic of responsibility and key players in the endeavour towards responsible antibiotic use.

Scientific, economic, regulatory challenges of antibiotic R&D have been described previously.[13-15] Recently, Morel et al. presented an elegant in depth-overview of societal and economical trade-offs associated with responsible antibiotic use.[16] Ethical aspects of antibiotic use including implications for elderly populations and responsibilities towards future generations were reviewed by others.[17, 18] While in these reviews barriers and facilitators were described from single perspectives (antibiotic R&D or ethics), our results provide insights and perceptions from third-party stakeholders from multiple sectors.

Our study has several strengths. To our knowledge this is the first qualitative study on barriers and facilitators of responsible antibiotic use from the perspectives of third-party stakeholders. Semi-structured interviews allowed the stakeholders to express their views in their own terms and showing their quotations should contribute to greater depth of understanding of the barriers and facilitators. Furthermore, the breadth of perspectives, from antibiotic development to medical ethics, allowed a wide exploration of barriers and facilitators. The findings of this study go beyond specific health care and country settings which make them relevant for both national- and worldwide-level policies.

Several limitations should be addressed. First, concerns could rise regarding the relatively small sample size of the interviewed stakeholders. In this exploratory interview study, an illustrative sample of third-party stakeholders were consulted. Whereas a quantitative study design would allow for more participants, this would lead to loss of depth of the answers. Second, the interview guide could be considered narrow considering the complexity of the ABR problem. However, the participating

stakeholders were given the opportunity to introduce additional interview topics. Third, this study reports opinions and perceptions of the interviewed stakeholders but these may not be representative of the entire community they portray and may not reflect all socio-economic and geographic settings. The results of this study can be used as building blocks to design research tools to investigate barriers and facilitators of responsible antibiotic in specific regions of the world with a more quantitative approach (e.g., questionnaires).

In conclusion, we recommend considering the identified barriers and facilitators when drafting future antibiotic policies. Some of the barriers and facilitators identified in our study (e.g., financial incentives, new economic models) were addressed more extensively in another work package of the DRIVE-AB project.[19] Cross-disciplinary international policy efforts should, informed by this analysis, work towards solutions to ensure the sustainable use and equitable availability of effective (existing and new) antibiotics.

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Chapter 5 - Supplementary data

Elements of responsible antibiotic use that will be addressed in the interview:

1. Access-Availability: Ensuring access and routine availability of quality antibiotics.
2. Costs: Using the most cost-effective antibiotic regimen.
3. Patient Outcome: Optimising outcome (reduced morbidity, mortality and length of hospital stay) following the treatment or prevention of bacterial infections.
4. Antibiotic Resistance: Limiting the emergence of antibiotic resistance.
5. Future Effectiveness: Conserving the effectiveness of antibiotics for the future.

Illustrative examples to expedite discussions:

- Example 1: Complicated *S. aureus* bacteraemia
  Setting: Hospital care in European countries.
  The prevalence of MRSA is unequally distributed across Europe and the epidemiology is changing.
  Often, MRSA therapy prescribed for non MRSA susceptible *S. aureus* bloodstream infections (MSSA): glycopeptides rather than an antistaphylococcal penicillin.

→ Need for limiting the use of newly developed MRSA-antibiotics in case of MSSA.

- Example 2: The gonorrhoea resistance problem
  Setting: Community care in developing countries.
  Gonorrhoea is a sexually transmitted infection (STI) with a serious public health impact worldwide, especially in developing countries.
  Emergence of resistance to several antibiotics over time; more recently quinolones and the oral cephalosporin cefixime.

→ Need for new oral drugs and for limiting the emergence of resistance for newly developed oral drugs in the future.

Interview questions

1. Access –Availability: Ensuring access and routine availability of quality antibiotics.
From the perspective of ... could you name facilitators and barriers to access and availability of antibiotics? In example 1? In example 2? And more in general?

2. Costs: Using the most cost-effective antibiotic regimen.
From the perspective of ... could you name facilitators and barriers to the most cost-effective antibiotic regimen? In example 1? In example 2? And more in general?

3. Patient Outcome: Optimising outcome (reduced morbidity, mortality and length of hospital stay) following the treatment or prevention of bacterial infections.
From the perspective of ... could you name facilitators and barriers to optimised patient outcome? In example 1? In example 2? And more in general?

4. Antibiotic Resistance: Limiting the emergence of antibiotic resistance.
From the perspective of ... could you name facilitators and barriers to limiting the emergence of resistance? In example 1? In example 2? And more in general?

5. Future Effectiveness: Conserving the effectiveness of antibiotics for the future.
From the perspective of ... could you name facilitators and barriers to conserving the effectiveness of the antibiotics? In example 1? In example 2? And more in general?

Supplementary Figure S1: Interview guide.

Supplementary Table S1 Additional barriers to and facilitators of responsible antibiotic use: care setting-specific, country-specific or relating to health care access in general.

Barrier or facilitator	Representative quote
Long-term care	
Lack of data	*'we don't have an overall view of the whole country and to some stakeholders long-term care is like the black hole of antimicrobial resistance and we should perform more surveillance studies, point-prevalence studies, look into the prevalence of antimicrobial resistance, resistant bacteria in the nursing home setting.'* (medical ethics) *'And then there is the uncertainty about the length of an antibiotic course, we have a lot of scientific questions unanswered there, we don't know what is the proper length of an antibiotic cure and there is a tendency to extend length of cures for vulnerable patients but there is no hard evidence for doing that. Doctors do that because they are afraid that because of the vulnerability of their patients the antibiotic, they need to be treated longer than other patients.'* (medical ethics)
Antibiotic route	*'part of them are practical barriers, the route of entrance of the antibiotic. If you have to give them intravenously it might be difficult in an out of hospital situation. So, this might need transfer of the patient and when it comes to older patients, frail, elderly especially, well physicians are frequently hesitant to transfer their patient to another setting. And if that is necessary to give them antibiotics intravenously,* *this is also a barrier*' (medical ethics)
Pricing	*'well a barrier for my field is the pricing of antibiotics, the necessity to work within strict budgetary restraints. That at least is what is happening in long-term care in [Country X]. […] long-term care has to be provided with limited budgets so this will put restraints on the availability of certain medicines, especially when they are expensive and not present in routine guidelines.* (medical ethics)
Infection control measures	*'the dominant care philosophy, dominant at this moment in the long-term care setting that more or less says that living in long-term care must mimic your home situation, must mimic a homelike situation.* *So, if it has to mimic a homelike situation then topics like infection prevention, careful use of antibiotics more or less belongs to a medical model and the medical model doesn't fit in with this homelike care philosophy.'* (medical ethics)
Lack of awareness	*'...there is culture of positive expectation in the nursing home setting. Family of our residents think well,* *if you're not sure whether it's wrong, just give them antibiotics because may it not work it will not harm? and this is also the expectation of the nursing staff'* (medical ethics)

Supplementary Table S1 Additional barriers to and facilitators of responsible antibiotic use: care setting-specific, country-specific or relating to health care access in general.

Barrier or facilitator	Representative quote
Long-term care	
Lack of incentive to improve	*'another barrier here is that we [in the Netherlands]] are performing quite well as a country compared to other countries in Europe, so why bother? Why change our policy, why should we do anything and who's going to pay for it? So, I think these are barriers.'* (medical ethics)
Hospital care	
Financial structure	*'I think that the unfortunate state of affairs is that because of our health care systems' limitations, we can't always use the best medicine in terms of reducing morbidity, we have to use what is available in a given system at any given time. The example of the new MRSA drug that you inject once a week are a perfect example because they, at least in theory, can negate the need to even be admitted to the hospital, at least in the developed world. But because of the cost structure we haven't been able to figure out how to use them so we still have to admit patients to the hospital so we're not able to optimise outcomes that way.'* (government) '*The way we get paid for hospital admissions in America is under the DRG diagnosis group. Once a patient gets admitted to the hospital, it becomes very important to use the most inexpensive antibiotic that we can for that patient and our stewardship programme precludes us from using these fancy drugs on our patients.* *Interviewer: So that could be a good way to preserve the new drugs? Interviewee: We don't know that. Maybe using these drugs is better because we could keep people out of hospital and stop the spread of MRSA, we just don't know.'* (government) '*On the cost piece, in US hospitals, this inpatient drug it will always be charged against the hospitals DRG, it's bundled payment. It's diagnostic group payment. So from the hospitals' perspective every dollar they spend on this antibiotic is a cost to the hospital that they cannot be reimbursed for. If they can somehow not give the drug as part of their hospital stay the hospital makes more money. So if they can give it as OPAT or if they can give it and send you home then it's easier for the hospital to make money'* (health law and bioethics) *'It's the local hospital managing it's pharmacy budget the way that see fit. There are some federal rules in this area but not many on what that hospital chooses to do. That hospital probably has some torque in some malpractice exposure if they fail to have a drug on hand because they excluded it form the formulary and the patient died. They could be negligent. Plus they just want to offer the best care for the patient. So they are trying to balance the economics as well as the medicine.'* (health law and bioethics)
Budget Holder	*'The main barrier of this is the budget holder […] The budget holder just looks at the budget and he doesn't, he's often not the one treating the patient. Also if there's savings at the hospital he doesn't care. So he's looking, if I can save let's say 100,000 in antibiotics and then I could put it into cardiovascular I can help more patients. So they're not looking by therapy area alone. Often they look, okay, it's a cost opportunity question. So there's education to be done and maybe also allocating budget in a review track or even here with harmonizing for the antibiotics.'* (Health economy)

Separate Budgets	*'In the United States at least, we sometimes have silo mentality, the pharmacy department is responsible for the pharmacy budget and they are going to try to optimise the cost by using the least expensive drugs but they may actually be costing the hospital increased costs'* (antibiotic R&D)
Health care access in general	
Collecting and using data	'*I think probably a lack of infrastructure. Collecting the appropriate data, would be more of an issue than in high income countries. I think it would be more of an issue in low income countries.'* (antibiotic R&D) *'And it can come from better use of probabilistic data, again, through this computerised decision support system that I was talking about. So, get better information that would be one answer.'* (medical ethics)
Financial priority	*'there's a lot of things for them to balance and they're balancing what's best for the institution long term versus what's best for this one patient'* (health law and bioethics)
Quality of generic drugs	*'a significant issue which in our drugs is quality and in many situations certain batches are generic drugs are not manufactured with the same high quality that other batches of generic drugs, the brand name is by contrast always held to a very high standard because the manufacturer depends upon the reputation of that drug throughout the world for it to be the best standard possible'* (antibiotic R&D)
Free drugs	*'[Company X] has spent many, many millions of dollars manufacturing [drug X] that it gives away for free in Africa. It does so in parts because it's the right thing to do but in terms of providing benefits to the company they're very good public affairs reactions about that and commentary and good will. It also gives individuals who work at [Company X] a sense of working for a company that cares about others and cares about general good. And it provides increased stimulation and loyalty among the employees. But you can't do that in companies that don't have the enormous deep pockets that a company like [Company X] has'* (antibiotic R&D)

Legend: DRG: Diagnosis-related group.

6

A case study on *Staphylococcus aureus* bacteraemia: available treatment options, antibiotic R&D and responsible antibiotic use strategies

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Abstract

Aim This case study addresses (I) antibiotic treatment options for *Staphylococcus aureus* bacteraemia (SAB), for both empirical and targeted therapy; (II) current status of and priorities for the antibiotic pipeline to ensure access of effective antibiotics for SAB; and (III) strategies for responsible antibiotic use relevant to the clinical management of SAB.

Methods Evidence to address the aims was extracted from the following information sources: (I) EUCAST and CLSI recommendations, summaries of product characteristics (SPCs), antibiotic treatment guidelines and textbook "Kucers' The Use of Antibiotics"; (II) the www.clinicaltrial.gov database; and (III) quality indicators (QIs) for responsible antibiotic use.

Results Current monotherapy treatment options for SAB include only three drug classes (beta-lactams, glycopeptides, lipopeptide) for SAB of which two also cover MRSA bacteraemia (glycopeptides, lipopeptide). The analysis of the antibiotic pipeline and ongoing clinical trials revealed that several new antibiotics with *S. aureus* (including MRSA) coverage were developed in the past decade (2009-2019). However, none belonged to a new antibiotic class or had superior effectiveness and their added clinical value for SAB remains to be proven. Responsible antibiotic use for the treatment of SAB was illustrated using eleven QIs.

Conclusion Awareness of the problem of a limited antibiotic arsenal together with incentives (e.g., push incentives) are needed to steer the R&D landscape towards the development of novel and effective antibiotics for treating SAB. In the meantime, responsible antibiotic use guided by quality indicators should preserve the effectiveness of currently available antibiotics for treating SAB.

Introduction

Staphylococcus aureus, a Gram-positive bacterium that is both a human commensal and an opportunistic pathogen, is a frequent cause of bacteraemia in industrialised nations.[1-3] The mortality associated with *Staphylococcus aureus* bacteraemia (SAB), estimated at 20-25 %, is considerable.[4, 5] Furthermore, the burden of SAB is increasing overtime.[6-8] SAB is a common healthcare associated infection, often linked with the use of intravascular catheters but can also be acquired in the community.

Over the past sixty years, *Staphylococcus aureus* has shown great aptitude for becoming resistant to antibiotics thereby posing challenges for clinical management of *S. aureus* infections. Currently, MRSA strains are resistant to several beta-lactam antibiotics including penicillins, cephalosporins, carbapenems,[9, 10] quinolones,[11] and even vancomycin.[12]

The MRSA epidemiology is continuously changing and shows a wide variation within and between geographical regions.[13] For example, methicillin resistance rates among *S. aureus* invasive isolates range from 1.2 to 50.5 % in European countries.[3]

The development of resistance by bacteria is a natural phenomenon and all use of antimicrobial drugs drives the development of resistance by selection pressure. At the level of the health care facilities, strategies to reduce the emergence of resistance should thus focus on limiting antibiotic use to appropriate clinical situations. These responsible antibiotic use strategies are the core focus of antibiotic stewardship. Containing the spread of MRSA is in the interest of both patient health and the hospital finances.[14] Quantity of hospital antibiotic use has previously been associated with frequency of MRSA acquisition.[15] Over the past years, remarkable decreases in MRSA rates were observed following infection control and stewardship activities in France and the United-Kingdom.[16]

Aims

This case study addresses (I) available antibiotic treatment options of SAB for both empirical and targeted therapy and (II) current status of and priorities for the antibiotic pipeline to ensure access of effective antibiotics for SAB. Finally, (III) strategies for responsible antibiotic use relevant to the clinical management of SAB are discussed. The case study focuses on the management of SAB in the hospital setting and does not address other treatment options such as source control, vaccines or antibodies against *S. aureus*.

Case study methodology

Definition

A case study can be defined as an intensive study about a person, a group of people or a unit, which is aimed to generalise over several units.[17] A case study is typically characterised by its subject (i.e., a phenomenon of scientific interest or 'unit') and its object (i.e., the analytical frame within which the case subject is understood and illustrated).[18] The present case study addresses (I) the available antibiotic arsenal, (II) the current status of and priorities for the antibiotic R&D and (III) responsible antibiotic use strategies (objects) for the treatment of *Staphylococcus aureus* bacteraemia (subject) in the hospital setting.

I. Staphylococcus aureus bacteraemia: current antibiotic treatment options

Empirical treatment options (**Table 1**) and targeted treatment options for *Staphylococcus aureus* bacteraemia and/or endocarditis (**Table 2**) were compiled using the information sources listed below:

- Clinical breakpoints were extracted from EUCAST.[19] When no clinical breakpoint was described in the EUCAST database, the CLSI library was searched.[20]
- Clinical use sections of the textbook Kucers' The Use of Antibiotics were searched for relevant human data on severe infections, bacteraemia and/or endocarditis, or empiric treatment of febrile neutropenic patients.[21] Kucers' The Use of Antibiotics is considered a leading source of information in the field of infectious diseases.[22]
- An illustrative sample of guidelines from Europe, the United-States and Australia accessible in English were searched for recommendations:
  - Clinical practice guidelines for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children by the Infectious Diseases Society of America (IDSA)[23]
  - Clinical practice guidelines for the diagnosis and management of intravascular catheter-related Infection by the IDSA[24]
  - European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia (ECIL)[25]
  - Guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC)[26]
  - *Staphylococcus aureus* Bacteraemia (SAB) Management Clinical Guideline developed by the South Australian expert Advisory Group on Antimicrobial Resistance (SAAGAR)[27]
  - Antibacterial therapy of adult patients with sepsis guideline by the Dutch Working Party on Antibiotic Policy (SWAB) (Revisions have been announced)[28]

  - ❖ Guidelines for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the United Kingdom[29]
  - ❖ UptoDate Chapter 'Clinical approach to *Staphylococcus aureus* bacteremia in adults' by Holland & Fowler (Last updated in July 2019)[30]
- When available, the Summary of Product Characteristics (SPC) of antibiotics approved by the regulatory agencies (EMA and/or FDA) were accessed online. When no harmonised EMA indication was available (e.g., for drugs already widely in use before the creation of the EMA in 1995 and not undergoing referral procedures at EMA afterwards), SPCs from EU National Regulatory Agencies (EU NRA) were searched. The sections "therapeutic indications" and "posology" were screened for one of the following indications: bacteraemia, sepsis, septicaemia, severe infections, endocarditis.

Additional information on the data extraction process:

- Antibiotics for which no literature on use as monotherapy was reviewed in Kucers' The Use of Antibiotics were not included (e.g., fosfomycin, rifampicin, aminoglycosides, ertapenem).[21]
- The level of evidence of the recommendations are not provided. However, the UptoDate Chapter on SAB[30] was included as an information source and the recommendations from UptoDate have previously been shown to adhere with the Grading of Recommendations Assessment Development and Evaluation (GRADE) framework.[31]
- No distinction was made between first or second choice of therapy. This case study should not be seen as a clinical practice guidance but rather as a reflection on the current antibiotic arsenal for SAB. Of note, antibiotics mentioned as alternative, third-line (i.e., very weak evidence) or salvage treatment options were not included.

II. Staphylococcus aureus bacteraemia: current status of and priorities for antibiotic R&D

Ongoing and recently completed (≤5 years) clinical trials for antibiotics for the treatment of SAB and/or endocarditis (**Table 3**) were searched in the www.clinicaltrial.gov database. Clinical trials were not included in the table when: trial status was 'unknown', completed before January 2014, when trials results were already published, when the interventions were not limited to the use of antibiotics (e.g., algorithm based therapies, adjunctive immunotherapeutics, other novel approaches); or when trials did not study any specific (combination of) antibiotics. Utilisation registry trials, observational and retrospective studies are not presented in **Table 3**.

III. Staphylococcus aureus bacteraemia: responsible antibiotic use strategies
Fifty-one generic inpatient quality indicators (IQIs) for antibiotic use were recently developed by the Driving Re-InVEstment in R&D and responsible AntiBiotic use (DRIVE-AB) consortium through an international and multidisciplinary consensus.[32] While we recognise that all 51 IQIs are relevant to the management of SAB, we highlight here a selection of themes and associated quality indicators, considered particularly pertinent to measure responsible antibiotic use for SAB. The original codes for the addressed IQIs are shown in the text.[32]

Study limitations

Limitation of case study research includes bias toward verification (i.e., the tendency to confirm the researcher's preconceived notions).[33] The data extraction performed among different international information sources and the collaboration with researchers from different backgrounds (including medical specialists, a health economist and a regulator) is expected to reduce risks for verification biases.

I. SAB: current treatment options

The clinical management of SAB requires a combination of effective antibiotic therapy and prompt removal of the source of infection such as catheter removal or abscess drainage. As with most infectious diseases, there is no 'one size fits all' antibiotic treatment for SAB as the appropriate dosage regimen is determined by a combination of pathogen-related factors (e.g., antibiotic susceptibility), patient-related factors, (e.g., antibiotic allergies, immune factors, comorbidities, concomitant therapy) and source of infection (e.g., skin and skin tissue versus pulmonary).
SAB can be classified as 'complicated' or 'uncomplicated.[23] One of the criteria used for this severity classification is whether an endocarditis is suspected or diagnosed. Indeed, *S. aureus* is the major causative pathogen of infective endocarditis in many regions of the world.[34] This distinction between complicated or uncomplicated SAB has a significant impact on clinical management by guiding the diagnostic procedures, the duration of antibiotic treatment, and the overall prognosis.[35]

Terminology: empirical versus targeted therapy

A crucial aspect of the clinical management of bacterial infections is the distinction between empirical therapy (also called initial therapy) and targeted therapy (or definitive therapy).[36] While the first should be based on clinical presentation and local epidemiology (i.e., a 'bacteriological educated guess' covering all suspected causative pathogens including *S. aureus*), the latter should be based on microbiology results (i.e., identification of *S. aureus* as the causative pathogen and antimicrobial

susceptibility data). In this case study, initial empirical therapy refers to the first days of therapy, i.e., 48-72 hours before the cultures identify the causative pathogen.

Antibiotic treatment options for S. aureus bacteraemia and endocarditis

Current treatment options for *S. aureus* bacteraemia and endocarditis are shown in **Table 1** and **Table 2**. Coverage of *S. aureus* infections should be guided by local epidemiology, however, there is no generally accepted consensus on an appropriate methicillin resistance threshold for bacteraemia. A threshold of 10 % resistance rate in bacteria has been recommended previously.[29] However, some argued that this 10 % resistance threshold is too low.[37] A threshold of 20 % has been advised to guide the choice of empirical therapy for non-bacteraemia infections when MRSA is suspected.[38] These percentages overlap with previous recommendations for a 10-20 % threshold, by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society for pneumonia.[39] Coverage of MRSA should also be opted for in presence of one or more risk factors such as recent antibiotic use or use of central venous catheters in settings where MRSA is prevalent, known nasal MRSA colonisation or prior MRSA infection.[40, 41]

Empirical therapy of SAB

Twelve beta-lactam and one glycopeptide antibiotics are described as empirical treatment options for SAB (**Table 1**). Ten antibiotics are recommended by at least one guideline or have an indication (from an EU NRA, EMA or FDA). Of these antibiotic options, eight have only MSSA coverage (beta lactams including cephalosporins and carbapenems) and two have also MRSA coverage (vancomycin and teicoplanin). Two more recent extended spectrum beta-lactam antibiotics, ceftaroline and ceftobiprole, for which there is no recommendation for the treatment of SAB to this date, are discussed more in detail in section II.

Targeted therapy of SAB

Fifteen antibiotics are described as targeted treatment options for SAB (**Table 2**). Seven antibiotics are recommended by at least one guideline or have an indication (from an EU NRA, EMA or FDA). Of these antibiotic options, three have only MSSA coverage (isoxazolyl penicillins, nafcillin and cefazolin) and four have also MRSA coverage (vancomycin, teicoplanin, daptomycin and linezolid). Of note, linezolid has no regulatory indication from FDA or EMA for bacteraemia and is only recommended for uncomplicated bacteraemia with confirmed MRSA by one guideline.[29]

Combination antibiotic therapy

There are two major rationales for combination therapies. The first is broadening the antibiotic spectrum of the empirical therapy. The second purpose of combinations is

Table 1 Options for broad-spectrum initial empirical antibiotic therapy of severe infections (i.e., suspected bacteraemia, sepsis and/or endocarditis) including coverage of *S. aureus*.

Antibiotic class	Antibiotic agent	Clinical breakpoint *S. aureus* (MIC)	Source[a]	MSSA		MRSA		References
				Bacteraemia	Endocarditis[b]	Bacteraemia	Endocarditis[b]	
Beta lactams								
Cephalosporin (2nd generation)	Cefuroxime	≤ 4 mg/L (S); > 4 mg/L (R) (inferred from MIC cefoxitin[19])	Mentioned in Kucers'	NO	NO	NO	NO	21
			Recommended by guideline(s)	YES	NO	NO	NO	28
			EMA harmonised indication	NO	NO	NO	NO	42
			FDA indication	YES	NO	NO	NO	43
Cephalosporin (3rd generation)	Cefotaxime	≤ 4 mg/L (S); > 4 mg/L (R) (inferred from MIC cefoxitin[19])	Mentioned in Kucers'	NO	YES	NO	NO	21
			Recommended by guideline(s)	YES	YES	NO	NO	26, 28
			EU NRA indication[c] (e.g., France)	YES	YES	NO	NO	44
			FDA indication	YES	NO	NO	NO	45
	Ceftriaxone	≤ 4 mg/L (S); > 4 mg/L (R) (inferred from MIC cefoxitin[19])	Mentioned in Kucers'	NO	YES	NO	NO	21
			Recommended by guideline(s)	YES	YES	NO	NO	28
			EMA harmonised indication	YES	YES	NO	NO	46
			FDA indication	YES	NO	NO	NO	47
	Ceftazidime	-	Mentioned in Kucers'	YES	NO	NO	NO	21
			Recommended by guideline(s)	NO	NO	NO	NO	
			EMA harmonised indication	NO	NO	NO	NO	48
			FDA indication	YES	NO	NO	NO	49
Cephalosporin (4th generation)	Cefepime	≤ 4 mg/L (S); > 4 mg/L (R) (inferred from MIC cefoxitin[19])	Mentioned in Kucers'	YES	NO	NO	NO	21
			Recommended by guideline(s)	YES	YES	NO	NO	25

			EU NRA indication[c] (e.g., United-Kingdom)	YES	NO	NO	NO	50
			FDA indication	YES	NO	NO	NO	51
Cephalosporin (5th generation)	Ceftaroline	≤ 1 mg/L (S); > 2 mg/L (R)[19]	Mentioned in Kucers'	NO	NO	NO	NO	21
			Recommended by guideline(s)	NO	NO	NO	NO	
			EMA harmonised indication	NO	NO	NO	NO	52
			FDA indication	NO	NO	NO	NO	53
	Ceftobiprole	≤ 2 mg/L (S); > 2 mg/L (R)[19]	Mentioned in Kucers'	NO	NO	NO	NO	21
			Recommended by guideline(s)	NO	NO	NO	NO	
			EU NRA indication [c, d] (e.g., United-Kingdom)	NO	NO	NO	NO	54
			FDA indication	Not available in the US				
Beta lactam/ beta-lactamase inhibitor combination	Piperacillin/ Tazobactam	≤ 4 mg/L (S); > 4 mg/L (R) (inferred from MIC cefoxitin[19])	Mentioned in Kucers'	YES	NO	NO	NO	21
			Recommended by guideline(s)	YES	NO	NO	NO	25, 28
			EMA harmonised indication	YES	NO	NO	NO	55
			FDA indication	YES	YES	NO	NO	56
Carbapenems	Imipenem/ Cilastatin	≤ 4 mg/L (S); > 4 mg/L (R) (inferred from MIC cefoxitin[19])	Mentioned in Kucers'	YES	YES	NO	NO	21
			Recommended by guideline(s)	YES	YES	NO	NO	28
			EMA harmonised indication	YES	NO	NO	NO	57
			FDA indication	YES	YES	NO	NO	58
	Meropenem	≤ 4 mg/L (S); > 4 mg/L (R) (inferred from MIC cefoxitin[19])	Mentioned in Kucers'	YES	YES	NO	NO	21
			Recommended by guideline(s)	YES	YES	NO	NO	28
			EMA harmonised indication	YES	NO	NO	NO	59
			FDA indication	YES	NO	NO	NO	60

Table 1 Continued.

Antibiotic class	Antibiotic agent	Clinical breakpoint *S. aureus* (MIC)	Source[a]	MSSA		MRSA		References
				Bacteraemia	Endocarditis[b]	Bacteraemia	Endocarditis[b]	
Glycopeptides								
	Vancomycin	≤ 2 mg/L (S); > 2 mg/L (R)[19]	Mentioned in Kucers'	YES	YES	YES	YES	21
			Recommended by guideline(s)	YES	YES	YES	YES	23, 24, 26, 27, 29, 30
			EMA harmonised indication	YES	YES	YES	YES	61
			FDA indication	YES	YES	YES	YES	62
	Teicoplanin	≤ 2 mg/L (S); > 2 mg/L (R)[19]	Mentioned in Kucers'	YES	YES	YES	YES	21
			Recommended by guideline(s)	YES	YES	YES	NO	24, 29, 30
			EMA harmonised indication	YES	YES	YES	YES	63
			FDA indication	Not available in the US				

Legend: S: Susceptible; R: Resistant; EU NRA: EU National Regulatory Agency; US: United-States; -: missing data.

[a] Sources: Mentioned in Kucers': YES means human clinical data reviewed; NO means no human clinical data reviewed. Recommended by guideline(s): YES means the antibiotic was recommended in at least one of the searched guidelines; specific guideline references are shown in the column 'references'; NO means the antibiotic was not recommended by any of the searched guidelines. EMA/EU NRA indication or FDA indication: YES means regulatory indication available; NO means no regulatory indication available.[b] No distinction was made between prosthetic or native valve endocarditis and between right- or left-sided endocarditis. [c] No harmonised EMA indication. [d] Refused authorisation for use in the European Union by the EMA: https://www.ema.europa.eu/en/medicines/human/EPAR/zeftera-previously-zevtera.

Table 2 Options for targeted antibiotic therapy of *Staphylococcus aureus* bacteraemia and endocarditis.

Antibiotic class	Antibiotic agent	Clinical breakpoint *S. aureus* (MIC)	Source[a]	MSSA		MRSA		References
				Bacteraemia	Endocarditis[b]	Bacteraemia	Endocarditis[b]	
Beta lactams								
Penicillins	Isoxazolyl Penicillins, e.g., Oxacillin, Cloxacillin, Dicloxacillin, Flucloxacillin	≤ 2 mg/L (S); > 2 mg/L (R) (MIC oxacillin[19])	Mentioned in Kucers'	YES	YES	NO	NO	21
			Recommended by guideline(s)	YES	YES	NO	NO	24, 26-28, 30
			EU NRA indication[c] (e.g., the Netherlands)	YES	YES	NO	NO	64
			FDA indication	All susceptible infections[d]	All susceptible infections[d]	NO	NO	65
	Nafcillin	≤ 2 mg/L (S); > 4 mg/L (R) (inferred from MIC oxacillin[20])	Mentioned in Kucers'	YES	YES	NO	NO	21
			Recommended by guideline(s)	YES	YES	NO	NO	24, 30
			EU NRA/EMA harmonised indication	Not available in Europe				
			FDA indication	All susceptible infections[d]	All susceptible infections[d]	NO	NO	66
Cephalosporins (1st generation)	Cefalothin	-	Mentioned in Kucers'	YES	YES	NO	NO	21
			Recommended by guideline(s)	NO	NO	NO	NO	
			EU NRA indication[c]	-		-		
			FDA indication	Not available in the US				

Table 2 Continued.

Antibiotic class	Antibiotic agent	Clinical breakpoint *S. aureus* (MIC)	Source[a]	MSSA		MRSA		References
				Bacteraemia	Endocarditis[b]	Bacteraemia	Endocarditis[b]	
Cephalosporins (1st generation)	Cefazolin	≤ 4 mg/L (S); > 4 mg/L (R) (inferred from MIC cefoxitin[19])	Mentioned in Kucers'	YES	NO	NO	NO	21
			Recommended by guideline(s)	YES	NO	NO	NO	24, 26, 27, 30
			EU NRA indication[c] (e.g., Belgium)	YES	YES	NO	NO	67
			FDA indication	YES	YES	NO	NO	68
Lipo(glyco)peptides								
Glycopeptide	Vancomycin	≤ 2 mg/L (S); > 2 mg/L (R)[19]	Mentioned in Kucers'	YES	YES	YES	YES	21
			Recommended by guideline(s)	YES	YES	YES	YES	23, 24, 26, 27, 29, 30
			EMA harmonised indication	YES	YES	YES	YES	61
			FDA indication	YES	YES	YES	YES	62
	Teicoplanin	≤ 2 mg/L (S); > 2 mg/L (R)[19]	Mentioned in Kucers'	YES	YES	YES	YES	21
			Recommended by guideline(s)	YES	YES	YES	NO	24, 29, 30
			EMA harmonised indication	YES	YES	YES	YES	63
			FDA indication	Not available in the US				
Lipoglycopeptide	Oritavancin	≤ 0.125 mg/L (S); > 0.125 mg/L (R)[19]	Mentioned in Kucers'	YES	NO	NO	NO	21
			Recommended by guideline(s)	NO	NO	NO	NO	
			EU NRA/EMA harmonised indication	NO	NO	NO	NO	69
			FDA indication	NO	NO	NO	NO	70

	Dalbavancin	≤ 0.125 mg/L (S); > 0.125 mg/L (R)[19]	Mentioned in Kucers'	YES	NO	YES	NO	21
			Recommended by guideline(s)	NO	NO	NO	NO	
			EMA harmonised indication	NO	NO	NO	NO	71
			FDA indication	NO	NO	NO	NO	72
	Telavancin	≤ 0.125 mg/L (S) (MIC MRSA[19])	Mentioned in Kucers'	YES	YES	YES	YES	21
			Recommended by guideline(s)	NO	NO	NO	NO	
			EU NRA/EMA harmonised indication	Not available in Europe				
			FDA indication	NO	NO	NO	NO	73
Lipopeptide								
	Daptomycin	≤ 1 mg/L (S); > 1 mg/L (R)[19]	Mentioned in Kucers'	YES	NO	YES	NO	21
			Recommended by guideline(s)	YES	NO	YES	YES	23, 30
			EMA harmonised indication	YES	YES	YES	YES	74
			FDA indication	YES	YES	YES	YES	75
Other antibiotics								
Oxazolidinone	Linezolid	≤ 4 mg/L (S); > 4 mg/L (R)[19]	Mentioned in Kucers	YES	NO	YES	YES	21
			Recommended by guideline(s)	NO	NO	YES	YES	29
			EU NRA indication[c] (e.g., the Netherlands)	NO	NO	NO	NO	76
			FDA indication	NO	NO	NO	NO	77
	Tedizolid	≤ 0.5 mg/L (S); > 0.5 mg/L (R)[19]	Mentioned in Kucers	NO	NO	NO	NO	21
			Recommended by guideline(s)	NO	NO	NO	NO	
			EMA harmonised indication	NO	NO	NO	NO	78
			FDA indication	NO	NO	NO	NO	79

Table 2 Continued.

Antibiotic class	Antibiotic agent	Clinical breakpoint *S. aureus* (MIC)	Source[a]	MSSA		MRSA		References
				Bacteraemia	Endocarditis[b]	Bacteraemia	Endocarditis[b]	
Macrolide-lincosamide-streptogramin	Quinupristin-Dalfopristin	≤ 1 mg/L (S); > 2 mg/L (R)[19]	Mentioned in Kucers'	YES	NO	YES	NO	21
			Recommended by guideline(s)	NO	NO	NO	NO	
			EU NRA indication [c]	-		-		
			FDA indication	NO	NO	NO	NO	80
Lincosamide	Clindamycin	≤ 0.25 mg/L (S); > 0.5 mg/L (R)[19]	Mentioned in Kucers'	YES	YES	NO	NO	21
			Recommended by guideline(s)	NO	NO	NO	NO	
			EU NRA (e.g., the Netherlands) [c]	NO	NO	NO	NO	81
			FDA indication	NO	NO	NO	NO	82
Combination of Dihydrofolate reductase inhibitor and a Sulfonamide antibiotic	Trimethoprim-Sulfamethoxazole (Cotrimoxazole)	≤ 2 mg/L (S); > 4 mg/L (R)[19]	Mentioned in Kucers'	YES	YES	NO	NO	21
			Recommended by guideline(s)	NO	NO	NO	NO	
			EU NRA indication[c] (e.g., United-Kingdom)	NO	NO	NO	NO	83
			FDA indication	NO	NO	NO	NO	84

Legend: S: Susceptible; R: Resistant; EU NRA: EU National Regulatory Agency; US: United-States; -: Missing data.
[a] Sources: Mentioned in Kucers': YES means human clinical data reviewed; NO means no human clinical data reviewed. Recommended by guideline(s): YES means the antibiotic was recommended in at least one of the searched guidelines; specific guideline references are shown in the column 'references'; NO means the antibiotic was not recommended by any of the searches guidelines. EMA/EU NRA indication or FDA indication: YES means regulatory indication available; NO means no regulatory indication available. [b] No distinction was made between prosthetic or native valve endocarditis and between right- or left-sided endocarditis. [c] No harmonised EMA indication; [d] Specific clinical indications (e.g., bacteraemia, sepsis, severe infections) were not documented.

improving targeted therapy. This case study does not address the options for combination therapy. Recommendations for initial empirical combination treatments for SAB are made in several guidelines.[25, 26, 28, 30] The available evidence and clinical added value for combination therapies for targeted SAB are reviewed elsewhere.[13, 85-88]

Oral step-down antibiotic therapy

Advantages of (early) oral step-down include a reduced duration of need for intravascular lines and associated complications, a reduced need for prolonged hospitalisation or professional home care and improved patient comfort (e.g., quality of life).[89, 90] The appropriateness of oral therapy depends on both the oral bioavailability of the antibiotic as well as patient factors.[29] Currently, there is only scarce clinical evidence to support an oral step-down approach for the treatment of SAB or endocarditis. However, new insights are likely on their way with an ongoing trial assessing whether early oral switch therapy is safe and effective for patients with SAB (**Table 3**).[91] Also, a recently approved project of the Antibacterial Resistance Leadership Group (ARLG) is testing new strategies for step-down therapy for MRSA bloodstream infections (BSIs).[92] A recent trial performed by Iversen et al. showed non-inferiority of oral switch compared to continued intravenous antibiotic treatment of stable patients with left sided endocarditis.[93]

II. SAB: curent status of and priorities for antbibiotic R&D

Our review of the current monotherapy treatment options for SAB showed a limited arsenal with only three drug classes (beta-lactams, glycopeptides, lipopeptide) for SAB of which two have MRSA coverage (glycopeptides, lipopeptide) (**Table 2**).

Output of the antibiotic pipeline in the past decade

The current antibiotic pipeline is not as productive and dynamic as it once was. However, 18 new antibiotics received FDA approval,[94] and 12 EMA approval in the past decade (2009-2019). Of these new antibiotics: none belonged to a new drug class or involved a (likely) new mechanism of action. Of note, daptomycin was the last discovery of a new class for the treatment of SAB with initial FDA approval in 2003.[75]

Eight of these new antibiotics could potentially be relevant to the treatment of SAB: ceftaroline fosamil (**Table 1**); dalbavancin, oritavancin, telavancin and tedizolid (**Table 2**); as well as delafloxacin, omadacycline and lefamulin.

Ceftaroline fosamil was approved by the FDA in 2011 for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired

pneumonia (CAP).[53] The approved indication covers CAP caused by *Streptococcus pneumoniae* including cases with concurrent bacteraemia. Regardless, ceftaroline fosamil remains of interest for the empiric treatment of SAB because of its rapid clearance of MSSA and MRSA blood stream infections.[95] New trials should provide further insights in clinical relevance for SAB therapy.

Some new targeted treatment options for MRSA bacteraemia (dalbavancin, oritavancin and telavancin) approved for the treatment of ABSSSIs, have been reviewed in **Table 2**. In addition, recent trial activities involving these new agents are listed in **Table 3**. Tedizolid is a fourth new agent that might have a therapeutic potential for MRSA bacteraemia.[96] However, so far no clinical trial has been registered to evaluate tedizolid for the treatment of SAB (**Table 3**).

A relatively new antibiotic with treatment potential for SAB (both MSSA and MRSA coverage) is ceftobiprole (**Table 2**). Ceftobiprole received refusals by the FDA in 2008 and consecutively in 2010 by the EMA based on lack of GCP compliance of the conducted trials and reliability of the yielded data.[97, 98] Currently, following re-submission with new clinical data at national agencies in the EU, ceftobiprole is approved for sale in 13 European countries (e.g., Germany, Italy, the UK, France, Austria and Switzerland) and several non-European countries for the treatment of adult patients with CAP and HAP, excluding ventilator-associated pneumonia (VAP).[99] In 2017, the manufacturer announced two studies of ceftobiprole for the treatment of SAB and ABSSSIs which would support regulatory approval for these indications.[99]

More recently, the FDA approved delafloxacin,[100] a new fluoroquinolone for ABSSSIs and omadacycline, a semisynthetic tetracycline derivative, for ABSSSIs and CAP.[101] The most recent FDA approval was for lefamulin, a pleuromutilin antibiotic for CAP.[102] Additional clinical trials are anticipated and should determine their clinical role for other indications. However, currently no trials for these new antibiotics are registered for SAB or endocarditis (**Table 3**).

The newly developed antibiotics ceftaroline, ceftobiprole, delafloxacin and omadacycline all have a very broad spectrum. Regardless of their activity, this feature makes them less suitable for targeted SAB treatment.

Current SAB trials

Ongoing and recently (<5 years) completed but not yet published clinical trials for SAB are shown in **Table 3**. Interestingly, several trials are being conducted with young infants (e.g., NCT04044703, NCT02790996) and children (e.g., NCT03688659, NCT03643952) (**Table 3**). It is expected that these trials should yield improved dosing regimens for these specific patient populations. Another observation is that seven trials out of 26 have ended prematurely over the past few years (**Table 3**). Reasons provided for early termination of the SAB trials included recruitment related issues (n=4), 'business reasons' (n=1), lack of statistical power (n= 1) and following a safety

recommendation (n=1). Exploring the barriers (e.g., financial, recruitment logistics, ethical or trial design related) that led to the discontinuation of antibiotic trials would be valuable to help work towards facilitators of antibiotic R&D. Results of recent completed or ongoing trials should be used to timely inform clinical practice guidelines.

What should guide R&D priorities for antibiotics against *S. aureus*?

The driving forces of antibiotic R&D should not be market based but rather based on public health unmet needs. SAB is a life-threatening condition. Even in cases with adequate source control, patients treated with available antibiotics are having positive blood cultures for several days. Therefore, there is a need for superior antibiotics (in terms of effectiveness and safety) for treating SAB, regardless of resistance to available antibiotics. Previous developments have mainly targeted resistance (MRSA), which led to expanding the number of drugs that target MRSA from classes that show no superior activity against MSSA. The added value of recently developed drugs can be considered related mainly to some minor improvement aspects such as ease of use within known antibiotics classes, e.g., once only dose oritavancin or the oral formulation of tedizolid.

Incontestable positive developments are the increased awareness of the urgency of the antimicrobial resistance issue as well as the 'high priority' label for methicillin-(and vancomycin-) resistant *S. aureus* from the WHO on its priority pathogen list (PPL) for antibiotic resistant bacteria.[108] In addition, MSSA infections remain an important burden. Currently, it is unclear whether MRSA bacteraemia is more dangerous than infections caused by MSSA.[109-111] Thus, there is a need for new potent drugs for both MSSA and MRSA bacteraemia. Decreases in MRSA colonisation and/or infections can be achieved through implementing antibiotic stewardship and infection control policies and needs more consideration as well.

In conclusion, progress has been made to address the coverage of MRSA as the antibiotic pipeline has yielded multiple new regulatory approvals; we call for awareness for the potentially overshadowed severe MSSA infections that do not require a broader spectrum but more potent molecules for treatment.

What could benefit the R&D strategy for antibiotics against *S. aureus* bacteraemia?

A few potential facilitators of SAB R&D which should speed up the process of drug development and lead to more efficient resource allocation, are addressed here.

Push incentives

The effective stimulation of antibiotic R&D calls for both *push* incentives (those designed to support R&D directly) and *pull* incentives (those designed to reward

Table 3 Ongoing and recently completed (≤5 years) clinical trials for antibiotics for the treatment of *S. aureus* bacteraemia and/or endocarditis.

Antibiotic class	Drug name	MRSA coverage	Endocarditis	Trial Phase	Drug Comparator[a]
Beta- lactam Cephalosporins	Cefazolin	NO	NO	Phase IV	Cloxacillin
	Cefotaxime	NO	Not documented	Phase IV	NA
	Ceftaroline fosamil + ampicillin + optional aminoglycoside	NO	Not documented	Phase II	NA
	Ceftaroline fosamil	YES	YES[b]	Phase IV	NA
	Ceftobiprole medocaril	YES	YES[b]	Phase III	Daptomycin
Beta-lactam, Penicillins	Cloxacillin + Levofloxacin	NO	NO	Phase III	Cloxacillin
	Cloxacillin + fosfomycin	NO	YES[c]	Phase IV	Cloxacillin
Glycopeptide	Daptomycin	YES	NO	Phase II	NA
	Daptomycin	YES	Not documented	Phase II	Vancomycin
	Daptomycin	YES	Not documented	Phase III	Vancomycin
	Daptomycin + Fosfomycin	YES	YES	Phase III	Daptomycin
	Daptomycin	YES	YES	Phase III	NA
	Vancomycin or daptomycin	YES	YES	Phase III	Vancomycin or Daptomycin + beta-lactam
	Daptomycin + beta-lactam	YES	YES	Phase IV	Placebo + beta-lactam
	Vancomycin	Not documented	YES	Phase II	NA
	Vancomycin	YES	Not documented	Phase IV	NA

Number of patients	Trial Status	Trial period	Countries	ClinicalTrials.gov identifier and other reference
300 (estimated)	Recruiting	Sept 2018 – *estimated* Sept 2022	France	NCT03248063 [103]
60 enrolled	Completed	Nov 2015 – Sept 2016	The Netherlands	NCT02560207
11 participants	Terminated (due to slow enrolment)	Aug 2015 – Dec 2017	US	NCT02424734
56 enrolled	Completed	Jan 2013 – July 2014	US	NCT01701219
390 (estimated)	Recruiting	Jun 2018 – *estimated* Aug 2021	US, Argentina, Brazil, Bulgaria, Georgia, Germany, Israel, Italy, Russia, Spain, Ukraine	NCT03138733[104]
1 enrolled (154 estimated)	Terminated (not participants inclusion)	May 2013 – Nov 2014	Spain	NCT01875263
366 (estimated)	Not yet Recruiting	May 2019 – *estimated* Aug 2021	Spain	NCT03959345
20 (estimated)	Recruiting	Dec 2018 e*stimated* May 2021	Japan	NCT03643952
14 enrolled (50 estimated)	Terminated (slow accrual of participants)	Jan 2014 – Dec 2015	Singapore	NCT01975662
10 enrolled (332 estimated)	Terminated (lack of inclusion)	May 2012 – July 2014	France	NCT01515020
167 enrolled	Completed	Dec 2013 – Jan 2018	Spain	NCT01898338 [105]
Not provided	Completed	March 2014 – Sept 2015	France	NCT02142075
358 enrolled (440 estimated)	Terminated (Recommendation of the Data Safety Monitoring Committee)	Aug 2015- Oct 2018	Australia, New Zealand, Singapore, Israel.	NCT02365493 [106]
102 (estimated)	Active, not recruiting	Nov 2016 – Sept 2019	Canada	NCT02972983 [107]
300 (estimated)	Recruiting	Feb 2017 – *estimated* Feb 2019	Estonia, Greece, Italy, Spain, United-Kingdom	NCT02790996
28 (estimated)	Recruiting	Aug 2019 – *estimated* Aug 2020	Australia	NCT04044703

Table 3 Continued.

Antibiotic class	Drug name	MRSA coverage	Endocarditis	Trial Phase	Drug Comparator[a]
Glycopeptide	Vancomycin	YES	Not documented	Phase IV	NA
	Vancomycin + Gentamicin	YES	YES	*Not documented*	NA
Lipoglycopeptide	Dalbavancin	YES	YES	Phase II	Standard of Care
	Oritavancin	YES	YES	Phase IV	NA
	Telavancin	YES	YES	Phase III	Vancomycin, Daptomycin, Synthetic penicillin, Cefazolin
	Telavancin	YES	NO	Phase II	-
Oxazolidinone	Tedizolid phosphate	YES	Unspecified	Phase III	Linezolid
Other antibiotics	Fosfomycin + imipenem	YES	YES	Phase IV	Vancomycin
Early Oral Switch	Trimethoprim-Sulfamethoxazole, Clindamycin, Linezolid, Flucloxacillin, Cloxacillin, Vancomycin, Daptomycin, Cefazolin	YES	NO	Phase III	NA
	Levofloxacin + Rifampicin	YES	YES	Phase III	Cloxacillin, Oxacillin, Gentamicin, Vancomycin, Rifampicin[d]

From www.clinicaltrials.gov, Accessed: December 2019.
Legend: NA: Not Applicable. US: United-States; [a] Not all the trials used a comparator drug (e.g., single-arm trial, pharmacokinetics trial, phase IV trial) [b] Exclusion criteria: Left-sided endocarditis; [c] Exclusion criteria: Prosthetic endocarditis;[d] Conventional intravenous treatment of staphylococci in infective endocarditis following European guidelines.[26]

Number of patients	Trial Status	Trial period	Countries	ClinicalTrials.gov identifier and other reference
222 (estimated)	Recruiting	Apr 2018 – *estimated* Dec 2022	Brazil	NCT03438214
30 (estimated)	Not yet recruiting	Jan 2019 – *estimated* Jan 2021	Egypt	NCT03688659
2 enrolled (150 estimated)	Stopped (due to business reasons)	May 2017 – Aug 2017	US	NCT03148756
15 estimated	Recruiting	Jul 2019 – *estimated* Dec 2019	US	NCT03761953
121 enrolled (248 estimated)	Terminated (Halted due to lack of statistical power. No safety concerns identified.	Dec 2014 – Apr 2018	US	NCT02208063
40 enrolled	Completed	Mar 2011 – Dec 2016	US	NCT01321879
125 enrolled	Completed	Nov 2013 – Oct 2016	Japan	NCT01967225
50 enrolled	Completed	Jun 2009 – Apr 2015	Spain	NCT00871104
215 (estimated)	Recruiting	Dec 2013 – Oct 2019	Germany	NCT01792804 [91]
324 (estimated)	Recruiting	Feb 2016- *estimated* Oct 2021	France	NCT02701608

successful outcomes from R&D).[112] The value of two push incentives as proposed by the DRIVE-AB consortium are discussed here.

- Pipeline coordinators (i.e., a governmental or non-profit organisation) act as monitors of the progress, or lack thereof, of the antibiotic pipeline.[113] By following closely new developments, they can steer R&D projects to address potential gaps (assessed through unmet public health priorities and priority pathogens list) and thereby ideally avoiding duplication. In addition, they may finance development activities or advance themselves specific programmes. Examples of pipeline coordinators include Global Antibiotic Research and Development Partnership (GARDP), BARDA (Biomedical Advanced Research and Development Authority) and CARB-X.
- A grant framework has been proposed as a second push incentive to stimulate R&D. This framework consists of four financial incentives to support early- and mid-stage R&D, complemented with two highly focused incentives: priority and clinical development grants.[114] Here again, the focus is to steering new development towards unmet public health needs in antimicrobial R&D.

Regulatory aspects of SAB

Registration for the indication bacteraemia is not common as it needs to rely on prior demonstration of efficacy at the infection source covering different body sites. A clear indication pathway defined by the regulatory agencies is expected to facilitate regulatory approval of new antibiotics. While the FDA recognises SAB as a unique severe infection regardless of the presence of an infection source, which is often not found, the EMA currently does not consider that an indication for treatment of bacteraemia can be in principle substantiated by a trial that enrols patients with bacteraemia due to a specific pathogen regardless of the primary focus of infection.[115] https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-revision-3_en.pdfHowever, it can be considered that the FDA position specifically for SAB has its rationale and therefore sponsors are encouraged to still discuss the options with the EMA.

Marketing incentives

An example of a marketing incentive to stimulate antibiotic R&D is the status of 'Qualified Infectious Disease Product' (QIDP) offered by the FDA since the Generating Antibiotic Incentives Now Act (GAIN) from 2012. This status promises manufacturers an accelerated review of the drug application and five additional years of marketing exclusivity. Unfortunately, GAIN has not set stringent requirements to ensure that qualifying antibiotics address unmet public health need.[116] Dalbavancin, tedizolid and oritavancin are novel antibiotics that benefited from these marketing incentives,

even if not having a major impact on unmet needs. More promising incentives that are expected to improve the profitability of the market are subscription-based payment models that will soon be piloted in Sweden and the United Kingdom.[117, 118] These models will test the concept of delinkage, i.e., paying to maintain access to an essential antibiotic rather than strictly reimbursing unit sales.

Clinical trial designs

Regulatory agencies can assist sponsors in the clinical development of new antibacterial drugs by developing guidance documents on innovative clinical trial designs. In 2013, EMA issued a new guidance document that described examples of streamlined clinical programmes that could allow granting approval for pathogen specific indications in areas of unmet medical needs.[119] In 2017, the FDA issued guidance on 'Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases'.[120] In addition, Holland et al. recently addressed key features to consider in designing an SAB trial for the different stakeholders, including investigators, sponsors, and regulators.[121] An example of innovative trial designs includes the *Staphylococcus aureus* Network Adaptive Platform Trial that aims to optimise management of SAB via the implementation of adaptive trials, in which design modifications (e.g., response adaptive randomisation) are made based on the results of interim analyses. Such trials are expected to help allocate resources more efficiently without lowering scientific and regulatory standards.[122, 123]

III. SAB: responsible antibiotic use strategies

A selection of quality indicators for responsible antibiotic use considered particularly pertinent to measure responsible antibiotic use for SAB are addressed.

Resistance Surveillance

The European Antimicrobial Resistance Surveillance Network (EARS-NET) provides insights in the evolving epidemiology of MRSA and largely relies on data input from national focal points of EU/EEA member states. Therefore, surveillance practice at the hospital level (IQI-41) is essential to inform upstream national focus points. Compliance with this IQI is key to monitor the epidemiology of MRSA and subsequently guide the selection of optimal antibiotic therapy for SAB.

Access-Availability

A selection of both empirical and targeted antibiotic drugs for SAB should be part of the hospital formulary and present at the hospital to facilitate optimal patient care (IQI-1).

Microbiological Diagnostic

Blood cultures are needed to perform antibiotic susceptibility testing (AST) that in turn will allow de-escalation from empirical to targeted therapy of SAB (IQI-31). Harmonisation of AST methods should be pursued. EUCAST provides guidelines for harmonisation of clinical breakpoints to guide AST reporting. In addition, rapid molecular tests such as the T2Bacteria magnetic resonance assay can be performed to identify MRSA and steer treatment choice for SAB.[124]

Expertise and Resources

Over the past decades, studies performed around the world have repeatedly shown that a bed-side consult from infectious disease specialists largely benefits patient outcomes (IQI-27).

Antibacterial Activity and Spectrum

Depending on the local epidemiology, empirical therapy should cover MRSA in patients with risk factors (IQI-3). In order to reduce broad spectrum antibiotic selection pressure on the commensal microbiome the antibiotic therapy should be changed to pathogen-directed as soon as the results of the microbiological diagnostic become available (i.e., de-escalation of antibiotic therapy) (IQI-5 and IQI-7).

Furthermore, a useful tool to stimulate the use of narrow-spectrum antibiotics is the selective reporting of antibiotic susceptibilities by the microbiology laboratory. Indeed, limiting the numbers of effective formulary drugs shown in the antibiotic susceptibility reports (e.g., showing only very few treatment options with a narrow activity spectrum) should improve the quality of antibiotic prescribing (IQI-4).

Evidence-Based Guidelines

Only few authoritative (i.e., endorsed by professional societies) English written clinical practice guidelines addressing BSI are available. This lack of guidelines for SAB may result in variation in clinical practice as well as in deviations from published evidence.[125] The few available evidence-based and graded guidelines available in English for SAB should be used in national (and possibly even more local) guideline developments based on geographical epidemiology (IQI-18). The ESCMID/IDSA guideline on *S. aureus* bacteraemia that is currently under preparation will contribute to improved evidence-based clinical practice as well as steer the development of more local guidelines within the European region.

Toxicity

Antibiotics are a common cause of drug allergies. To avoid unnecessary complications in patients with SAB, allergies to penicillins, cephalosporins and glycopeptides should be taken into account (IQI-47).

Timing

In view of the severity of SAB timely administration of initial empirical therapy is required. Following the recommendation of the SWAB guideline on sepsis, antibiotics should be started as soon as possible, preferably within the first hour of diagnosis for patients with severe sepsis and septic shock (IQI-45).[28]

Conclusion

Case study research allows for the study of complex issues in real world settings. Consultation of different information sources and involvement of researchers with various backgrounds should limit verification bias. While much research attention is given to (multi-)resistant Gram-negative bacteria, it is important not to underestimate the burden of Gram-positive species. With the aging of the world population the burden of SAB is expected to expand further. Another important evolution is the increased incidence of MSSA SAB independently from the epidemiologic evolution of MRSA bacteraemia. The analysis of the antibiotic pipeline and ongoing clinical trials revealed that several new antibiotics with *S. aureus* (including MRSA) coverage were developed in the past decade (2009-2019). However, none belonged to a new antibiotic class or had superior effectiveness and their added clinical value for SAB remains to be proven. Clinical trials are needed to fill current gaps and to inform best practices for the clinical management of SAB. Awareness of the limited antibiotic arsenal together with incentives are needed to steer the R&D landscape towards the development of novel and effective drugs for SAB. In the meantime, responsible antibiotic use guided by the use of quality indicators should preserve the effectiveness of currently available antibiotics for treating SAB.

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7

General Discussion

This thesis explored responsible antibiotic use. A search for a global definition, associated quality indicators, barriers and facilitators was conducted involving a wide range of stakeholders. In this final chapter, the main findings are summarised. Furthermore, reflections on the findings are provided and methodological considerations are discussed. Finally, implications and recommendations for practice, policy and research are presented.

Main findings

Definition and measurement of responsible antibiotic use

International and multidisciplinary consensus was established on 22 elements of *responsible antibiotic use* (**Chapter 2**). The large number of elements comprised in the definition highlights the complexity of the concept of responsible antibiotic use. Elements were grouped into patient-level (e.g., Indication, Documentation) or societal-level elements (e.g., Education, Future Effectiveness). Seventeen synonyms of responsible antibiotic use that can be seen as interchangeable were identified in the scientific literature (e.g., adequate, appropriate).

An international and multidisciplinary consensus procedure led to the development of 51 generic quality indicators (QIs) for responsible antibiotic use in the inpatient setting (**Chapter 3**). Most of the inpatient quality indicators were classified as process, about one third as structure and two as outcome indicators according to the Donabedian model. Altogether, the QIs covered a wide range of 19 different themes of responsible inpatient antibiotic use, of which the majority overlap with the elements of the definition of responsible use (**Chapter 2**). Responsible antibiotic use practices for the treatment of *Staphylococcus aureus* bacteraemia (SAB) in the hospital setting were illustrated using a selection of 11 QIs in **Chapter 6**.

Patients' experiences with antibiotic treatment and responsible antibiotic use cluster into five main themes (**Chapter 4**):

- patients trust their doctors for antibiotic treatment decisions;
- patients perceive a lack of prioritisation of communication on antibiotic treatments and a lack of tailoring of information on antibiotics;
- patients differ in their wish to be informed but overall want to receive information on main aspects of their antibiotic treatments (i.e., clinical indication, adverse events, duration, frequency and timing of antibiotic intake) in an understandable way;
- patients find it reassuring to share information about their antibiotic treatment with close family;

- health care professionals should explore patients' preferences for being involved in shared decision-making for their antibiotic treatments.

Concerning ABR, patients acknowledged the problem but seemed to prioritise the individual perspective over the societal perspective.

Barriers to and facilitators of responsible antibiotic use

International *third-party* stakeholders (i.e., involved with antibiotics but outside the medical and patient communities) described barriers and facilitators – hindering or helping, respectively, responsible antibiotic use – that can be grouped into seven categories (**Chapter 5**):

- scientific (e.g., uncertainty of future medical needs);
- economic (e.g., financial incentives);
- regulatory (e.g., regulatory harmonisation, **Box 1**);
- ethical (e.g., responsibility for future generations);
- societal (e.g., invisibility of antibacterial resistance);
- political (e.g., changing political environment);
- medical practice (e.g., alternatives for antibiotics).

Moreover, several contrasts highlighting the complexity of responsible antibiotic use emerged across these categories. Examples include the alarming worldwide spread of ABR as opposed to its invisibility, the conflicts between antibiotic stewardship principles and incentives for antibiotic research and development (R&D) with current economic models, and the contradiction between research based on current unmet needs versus the uncertainty of future medical needs.

A case study of responsible antibiotic use practices for the treatment of SAB identified a limited antibiotic arsenal with only three drug classes (beta-lactams, glycopeptides, lipopeptide) of which two cover MRSA bacteraemia (glycopeptides, lipopeptide). In addition, limited R&D progress on new drugs for SAB was reported in the last decade.

Stakeholder involvement

The input of 112 stakeholders from 25 countries was included in the work presented in this thesis. **Table 1** summarises the expertise and geographic spread of the stakeholders consulted in the different studies.

Reflection on the findings

The work performed in this thesis was performed in parallel to the development of numerous initiatives on responsible antibiotic use and initiatives to tackle resistance. A reflection on the findings of this thesis is provided in the context of these recent developments. Of note, the initiatives discussed here are not meant as a comprehensive list but should rather be seen as illustrative examples of developments contemporary to the work presented in this thesis.

Responsible antibiotic use and antibiotic stewardship

This thesis focused on exploring and defining responsible antibiotic use. Multidisciplinary consensus on a definition of responsible antibiotic use with a global scope was established (**Chapter 2**). In the meantime other researchers explored the emergence and evolution of the term *antimicrobial stewardship*.[1] Antimicrobial or antibiotic stewardship, a term coined in the mid 1990's, can be considered as a successor of the term *antimicrobial* or *antibiotic policies*. A review of the literature revealed variation in how antimicrobial stewardship has been defined or conceptualised over the past years.[1] Subsequently, reflection on the different definitions used led to a newly introduced definition: 'a coherent set of actions which promote using antimicrobials responsibly'.[1] This new definition of stewardship does not specify what 'using responsibly' entails. Therefore, the definitions of responsible antibiotic use and of stewardship can be seen as complementary.

Perhaps an important consideration is the distinction between *what is responsible antibiotic use* and *how to achieve responsible antibiotic use*.[2] While the studies on responsible antibiotic use presented in this thesis mainly answer the *what* or the objectives, stewardship as defined by Dyar et al. refers more specifically to the *how* or means to meet the *what*. The fourteen objectives of stewardship reported by Schuts et al.[3] match the elements and themes of responsible antibiotic use as reported in this thesis. Thus, stewardship activities can be seen as necessary for achieving responsible antibiotic use. All the same, responsible use and stewardship practices are both crucial for conserving the effectiveness of our antibiotic arsenal for the future. However, discussions on how responsible use and stewardship relate to each other and associated semantics are likely to persist due to the rapid evolution of terminologies over the past few decades.

Quality and quantity of antibiotic use in the inpatient setting

The research presented in this thesis was embedded in work package 1A of the DRIVE-AB (Driving Re-InVEstment in R&D and responsible AntiBiotic use) project.[4] The aim of this work package was to develop an evidence-based consensus definition and framework for *responsible antibiotic use*, with standardised measures

to assess the quality and the quantity of antibiotic use. The review performed by Zanichelli et al. confirmed heterogeneity of reported measures and clearly showed a need for standardisation of measures of antibiotic use.[5] Within the DRIVE-AB project, an important distinction was established between two different types of measures of antibiotic use. On the one hand, indicators to measure the quality of antibiotic use (i.e., quality indicators) and on the other hand, metrics to measure the quantity of antibiotics use. A QI reflects the degree to which antibiotic is used correctly or appropriately while, in contrast, a quantity metric reflects the volume or the costs of antibiotic use.[6] Consequently, a QI has a value on its own while a quantity metric only gains value when comparisons are made between, e.g., wards, hospitals or countries. Following the same methodology as for the QIs, broadly supported quantity metrics were selected for the inpatient setting.[7] For ABS activities in the inpatient setting, monitoring antibiotic prescriptions using standardised QIs and quantity metrics are both of added value to measure and compare antibiotic use. The results of the work on quality indicators and quantity metrics for responsible antibiotic use performed by the DRIVE-AB were consulted during the drafting of the 'Proposals for EU guidelines for the Prudent Use of Antimicrobials in Human Medicine' written by the European Centre for Disease Prevention and Control (ECDC) in 2017.[8]

Other researchers have developed QIs for antibiotic use for the inpatient setting during the timeframe of this thesis. The QIs developed in **Chapter 3** overlap with all 11 QIs for the hospital setting identified by van den Bosch et al. using a similar methodology with a European expert panel in which all the main medical specialties involved in antibiotic treatment were represented.[9] However, the panel did not include representatives of international professional clinical societies or stakeholders from outside the medical community. In another initiative, the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), experts from the EU and the US identified 17 core indicators and 16 optional indicators for inpatient antibiotic use addressing the organisation of ASPs. While the van den Bosch study aimed at developing a concise set of non-disease-specific QIs from the literature, the list of TATFAR indicators resulted from comparisons between antibiotic stewardship programmes in EU and US hospitals.[10] All these QIs should be seen as complementary output of international and cross-disciplinary efforts to improve antibiotic use. A review of the literature on quality indicators for antibiotic use in the inpatient setting concluded that the QIs developed in **Chapter 3** are currently the most comprehensive set of QIs for the inpatient setting.[11]

Van Den Bosch and colleagues were the first group to both develop and test the clinimetric properties of a set of generic QIs for appropriate antibiotic treatment in the hospital setting.[9, 12] They found that 64% of the generic QIs showed sound clinimetric properties following data extraction in the selected 22 Dutch hospitals and thereby highlighted the importance of testing the clinimetric properties of QIs before using

them in a specific setting.[12] A first practice test of a selection of the QIs for responsible antibiotic use developed in this thesis (**Chapter 3**) is currently work in progress; results are expected later this year. The practice test is performed within a network of hospitals in the Dutch-Belgian border area working towards the implementation of the Infection RIsk Scan (IRIS).[13] Joining a pre-existing collaboration is expected to lead to efficient data collection for the evaluation of the relevance of the QIs in hospitals in the Dutch-Belgian border region. The work is performed within the i41health project funded by the EU INTERREG.[14] In addition, translation and adaptation of the QIs reported in **Chapter 3** to the Portuguese context is the aim of a PhD project currently being performed in a hospital in Portugal.[15]

The patients' perspective

Patients are only rarely included in ABS efforts,[16] even though patient engagement and shared decision-making are known to positively impact health-related behaviours and health outcomes.[17-19] So far, most studies into patient-related determinants of antibiotic use were performed in the outpatient setting while inpatient studies are lacking.[20] In an era where resistance is becoming an increasing obstacle to the delivery of safe health care, it seems essential to learn more about the experiences of hospitalised patients and to better define their role with regard to inpatient antibiotic stewardship. The patients' perspective on responsible antibiotic use was explored in this thesis. In the consensus procedures towards a definition (**Chapter 2**) and quality indicators (**Chapter 3**) for responsible antibiotic use, stakeholders were consulted to represent the patient and public health perspectives. Furthermore, in **Chapter 4**, views and experiences of hospital patients with antibiotics were explored to understand what responsible antibiotic use entails for them. While the findings of **Chapters 2 and 3** focussed more on evidence-based medical procedures, the themes that emerged from **Chapter 4** were more patient oriented, e.g., patients wish for doctors to explore their preferences for shared decision-making, patients wish to receive tailored information. Ultimately, efforts to improve responsible antibiotic use should focus on improving both the recommended medical-oriented procedures and patient-oriented aspects.

The complexity of responsible antibiotic use

Antibiotic consumption is on the rise globally[21] and resistance could cause up to 10 million deaths a year by 2050.[22, 23] Even though discussions within the scientific community remain on how to best quantify the burden of resistance, its clinical and public health impact is expected to be enormous.[24] As a result, responsible antibiotic use is probably more relevant and urgent than ever. The findings presented in this

thesis illustrate the complexity of responsible antibiotic use through the large numbers of elements (n=22 elements) constituting the definition and the large number of QIs for the inpatient setting (n=51 QIs covering 19 themes). In addition, seven categories of barriers and facilitators were identified by third-party stakeholders (**Chapters 5 and 6**). While below the barriers and facilitators are addressed separately, it should be acknowledged that they are closely interconnected. Recent initiatives and developments relating to a selection of these barriers and facilitators are addressed here.

Scientific challenges

The need for a robust pipeline was expressed by the third-party stakeholders to develop new and better antibiotics, e.g., antibiotics with fewer side effects and that are less resistance inducing. The importance of this robust pipeline was underscored by the uncertainty of future medical needs (**Chapter 5**). A recent report by the WHO revealed that the current antibiotic pipeline remains insufficient to tackle the challenge of increasing emergence and spread of resistance.[25] Another conclusion by the WHO was that new antibiotics present overall limited clinical benefits. These conclusions align with the findings presented in our analysis of the output of the antibiotic pipeline concerning new antibiotics with *S. aureus* (including MRSA) coverage in the past decade. Indeed, none belonged to a new antibiotic class or had superior effectiveness, and their added clinical value for SAB remains to be proven (**Chapter 6**).

Economic challenges

New economic models that create incentives for the discovery of new antibiotics and microbiologic diagnostics, while at the same time safeguarding responsible antibiotic use, were reported by stakeholders to be key (**Chapter 5**). Four incentives to boost antibiotic R&D have recently been advocated for by the DRIVE-AB project.[26] These included *push* incentives (i.e., designed to support R&D directly) such as a grant framework and pipeline coordinators and two *pull* incentives (i.e., designed to reward successful outcomes from R&D) including market entry reward and the long-term continuity model (**Box 1**).[26] Push incentives to steer new development towards antibiotics for treating SAB were addressed in more detail in our case study (**Chapter 6**). Each of the four recommended incentives is intended to stimulate specific phases of the R&D process. The incentives should not be considered separately but rather as complementary to maximise their impact on the development of news antibiotics.[26] The proposed incentives have not yet been implemented. The antibiotic pipeline can be considered to have improved in terms of number of antibiotic candidates since the start of the research for this thesis, however, in the meantime, several companies fell into bankruptcy and large pharmaceutical companies left antibiotic R&D.[27, 28]

Regulatory challenges

Regulatory harmonisation (**Box 1**) was proposed by third-party stakeholders to expedite antibiotic R&D and reduce duplication of work by regulatory authorities in different countries or regions (**Chapter 5**). Harmonisation should thus be paired with important savings in financial resources. In 2017, the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Japanese Pharmaceutical and Medical Devices Agency reached an agreement to align data requirements for the clinical development of new antibiotics.[29] This tripartite collaboration is expected to facilitate a common development programme for new antibiotics in compliance with the regulatory requirements of all three agencies. Challenges regarding clinical trial designs were also discussed during stakeholder interviews (**Chapter 5**).

Box 1: Definitions and terminology

Grant framework	Push incentive (i.e., designed to support R&D directly) proposed by the DRIVE-AB project. Involves non-repayable funds for R&D given to academic institutions, companies, and others.[26]
Pipeline coordinators	Push incentive (i.e., designed to support R&D directly) proposed by the DRIVE-AB project. Involves governmental or non-profit organisations that closely track the antibiotic pipeline, identify gaps, and actively support R&D projects both financially and technically to fill these gaps.[26]
Market entry reward	Pull incentive (i.e., designed to reward successful outcomes from R&D) proposed by the DRIVE-AB project. Involves series of financial payments to an antibiotic developer for successfully achieving regulatory approval for an antibiotic that meets specific, pre-defined criteria to address a defined public health need, with obligations for sustainable use, equitable availability, and supply.[26]
Long-term continuity model	Pull incentive (i.e., designed to reward successful outcomes from R&D) proposed by the DRIVE-AB project. Involves a delinked payment to create a predictable supply of important generic antibiotics). Delinking means that revenues for the new antibiotic are either partially or fully delinked from the number of units sold, allowing for the revenues to be based on the value to society.[26]
Regulatory harmonisation	The process by which technical guidelines are developed to be uniform across participating authorities.[60]
Shortage	A shortage can be defined as a shortcoming in the supply of a drug that affects the patient's ability to access the required treatment in due time.[61]

In **Chapter 6**, several facilitators were addressed including the development of guidance documents on innovative clinical trial designs by regulatory agencies to assist sponsors in the clinical development of new antibiotics such as recently published by EMA and FDA.[30, 31] An example includes the *Staphylococcus aureus* Network Adaptive Platform Trial that aims to optimise management of SAB via the implementation of adaptive trials, in which design modifications, e.g., response adaptive randomisation, are made based on the results of interim analyses (**Chapter 6**). Such trials are expected to help allocate resources more efficiently without lowering scientific and regulatory standards.[32, 33]

Societal challenges

Important identified societal challenges included the invisibility of the problem of resistance, the lack of awareness of the resistance problem and the lack of understanding of the true societal value of effective antibiotics (**Chapter 5**). Efforts are being made by public health organisations and agencies to remedy these shortcomings. Since 2015, the WHO organises the World Antibiotic Awareness Week every November to increase awareness of global antibiotic resistance and to encourage best practices among the general public, health workers and policy makers.[34] Similarly, ECDC aims at increasing awareness by coordinating the yearly European Antibiotic Awareness Day (EAAD) and publishes patient stories to illustrate the consequences of resistance. In 2016, an international group of scientists introduced the concept of *antibiotic footprint* as a global tool for the public communication of the magnitude of antibiotic use in humans, animals and industry, which could build on the success of the concept of the carbon footprint.[35] Even though concerns have been expressed whether the concept of *footprint* is indeed applicable to antibiotics,[36, 37] it might constitute a valuable instrument to increase antibiotic awareness among the general public.

Ethical challenges

Several ethical dilemmas associated with responsible antibiotic use emerged during stakeholder interviews (**Chapter 5**). An important challenge is achieving the balance between ensuring access to patients in need of antibiotics and restricting them when there is no clinical indication in order to limit excess use of antibiotics. Until now, access to antibiotics for all in need of them remains unrealised, especially in low income countries. The annual burden of infectious diseases is estimated at 5,7 million deaths worldwide, most of which are treatable with antibiotics.[38] The WHO launched the Medicines and Health Products Programme Strategic Framework 2016–2030 to reinforce universal access to safe and quality-assured health products, including antibiotics, and universal health coverage. Shortages (**Box 1**) hinder access to antibiotics and are known to negatively impact antibiotic prescribing policies and

expenses. Recent initiatives to solve shortages include the Access to Medicines Foundation's six steps for implementation by pharmaceutical companies (e.g., holding local inventory in regional buffer stocks).[28] Another ethical dilemma is how to balance the needs of current patients and possible damage to future generations and how to integrate these responsibilities in current antibiotic policies. Addressing questions of intergenerational justice implies reflections on the rights of future patients, on whether our society has a role in defending these rights and on what risks our society is willing to take to safeguards their rights.[39, 40] Clear-cut answers on these matters are highly unlikely in view of the complexity of the problem.

Political challenges

A steep increase in political attention was observed during these past few years. Highlights include the presentation of the WHO Global Action Plan (2015) and the Review on Antimicrobial Resistance commissioned by the United-Kingdom prime minister (2014-2015). Very importantly, resistance was put on the agenda of the United Nations (UN) General Assembly as a major global health priority in September 2016. Following the assembly meeting, the UN created the Interagency Coordination Group (IACG) that recently published the report 'No time to wait'.[23] More locally, resistance constituted one of the political priorities during the Dutch Presidency of the EU in the first half of 2016 with a specific focus on the *One Health* approach.[41] All these initiatives support an international and multi-stakeholder approach, including, e.g., governments, public health, non-political organisations, manufacturers and the general public, in alignment with facilitators and/or solutions proposed by the interviewed stakeholders (**Chapter 5**). The increasing political attention might help to work on lifting the barriers identified in stakeholder interviews, e.g., changes in political environment, lack of outcomes expectancy from policy makers (**Chapter 5**).

Medical practice:

Stakeholders advised to restrict antibiotic use and the need for antibiotics by enhancing stewardship, establishing infection prevention policies, providing education and stimulating alternatives for antibiotics (e.g., vaccines) (**Chapter 5**). Over the past few years, several tools have become available to support these efforts. Examples include a free online course on antibiotic stewardship for clinicians by the WHO,[42] several guidance documents to facilitate and support stewardship activities at the health care facility level including a legal framework of stewardship and a list of generic competencies in antimicrobial prescribing and stewardship produced by the ESCMID Study Group for Antimicrobial Stewardship (ESGAP).[43, 44] In addition, ESGAP regularly publishes survey studies that explore differences in national guidelines and organisation of stewardship programs and efforts across European countries for international cross-fertilisation of practices.[45-48] Ideally, these tools

could help reach the cultural paradigm shift in medical professionals needed for achieving responsible antibiotic use (**Chapter 5**). Furthermore, stakeholders expressed their concern about financial incentives for antibiotic prescribing (**Chapter 5**). Financial incentives are indeed known to contribute to irrational prescribing of drugs[49, 50] and should thus be removed from clinical practice. In parallel, the promotion of antibiotics by the drug industry should be abolished. Interestingly, more companies are reporting actions including decoupling sales volumes from sales agents' revenues.[28]

Thus, efforts towards responsible antibiotic use to curb resistance require synergistic, overlapping and complementing approaches.[51] The complexity of the issues at stake previously led to the labelling of resistance as a *wicked problem* and even more recently as a *super wicked problem*.[52]

Methodological considerations

Scope of the thesis

Reflections on the scope of the thesis are addressed below.

- The thesis focused on human medicine. However, ABR has been recognised to be a One Health issue as human health, animal health and the environment are closely interrelated.[53] Therefore, a One Health approach for curbing ABR is of paramount importance.
- When defining quality in healthcare, the focus is usually on a specific disease or disorder (e.g., breast cancer), delivered by a specific health care worker (e.g., oncology nurse) for a specific patient group (e.g., women aged 30-60).[54] However, in this thesis the aim was to define responsible antibiotic use for a wide range of bacterial infections, delivered by a range of healthcare professionals. The scope of the research was even global, that is, applicable anywhere worldwide. Therefore, the results of this thesis can be considered as generic findings (i.e., definition, quality indicators, barriers and facilitators) for responsible antibiotic use regardless of geography, disease or population specifics. A potential risk of such a generic approach can be the oversimplification of study results.

Stakeholder involvement

This thesis aimed at including a wide range of stakeholders and experts involved in antibiotics from molecule to prescribed drug (**Table 1**). The involvement of stakeholders and experts in one's research is inexorably linked with questions concerning the levels and/or quality of the expertise of the solicited individuals. In the studies presented in this thesis, the invitation of international stakeholders and experts for

participation was based on demonstrated experience and expertise in the topic of antibiotic use and/or stewardship, or in different perspectives of antibiotic use. Examples of considered criteria for demonstrated experience and expertise included professional activities and positions as well as research output. However, no systematic system was applied for the selection of the stakeholders. Stakeholders among the extended international network of academic and European Federation of Pharmaceutical Industries and Associations (EFPIA) partners of the DRIVE-AB project were invited for participation. Participation as a stakeholder to the studies presented in this thesis was not financially compensated. Thus, the results of this thesis are prone to an inevitable risk of bias towards motivated, available stakeholders within this network. All participating stakeholders are listed in the acknowledgments and/or supplementary materials of the published manuscripts for transparency purposes.
In **Chapters 2 and 3**, stakeholders and experts were categorised into four groups aiming at representing all parties involved with antibiotic use: (i) medical community; (ii) public health and patients; (iii) antibiotic R&D; (iv): payers, policy makers, governments and regulators (**Table 1**). These groups were introduced for a better overview of the invited stakeholders. During the analysis of the results of the Delphi questionnaires, the scores for each stakeholder subgroup were not calculated separately, but rather across the four stakeholder groups, as the aim of the study was to identify elements of responsible antibiotic use and QIs taking into account different perspectives. Also, the number of stakeholders in each subgroup was relatively small so analysis at the subgroup level was not considered meaningful.
The widely diverging perspectives of stakeholders providing input is expected to ensure comprehensiveness and wide support of the results across the different sectors. However, while the diversity in background and geography of the stakeholders may emphasise the potential for acceptance of the results, this may also potentially lead to a lack of confidence in the research findings (e.g., involvement of the pharmaceutical industry in defining responsible antibiotic use). An evaluation on how the research output was valued by the participating stakeholders and sectors was beyond the scope of this thesis.

Research methodology

The results presented in this thesis were collected via various research methods including the (RAND-modified) DELPHI method, individual interviews, focus groups and a case study.

The Delphi method is used to systematically integrate scientific evidence from literature and expert opinion.[55] This method involves an iterative process of rating and soliciting expert input with multiple opportunities for feedback.[56] Whether the Delphi technique should be considered a qualitative, quantitative or mixed-method

Table 1 Expertise and geographic spread of stakeholders (N=112*) consulted for input.

Medical Community	Patients, Public Health, Ethics	Antibiotic R&D, (health)- economists	Policy Makers, Governments, Regulators, Payers	Geographic representation
Definition of Responsible Antibiotic Use (Chapter 2) (n=50)**				
n=13 • Infectious diseases: n=3 medical specialist; n=1 nurse; n=2 professional societies (API, ISC) • Pharmacy (n=3) • Clinical Microbiology (n=2) • General Practice (n=1) • Paediatrics (n=1)	**n=12** • International public health organisation (WHO, PAHO) (n= 4) • International medical humanitarian organisation (MSF (n=1) • National public health institutes (n=3) • Chennai Declaration group (n=1) • (Medical) ethics (n=2) • Global network dedicated to ABR (ReAct) (n=1)	**n=13** • Antibiotic R&D and pharmaceutical companies (large n=5; SME n=3) • Economics (n=1) • Health economics (n=3) • European Investment Bank (n=1)	**n=12** • Drug regulatory agencies (EMA, FDA) (n=3) • National health insurance advisor (n=1) • Public health agencies (CDC, ECDC) (n=3) • Departments of Health (n=4) • Policy Maker (n=1)	• Africa (Nigeria, South-Africa; Tanzania) • Asia (India, Thailand) • Australia (Australia) • Europe (Belgium, France, Luxembourg, Norway, Spain, the Netherlands, Sweden, Switzerland, United-Kingdom) • North-America (United-States) • South-America (Argentina, Chile)
Quality Indicators for responsible antibiotic use (Chapter 3) (n=25)				
n=10 • Infectious diseases: n=3 medical specialist; n=3 professional societies: ESCMID study group for Antibiotic Policies – ESGAP, SPILF, Hellenic Society for Chemotherapy. • Pharmacy (n=4)	**n=3** • International public health Organisation (WHO) (n= 1) • Chennai declaration group (n=1) • National public health institute (n=1)	**n=7** • Antibiotic R&D and pharmaceutical companies (large n=3; SME n=1) • Economics (n=1) • Health-economics (n=2)	**n=5** • Drug regulatory agency (EMA) (n=1) • National health insurance advisor (n=1) • Public health agency (CDC) (n=1) • Institute for Health Technology Assessment (n=1) • Department of Health (n=1)	• Asia (Israel, Thailand, India) • Australia (Australia) • Europe (Austria, Belgium, France, Greece, Malta, United-Kingdom, Slovenia, Spain, Sweden, the Netherlands) • North-America (United-States)

Patients' views on responsible antibiotic use (Chapter 4) (n=42)				
	• Patients			• Europe (Belgium, Croatia, France, the Netherlands, Switzerland)
Barriers to and facilitators of responsible antibiotic use (Chapter 5) (n=12)				
	• Medical ethics (n=3) • Health law and bioethics (n=1) • Public health (n=1)	• Antibiotic R&D (n=3) • Health economics (n=1)	• Drug regulatory agency (FDA) n=1 • Public health agency (ECDC) (n=1) • US presidential advisory council on combating antibiotic-resistant bacteria (n=1)	• Asia (Israel) • Europe (France, Sweden, the Netherlands, United-Kingdom) • North-America (United-States)

Legend: * Ten stakeholders participated in the studies of Chapters 2 and 3; five stakeholders participated in the studies of Chapters 2 and 5; one stakeholder participated in the studies of Chapters 2, 3 and 5. ** n= 2 answers missing; therefore N= 48 answers were used for data analysis. ABR: Antibiotic Resistance; API: Asociación Panamericana de Infectiología; CDC: US Centers for Disease Control and Prevention; ECDC: European Centre for Disease Prevention and Control; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; FDA: US Food and Drug Administration; ISC: International Society of Chemotherapy; MSF: Médecins Sans Frontières; PAHO: Pan American Health Organization; R&D: Research and Development; SME: Small and Medium-sized Enterprise; SPILF: Société de Pathologie Infectieuse de Langue Française WHO: World Health Organization.

approach remains a topic of debate.[57] Delphi studies allow for more participants than can effectively interact in a face to face meeting (i.e., without dominance by only a few) and often lifts many practical barriers (e.g., costs, time, logistics).[58, 59] There are currently no clear criteria, definitions or agreement on how to perform Delphi studies, resulting in variation in designs used.[56] For the development of the QIs for responsible antibiotic use (**Chapter 3**), a four step RAND modified DELPHI design was chosen as it was previously used for the development of QIs for antibiotic use.[62, 63] (Of note, RAND refers to the RAND Corporation, a non-profit research organisation, which developed the Delphi method in the 1950s.[64]) The four steps included: (1) systematic review of scientific literature and web sites of relevant public health organisations; (2) first questionnaire to a multidisciplinary international stakeholder panel for appraisal of relevance; (3) discussion of questionnaire results in a consensus meeting (via a web conferencing interface); (4) second questionnaire for final validation of the QIs. The Delphi design was adapted for the study on the definition of responsible antibiotic use, as the fourth step was judged to be unnecessary after the consensus meeting on the definition of responsible antibiotic use. Indeed, during the consensus meeting agreement was already reached between the participating stakeholders on the rephrasing of the elements and exclusion of the newly suggested elements. Methodologic criteria for reporting Delphi studies have been recommended and these were followed in the performed Delphi studies (e.g., criteria for dropping items at each round).[56]

The main shortcoming of a Delphi method is its limited generalisability inherent to its reliance on stakeholder/expert opinion.[65] However, the aim of the Delphi studies was to reach consensus on generic elements of and quality indicators for responsible antibiotic use with a global scope regardless of contextual factors (see section *Scope of the thesis* above). Also, in both Delphi studies an overview of the literature and website searches (i.e., the results of step 1) was provided to the stakeholders to help them rate the relevance of the elements for defining responsible antibiotic use and of the QIs. Altogether, this should have ensured that the findings presented in **Chapters 2 and 3** are only moderately affected by problems of generalisability.

In this thesis we used individual interviews and focus groups to explore opinions, views, perceptions of patients and stakeholders. Qualitative data primarily consists of words rather than numbers and thus allows for in-depth understanding of, e.g., experiences, viewpoints, beliefs or systems.[66, 67] Indeed, in contrast to quantitative research, qualitative research does not aim at quantification of opinions, variables, factors or any kind of data. In this thesis, individual interviews and focus groups were performed with patients in four European countries to explore inpatients' experiences concerning antibiotic treatment and views on responsible antibiotic use (**Chapter 4**). In **Chapter 5**, semi-structured interviews were conducted to explore barriers to and

facilitators of responsible antibiotic use from the perspective of third-party stakeholders. In both studies, an interview guide (and focus group guide for **Chapter 4**) was developed based on elements of the definition of responsible antibiotic use. Semi-structured interviews allowed interviewees to introduce additional and not predetermined interview topics to ensure that important topics were not missed.
The main limitation inherent to the use of qualitative semi-structured interviews concerns the relatively small sample sizes and its consequence on the interpretation of the findings. The purpose of qualitative research is often exploratory and therefore requires the opportunity for in-depth data collection. In **Chapter 4**, 42 patients from four European countries were consulted on their views on responsible antibiotic use. Inclusion was suspended upon data saturation, i.e., when no new concept emerged from the data. In contrast, in **Chapter 5**, data saturation was not pursued due to the wide variation of backgrounds of the consulted stakeholders. Instead, an illustrative sample of 12 stakeholders were interviewed on barriers to and facilitators of responsible antibiotic use. Whereas a quantitative study design would allow for more participants, this would lead to loss of depth of the answers. Often, the results of qualitative interviews can be used as building blocks to design research tools to further investigate the research topic with a more quantitative approach, e.g., an online questionnaire. Strategies have been formulated to help researchers ensure the credibility of qualitative research findings. Examples of strategies followed in this thesis include the report of stakeholders' and patients' verbatim quotes for transparency and support of the research findings as well as the use of the COREQ guidelines for reporting qualitative studies.[68, 69]

Case study research is defined as 'a qualitative approach in which the investigator explores a real-life, contemporary bounded system (a case) or multiple bound systems (cases) over time, through detailed, in-depth data collection involving multiple sources of information, and reports a case description and case themes'.[70] The case study presented in **Chapter 6** allowed for an illustration of responsible antibiotic use principles for a specific infectious disease, i.e., *Staphylococcus aureus* bacteraemia (SAB). SAB was chosen as Methicillin Resistant *S. aureus* (MRSA) is classified as a high priority pathogen by the WHO[71] and Methicillin susceptible *S. aureus* (MSSA) still has a substantial burden. The case study displayed the consequences of ABR on the availability of treatment options for SAB. Criticism of case study research mainly refers to its limited generalisability and the bias toward verification (i.e., the tendency to confirm the researcher's preconceived notions).[72] The data extraction performed among different international information sources and the collaboration with researchers from different backgrounds (e.g., medical specialists, health economist, regulator) is expected to reduce risks for generalisation and verification biases.

Recommendations for future directions

The results of this thesis yielded the following recommendations for future practice, policy and research.

Practice

- Health care facilities should use the definition and quality indicators in daily practice to increase their responsible antibiotic use. Indeed, the definition of responsible antibiotic use (**Chapter 2**) and the inpatient quality indicators for responsible antibiotic use (**Chapter 3**) can be translated and tailored to the local health care setting to inform the quality of the antibiotic use and guide further antibiotic prescription improvement efforts. Not only the quality but also the quantity of use should be monitored at the health care facility. In addition, efforts to reduce the overall consumption of antibiotics should be implemented, such as infection prevention measures and when possible vaccines.
- Health care professionals should be educated on responsible antibiotic use. The definition (**Chapter 2**) and the inpatient quality indicators (**Chapter 3**) may constitute a valuable educational tool for use in different healthcare curricula (physicians, nurses, pharmacists), including undergraduate education. For example, the infographic illustrating the 22 elements of the definition responsible antibiotic use can facilitate understanding and dissemination of the findings (**Chapter 2**). The negative consequences of antibiotic use should be clearly emphasised, including toxicity (i.e., side effects), interactions with other drugs, unintended consequences ('i.e., *C. difficile* infection, long lasting impact on microbiome) and the development of resistance.
- Health care professionals should improve communication with patients on responsible antibiotic use to promote patient involvement. The findings presented in this thesis describe responsible antibiotic use from the hospitalised patient's perspective. Health care professionals should focus on providing tailored and understandable information to the patients (on clinical indication, side effects, duration, frequency and timing of antibiotic intake) and explore their preferences for shared decision-making. (**Chapter 4**) More information on antibiotic use should also increase awareness and engage patients on the problem of resistance.

Policy

- International policies on responsible antibiotic use should be pursued. Bacteria and their resistance genes spread rapidly across the globe without considerations for country borders. The quality indicators reported in this thesis (**Chapter 3**) were consulted in the drafting of the 'Proposals for EU guidelines for the Prudent Use of Antimicrobials in Human Medicine' written by the European Centre for Disease

Prevention and Control (ECDC) in 2017. Future international policy efforts should focus on the use of standardised measures to assess the quality and quantity of antibiotic use across different countries. Indeed, standardised measures should facilitate informative comparisons between different countries.

- Awareness on the need for multi-sectoral action to address ABR should be increased. This thesis sought to bring together various stakeholders involved in antibiotics from molecule to prescribed drug to trigger reflections on responsible antibiotic use. The research performed in this thesis can therefore be considered as an intervention to increase awareness among international multidisciplinary stakeholders. Future policy efforts should continue to address the urgency for change among the general public and all concerned sectors (**Chapter 5**).
- Focus and priorities of multi-sectoral action to address ABR should be aligned. Aligning improvement targets and priorities of all involved stakeholders is needed to steer progress and avoid fragmentation of policy efforts (**Chapter 5**). This thesis reports the results of a broad exploration of responsible use from various sectors and perspectives concerned with antibiotic use and the development of resistance. Many different perspectives were gathered together for the development of a definition (**Chapter 2**) and quality indicators (**Chapter 3**) for responsible antibiotic use as well as the exploration of barriers that should be lifted (**Chapter 5**). Indeed, finding common grounds between all concerned sectors might help to tackle the super wicked antibiotic resistance problem.

Research

- Multidisciplinary and multi-sectoral collaboration on responsible antibiotic use should be evaluated. Future studies should explore how the collaboration was experienced by the stakeholders and evaluate its outcomes.
- Quality indicators for responsible antibiotic use should be used as outcomes for antibiotic stewardship intervention studies. Future quality improvement studies should use the QIs (**Chapter 3**) to monitor and evaluate the impact of antibiotic stewardship activities at inpatient health care facilities. The use of standardised quality indicators for antibiotic use should facilitate informative comparisons between different health care settings, or within a single health care setting over time.
- Case studies on infectious diseases should be used more often to illustrate the consequences of resistance on available effective antibiotics and medical unmet needs. Performing case studies for specific infectious diseases, following the example reported in the thesis, increases reflection on the available antibiotic arsenal and highlights important medical unmet needs (new antibiotics classes or antibiotics with new mechanisms of actions) to steer antibiotic R&D (**Chapter 6**). This should, in turn, ensure availability of effective antibiotics in the future.

Final conclusion

This thesis presents the results of a broad exploration of responsible antibiotic use. The research performed in this thesis yielded a multidisciplinary and multisector consensus based definition of responsible antibiotic use and associated quality indicators. In addition, views from inpatients on responsible antibiotic use were elucidated. Finally, barriers and facilitators of responsible antibiotic were explored from the perspectives of third-party stakeholders (i.e., stakeholders outside the medical and patient communities). The research presented in this thesis contributes to the body of knowledge on the complexity of using antibiotics responsibly and sought to include stakeholders involved in antibiotics from molecule to prescribed drug. The findings of this thesis are embedded in a context of increasing awareness of the societal implications of ABR and of the need for multi-sectoral actions to address the issue.

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8

Summary
Samenvatting
Résumé

Summary

In Chapter 1 we provided the background and rationale for the work of this thesis. The world is facing the fast-growing public health threat of antibiotic resistance (ABR), i.e., the ability of a bacterium to resist the action of an antibiotic. As a result, antibiotics are losing their potential to prevent and treat bacterial infections. The development of resistance is a natural phenomenon that occurs when bacteria are exposed to antibiotics following the Darwinian principle of *survival of the fittest*. Indeed, susceptible bacteria are killed or inhibited by the antibiotic, while bacteria that are naturally resistant or that have acquired resistance features have better odds at survival and proliferation. Therefore, antibiotic use is an important driver of resistance. Limiting antibiotic use to appropriate clinical indications should curb the development of resistance by reducing the selection pressure for the bacteria.
ABR is a complex societal problem that requires action from multiple sectors. However, up to the start of this thesis in 2014, involvement of stakeholders from different relevant sectors (e.g., public health, governments, regulators, antibiotic R&D) was relatively limited. Furthermore, there was no general consensus between all sectors on a definition of *responsible antibiotic use* and many different measures were used to evaluate the quality of antibiotic prescriptions. The identification of bottlenecks and levers from the perspective of a wide range of stakeholders is key to steer the focus of research and policy efforts towards solutions for ABR. So far, barriers to and facilitators of responsible antibiotic use have mainly been studied among the prescribers of the antibiotics. However, stakeholders and experts involved in the processes of drug development, drug regulation and dispensing (i.e., outside the medical and patient communities) are increasingly expected to contribute to efforts towards solutions.
The aim of this thesis was to explore responsible antibiotic use. A search for a global definition, quality indicators (QIs), barriers and facilitators was conducted involving a wide range of stakeholders.

In **Chapter 2**, we identified key elements for a global definition of responsible antibiotic use based on input from various stakeholders. The aim was a definition relevant for any setting worldwide regardless of the socio-economic, cultural or care-setting factors. A Delphi study allowed us to combine concepts from scientific literature and stakeholder opinion into a definition of responsible antibiotics use. Elements of the definitions identified in the literature were appraised by 50 international stakeholders with diverse backgrounds (e.g., medical community, public health organisations, pharmaceutical companies, regulators, governments). Finally, international multidisciplinary consensus was reached on 22 elements to be considered when defining responsible use. Two groups were identified: patient-level

(e.g., Indication, Documentation) and societal-level (e.g., Education, Future Effectiveness) elements. The widely diverging perspectives of stakeholders providing input should ensure the comprehensiveness and relevance of the definition for both individual patients and society. The large number of elements contained in the definition of responsible antibiotic use highlights the complexity of this concept. An aspirational goal would be to address them all when using antibiotics.

In **Chapter 3**, we developed generic quality indicators for responsible antibiotic use in the inpatient setting (including hospitals). A Delphi study allowed us to combine concepts from the scientific literature and stakeholder opinion into generic quality indicators for responsible antibiotics use. Potential indicators identified in the literature were appraised by 25 international stakeholders with diverse backgrounds (e.g., medical community, public health, antibiotic research and development, regulators, governments). This international and multidisciplinary consensus procedure led to the development of 51 generic QIs for responsible antibiotic use. These QIs are intended to be universally applicable, i.e., regardless of infectious disease type, geographical or socioeconomic setting. Moreover, the broad background range of the stakeholders that selected them is expected to lead to widespread support for the QIs. Most of the QIs were classified as process, about one third as structure and only two as outcome indicators according to the Donabedian model. The QIs were phrased as recommendations. Altogether, the QIs covered a wide range of 19 different themes of responsible inpatient antibiotic use, of which the majority overlap with the elements of the definition of responsible use (described in **Chapter 2**). The QIs can be used to evaluate the quality of antibiotic use and to identify targets for quality improvement projects of antibiotic use (i.e., antibiotic stewardship) in hospitals or other inpatient health care facilities.

In **Chapter 4**, we explored patients' views and experiences concerning antibiotic treatments and responsible antibiotic use. Interviews and focus groups were held with 42 patients in five European hospitals. The topics of the interviews and focus groups were based on elements from the definition of responsible antibiotic use that was established in **Chapter 2**. Five main themes emerged:

- patients trust their doctors for antibiotic treatment decisions;
- patients perceive a lack of communication on antibiotic treatments and a lack of tailoring of information on antibiotics;
- patients differ in their wish to be informed but overall want to receive information on main aspects of their antibiotic treatments (i.e., clinical indication, adverse events, duration, frequency and timing of antibiotic intake) in an understandable way;
- patients find it reassuring to share information about their antibiotic treatment with close family;

- health care professionals should explore patients' preferences for being involved in shared decision-making for their antibiotic treatments.

Concerning ABR, patients acknowledged the problem but seemed to prioritise the individual perspective over the societal perspective. Hospital patients often doubt their ability to understand medical information and trust their physicians to make the best decisions for them. In order to promote patient involvement, communication strategies to inform hospitalised patients should be tailored to their concerns and preferences.

In **Chapter 5**, we explored barriers to and facilitators of responsible antibiotic use according to *third-party* stakeholders (i.e., stakeholders involved with antibiotics but outside the medical and patient communities). Twelve individual interviews were conducted with international third-party stakeholders. The interview topics were based on elements from the definition established in **Chapter 2**. Seven categories of barriers and facilitators were identified: scientific (e.g., uncertainty of future medical needs), economic (e.g., financial incentives), regulatory (e.g., regulatory harmonisation), ethical (e.g., responsibility for future generations), societal (e.g., invisibility of antibacterial resistance), political (e.g., changing political environment) and medical practice (e.g., alternatives for antibiotics). Furthermore, several contrasts highlighting the complexity of responsible antibiotic use emerged across the categories. Examples include the alarming worldwide spread of ABR as opposed to its invisibility, and the paradox between research based on current unmet needs versus the uncertainty of future medical needs. The identified barriers and facilitators should be considered when drafting future antibiotic policies.

In Chapter 6, we conducted a case study to address (I) antibiotic treatment options for *Staphylococcus aureus* bacteraemia (SAB); (II) current status of and priorities for the antibiotic pipeline to ensure access of effective antibiotics for SAB; and (III) strategies for responsible antibiotic use relevant to the clinical management of SAB. Information was collected from different sources including labels from available antibiotics, antibiotic treatment guidelines, a leading textbook and a database of clinical trials. The case study revealed that current treatment options for SAB include only three drug classes (beta-lactams, glycopeptides, lipopeptide) of which two also cover MRSA bacteraemia (glycopeptides, lipopeptide). The analysis of the antibiotic pipeline and ongoing clinical trials revealed that several new antibiotics with *S. aureus* (including MRSA) coverage were developed in the past decade (2009-2019). However, none belongs to a new antibiotic class or has superior effectiveness. Their added clinical value for SAB remains thus to be proven. Responsible antibiotic use for the treatment of SAB was illustrated using eleven QIs developed in **Chapter 3**. The case study highlights the need for awareness surrounding the problem of a limited

antibiotic arsenal to steer the R&D landscape towards the development of novel and effective antibiotics for treating SAB. In the meantime, responsible antibiotic use guided by quality indicators should preserve the effectiveness of currently available antibiotics for treating SAB.

In **Chapter 7**, we presented the general discussion of this thesis. We summarised the main findings and discussed these findings in the context of developments contemporary to the work of this thesis. We also addressed methodological considerations. As a result, the following recommendations for future directions were formulated:

Practice

- Health care facilities should use the definition and quality indicators in daily practice to increase their responsible antibiotic use.
- Health care professionals should be educated on responsible antibiotic use.
- Health care professionals should improve communication with patients on responsible antibiotic use to promote patient involvement.

Policy

- International policies on responsible antibiotic use should be pursued and should focus on the use of standardised measures to assess the quality and quantity of antibiotic use.
- Awareness on the need for multidisciplinary and multi-sectoral action to address ABR should be increased.
- Focus and priorities of multi-sectoral action to address ABR should be aligned.

Research

- Multidisciplinary and multi-sectoral collaboration on responsible antibiotic use should be evaluated.
- Quality indicators for responsible antibiotic use should be used as outcomes for antibiotic stewardship intervention studies.
- Case studies on infectious diseases should be performed more often to illustrate the consequences of resistance on the availability of effective antibiotics. In addition, case studies help to reflect on medical unmet needs (i.e., new antibiotic classes or antibiotics with new mechanisms of action) and the need for responsible antibiotic use practices.

Final conclusion

This thesis reports the findings of a broad exploration of responsible antibiotic use for which many different concerned stakeholders, involved from antibiotic molecule to prescribed drug, were consulted. These results contribute to the body of knowledge regarding the complexity of using antibiotics responsibly. The findings of this thesis are embedded in a context of increasing awareness of the societal implications of ABR and of the need for multi-sectoral actions to address the issue.

Samenvatting

In **Hoofdstuk 1** presenteren we de achtergrond en de onderbouwing van dit proefschrift. Antibioticaresistentie (ABR), oftewel wanneer een bacterie niet meer gevoelig is voor een bepaald antibioticum of meerdere antibiotica, is een belangrijke wereldwijde dreiging voor de volksgezondheid. Het gevolg van ABR is dat antibiotica niet meer voldoende helpen om bacteriële infecties te voorkomen en te behandelen. De ontwikkeling van resistentie is een natuurlijk fenomeen dat plaatsvindt wanneer bacteriën worden blootgesteld aan antibiotica, volgens het Darwin geïnspireerde principe van *survival of the fittest*. Bacteriën die gevoelig zijn voor het antibioticum worden gedood of geremd in hun groei, terwijl bacteriën die uit zichzelf resistent zijn of resistentie mechanismen hebben verworven, betere kansen hebben om te overleven en zich verder voor te planten. Antibioticagebruik heeft daarom een belangrijke rol in de ontwikkeling van ABR. Het beperken van antibioticagebruik tot de juiste klinische indicaties zorgt voor minder selectiedruk op de bacteriën en vermindert daarmee het ontstaan van resistentie.
ABR is een complex maatschappelijk probleem waarvoor een gezamenlijke aanpak van meerdere sectoren nodig is. Voor het starten van dit proefschrift in 2014 was de betrokkenheid van verschillende sectoren (bijv. volksgezondheid, overheden, toezichthouders, antibiotica ontwikkelaars) echter nog redelijk beperkt. Daarnaast bestond er geen algemene consensus tussen de betrokken sectoren over een definitie van *verantwoord antibioticagebruik* en werden er veel verschillende maatstaven gebruikt voor het evalueren van de kwaliteit van antibioticavoorschriften. Het identificeren van knelpunten en bevorderende factoren vanuit het perspectief van verschillende stakeholders is belangrijk voor onderzoek naar en beleid over oplossingen voor ABR. Tot nu toe zijn belemmerende en bevorderende factoren van verantwoord antibioticagebruik voornamelijk bestudeerd onder antibiotica voorschrijvers. Echter wordt er van stakeholders en experts, betrokken bij de ontwikkeling, regelgeving en verstrekking van geneesmiddelen, ook steeds meer verwacht dat ze gaan bijdragen aan inspanningen voor oplossingen.
Dit proefschrift heeft als doel om *verantwoord antibioticagebruik* te onderzoeken. Er is gezocht naar een definitie, kwaliteitsindicatoren en bevorderende en belemmerende factoren van *verantwoord antibioticagebruik*. Voor de totstandkoming van dit proefschrift zijn veel verschillende stakeholders geraadpleegd.
In **Hoofdstuk 2** hebben wij de belangrijkste elementen voor een definitie van verantwoord antibioticagebruik geïdentificeerd op basis van de input van verschillende stakeholders. Het doel was een definitie, relevant voor verschillende contexten wereldwijd, los van sociaaleconomische, culturele of zorginstelling factoren. Met behulp van een Delphi studie werden bevindingen uit de wetenschappelijke literatuur samengevoegd met de meningen en ervaringen van stakeholders tot een definitie

van verantwoord antibioticagebruik. Elementen van definities uit de literatuur werden beoordeeld door 50 internationale stakeholders met verschillende achtergronden (bijv. medische gemeenschap, volksgezondheidsorganisaties, farmaceutische bedrijven, toezichthouders, overheden).
Uiteindelijk werd er internationaal en multidisciplinair consensus bereikt over 22 elementen die samen verantwoord antibioticagebruik definiëren. Twee groepen worden onderscheiden: patiënt gerelateerde elementen (bijv. Indicatie, Documentatie) en maatschappelijke elementen (bijv. Educatie, Toekomstige Effectiviteit). De zeer uiteenlopende perspectieven van de betrokken stakeholders zouden moeten zorgen voor volledigheid en relevantie van de definitie voor zowel de individuele patiënt als de maatschappij. Het grote aantal elementen van de definitie geeft de complexiteit van het concept *verantwoord antibioticagebruik* weer. Bij het gebruik van antibiotica worden idealiter alle elementen nagestreefd.

In **Hoofdstuk 3** hebben wij generieke kwaliteitsindicatoren voor verantwoord antibioticagebruik ontwikkeld voor de intramurale zorg (inclusief ziekenhuizen). Middels een Delphi studie werden bevindingen uit de wetenschappelijke literatuur samengevoegd met meningen en ervaringen van stakeholders tot generieke kwaliteitsindicatoren voor verwantwoord antibioticagebruik. Potentiële indicatoren geëxtraheerd uit de literatuur werden beoordeeld door 25 internationale stakeholders met verschillende achtergronden (bijv. medische gemeenschap, volksgezondheidsorganisaties, farmaceutische bedrijven, toezichthouders, overheden). Deze internationale en multidisciplinaire consensus procedure leidde tot de ontwikkeling van 51 generieke kwaliteitsindicatoren voor verantwoord antibioticagebruik. Deze kwaliteitsindicatoren zijn bedoeld om wereldwijd toepasbaar te zijn, ongeacht het type infectieziekte en geografische of socio-economische aspecten.
Door de diversiteit aan stakeholders betrokken bij dit onderzoek zou een breed draagvlak gecreëerd moeten zijn voor de kwaliteitsindicatoren. De meeste kwaliteitsindicatoren zijn op basis van het Donabedian model geclassificeerd als procesindicatoren, een derde als structuurindicatoren en enkel twee als uitkomstindicatoren. De kwaliteitsindicatoren zijn geformuleerd als aanbevelingen. Samen omvatten de kwaliteitsindicatoren een breed scala van 19 thema's van verantwoord antibioticagebruik voor de intramurale zorg. De meeste thema's overlappen met de elementen van de definitie van antibioticagebruik (beschreven in **Hoofdstuk 2**). De kwaliteitsindicatoren kunnen gebruikt worden voor het evalueren van de kwaliteit van antibioticagebruik en voor het bepalen van doelstellingen voor kwaliteitsverbeteringsprojecten van antibioticagebruik (ook wel antibiotica stewardship genoemd) in ziekenhuizen of andere intramurale zorginstellingen.

In **Hoofdstuk 4** hebben wij opvattingen en ervaringen van patiënten met antibioticabehandelingen en verantwoord antibioticagebruik onderzocht. Interviews en focusgroepen zijn gehouden met 42 patiënten in vijf Europese ziekenhuizen. De interview en focusgroep onderwerpen waren gebaseerd op elementen van de definitie van antibioticagebruik uit Hoofdstuk 2. Vijf thema's kwamen naar voren:

- patiënten vertrouwen hun artsen m.b.t. beslissingen over antibioticabehandelingen;
- patiënten ervaren dat communicatie over antibioticabehandelingen en toegespitste informatie over antibiotica ontbreken;
- patiënten verschillen in hun wensen om geïnformeerd te worden maar willen in het algemeen geïnformeerd worden over de belangrijkste aspecten van hun antibioticabehandelingen (klinische indicatie, bijwerkingen, duur, frequentie en moment van antibiotica inname) op een begrijpelijke manier;
- patiënten vinden het geruststellend om informatie over hun antibioticabehandelingen met hun naaste familie te delen;
- Zorgverleners zouden voorkeuren van patiënten moeten verkennen m.b.t. gedeelde besluitvorming (*shared decision-making*) over hun antibioticabehandelingen.

Wat betreft ABR erkenden patiënten het probleem, maar ze leken prioriteit te geven aan het individuele boven het maatschappelijke perspectief. Ziekenhuispatiënten twijfelen vaak aan hun vaardigheid om medische informatie te begrijpen en vertrouwen erop dat hun artsen de juiste beslissingen voor ze maken. Communicatiestrategieën voor het informeren van ziekenhuispatiënten zouden aangepast moeten worden naar hun bezorgdheden en voorkeuren om hun betrokkenheid te stimuleren.

In **Hoofdstuk 5** hebben wij bevorderende en belemmerende factoren van verantwoord antibioticagebruik onderzocht vanuit het perspectief van *third-party* stakeholders (d.w.z. stakeholders betrokken bij antibiotica, maar buiten de medische gemeenschap en patiënten). Twaalf individuele interviews zijn afgenomen met internationale third-party stakeholders. De interview onderwerpen waren gebaseerd op de elementen van de definitie van antibioticagebruik uit **Hoofdstuk 2**. Zeven categorieën van bevorderende en belemmerende factoren zijn geïdentificeerd: wetenschappelijk (bijv. onzekerheden over toekomstige medische behoeften), economisch (bijv. financiële prikkels), regelgevend (bijv. harmonisatie van regelgeving), ethisch (bijv. verantwoordelijkheid voor toekomstige generaties), maatschappelijk (bijv. onzichtbaarheid van antibioticaresistentie), politiek (bijv. veranderende politieke omgeving) en medische praktijk (bijv. alternatieven voor antibiotica). Tevens illustreren verschillende contrasten binnen en tussen de categorieën de complexiteit van verantwoord antibioticagebruik. Voorbeelden hiervan zijn de alarmerende wereldwijde spreiding van ABR tegenover haar onzichtbaarheid en de paradox tussen onderzoek gebaseerd op huidige onvervulde medische behoeften versus de onzekerheden

over toekomstige medische behoeften. Bij het opstellen van toekomstig antibioticabeleid zou rekening gehouden moeten worden met de geïdentificeerde bevorderende en belemmerende factoren.

In **Hoofdstuk 6** hebben wij een *case study* onderzoek verricht naar (I) de behandelingsopties met antibiotica voor *Staphylococcus aureus* bacteriëmie (SAB), (II) de huidige status en prioriteiten van de antibioticapijplijn en (III) strategieën voor verantwoord antibioticagebruik relevant voor de klinische behandeling van SAB. Informatie werd verzameld uit verschillende bronnen waaronder: bijsluiters van beschikbare antibiotica, antibioticagebruik richtlijnen, een belangrijk leerboek en een database van klinische studies. De casestudie liet zien dat de huidige behandeling opties voor SAB uit enkel drie antibioticaklassen bestaan (beta-lactams, glycopeptiden, lipopeptide) waarvan twee ook MRSA bacteriëmie dekken (glycopeptiden, lipopeptide). De analyse van de antibioticapijplijn en lopende klinische studies liet zien dat verschillende nieuwe antibiotica werkzaam tegen *S. aureus* (inclusief MRSA) ontwikkeld zijn in het laatste decennium (2009-2019). Echter, geen van deze behoren tot een nieuwe antibioticaklasse of hebben een superieure werking. Hun toegevoegde klinische waarde zal dus nog aangetoond moeten worden. Verantwoord antibioticagebruik voor de behandeling van SAB was geïllustreerd aan de hand van 11 kwaliteitsindicatoren ontwikkeld in **Hoofdstuk 3**. De casestudie benadrukt de noodzaak voor bewustwording van het probleem van een beperkt antibiotica arsenaal met als doel het R&D landschap te bewegen naar de ontwikkeling van nieuwe en effectieve antibiotica voor de behandeling van SAB. In de tussentijd zou de effectiviteit van beschikbare antibiotica voor de behandeling van SAB behouden moeten worden door hun verantwoorde inzet geleid door kwaliteitsindicatoren.

In **Hoofdstuk 7** presenteren wij de discussie van dit proefschrift. We vatten de hoofdbevindingen samen en bediscussiëren deze in de context van actuele ontwikkelingen. We bespreken ook de methodologische afwegingen. Uiteindelijk werden de volgende aanbevelingen opgesteld:

Praktijk

- Zorginstellingen zouden de definitie en kwaliteitsindicatoren in de dagelijkse praktijk moeten gebruiken om verantwoord antibioticagebruik te verhogen.
- Zorgverleners zouden geschoold moeten worden in verantwoord antibioticagebruik.
- Zorgverleners zouden communicatie met patiënten over verantwoord antibioticagebruik moeten verbeteren om patiëntenbetrokkenheid te stimuleren.

Beleid

- Internationaal beleid over verantwoord antibioticagebruik zou moeten worden voortgezet en zou moeten focussen op het gebruik van gestandaardiseerde maten voor het evalueren van de kwaliteit en kwantiteit van antibioticagebruik.
- Bewustwording van de noodzaak voor multidisciplinaire en multisectoriële inspanningen om het ABR probleem aan te pakken zou vergroot moeten worden.
- De focus en de prioriteiten van de multisectoriële aanpak voor ABR moeten op elkaar worden afgestemd.

Onderzoek

- Multidisciplinaire en multisectoriële samenwerking m.b.t. verantwoord antibioticagebruik zou moeten worden geëvalueerd.
- Kwaliteitsindicatoren voor verantwoord antibioticagebruik zouden moeten worden gebruikt als uitkomstmaten voor antibiotica *stewardship* interventies.
- Casestudies over infectieziektes zouden vaker toegepast moeten worden om de consequenties van resistentie op de beschikbare van effectieve antibiotica in kaart te brengen. Daarnaast helpen ze te reflecteren over onvervulde medische behoeften (d.w.z. nieuwe antibioticaklassen of antibiotica met nieuwe werkingsmechanismen) en over de noodzaak voor verantwoord antibioticagebruik.

Slotconclusie

Dit proefschrift beschrijft de bevindingen van een brede verkenning van verantwoord antibioticagebruik waarin veel verschillende stakeholders, betrokken van antibioticum molecuul tot voorgeschreven medicijn, zijn geraadpleegd. Deze resultaten dragen bij aan de kennis over de complexiteit van het verantwoord gebruik van antibiotica. De resultaten van dit proefschrift zijn onderdeel van een groeiend bewustzijn van de maatschappelijke implicaties van ABR en de noodzaak voor een multisectoriële aanpak van dit probleem.

Résumé

Dans le **Chapitre 1**, nous décrivons le contexte et le fondement de cette thèse. Le monde est confronté à une menace grandissante concernant la santé publique, celle de l'antibiorésistance (ABR), c.-à-d. la capacité d'un micro-organisme à résister aux effets d'un antibiotique. Les antibiotiques perdent donc leurs capacités à prévenir et soigner les infections bactériennes. Le développement de l'ABR est un phénomène naturel qui se produit lorsque des bactéries sont exposées aux antibiotiques suivant le principe Darwinien de la *survie du plus fort*. En effet, les bactéries sensibles sont tuées ou inhibées par l'antibiotique alors que celles naturellement résistantes ou ayant acquis des mécanismes de résistance ont de meilleures chances de survivre et de proliférer. L'utilisation des antibiotiques est donc un vecteur important entrainant l'ABR. Limiter l'utilisation des antibiotiques aux situations cliniques appropriées devrait freiner le développement de l'antibiorésistance par la réduction de la pression sélective exercée sur les bactéries.

L'ABR est un problème sociétal complexe qui exige des démarches convergentes de plusieurs secteurs. Cependant, jusqu'au début de cette thèse en 2014, l'implication de stakeholders de différents secteurs importants (par ex. santé publique, gouvernements, régulateurs, R&D antibiotique) était relativement limitée. De plus, il n'y avait pas de consensus général entre tous les secteurs sur une définition de l'utilisation responsable des antibiotiques et beaucoup de mesures différentes étaient employées pour évaluer la qualité des prescriptions antibiotiques. L'identification de facteurs limitants et favorisants depuis le point de vue d'une grande diversité de stakeholders est cruciale pour orienter les efforts de recherche et les efforts politiques quant aux solutions pour l'ABR. Jusqu'à présent, les facteurs limitants et favorisants l'utilisation responsable des antibiotiques ont été principalement étudiés parmi les prescripteurs d'antibiotiques. Cependant, les attentes se font de plus en plus importantes au niveau des stakeholders et experts impliqués dans les procédés de développement, régulation et distribution des médicaments (en dehors des communautés médicales et de patients) qu'ils contribuent aux efforts visant à trouver des solutions.

L'objectif de cette thèse était une exploration de l'utilisation responsable des antibiotiques. Des recherches pour une définition universelle, des indicateurs de qualité ainsi que de facteurs limitants et favorisants ont été menées en incluant une grande variété de stakeholders.

Dans le **Chapitre 2**, nous avons identifié les éléments clés pour une définition universelle de l'utilisation responsable des antibiotiques en se basant sur la contribution de divers stakeholders. L'objectif était de présenter une définition pertinente pour n'importe quel contexte à travers le monde, indépendamment de

facteurs socio-économiques, culturels ou de l'environnement de soins. Une étude Delphi nous a permis de combiner des concepts de la littérature scientifique avec les opinions de stakeholders sur une définition de l'utilisation responsable des antibiotiques. Les éléments des définitions identifiées dans la littérature ont été évalués par 50 stakeholders avec diverses expertises (par ex. communauté médicale, organisations de santé publique, entreprises pharmaceutiques, régulateurs, gouvernements). Finalement, nous sommes parvenus à un consensus international et multidisciplinaire sur 22 éléments à considérer pour définir l'utilisation responsable des antibiotiques. Deux groupes d'éléments ont été identifiés : ceux au niveau du patient (par ex. Indication, Documentation) et ceux au niveau de la collectivité (par ex. Education, Efficacité Future). La divergence des points de vue des stakeholders ayant contribué devrait assurer l'exhaustivité intégralité et la pertinence de la définition à l'échelle du patient ainsi que de la société. Le grand nombre d'éléments contenus dans la définition de l'utilisation responsable des antibiotiques souligne la complexité de ce concept. Idéalement, tous devraient être abordés pour une utilisation responsable des antibiotiques.

Dans le **Chapitre 3**, nous avons développé des indicateurs de qualité pour l'utilisation responsable des antibiotiques dans les établissements de santé dont les hôpitaux. Une étude Delphi nous a permis de combiner des concepts de la littérature scientifique avec les opinions de stakeholders sur des indicateurs de qualité pour l'utilisation des antibiotiques. Les indicateurs potentiels identifiés dans la littérature ont été évalués par 25 stakeholders avec diverses expertises (par ex. la communauté médicale, organisations de santé publique, entreprises pharmaceutiques, régulateurs, gouvernements). Un consensus international et multidisciplinaire a été obtenu pour 51 indicateurs de qualité génériques pour l'utilisation responsable des antibiotiques. Ces indicateurs de qualité ont été conçus pour être utilisés universellement, c.-à-d. indépendamment du type d'infection, de la situation géographique ou contexte socio-économique. De plus, la divergence des expertises des stakeholders ayant contribué devrait assurer un vaste soutient des indicateurs. La plupart des indicateurs de qualité sont classifiés comme processus, un tiers comme structure et seulement deux comme résultat d'après le modèle Donabedien. Les indicateurs de qualité sont formulés comme des recommandations. Ensemble les indicateurs couvrent une vaste gamme de 19 thèmes sur l'utilisation responsable des antibiotiques dont la majorité correspondent aux éléments de la définition (décrit dans le **Chapitre 2**). Les indicateurs de qualité peuvent être utilisés pour évaluer la qualité de l'utilisation des antibiotiques et pour identifier des objectifs pour des projets d'amélioration de la qualité de l'utilisation des antibiotiques dans les hôpitaux.

Dans le **Chapitre 4**, nous avons exploré les expériences de patients avec des traitements antibiotiques et les points de vue sur l'utilisation responsable des antibiotiques. Des interviews et des groupes de discussions ont été menés avec 42 patients de 5 hôpitaux Européens. Les sujets abordés lors des interviews et groupes de discussions étaient basés sur des éléments de la définition de l'utilisation responsable des antibiotiques établie au **Chapitre 2**. Cinq principaux thèmes ont émergé :

- les patients font confiance à leurs médecins quant aux décisions sur les traitements antibiotiques ;
- les patients perçoivent un manque de communication sur les traitements antibiotiques et un manque d'adaptation des informations sur les antibiotiques ;
- les patients diffèrent dans leurs souhaits d'être informés mais en général souhaitent recevoir des informations compréhensibles sur les aspects importants de leurs traitements antibiotiques (c.-à-d. l'indication clinique, les effets secondaires, la durée, la fréquence et le moment de la prise des antibiotiques) ;
- les patients trouvent rassurant de partager d'informations sur leur traitement antibiotique avec leur famille proche ;
- les patients souhaitent que les professionnels de santé explorent leurs préférences quant à la prise de décision partagée au sujet des traitements antibiotiques ;

En ce qui concerne l'ABR, les patients reconnaissent le problème mais semblent prioriser l'intérêt individuel sur l'intérêt collectif. Les patients hospitalisés doutent souvent de leurs capacités à comprendre les informations médicales et font confiance à leurs médecins pour prendre les meilleures décisions pour eux. Pour encourager l'implication des patients, des stratégies de communications pour informer les patients hospitalisés devraient être adaptées à leurs inquiétudes et préférences.

Dans le **Chapitre 5**, nous avons exploré les facteurs limitants et favorisants de l'utilisation responsable des antibiotiques selon des *third-party* stakeholders (c.-à-d. des stakeholders concernés par les antibiotiques mais en dehors des médecins et des patients). Douze interviews ont été menées avec des third-party stakeholders internationaux. Les sujets abordés lors des interviews étaient basés sur des éléments de la définition de l'utilisation responsable des antibiotiques établie au **Chapitre 2**. Sept catégories de facteurs limitants et favorisants ont été identifiés : scientifique (par ex. incertitude des futurs besoins médicaux), économique (par ex. incitations financières), régulatoire (par ex. harmonisation régulatoire), éthique (par ex. responsabilités pour les futures générations), sociétale (par ex. invisibilité de l'antibiorésistance), politique (par ex. environnement politique changeant). Différents contrastes entre les catégories ont émergé accentuant d'autant plus la complexité de l'utilisation responsable des antibiotiques. Par exemple, la propagation alarmante opposée à l'invisibilité de l'ABR et le paradoxe entre la recherche basée sur les besoins médicaux

actuels contre l'incertitude des futurs besoins médicaux. Les obstacles et les facilitateurs identifiés devraient être considérés pour l'élaboration de futures politiques de gestion responsable des antibiotiques.

Dans le **Chapitre 6**, nous avons mené une étude de cas pour traiter (I) les options de traitements antibiotiques pour la bactériémie à *Staphylococcus aureus* (SAB) ; (II) la situation et les priorités pour le pipeline antibiotique pour assurer l'accès à des antibiotiques efficaces pour SAB ; et (III) les stratégies d'utilisation responsable des antibiotiques pertinents pour la gestion clinique de SAB.
Des informations ont été recueillies depuis différentes sources dont les notices d'antibiotiques disponibles, des directives de traitements antibiotiques, un manuel reconnu et une base de données d'essais cliniques. L'étude de cas a révélé que les options de traitements antibiotiques actuelles contiennent seulement trois classes de médicaments (bêta-lactamines, glycopeptides et lipopeptides) dont deux couvrent aussi les *S. aureus* résistants à la méthicilline (SARM) (glycopeptides, lipopeptide). L'analyse du pipeline antibiotique et des essais cliniques en cours a révélé que plusieurs nouveaux antibiotiques avec une couverture pour *S. aureus* (incluant SARM) ont été développés dans la dernière décennie (2009-2019). Cependant aucun n'appartient à une nouvelle classe antibiotique ou ne possède une efficacité supérieure. Leur plus-value clinique pour SAB reste à prouver.
L'utilisation responsable des antibiotiques pour le traitement de SAB a été illustrée avec onze indicateurs de qualité développés dans le **Chapitre 3**. L'étude de cas souligne le besoin de prise de conscience d'un arsenal antibiotique limité pour orienter la R&D vers le développement de nouveaux antibiotiques efficaces pour le traitement de SAB. En attendant, l'utilisation responsable des antibiotiques devrait préserver l'efficacité des antibiotiques actuellement disponibles pour traiter SAB.

Dans le **Chapitre 7**, nous présentons la discussion générale de cette thèse. Nous résumons les résultats principaux et les abordons dans le contexte de développements et travaux contemporains à cette thèse. Nous traitons aussi les réflexions méthodologiques. Finalement, les recommandations suivantes ont été formulées :

Pratique

- Les établissements de santé devraient employer la définition et les indicateurs de qualité dans leur pratique quotidienne pour augmenter l'utilisation responsable des antibiotiques.
- Les professionnels de santé devraient être formés et sensibilisés à l'utilisation responsable des antibiotiques.
- Les professionnels de santé devraient améliorer la communication avec les patients sur l'utilisation responsable des antibiotiques pour encourager l'implication des patients.

Politique

- Les politiques de gestion responsable des antibiotiques internationales devraient être poursuivies et devraient se concentrer sur l'emploi de mesures standardisées pour évaluer la qualité et la quantité d'antibiotiques utilisés.
- La prise de conscience du besoin d'actions multidisciplinaires et multisectorielles pour faire face à l'ABR doit être augmentée.
- L'objectif et les priorités de l'approche multisectorielle pour faire face à l'ABR doivent s'accorder.

Recherche

- La collaboration multidisciplinaire et multisectorielle sur l'utilisation responsable des antibiotiques devrait être évaluée.
- Les indicateurs de qualité pour l'utilisation responsable des antibiotiques devraient être employés en tant que mesures de résultats pour des études de bonne gestion des antibiotiques (ou *antibiotic stewardship*).
- Des études de cas sur les maladies infectieuses devraient être réalisées plus souvent pour illustrer les conséquences de l'antibiorésistance sur la disponibilité d'antibiotiques efficaces. De plus, les études de cas aident à mettre en lumière les besoins médicaux non satisfaits (c.-à-d. de nouvelles classes antibiotiques ou des antibiotiques avec de nouveaux mécanismes d'action) et le besoin de pratiques d'utilisation responsable des antibiotiques.

Conclusion finale

Cette thèse présente les résultats d'une large exploration de l'utilisation responsable des antibiotiques pour laquelle beaucoup de différents stakeholders, impliqués de la molécule antibiotique au médicament prescrit, ont été consultés. Ces résultats contribuent à l'ensemble des connaissances sur la complexité de l'utilisation responsable des antibiotiques. Les résultats de cette thèse s'inscrivent dans un contexte de prise de conscience grandissante des implications sociétales de l'ABR et du besoin d'actions multi-sectorielles pour faire face au problème.

Appendices

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PhD Portfolio
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Data Management

Data management refers to the collection, handling and storage of data in a transparent and reliable manner.

Data collection

- All participating stakeholders gave consent for participation to the studies reported in this thesis.
- Written informed consent was obtained from the participants of the interview studies (Chapters 4* and 5).
- Medical ethical approval was thought for the study involving patients (Chapter 4*). Medical ethics committees were consulted and approval was obtained in all participating hospitals. In the Netherlands, the ethics committee of the region Arnhem-Nijmegen (Commissie Mensgebonden Onderzoek regio Arnhem-Nijmegen) was consulted (application number 2016-2438). In Belgium, the ethics committee (Ethische Toetsingcommissie) of the Jessa Hospital was consulted (application number B243201628932).

Data handling

- Questionnaire (Chapters 2 and 3) and interview data (Chapters 4 and 5) were coded before data analysis.
- The audio files of the interviews (Chapters 4 and 5) were deleted after transcription and data analysis.
- For transparency purposes, the consulted stakeholders in Chapters 2, 3 and 5 were listed with full name and affiliation in the acknowledgment sections and/or the supplementary material sections of the publications. All stakeholders were informed about this procedure and gave consent prior to the submission of the manuscripts.

Data storage

- The hard copy informed consent forms of patients interviewed in Chapter 4* are stored in a locked archive of the Radboudumc, department of Internal Medicine.
- The data files of the work presented in this thesis and the digital informed consent forms of stakeholders interviewed in Chapter 5 are stored on the Radboudumc, department of Internal Medicine server (\\Umcms35\aig_opslag$). Access to these files is limited to authorised personnel (i.e., the secretarial office of the department of Internal Medicine).
- The data generated or analysed in this thesis are included in published articles. Requests for additional data can be made to the corresponding authors. A suitable way to share the data will then be sought.

* Of note, this data management plan is limited to the data collected by the author of the thesis, thus limited to the interviews performed with patients in the Netherlands and Belgium.

PhD Portfolio

Name	Annelie Alicia Monnier
Departments	Internal Medicine and Scientific Center for Quality of Healthcare (IQ healthcare), Radboudumc Faculty of Medicine and Life Sciences, Hasselt University
Graduate School	Radboud Institute for Health Science (RIHS)
PhD period	2014 – 2018

Courses	Year	ECTS
RIHS introductory course, Radboudumc, Nijmegen, the Netherlands	2015	1
Literature searches and systematic reviews, Medical library of the Radboudumc in collaboration with prof. dr. M.E. Hulscher, Nijmegen, the Netherlands	2015	0.5
Management and control of health care-associated bloodstream infections, European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Copenhagen, Denmark – *supported by an ESCMID travel grant*	2015	1
Achieving your goals and performing more successfully in your PhD, Radboud University, Nijmegen, the Netherlands	2015	1.5
Scientific integrity, Radboudumc, Nijmegen, the Netherlands	2015	1
Training in qualitative research methods, IQ Healthcare, Radboudumc, Nijmegen, the Netherlands	2016	0.5
Refresher course in statistics for PhD candidates, Radboud University, Nijmegen, the Netherlands	2016	1.5
Antibiotic stewardship, ESCMID Study Group for Antimicrobial StewardshiP (ESGAP), Ijmuiden, the Netherlands	2016	1
The art of presenting science, Radboud University, Nijmegen, the Netherlands	2016	1.5
Qualitative research methods and analysis, Radboud University, Nijmegen, the Netherlands	2016	3
Basic course for clinical investigators (eBROK), Netherlands Federation of University Medical Centres (NFU), the Netherlands	2017	1.5
PhD in the lead (pilot programme), Radboudumc, Nijmegen, the Netherlands	2017	2.5
Introduction to bioethics (online course), the Kennedy Institute of Ethics, Georgetown University, Washington, D.C., United-States	2018	1
Scientific writing for PhD candidates, Radboud University, Nijmegen, the Netherlands	2018	3
Analytic storytelling, Radboud University, Nijmegen, the Netherlands	2018	1

Courses	Year	ECTS
Career guidance for PhD students, Radboud University, Nijmegen, the Netherlands	2018	1
ESCMID observership, European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden	2018	2

Conferences, symposia and expert meetings	Year	ECTS
4th IQ Healthcare conference, Nijmegen, the Netherlands	2014	0.25
25th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Copenhagen, Denmark	2015	1
Conference 'Fighting antimicrobial resistance: a One Health perspective', The Dutch Pharmaceutical Law Association (VFenR), Amsterdam, the Netherlands – *on behalf of prof. dr. I.C. Gyssens*	2015	0.5 [a]
Expert meeting with the 'Antibiotic resistance' committee, Ministry of Health, Welfare and Sport, The Hague, the Netherlands – *on behalf of prof. dr. I.C. Gyssens*	2015	0.5 [a]
26th ECCMID, Amsterdam, the Netherlands	2016	1.5 [a]
Expert meeting on EU guidelines on the prudent use of antimicrobials in human medicine, ECDC, Stockholm, Sweden – *on behalf of prof. dr. I.C. Gyssens*	2016	1.5 [a]
Annual general assembly, DRIVE-AB project, Oslo, Norway	2016	1 [b]
Symposium on antibiotic resistance, the Ministry of Health, Welfare and Sport, The Hague, the Netherlands	2016	0.25
Science day 'Infectious diseases & global health', Radboud Center for Infectious diseases (RCI), Nijmegen, the Netherlands	2016	0.5 [c]
27th ECCMID, Vienna, Austria – *supported by an ESCMID travel grant*	2017	1.5 [b]
Debate on antimicrobial resistance, European Parliament, Brussels, Belgium	2017	0.1
Final conference, DRIVE-AB project, Brussels, Belgium	2017	1 [b]
Biannual meeting, i-4-1-Health project, Ghent, Belgium	2017	0.5
Conference 'Antibiotic resistance and elderly care', the Dutch National Institute for Public Health and the Environment (RIVM), Utrecht, the Netherlands	2017	0.25
Science day 'Infectious diseases & global health', RCI, Nijmegen, the Netherlands	2017	0.5 [c]
28th ECCMID, Madrid, Spain	2018	1.5 [b]
Conference 'Antibiotic surveillance: from data to action', the Dutch National Institute for Public Health and the Environment (RIVM), Amersfoort, the Netherlands	2018	0.25

Conferences, symposia and expert meetings	Year	ECTS
Scientific symposium, Innovative Medicines Initiative (IMI), Brussels, Belgium – *supported by an IMI travel grant*	2018	1 [b]
Others		
Various workshops (e.g., Radboudumc, Radboud University)	2014-2018	1.6
Various seminars and lectures (e.g., Radboudumc, Radboud University, Hasselt University)	2014-2018	2.6
Board member of PhD Organisation Nijmegen (PON)	2015-2016	1
Reviews of scientific publications	2016-2017	0.2
Study group 'Principles of antibiotic prescribing' for bachelor medical students, Hasselt University, Belgium	2018	0.5
TOTAL		**44**

Legend: [a] Oral presentation; [b] Poster presentation; [c] Laptop presentation.

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Annelie, Augustus 2020

Curriculum Vitae

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2008	**Baccalaureat Scientifique**, with honors *Lycée Val de Garonne, France*
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Publication List

This thesis:

Monnier AA, Tacconelli E, Årdal C, Cavaleri M, Gyssens IC. A case study on *Staphylococcus aureus* bacteraemia: available treatment options, antibiotic R&D and responsible antibiotic use strategies. JAC Antimicrob. Resist. 2020; 2(2).

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