JAC Antimicrob Resist
doi:10.1093/jacamr/dlab074

JAC-Antimicrobial Resistance

Antimicrobial guidelines in clinical practice: incorporating the ethical perspective

Merel Lambregts [1]*, Babette Rump [2], Fabienne Ropers[3], Martijn Sijbom [4], Mariska Petrignani[5]†, Leo Visser[1], Martine de Vries[6] and Mark de Boer[1]

[1]Department of Infectious Diseases, Leiden University Medical Center, Albinusdreef 2, 2333ZA, Leiden, The Netherlands; [2]National Institute of Public Health and the Environment, Centre for Infectious Diseases Control (RIVM-LCI), Antonie van Leeuwenhoeklaan 9, 3721MA, Bilthoven, The Netherlands; [3]Department of Epidemiology, Biostatistics and Bioinformatics, Amsterdam University Medical Center, Meibergdreef 9, 1105AZ, Amsterdam, The Netherlands; [4]Department of Public Health and Primary Care, Leiden University Medical Center, Albinusdreef 2, 2333ZA, Leiden, The Netherlands; [5]Department of Infectious Diseases, Haaglanden Municipal Health Service, Westeinde 128, 2512HE Den Haag, The Netherlands; [6]Leiden University Medical Center, Department of Medical Ethics and Law, Albinusdreef 2, 2333ZA, Leiden, The Netherlands

*Corresponding author. E-mail: m.m.c.lambregts@lumc.nl
†Present address: Amsterdam Municipal Health Service, Amsterdam, The Netherlands.

Received 16 December 2020; accepted 23 April 2021

Introduction: Guidelines on antimicrobial therapy are subject to periodic revision to anticipate changes in the epidemiology of antimicrobial resistance and new scientific knowledge. Changing a policy to a broader spectrum has important consequences on both the individual patient level (e.g. effectiveness, toxicity) and population level (e.g. emerging resistance, costs). By combining both clinical data evaluation and an ethical analysis, we aim to propose a comprehensive framework to guide antibiotic policy dilemmas.

Methods: A preliminary framework for decision-making on antimicrobial policy was constructed based on existing literature and panel discussions. Antibiotic policy themes were translated into specific elements that were fitted into this framework. The adapted framework was evaluated in two moral deliberation groups. The moral deliberation sessions were analysed using ATLAS.ti statistical software to categorize arguments and evaluate completeness of the final framework.

Results: The final framework outlines the process of data evaluation, ethical deliberation and decision-making. The first phase is a factual data exploration. In the second phase, perspectives are weighed and the policy of moral preference is formulated. Judgments are made on three levels: the individual patient, the patient population and society. In the final phase, feasibility, implementation and re-evaluation are addressed.

Conclusions: The proposed framework facilitates decision-making on antibiotic policy by structuring existing data, identifying knowledge gaps, explicating ethical considerations and balancing interests of the individual and current and future generations.

Introduction

Worldwide, antimicrobial therapy is the cornerstone in the management of patients with bacterial infections. Guidelines on empirical antibiotic therapy are subject to constant revision, for example in response to new scientific knowledge, advancing clinical understanding and changing epidemiology. Identifying the optimal empirical antimicrobial therapy has always been a challenge, but with the emergence of antimicrobial resistance (AMR) it is becoming an even more complex issue.

When antimicrobial resistance rates increase, the question arises whether the empirical therapy for a specific infectious disease should be adjusted to include a broader spectrum. Scientific and clinical as well as ethical arguments need to be taken into account and integrated in antimicrobial policymaking. Upscaling an antibiotic regimen may have important consequences for the individual patient in terms of effectiveness and toxicity, as well as for the population at large. Today's antimicrobial use impacts the health of both current and future societies, as antimicrobial

consumption is the major driver of AMR. As a result, antibiotic effectiveness is decreasing and ultimately a post-antibiotic era with pan-resistant pathogens is lurking.[1,2] Nevertheless, there is no clearly defined antimicrobial resistance threshold, i.e. a percentage, above which a more broad spectrum treatment should be adopted in routine practice, potentially—and acceptably—at the expense of future generations.[3]

It is untenable to expect doctors to balance this trade-off during individual patient encounters, stressing the importance of guidelines for the treatment of infectious diseases. Remarkably, these guidelines rarely make explicit the ethical considerations that lie at the base of their recommendations.[4] This may be explained by the complexity and multitude of ethical issues concerned.[5]

A framework to guide these complicated decisions, making the arguments explicit and facilitating ethical judgements, has not been available so far. In the literature, local microbiological resistance rates are the predominant argument for antibiotic policy-making, followed by disease severity and the attributable risk of developing future resistance.[6–10] Multiple publications on the ethical challenges related to empirical antibiotic therapy provide valuable insight into the relevant ethical principles.[11,12] However, these theoretical exercises have not yet been translated into a practical framework on how to balance benefits and harms of a proposed alteration in empirical treatment, incorporating both clinical and epidemiological data and the interests of current and future generations.

In this article we propose a method to support antibiotic policy and guideline committees when deciding on antibiotic therapy guidelines, incorporating both epidemiology and ethics.

Methods

In this study a developmental approach was taken, with the primary aim to construct a conceptual framework that is complete and practical, whilst acknowledging different stakeholders and addressing the ethical issues related to antibiotic policy. The framework was developed and evaluated through an iterative process, outlined in Figure 1.

Development of the preliminary framework

The developmental panel was formed by a pharmacist (B.H.), an internist/infectious diseases physician (M.L.), a member of the national antibiotic policy organization (M.d.B.), a general practitioner (M.S.), a public health physician (M.P.) and two medical ethicists (B.R. and M.d.V.). General themes regarding antibiotic therapy, relevant for any discussion over optimal empirical therapy for clinical management of patients with bacterial infections, were identified, based on available literature and experience of the panel members. Secondly, these themes were categorized and translated into specific framework elements. The importance of each element and the preferable order of elements were discussed in group discussions with the developmental panel. This resulted in a preliminary framework, consisting of three phases: data exploration, ethical deliberation and evaluation.

Evaluation and optimization of the framework

The applicability of the preliminary framework to real-life clinical practice was assessed by applying the framework to policy dilemmas in healthcare institutions. The dilemmas used for this evaluation were collected through an online survey among relevant regional stakeholders, including hospitals, primary care offices, long-term care facilities, pharmacies and municipal health services. The dilemmas were discussed in the panel group and the arguments were compared with elements of the preliminary framework.

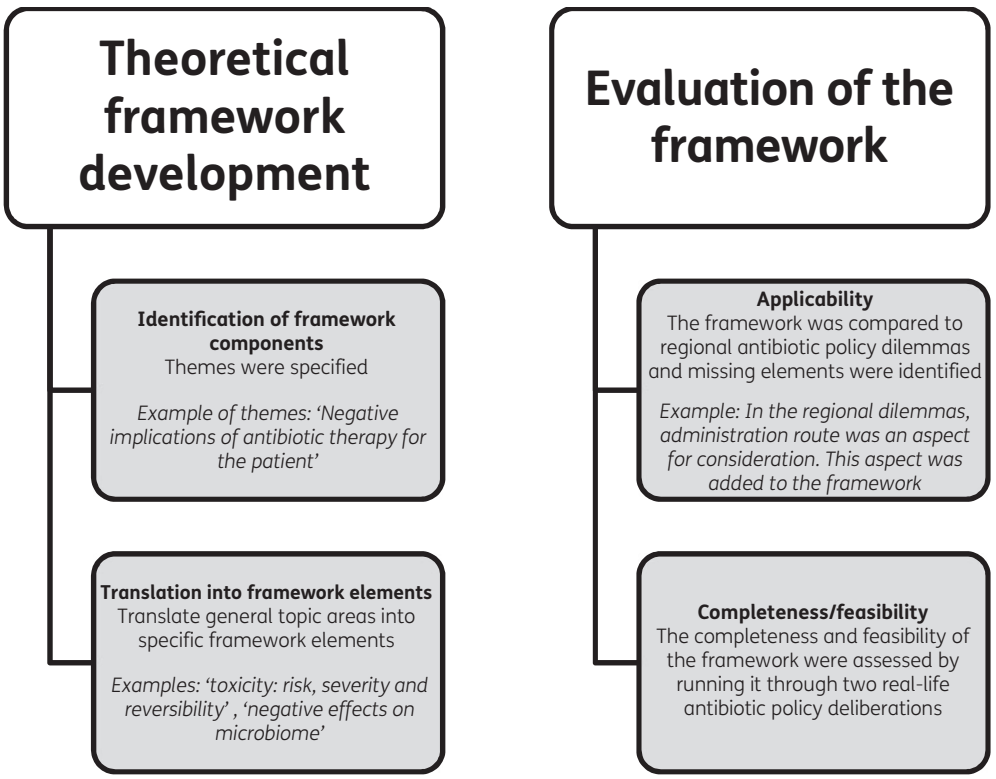

Figure 1. Construction of the framework.

Therapeutic dilemma

In a local hospital, the current guideline for treatment of sepsis is cefuroxime combined with gentamicin. However, a local analysis performed by the microbiology department shows that resistance to both antimicrobial agents is increasing in Gram-negative pathogens. The current resistance rate of Gram-negative pathogens in blood culture samples is 8.8%. Resistance to carbapenems is very rare. The question presented to the antibiotic policy committee was whether empirical treatment (awaiting cultures and susceptibility patterns) should be changed to a carbapenem.

Prophylactic dilemma

In a local hospital, the guideline for antibiotic prophylaxis for prosthetic joint implantation following low energetic fractures is cefazolin. Despite prophylaxis, 5%–10% of patients develop a postoperative wound infection and/or prosthetic joint infection (PJI). Cultures often reveal pathogens that are not covered by the current prophylactic therapy, e.g. Gram-negatives and anaerobic pathogens. The question presented to the antibiotic policy committee is whether the prophylactic therapy should be adjusted to a broader spectrum one, more specifically a second-generation cephalosporin combined with metronidazole, to prevent wound infection but more importantly PJI.

Figure 2. Antibiotic policy cases.

Newly identified elements were added to the framework, aiming for an optimal fit to the clinical need.

Subsequently, the completeness and feasibility of the framework was tested by applying it in two separate moral deliberation sessions: one prophylactic and one therapeutic dilemma (Figure 2). To this end, a moral deliberation group was composed representing all relevant stakeholders in the context of developing antimicrobial treatment guidelines: patient, healthy individual, pharmacist, specialist medical microbiology, hospital physician, infectious disease consultant, nursing home medical specialist, general practitioner, public health specialist and hospital manager (Appendix S1, available as Supplementary data at *JAC-AMR* Online). Additional stakeholders were invited to the moral deliberation according to the type of dilemma and setting. For example, a surgeon was invited for a pre-operative prophylaxis dilemma. The moral deliberation sessions were moderated by a medical ethicist (B.R.).

The two sessions were recorded (transcript verbatim) with permission of the participants and analysed by two researchers (B.R./M.L.). The aim of the analysis was to assess the feasibility and completeness of the preliminary framework. Arguments were coded and categorized by the two researchers and inconsistencies were resolved through discussion. ATLAS.ti statistical software Version 8.4.18 (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany) was used to perform these analyses.[13] The conceptual framework was thereafter optimized to include all additionally identified arguments/aspects.

Results

The framework

Figure 3 (Figure S1 for the abbreviated version) presents the proposed framework for a deliberation on antibiotic policy. The framework outlines the process of data evaluation and decision-making in which subsequent phases can be recognized. The first phase is a factual data exploration (IA) and evaluation (IB). The second phase is an ethical deliberation in which data and perspectives are weighed and the policy of moral preference is formulated. In the final phase (III), feasibility, implementation and re-evaluation are addressed.

Preparation (not in the figure)

The deliberation session is preceded by a preparation phase, aiming to identify and involve stakeholders and retrieve the data needed for phase I of the deliberation session. Great care is taken to address the needs of those stakeholders without a medical background, notably representatives of the patient council or civilians. In anticipation of a knowledge gap that may hamper participation, all participants are provided with additional basic background information, to enable all stakeholders to actively participate in the discussion.

Phase I: data exploration (IA) and evaluation (IB)

During the first phase of the deliberation, the case is summarized and further explained. The available data from the preparation phase are reviewed and structured in four individual steps, which are described in Table 1. This includes factual information about patient population, setting and syndrome. The anticipated health gain of the proposed alternative and the number needed to treat (NNT) with antibiotics to prevent one adverse outcome are estimated. Furthermore, the harm of antibiotic policy on an individual and societal level are addressed. Finally, possibilities for

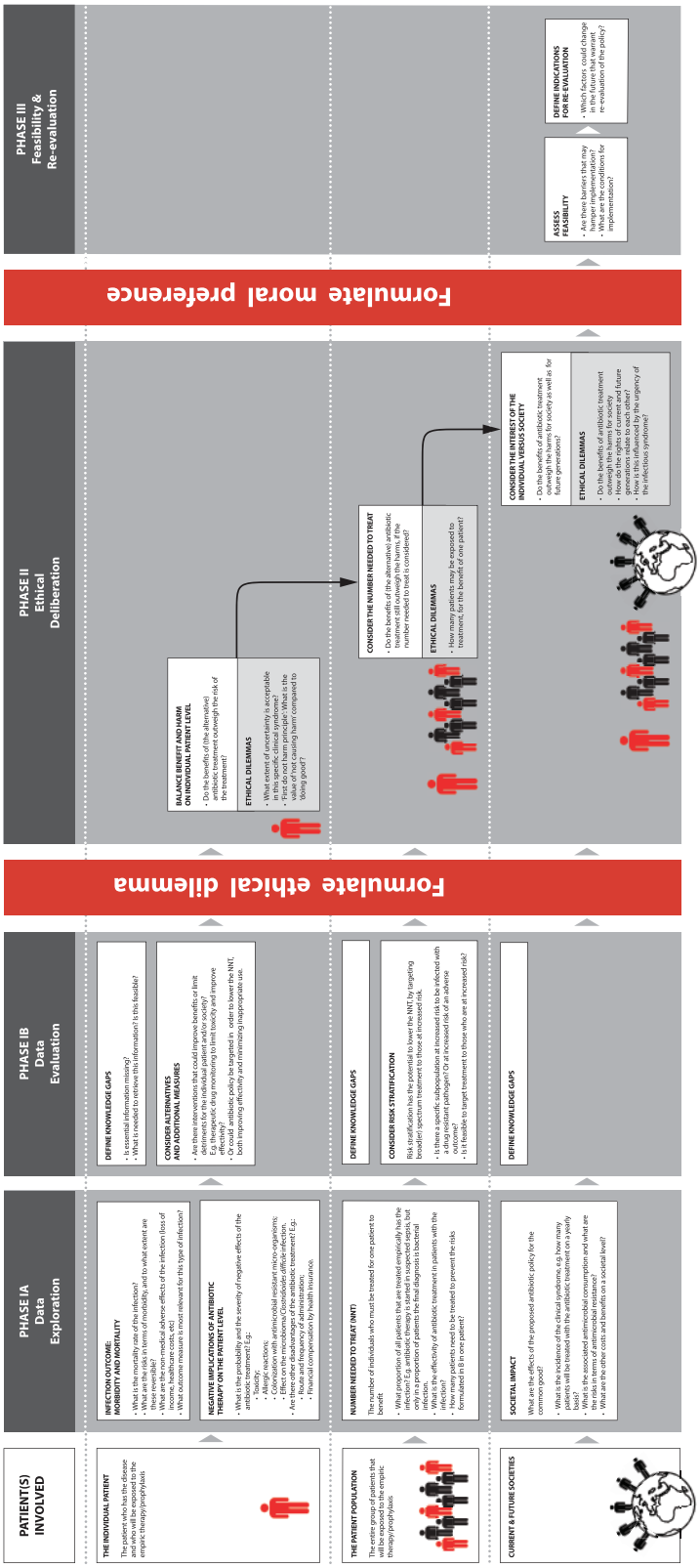

Figure 3. The final framework on dilemmas in antibiotic policy.

Table 1. Factual data exploration and evaluation

Factor	Description	Example[a]
Case summary	Describe the patient population, the setting and the dilemma. *Which patients will the guideline apply to? Can a subpopulation be identified?* *What is the setting? E.g. general practice, hospital, long-term care facility.*	In a local hospital the guideline for treatment of sepsis is cefuroxime combined with gentamicin. However, a local analysis of blood culture samples shows that the resistance rates for this combination is rising in Gram-negative pathogens. The question presented is whether empirical treatment (awaiting cultures) should be changed to a carbapenem. Population: adult patients that present at the emergency department of a Dutch hospital with suspected community-acquired sepsis.
1. Infection outcome: morbidity and mortality	Describe the most important outcome measures. *What is the risk of the clinical syndrome in terms of morbidity and mortality? What are the non-medical detriments?*	The clinical syndrome of sepsis is diverse, with mortality ranging from 10% to 52%, depending on subpopulation and severity. There can be long-term sequelae, including chronic kidney dysfunction and ICU-acquired weakness with impact on quality of life.
2. Negative implications of antibiotic therapy	What are the negative effects of the antibiotic treatment on the individual patient level? Consider probability and severity. *Relevant detriments are toxicity, allergic reactions, future infections with MDR organisms and impact on the microbiome. Practical disadvantages, such as dosing, route of administration and costs, may also be relevant.*[b]	Gentamicin is oto- and nephrotoxic. It is only administered in the empirical time window, limiting toxicity. Toxicity in meropenem and cefuroxime is rare. Meropenem covers a broader spectrum, including anaerobes, and impacts the microbiome more than the cefuroxime/gentamicin combination. The risk of *Clostridioides difficile* infections and candidaemia is therefore higher. Antibiotic therapy selects drug-resistant pathogens/resistance genes in the host and is accompanied by a risk of infections with MDR microorganisms in the future. The effect is most pronounced in the months following antibiotic therapy. All therapies are administered IV and are covered by health insurance.
3. Number needed to treat	How many patients will have to be treated with the proposed treatment to prevent the risks defined in step 2? *To answer this question: what proportion of the patients that will receive the empirical treatment truly has the infection? How effective is antibiotic treatment in averting morbidity and mortality in this patient population (see 1)?*	Of all patients that present with sepsis, 6.7% have blood cultures positive for a Gram-negative pathogen. Resistance to cefuroxime/gentamicin is 8.8%. Thus, 170 patients would have to be treated with a carbapenem to treat one additional patient effectively. This does not account for (potentially severe) Gram-negative bacterial infections without bacteraemia, therefore, the actual NNT will be lower. Management of sepsis comprises more than antibiotic therapy only (fluid resuscitation, source control, etc.). Evidence of the magnitude of the effect of adequate empirical antibiotic therapy on outcome is conflicting, but is presumed essential, especially in severe sepsis.
4. Societal impact	What are the effects of the proposed antibiotic policy for the common good? *What is the incidence of the clinical syndrome, e.g. how many patients will be treated with the antibiotic treatment on a yearly basis? What is the associated antimicrobial consumption and what are the risks in terms of antimicrobial resistance? What are the other costs and benefits on a societal level?*	Empirical treatment is relatively short (24–48 h). However, because of the frequency of sepsis, the associated antibiotic consumption is moderate to high. According to estimations, the incidence of sepsis is 13 000 patients/year in the Netherlands. Meropenem is a reserve antimicrobial agent, meaning it should be prescribed with caution and reserved for strict indications. It is impossible to quantify the effect of routine administration of meropenem for sepsis on the emergence of resistance in the Netherlands. There will be an effect, and it may lead to treatment difficulties for patients with Gram-negative infections in the (near) future. At the moment alternatives to meropenem are limited, but the future may bring new treatment strategies.
Alternatives, risk stratification, and additional measures	Are there interventions that could improve benefits or limit detriments for the individual patient and/or society?	According to local data, risk factors for a cefuroxime/gentamicin-resistant pathogen are prior colonization with an MDR pathogen and recent antibiotic therapy. Restricting carbapenems to

Continued

Table 1. *Continued*

Factor	Description	Example[a]
	For example, therapeutic drug monitoring to limit toxicity and improve effectiveness. Or could antibiotic policy be targeted in order to lower the NNT, both improving effectiveness and minimizing inappropriate use?	patients with risk factors of cefuroxime/gentamicin resistance would result in an estimated adequacy rate of 95% to 99%, depending on the strategy. Compared with treating all patients with a carbapenem empirically, the NNT with a carbapenem in the targeted approaches was a factor of 2.3 to 4.6 lower.[30]

[a]To exemplify the steps, the following antibiotic policy case was used.
[b]Practical issues (route of administration and dosing frequency) costs for the individual patient (health insurance coverage) were added to the framework as a result of the evaluation phase.

mitigation are addressed: is there a less burdensome alternative, e.g. is there a possibility for risk stratification in order to minimize the negative effects on an individual and/or societal level? During this review of the available data uncertainties and knowledge gaps are identified.

After this phase, the definite moral dilemma is formulated.

Phase II: ethical deliberation

In the second phase, the data acquired in phase I are weighed on both the individual patient level and a societal level. The first question is whether the benefits of an antibiotic strategy outweigh the related risks on the individual patient level. Secondly, in case of empirical therapy, proportionality is discussed: is the NNT proportional to the anticipated benefits? Thirdly the societal burden is to be considered. The following questions need to be addressed. What are the additional costs of a specific antibiotic strategy and the associated antibiotic consumption for society? What are the additional burdens in terms of antimicrobial resistance and are these in proportion to the expected benefits for the individual patients? The ethical deliberation is finalized with a conclusion on the desirability of changing the antimicrobial policy to the proposed alternative and a proposition for a course of action.

Phase III: feasibility and future evaluation

In the last phase, the feasibility of the proposed strategy is considered and whether there are factors that may hamper implementation of the proposed course of action. Finally, the key arguments that drive the preference for one policy over another are summarized. If one of these arguments would significantly change in the future, this should prompt re-evaluation of the antimicrobial policy. For example, changing epidemiology of pathogens, or newly available therapeutic agents, may shift the balances in phase II and therefore warrant re-evaluation.

Evaluation of the framework

Applicability to clinical practice

The online survey for representative ethical dilemmas resulted in a total of 24 dilemmas representing four healthcare settings (hospital $n = 13$, municipal health service $n = 2$, primary care $n = 3$, long-term care facilities $n = 6$). The 'cases' addressed mainly therapeutic dilemmas (18/24) and, to a lesser extent, prophylactic dilemmas (6/24). Two aspects of the dilemmas in the primary care setting were insufficiently addressed by the framework elements. The first considered practical issues (route of administration and dosing frequency). The second addressed financial costs for the individual patient (health insurance coverage). These shortcomings were resolved by adding two elements to the data exploration phase of the framework. No framework elements were removed in this phase.

Completeness and feasibility

Qualitative analyses of both moral deliberation sessions (Appendix S2 and Table S1) showed that all framework elements were addressed in the deliberation sessions. No additional clinical or ethical elements were retrieved that were not yet captured in the preliminary framework.

During the data exploration phase, the limited availability of data—regarding effectiveness, detriments and future implications of a certain antibiotic treatment policy—provided a challenge in both deliberation meetings. However, an approximation of the NNT to prevent one adverse outcome, and the acknowledgement of the uncertainties that accompanied the estimations and assumptions, formed an appropriate foundation for further discussion of the dilemma in the ethical deliberation phase.

Discussion

In this study, we developed a comprehensive framework for antimicrobial policymaking, that supported the integration of epidemiological data and ethical principles in antibiotic policymaking. Despite the fact that decisions on antimicrobial policy have to be taken repeatedly in various committees and healthcare institutions, little is known about the optimal approach. The fact that future generations are an important stakeholder in today's antimicrobial policy makes antibiotic guidelines unique compared with other healthcare guidelines. Remarkably, most antibiotic policy guidelines do not discuss the ethical aspects of their recommendations.[14] If these aspects are not explicitly addressed, they are unavoidably dealt with implicitly. The proposed framework aims to address the ethical challenges explicitly and transparently. To the best of our knowledge, this is the first conceptual framework that aims to facilitate the incorporation of ethical issues in antibiotic policy decision-making.

The four principles of Beauchamp and Childress

The four principles described by Beauchamp and Childress—autonomy, beneficence, non-maleficence and justice—are generally considered as the standard structure to analyse ethical dilemmas in medicine.[15] (Appendix S3). They provide an excellent starting point for a wide spectrum of medical dilemmas, but there are limitations when it comes to the applicability to antibiotic policy. They are four individual principles that lack interconnectivity and do not provide hierarchy. A second point of criticism is that the principles are unable to cover the different levels at which judgements need to be made. This limits their application to antibiotic policy dilemmas, which are multilayered, encompassing not merely the individual patient but also groups of patients and current and future societies. The proposed framework breaks the ethical dilemma down to single layers and interconnects the ethical issues involved. The four principles of Beauchamp and Childress are still interwoven in the proposed framework, but with a different approach to the concept justice. Justice is the principle that emphasizes equality among individuals, considers whether like cases are treated similarly and is concerned with global inequalities. In antimicrobial policy specifically, the concept justice is not limited to inequalities between patients with a well-defined infectious syndrome. In the framework, the benefits and harms of antibiotic policy changes are therefore visualized for different stakeholders and in different timeframes (present and future) to provide insight in the multiple dimensions of justice.

Intergenerational justice

Antibiotic effectiveness can be considered a scarce public good that must be fairly distributed both within and across generations.[16] This raises the question whether and to what extent withholding antibiotics now—which may be beneficial—is justified in order to preserve future antibiotic effectiveness. Different theoretical frameworks have been used to address this issue.[14,17–19] According to utilitarianism, the goal should be to maximize total utility of antibiotics, regardless of place and time. Are the 'antibiotic rights' of the future unidentified patients equal to that of known patients requiring antibiotic therapy today? Uncertainty regarding the burden of AMR over time, and the development of new treatment modalities, complicates this dilemma.[20,21] Some have proposed a temporal discount rate, giving more weight to the present patient and taking into account the discovery of new therapies.[19] In both deliberation sessions, the threshold of acceptable risk of irreversible damage due to inadequate empirical coverage depended on the severity of the clinical syndrome and the estimated consequences of inadequate therapy. Disease severity may justify broad-spectrum antimicrobial therapy in specific circumstances, regardless of the risk for future patients.[19,22]

In today's clinical practice, patients are generally not asked consent for being prescribed less than the maximum antibiotic therapy available.[19] Whether it is acceptable to curtail the autonomy of current patients in the interest of (future) societal health is a another dilemma in ethics. In both moral deliberation groups, all stakeholders, including patient and citizen representatives, agreed that autonomy of patients can—and should be—restricted when it comes to empirical antibiotic therapy, in order to prevent AMR-related harm to future patients. The fact that antibiotic effectiveness should be regarded a scarce good was the most important argument to support a suboptimal coverage and thus a risk of irreversible damage.

Applicability of the framework

The most widely adopted tool for guideline development is the GRADE methodology.[23] The strength of GRADE lies in a thorough analysis of the quality of available evidence and grading of the corresponding recommendations. However, there are specific aspects that are unique to antibiotic policymaking that are not optimally answered by GRADE, such as the variability of epidemiology of pathogens, the empirical nature of antimicrobial policymaking and the compelling interests of society.[24] Though the concept of equity has been added to the GRADE framework, this does not sufficiently cover the multilayered dilemma of effects on patients, patient groups and current and future societies. The proposed framework is designed to match the specific aspects of antimicrobial policymaking and is therefore complementary to GRADE.

The framework may support antibiotic policymaking on a national level. In addition, it may be employed to guide translation of national guidelines to local policy. The latter aspect is important as there are significant local differences in antimicrobial resistance rates. A structured analysis enables efficient revision of the antimicrobial policy when epidemiology changes. Furthermore, it enables benchmarking of antimicrobial policy between different healthcare institutions, despite differences in local epidemiology of pathogens.

Worldwide, there are intercultural, judicial and societal factors that impact the weight attributed to different aspects in phase II. For example, the visibility of AMR, the priority directed to antibiotic stewardship, the appreciation of moral equality of current and future patients and the handling of uncertainty may all impact the outcome of a moral deliberation.[25,26] The proposed framework was not designed to result in uniform decision-making. However, its aim and strength are that it puts forward the ethical issues interconnected with AMR, thereby advocating for these to be addressed instead of neglected or marginalized.

Strengths and weaknesses of the framework

An important strength of the proposed method is that all stakeholders are represented during the process. Patient participation is regarded one of the cornerstones of modern medicine. Involving patients and other individuals without medical training provides a relevant perspective.[27] This perspective goes unrevealed in the majority of antibiotic policy decisions that are being made today, even though it may be of additional importance because of the specific ethical aspects concerned.

The involvement of all stakeholders is time-consuming, which may hamper the feasibility of the proposed framework, especially for—often understaffed—local antibiotic committees. The proposed framework may be applied in a smaller committee. In that case, it should be acknowledged which perspectives were not represented.

A second challenge may be posed by incomplete data, making it impossible to calculate an accurate NNT, which is central in the proposed framework. When clinical data are lacking and

future risks can only be estimated, it is difficult to make up the balance.[28] However, there is no realistic prospect of filling in all knowledge gaps in the near future and clinical dilemmas need to be dealt with now, in order to prevent escalation of the emergence and spread of antimicrobial drug resistance in the (very) near future. Even in the absence of this complete information, the systematic evaluation of the available data and being able to determine the uncertainties at hand contributes to the outcome of the process.

Conclusions

As antibiotic resistance has an impact that transcends individual patients and persists over time, dilemmas in antibiotic policy can't be solved by science alone.[29] Even the most accurate epidemiological data and trials need to be complemented with value-based judgements to solve real-life dilemmas in antibiotic policy. The proposed framework supports decision-making on antibiotic policy by concretizing the dilemma, structuring existing data, identifying relevant knowledge gaps and, importantly, integrating and explicating ethical issues in the deliberation. A structured ethical assessment, especially concerning therapeutic effectiveness for future generations, deserves a prominent place in the development of guidelines on antimicrobial therapy. Ultimately thresholds of acceptable risks need to be defined.

Acknowledgements

We thank all members of the deliberation sessions for participating and providing their knowledge and experience, Julia Wubbolts for assisting with the data-analysis and Jos van den Broek for designing the framework illustration.

Funding

This project was funded by the Dutch Ministry of Health, reference number 327952.

Transparency declarations

None to declare.

Author contributions

M.L.: conception and design, literature search, framework development and revisions, qualitative data-analysis, first draft of the manuscript and revisions. B.R.: framework development, moderation of moral deliberation sessions, manuscript revisions. M.S.: development of the framework, manuscript revisions. M.P.: development of the framework, manuscript revisions. F.R.: development of the framework, manuscript revisions. L.V.: conception and design, manuscript revisions. M.d.V.: conception and design, development of the framework, manuscript revisions. M.d.B.: conception and design, development of the framework, data analysis, manuscript revisions.

Supplementary data

Appendices S1 to S3, Table S1 and Figure S1 are available as Supplementary data at *JAC-AMR* Online.

References

1 Fowler T, Walker D, Davies SC. The risk/benefit of predicting a post-antibiotic era: Is the alarm working? *Ann N Y Acad Sci* 2014; **1323**: 1–10.

2 Smith RA, M'ikanatha NM, Read AF. Antibiotic resistance: a primer and call to action. *Health Commun* 2015; **30**: 309–14.

3 Daneman N, Low DE, McGeer A *et al.* At the threshold: defining clinically meaningful resistance thresholds for antibiotic choice in community-acquired pneumonia. *Clin Infect Dis* 2008; **46**: 1131–8.

4 Weinstein MC. Should physicians be gatekeepers of medical resources? *J Med Ethics* 2001; **27**: 268–74.

5 Selgelid MJ. Ethics and drug resistance. *Bioethics* 2007; **21**: 218–29.

6 Averbuch D, Orasch C, Cordonnier C *et al.* 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. *Haematologica* 2013; **98**: 1826–35.

7 Maseda E, Gimenez MJ, Gilsanz F *et al.* Basis for selecting optimum antibiotic regimens for secondary peritonitis. *Expert Rev Anti Infect Ther* 2016; **14**: 109–24.

8 Pong AL, Bradley JS. Guidelines for the selection of antibacterial therapy in children. *Pediatr Clin North Am* 2005; **52**: 869–94.

9 File TM Jr. Appropriate use of antimicrobials for drug-resistant pneumonia: focus on the significance of β-lactam-resistant *Streptococcus pneumoniae*. *Clin Infect Dis* 2002; **34** Suppl 1: S17–26.

10 Dupont H. The empiric treatment of nosocomial intra-abdominal infections. *Int J Infect Dis* 2007; **11** Suppl 1: S1–6.

11 Leibovici L, Shraga I, Andreassen S. How do you choose antibiotic treatment? *BMJ* 1999; **318**: 1614–6.

12 Leibovici L, Paul M, Andreassen S. Balancing the benefits and costs of antibiotic drugs: the TREAT model. *Clin Microbiol Infect* 2010; **16**: 1736–9.

13 Soratto J, Pires DEP, Friese S. Thematic content analysis using ATLAS.ti software: potentialities for researchs in health. *Rev Bras Enferm* 2020; **73**: e20190250.

14 Littmann J, Rid A, Buyx A. Tackling anti-microbial resistance: ethical framework for rational antibiotic use. *Eur J Public Health* 2018; **28**: 359–63.

15 Beauchamp TL. Methods and principles in biomedical ethics. *J Med Ethics* 2003; **29**: 269–74.

16 Foster KR, Grundmann H. Do we need to put society first? The potential for tragedy in antimicrobial resistance. *PLoS Med* 2006; **3**: e29.

17 Millar M. Can antibiotic use be both just and sustainable. . . or only more or less so? *J Med Ethics* 2011; **37**: 153–7.

18 Millar M. Constraining the use of antibiotics: applying Scanlon's contractualism. *J Med Ethics* 2012; **38**: 465–9.

19 Leibovici L, Paul M, Ezra O. Ethical dilemmas in antibiotic treatment. *J Antimicrob Chemother* 2012; **67**: 12–6.

20 Coast J, Smith R, Karcher AM *et al.* Superbugs II: how should economic evaluation be conducted for interventions which aim to contain antimicrobial resistance? *Health Econ* 2002; **11**: 637–47.

21 Littmann J, Buyx A, Cars O. Antibiotic resistance: an ethical challenge. *Int J Antimicrob Agents* 2015; **46**: 359–61.

22 Leibovici L, Paul M. Ethical dilemmas in antibiotic treatment: focus on the elderly. *Clin Microbiol Infect* 2015; **21**: 27–9.

23 Guyatt GH, Oxman AD, Vist GE *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**: 924–6.

24 Weiss MJ, Hornby L, Shemie SD *et al.* GRADEing the un-GRADE-able: a description of challenges in applying GRADE methods to the ethical and

implementation questions of pediatric organ donation guidelines. *J Clin Epidemiol* 2018; **103**: 134–7.

25 Fitzpatrick F, Tarrant C, Hamilton V *et al*. Sepsis and antimicrobial stewardship: two sides of the same coin. *BMJ Qual Saf* 2019; **28**: 758–61.

26 Krockow EM, Tarrant C. The international dimensions of antimicrobial resistance: Contextual factors shape distinct ethical challenges in South Africa, Sri Lanka and the United Kingdom. *Bioethics* 2019; **33**: 756–65.

27 Parsonage B, Hagglund PK, Keogh L *et al*. Control of antimicrobial resistance requires an ethical approach. *Front Microbiol* 2017; **8**: 2124.

28 de Kraker ME, Stewardson AJ, Harbarth S. Will 10 million people die a year due to antimicrobial resistance by 2050? *PLoS Med* 2016; **13**: e1002184.

29 Hernandez-Marrero P, Martins Pereira S, de Sa Brandao PJ *et al*. Toward a bioethical framework for antibiotic use, antimicrobial resistance and for empirically designing ethically robust strategies to protect human health: a research protocol. *J Int Med Res* 2017; **45**: 1787–93.

30 Lambregts MMC, Hendriks BJC, Visser LG *et al*. Using local clinical and microbiological data to develop an institution specific carbapenem-sparing strategy in sepsis: a nested case-control study. *Antimicrob Resist Infect Control* 2019; **8**: 19.