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Rational empiric antibiotic therapy in clinical practice and policy making: uncertainties, probabilities, and ethics

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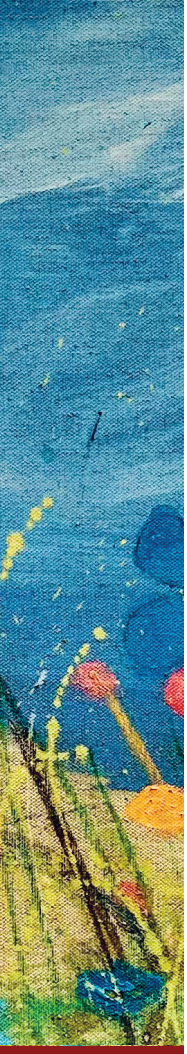

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Antimicrobial guidelines in clinical practice: incorporating the ethical perspective

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ABSTRACT

Introduction: Guidelines on antimicrobial therapy are subject to periodic revision to anticipate on 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. efficacy, 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 analyzed 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]

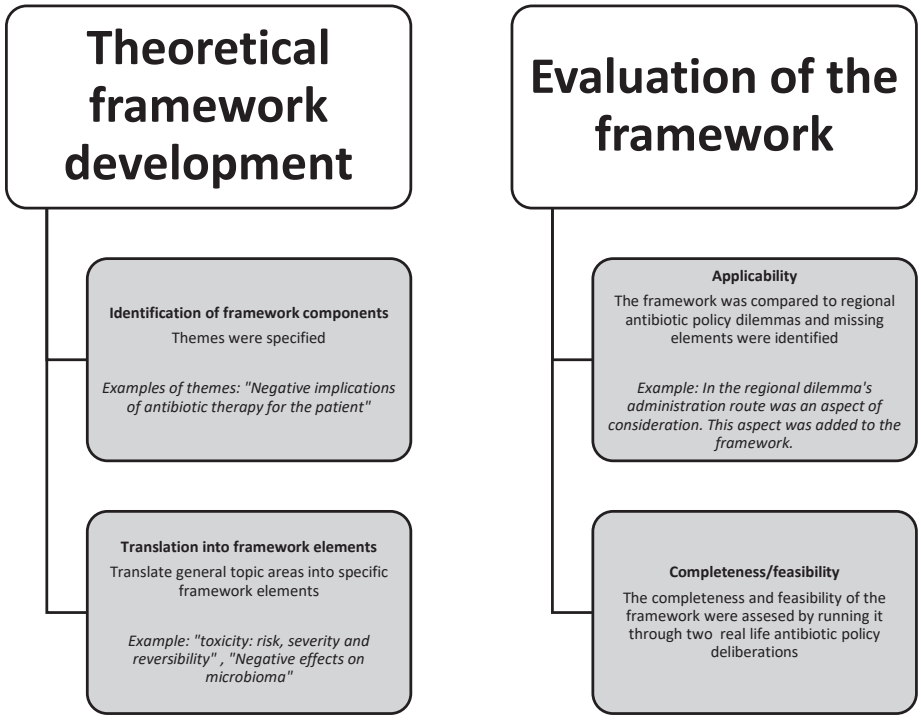
It is untenable to expect doctors to balance this trade-off during individual patient encounters, stressing the importance of guidelines for the treatment of infectious diseases. Remarkably, these guidelines rarely make explicit the ethical considerations that lie at the base of their recommendations.[4] 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 policymaking, 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.

Figure 1. Construction of the framework.



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. 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 (Box 1). 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. 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.

Box 1. Antibiotic policy cases

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 empiric 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, more specifically a second generation cephalosporin combined with metronidazole, to prevent wound infection, but more importantly PJI.

RESULTS

The framework

Figure 2 (Supplementary data for the detailed 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.

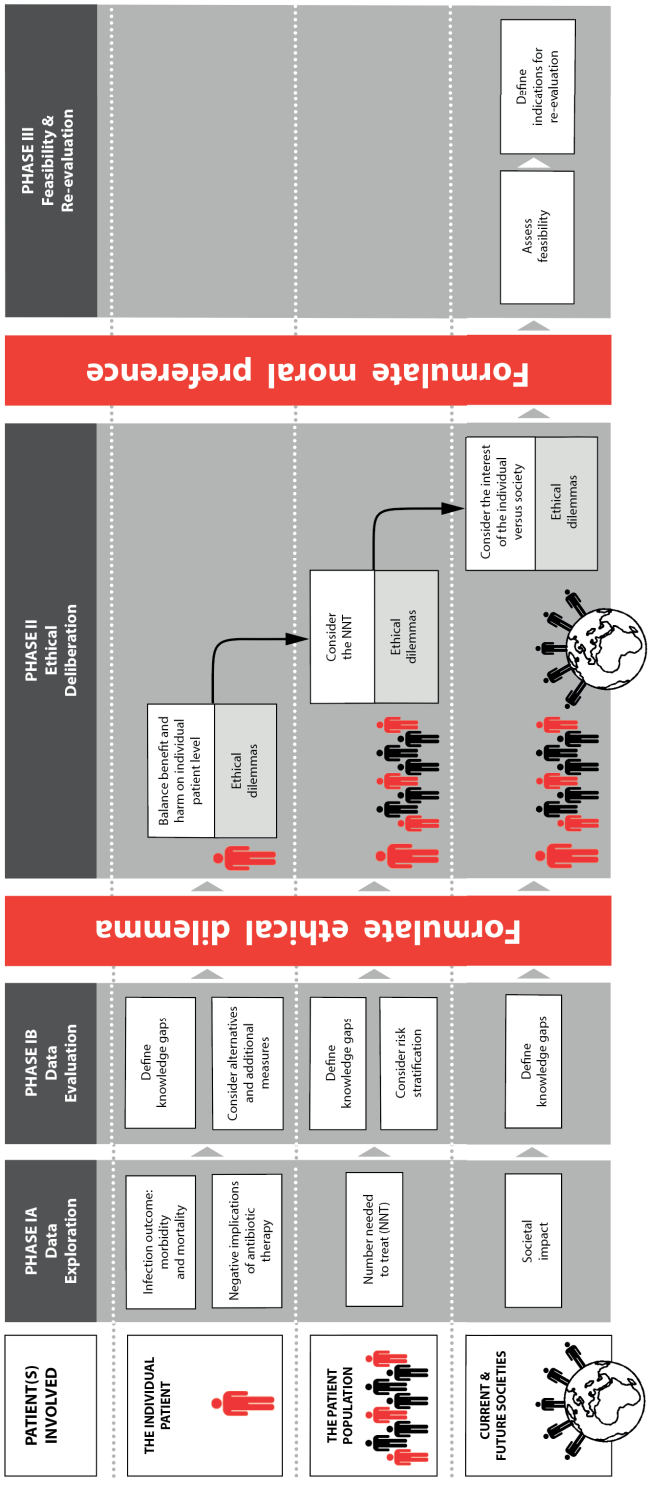


Figure 2. The final framework on dilemmas in antibiotic policy.

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 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.

Table 1. Factual data exploration and evaluation

Factor	Description	Example*
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 empiric treatment (awaiting cultures) should be changed to a carbapenem. Population: Adult patients that present at the first aid department of a Dutch hospital with suspected community acquired sepsis.
1. Infection outcome: morbidity and mortality	**Describe the most important outcome measures.** *What are 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 percent, 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 MDROs, impact on the microbioma. Practical disadvantages, such as dosing and route of administration and costs may also be relevant. ***	Gentamicin is oto- and nephrotoxic. It is only administered in the empiric time window, limiting toxicity. Toxicity in meropenem and cefuroxime is rare. Meropenem is more broad-spectrum, including anaerobes, and impacts the microbiome more than the cefuroxime/gentamicin combination. The risk of *Clostridium difficile* infections and candidemia is therefore higher. Antibiotic therapy selects drug-resistant pathogens/ resistance genes in the host and is accompanied by a risk of infections with multi-resistant micro-organisms in the future. The effect is greatest in the months following antibiotic therapy. All therapies are administered intravenously and are covered by health insurance.
3. Number needed to treat (NNT)	**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 % has positive blood cultures for a Gram-negative pathogen. Resistance to cefuroxime/gentamicin is 8.8%. 170 patients would have to be treated with 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 empiric antibiotic therapy on outcome is conflicting, but is presumed essential, especially is severe sepsis.

Table 1. Factual data exploration and evaluation (*continued*)

Factor	Description	Example*
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.*	Empiric treatment is relatively short (24/48 hours). 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 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 and additional measures	***Are there interventions that could improve benefits or limit detriments for the individual patient and/or society?*** *For example therapeutic drug monitoring to limit toxicity and improve effectivity. Or could antibiotic policy be targeted in order to lower the NNT, both improving effectivity, but minimizing inappropriate use.*	According to local data, risk factors for a cefuroxime/gentamicin resistant pathogen are prior colonization with a multidrug resistant pathogen, and recent antibiotic therapy. Restricting carbapenem for patients with risk factors of cefuroxime/gentamicin resistance, would result in an estimated adequacy rate of 95 to 99%, depending on the strategy. Compared to treating all patients with a carbapenem empirically, the NNTC in the targeted approaches was a factor 2.3 to 4.6 lower.[30]

Legend: * To exemplify the steps, the following antibiotic policy case was used: . ** 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. Abbreviations: NNT: number needed to treat.

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 (Supplementary data, 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] (Supplementary data). 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 multi-layered, 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 multi-layered 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 is-

sues 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.

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SUPPLEMENTARY DATA

Qualitative analyses of moral deliberation sessions

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.[1]

The assessment of feasibility and completeness of the preliminary framework through identification of recurrent questions and statements in the two group discussions 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 (Table S1).

On the individual patient level, the most frequently addressed framework elements regarded balancing the expected benefit and adverse effects of broader empirical treatment. Beneficence and non-maleficence were considered equally important ethical principles, as long as there is a proper balance between the (intended) benefit and the risks.[2,3] In severe sepsis, the benefit associated with appropriate treatment was considered so substantial, that toxicity may become a secondary consideration

On the population level, the NNT was a central theme in both sessions. Because of the empiric nature of the two dilemmas, a proportion of patients is exposed to an antibiotic therapy that is unnecessarily broad or from which they will not benefit at all, because their illness is not caused by a bacterial infection. At the same time, applying the standard empiric therapy, a proportion of patients is withheld potentially life-saving treatment. These aspects are reflected in the NNT, and dictated the discussion on the patient population level.

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Table S1. Summary of topics with quotes from the two moral deliberation sessions.

Phase in Framework	Topic	Quote
Patient(s) involved	The individual patient	"… What kind of patient should I think of, what kind of patient is it? If we are going to discuss this, this is important to me. Are this mainly 40 years old patients who are snatched away in in the mids of their life by the sepsis or … […]. Indeed what kind of patients, how ill are they upon admission and what are their other characteristics…?"
Phase IA	The individual patient: Infection outcome	"… In our hospital […] everyone actually just gets cefuroxime gentamicin because, even if they end up at the Intensive care unit, we are just doing fine with it…" "Based on the available microbiological data the proposed alternative treatment would target 75% of pathogens [that are not coverd by the current prophylactic therapy]"
	The individual patient: Negative implications of antibiotic therapy	"… Are there downsides on an individual level? Thus are there adverse consequences for the patient if you change the policy..?" " Well..if you have seen a few patients with refractory *Clostridium difficile* infections…"
	The patient population: Number needed to treat	"… Shouldn't we also summarize all assumptions in ms. X comment, that is with the new policy you treat 6-7 patients to prevent 1 infection…"
	Current and future societies	" There are also data that if you treat 1000 patients with a carbapenem, you could induce colonization with a resistant pathogen in 14 patients. Yes 14 out of 1000 " "Quality of care is less in patients that have to be isolated [because of colonization with a resistant pathogen]"
Phase IB	Defining knowledge gaps	"…But is all of this a problem? There is little data on that…" "..Propensity score studies have limitations ofcourse, we don't know exactly the increase in mortality as a consequence of inadequate empirc therapy."
	Consider risk stratification	"Our hospital data show that for a proportion of patients that is infected with a resistant pathogen this is predictable, risk factors being immunocompromised patients, prior hospitalization for example. You could potentially apply risk stratification…"

Table S1. Summary of topics with quotes from the two moral deliberation sessions .(*continued*)

Phase in Framework	Topic	Quote
Phase II	Balance benefit and harm on the individual patient level	" I am thinking, in many patients I know, when I do nothing, they will be fine tomorrow. In others, whatever I prescribe, he will not survive. In-between there is a large area where there is a certain benefit, we have to find the cut-off" "Not the most effective, but the best balance between advantages and disadvantages" "Based on these numbers, to treat 80 people adequately, you will induce resistance in 800 patients. […] To me that is unacceptable"
	Consider the NNT	"Patients on the ICU are given meropenem, they rarely have a resistant pathogen, but we have decided it, because we really do have our backs to the wall" "With the newly proposed prophylaxis you will have to treat 6-7 patients to prevent one post-operative infection"
	Consider the interest of the individual versus society	"… Okay, so we have patients, we have resources to help those patients. But if we take substance B the consequence might be situations such as in Tuscany or Spain […]. You also mentioned this earlieron, this aspect shouldn't we give this aspect more weight from a moral perspective than the costs or an elaboration on certain numbers..?"" " Isn't it all about what risk of mortality do you want to accept in order to save the population..?" "What is the value of one life now, compared to an entire future population in which mortality will be high because of ordinary post-operative complications, that is hard to quantify"
Phase III	Assess feasibility	"… We indeed focus strongly on todays numbers and future numbers and so on, but I think that these indeed are important for feasibility and acceptance, because if you are the one who has to implement the policy, it helps enormously to know what the effect of your actions will be…"
	Define indications for re-evaluation	"We are focusing on the 8.8 % resistance rate….but in 10 years it will be 20% or 30%, it will increase with time , at a certain point, when will we have to reconsider?"

Legend: Two moral deliberation sessions were analyzed, one regarded empiric sepsis therapy, one regarded antibiotic prophylaxis for prosthetic joint implantation. Arguments were categorized using the framework elements. The questions and statements in the third columns "Quotes" are derived from these moral deliberation sessions.

The four principles of Beauchamp and Childress: ethical areas of conflict in the moral deliberation sessions

The four principles described by Beauchamp and Childress -beneficence, non-maleficence, justice and autonomy- are generally considered as the standard structure from which to analyse ethical dilemmas in medicine.[1] In this appendix we will describe these 4 individual principles, that have not been assigned an hierarchal order.

Beneficence and non-maleficence

Beneficence is the principle to act in the best interest of the patient, balancing the benefits of treatment against the risks. Non-maleficence is avoiding the causation of harm, for example toxicity. Non-maleficence is often attributed more weight, compared to beneficence; as is reflected in the Hippocratic oath: 'first do no harm'.[2] When in conflict, the risk of adverse effects of antibiotic therapy, such as toxicity and future drug resistant infections, could be regarded more important than the beneficence of adequate therapy.[3] In the moral deliberation sessions, beneficence and non-maleficence were considered equally important ethical principles, as long as there is a proper balance between the (intended) benefit and the risks. In severe clinical infectious syndromes, the benefit associated with appropriate treatment is so great, that toxicity may become a secondary consideration.[4,5] Because of the empiric nature of the dilemmas, a proportion of patients is exposed to an antibiotic therapy that is unnecessarily broad or they will not benefit from at all, because their illness is not caused by a bacterial infection. At the same time, applying the same standard empiric therapy, a proportion of patient is withheld potentially life-saving treatment. Hence, this aspect regarding the NNT and non-maleficence dictated the discussion on the individual patient level.

Justice

The concept of Justice concerns a fair distribution of health resources. Antibiotics, or more specifically antibiotic effectiveness, is a resource which can be depleted. According to 'justice' it should be fairly distributed between people. Uncertainty regarding the burden of AMR over time, and the development of new treatment modalities, complicates this dilemma.[6,7] The fact that antibiotic effectiveness should be regarded a scarce good and interests of society should also be observed, was the most important argument to support a sub-optimal coverage and thus a risk of irreversible damage for an individual patient.

Autonomy

Whether curtailing the autonomy of patients in the interest of (future) societal health is acceptable, is a recurrent dilemma in ethics. In utilitarianism, patient autonomy is neglected, as long as it does not interfere with over-all antibiotic effectiveness.[8,9] Auton-

omy is however an important aspect of principalism. In both moral deliberation groups, all stakeholders, including patients and healthy individuals, agreed that autonomy of patients can -and should be- restricted when it comes to empiric antibiotic therapy, in order to prevent AMR related harm in future patients.

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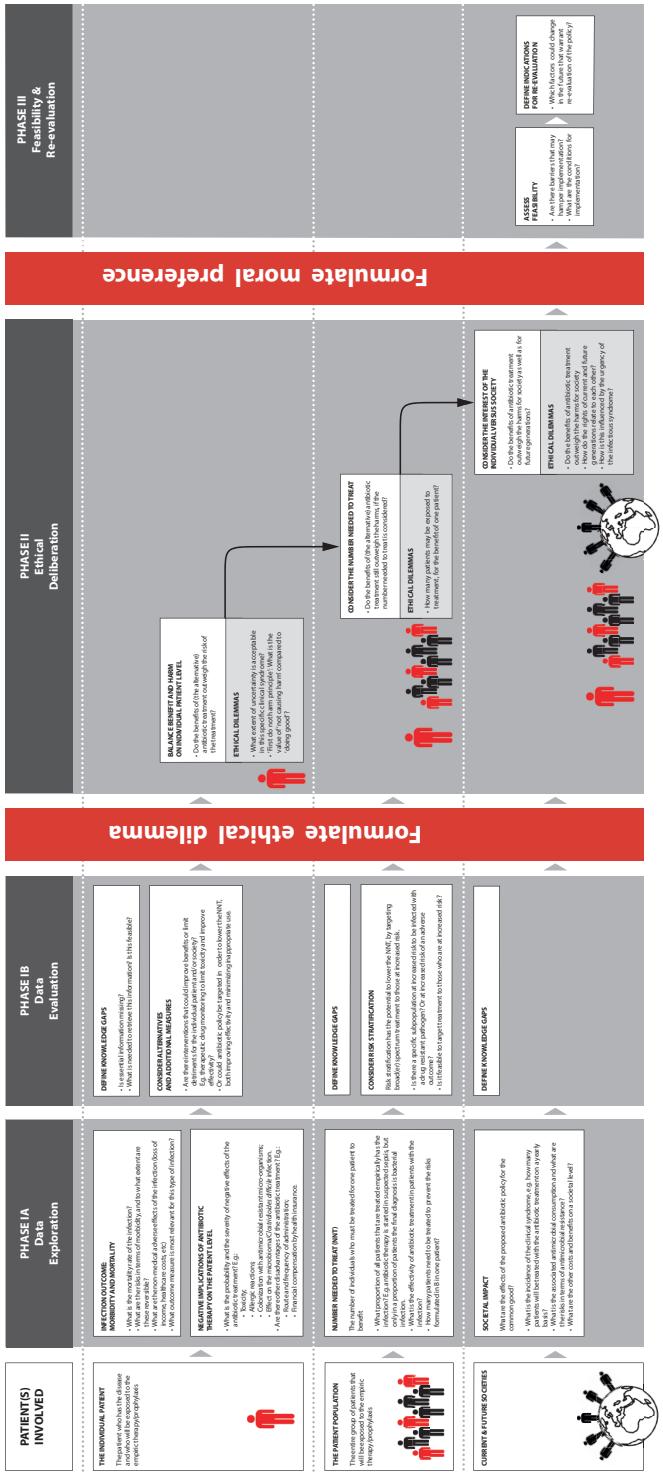
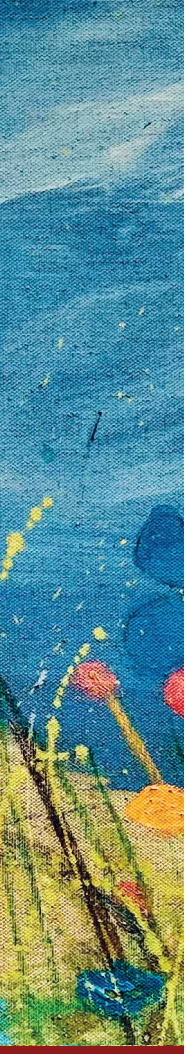
Figure S1: Detailed version of the framework on dilemmas in antibiotic policy.





Decision making in antibiotic prophylaxis: a bioethical approach

Letter

The following letter was written in response to a randomized controlled study that investigated the use of preoperative oral antibiotics in colon surgery, the ORALEV trial. In this study, patients were randomized to receive either oral prophylaxis with ciprofloxacin and metronidazole or placebo. As less surgical site infections occurred in the intervention group, the authors conclude that oral prophylaxis should be implemented in daily practice. In our letter we illustrate how using a systematic approach to decide on antibiotic therapy – as described in the first part of this Chapter- may result in a different conclusion.

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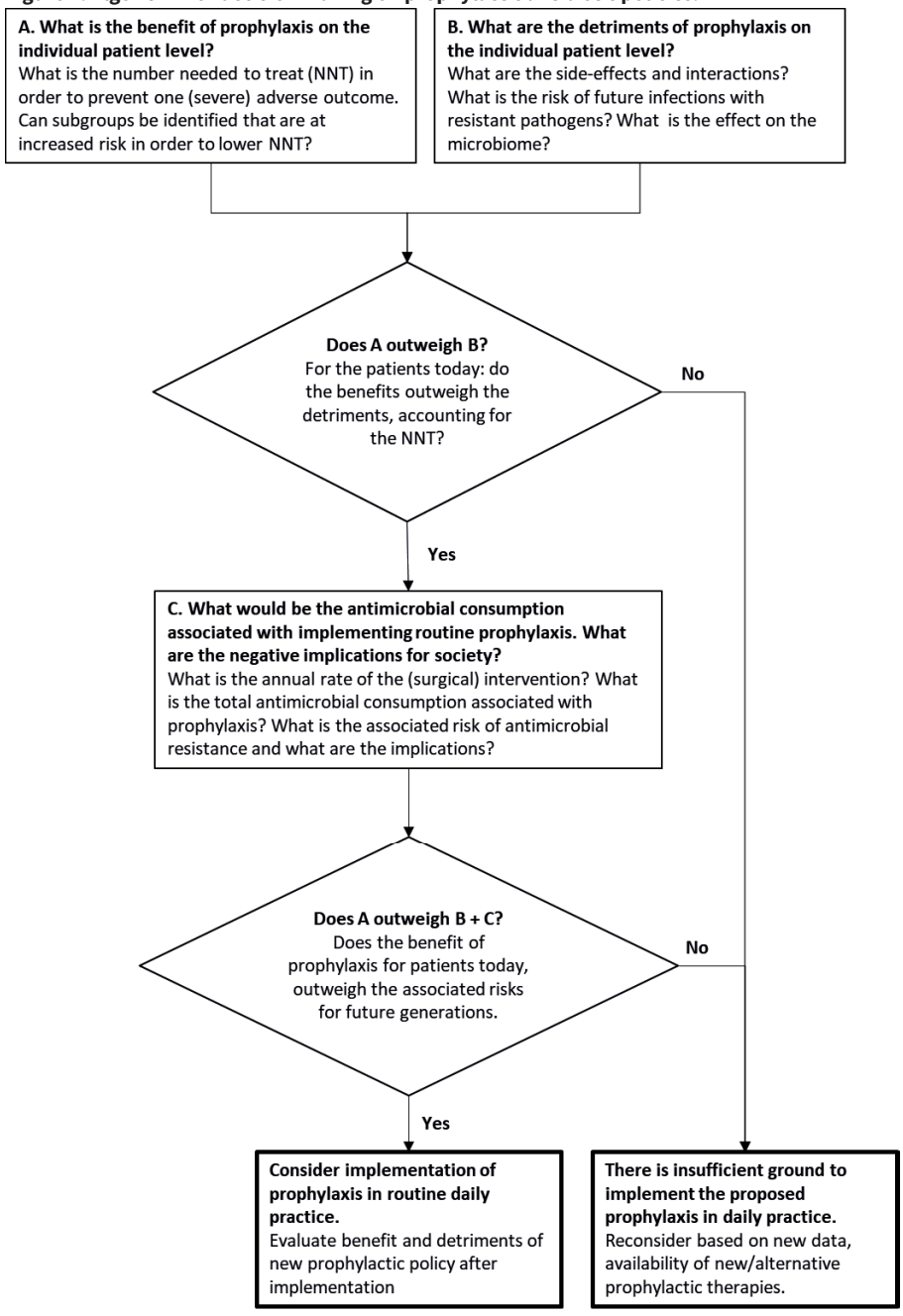
We read with great interest the Article by Eloy Espin Basany and colleagues reporting the results of the ORALEV trial, which examined the use of preoperative oral antibiotics in colon surgery.[1] The authors concluded that oral prophylaxis with ciprofloxacin and metronidazole the day before colon surgery should be routinely adopted. However, a statistically significant effect on infectious complications might not be enough to support their conclusion. To come to a change in antibiotic policy, a systematic approach is warranted, that comprises more than the effect of prophylaxis on infectious complications alone (Figure). From the data presented by Espin Basany and colleagues,[1] we calculate that the number needed to treat (NNT) to prevent one surgical-site infection (primary endpoint) is approximately 16 (95% CI 9–58), which appears low. However, most of the infections were superficial. When focusing on more severe complications—eg, deeper infections and organ space infections—the difference is small (16 of 269 patients in the control group vs seven of 267 patients in the preoperative antibiotics group) and not statistically significant. Antibiotic prophylaxis did not have any effect on the need for an intervention (drainage or re-operation) or duration of hospital stay. Furthermore, microbiological data to support or oppose the findings were not provided. Hence, it remains unclear to what extent the proposed prophylaxis prevents (serious) infectious complications. The benefit of any preventative treatment must be weighed against the side-effects across the entire exposed population. Both antibiotics used in the ORALEV trial have side effects. The safety profile of quinolones has fallen into disrepute cause of the association with vascular complications. Although in the context of 1-day preoperative prophylaxis, the effect on the microbiome will be low compared to prolonged therapy, even a single dose has an impact.[2] Even if the benefits of preoperative antibiotics outweighed the risks at the individual patient level, there is a third aspect that should be given thought. Today's guidelines have responsibilities towards future generations as well, and should safeguard the long-term efficacy of antibiotics. Even though the prophylaxis proposed in the ORALEV study is given only for 24 h, the associated antimicrobial consumption is considerable, since colon surgery is a high frequency procedure worldwide.(3) Quinolones should be prescribed with caution because of concerns about development of antibiotic resistance. Decreased susceptibility to quinolones rises mainly by single-step mutations, as reflected by increasing resistance rates globally.[4] Balancing the interests of patients with the—often opposed— interest of (near) future generations, is a substantial bioethical dilemma, but should be considered part of our professional duty.[5] As such, we believe that Espin Basany and colleagues' statement that oral prophylaxis the day before colon surgery should be routine practice worldwide appears premature.

Figure 1. Algorithm for decision making on prophylactic antibiotic policies.



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