Antimicrobial stewardship programs; a two-part narrative review of step-wise design and issues of controversy. Part II: Ten questions reflecting knowledge gaps and issues of controversy in the field of antimicrobial stewardship

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Abstract: Regardless of one's opinion on antimicrobial stewardship programs (ASPs), it is hardly possible to work in hospital care and not be exposed to the term or its practical effects. Despite the term being relatively new, the number of publications in the field is vast, including several excellent reviews of general and specific aspects. Work in antimicrobial stewardship is complex, and include aspects not only of infectious disease and microbiology, but also of epidemiology, genetics, behavioural psychology, systems science, economics and ethics, to name but a few. This review aims to take several of these aspects and the scientific evidence from antimicrobial stewardship studies and merge them into two questions: How should we design ASPs based on what we know today? and Which are the most essential unanswered questions regarding antimicrobial stewardship on a broader scale? This narrative review is written in two separate parts aiming to provide answers to the two questions. The first part, published separately, is written as a step-wise approach to designing a stewardship intervention based on the pillars of unmet need, feasibility, scientific evidence and necessary core elements. It is written mainly as a guide to someone new to the field. It is sorted into five distinct steps; (a) focusing on designing aims; (b) assessing performance and local barriers to rational antimicrobial use; (c) deciding on intervention technique; (d) practical, tailored design including core element inclusion; and (e) evaluation and sustainability. This second part formulates 10 critical questions on controversies in the field of antimicrobial stewardship. It is aimed at clinicians and researchers with stewardship experience and strives to promote discussion, not to provide answers.

Keywords: Antimicrobial stewardship, antimicrobial resistance

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Introduction

As a complement to Part I of this two-part review, which outlines some of the things we do know within the field of antimicrobial stewardship in a five-step guide, this second part highlights some of the questions in the field that remain to be definitively answered. Antimicrobial stewardship research is a comparatively young field applied to a very complex context, and there are thus several areas of uncertainty and issues of controversy. Table 1 lists 10 questions emphasizing such areas or issues. The questions have been chosen subjectively, and the list is by no means exhaustive. Furthermore, the questions are wide in scope,

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Table 1. The 10 questions posed.

1. Can antimicrobial resistance be reversed and can this reversal be obtained through ASPs?
2. Are potential aims of ASPs causally linked to overall objectives?
3. Is there a level of antimicrobial use that balances collective risk, and if so, what is it?
4. How should we address apparent differences in levels of use of antibiotics in the world?
5. How do we address the perceived sepsis/stewardship dichotomy in a balanced way?
6. How do we balance the trade-off between individual and collective risks, patient participation and essentialism?
7. Should individual dysbiosis from antimicrobials be a part of the antimicrobial stewardship discussion and what role should it play?
8. How do we balance the need for uniform methodological evidence with limited evidence for generalizability?
9. What are the potential consequences of an effective ASP on the supply of antibiotics?
10. Is there a risk of 'crowding out' effects from ASPs?

ASP, antimicrobial stewardship program.

each warranting separate reviews, and are here touched upon only briefly to stimulate further discussion. The preliminary reply given to each question is the author's personal reflection, and should thus not be read as the definite answers based on scientific evidence. During the completion of this review, two excellent reviews, including a Society for Healthcare Epidemiology of America (SHEA) white paper, have been published, reviewing knowledge gaps and research needs in antibiotic stewardshipprogrammes (ASPs) in hospital and non-hospital settings.[1,2] Some of the issues mentioned in these reviews overlap the questions in the following.

The 10 questions

1. Can antimicrobial resistance be reversed and can this reversal be obtained through ASPs?

If resistance cannot be reversed, why all the effort? The answer is straightforward. Even if reversal of resistance is deemed not feasible, just stopping or slowing down resistance development are objectives worth striving for, while at the same time aiming to improve the pipeline of antibiotics, vaccines and diagnostic measures.

Regarding potential of reversibility, the traditional theoretical assumption is that the uptake of a resistance mechanism provides a selection advantage in the presence of an antibiotic, but infers a fitness cost that, in the absence of the antibiotic, translates to a selection disadvantage.[3,4] This fitness cost is a prerequisite for reversibility of resistance, and it may be possible to predict the rate of reversibility during withdrawal of antibiotics.[5]

However, the clinical evidence for reversibility is less clear. There are quite a few studies that do show reversibility following reduction of specific antibiotics, but also others that do not.[6–10] There are modelling studies that imply that restriction in very specific situations may facilitate resistance.[11] These varying results are attributed to the complexity of the situation, including attributes of the specific bacterium, the specific antibiotic, the potential of compensatory chromosomal mutations or plasmid-mediated increases in fitness that offset fitness costs, the transmission routes, antibiotic residues in the environment, pandemics of susceptible or resistant bacteria with propensity for spread, co-carriage of other resistance determinants and resistance dilution in the population.[12,13] Moreover, there is little information on thresholds of use on a population level or on exposure levels in individuals (concentration and duration of treatment courses) that favour reversibility potential, if such can be defined.

The answer to the question can thus be a clear yes, there is potential of reversibility of resistance (but not in all cases) and yes, reversibility can possibly be accomplished by a reduction of antimicrobial use through ASP in some cases, but the issue is complex and is one where more research is needed to properly assign aims of ASPs to achieve the intended impact.

2. Are potential aims of ASPs causally linked to overall objectives?

Rephrased; is reduction of antibiotic use, improvement of prescription quality, improved clinical or microbial outcomes or reduced costs

consistent with 'using antibiotics in a way that aims to optimise healthcare outcomes while minimising unintended consequences of antibiotic use' or 'using antibiotics in a way that aims to ensure sustainable access for all who need them'?[14,15] Even if cost outcomes and cost-benefit/cost-effectiveness outcomes (which are necessary in a broader context but perhaps not for these particular objectives) are excluded, the answer is still far from certain. If patient outcomes are improved as a result of ASPs, this is consistent with the objectives mentioned previously, but this is far from generally being the case based on available research. If a reduction in the use of antibiotics is achieved with no negative effect on patient outcomes, or if improved guideline adherence is achieved, it is still not clear that such an outcome ensures sustainable access to all who need it. This leads the discussion back to question 1, whether resistance development can be slowed or reversed by reducing antimicrobial use in general. This leads back to the reply that the issue is quite complex and the effect will likely depend on the contextual factors discussed in question 1.

The answer therefore can again be: potentially yes, but we need better ways of predicting which aims provide the greatest impact, to be able to steer interventions towards specific aims for which the overall objectives are best aligned.

3. Is there a level of antimicrobial use that balances collective risk and, if so, what is it?

When we strive to reduce the use of unnecessary antimicrobials, what levels of use should we aim for? Naturally, levels and proportion of use in a population have to be adjusted to demography as well as infection and resistance epidemiology, and in hospital care adjusted for patient case-mix and hospital characteristics.[16] But can thresholds of use that limit the development of further resistance be identified for antibiotics, all other factors contributing to resistance being optimised?

Some guidelines stress the importance of stating qualitative and quantitative targets of antimicrobial use as a part of steering responsible use of antibiotics,[17] and there have been specific suggestions of target levels published. In a 2016 Science manuscript, a collaboration of international scientists suggested that no country should consume more than the then current global median level [8.54 defined daily doses (DDD) per capita per year],[18] but this should be viewed as a symbolic target and has limited relevance to exact target levels where accelerated resistance may be prevented. In a review studying TATFAR partner countries, several countries had developed, or were developing, quantitative target levels for reduction in use or absolute use.[19] A total of 9 countries presented target levels and 17 indicated that development of target levels were underway. In Belgium (<600 by 2020), Sweden (<250) and Norway (<250), absolute targets for numbers of prescriptions per 1000 individuals and year were proposed. In a number of countries (Belgium, France, Norway and Sweden), precise targets for proportions of certain antibiotics for specific conditions exist. In yet five other TATFAR countries [United Kingdom (UK), United States (US), Malta, Slovenia and the Netherlands], target levels for the degree of reduction of antimicrobial use, in general or specifically, were reported.

Extensive modelling of the dynamics of resistance in relation to the volume of antimicrobial use has been performed,[20] and suggests that if use of antimicrobials for which resistance is increasing is reduced and external sources of resistance are stopped from entering into a community, resistance levels may be maintained.[21] Applied to an epidemiological context, studies regarding threshold levels/quota of use to contain resistance have been performed based on adaptive regression splines that allow assessment of non-linear relationships between levels of use and resistance development. Such studies suggest that thresholds can be identified,[22] but are subject to variation between specific populations and specific time-points in the same populations. Thus, to inform quotas and threshold levels, intense local surveillance and continuous modelling are required. Individuals responsible for ASPs should strive to increase reflection on target levels.

The answer therefore may be: such levels likely exist and can be calculated if surveillance is detailed enough, but they are not uniform, across either different antimicrobials, different geographical areas, or time.

4. How should we address apparent differences in levels of use of antibiotics in the world?

Without discussing the reasons behind this fact, it is undisputable that there are differences in levels of use of antimicrobials between different

physicians, different regions and different nations, even though trends of use suggest convergence.[23–25] The short-term consequences of such differences will initially be mainly local, but in the long run likely carry a global component. Moreover, the global consequences of antimicrobial overuse will likely be unevenly distributed around the world – an analogy of the injustice of the effects of climate change.[26] A disproportionate impact is predicted to occur in regions with mainly lower-income and middle-income countries.[27]

Some of the differences in levels of use mirror differences in epidemiology, and some depend on availability of diagnostics or lack of access to both narrow-spectrum and broad-spectrum antibiotics. However, some of the differences suggest different cultures of antibiotic use. Just like the case in many other issues in healthcare, differences in organisation, demand/supply of healthcare, including competition between providers, patient/physician relations, liability costs or culture may lead to higher objective or subjective cost of uncertainty/risk in treatment decisions compared with other settings. The pressing questions are: are differences acceptable when they may cause negative consequences in areas where the perception of the cost of uncertainty is lower and how should we address them?

In the climate change policy debate, the most common suggestions to effectively reduce emissions are strict international regulation and/or carbon pricing/taxing. In contrast, in the field of antimicrobial resistance there are no uniform target levels of use that are deemed reasonable (see question 3), either in use of DID (DDD per 1000 inhabitants per day), or in the proportion of narrow-spectrum agents. Until such levels, in relation to resistance levels, are approximately suggested and agreed upon, it is difficult to argue that a certain level is unacceptably high (or low). We thus have to rely on global coordination of efforts with quantitatively vague ambitions. However, whenever possible, incentives that add external barriers to rational use of antibiotics should be removed.

Thus, until target levels/intervals are defined, there seems to be no simple and straightforward solution to this question, except for global coordinated action.

5. How do we address the perceived sepsis/stewardship dichotomy in a balanced way?

Is there a conflict between optimising awareness and empirical therapy for acute, potentially severe infections (most notably sepsis) and the objectives of ASPs? Development of machine-learning algorithms with great potential to improve early identification of sepsis are underway,[28] but as long as widely used clinical algorithms for early identification of potentially severe infections, such as sepsis, have limited sensitivity and specificity, a tension between the objective of early identification and treatment of potentially severe infections and limiting over-use of antibiotics may be difficult to avoid entirely.[29] The ambition to increase awareness of sepsis and the ambition to promote antimicrobial stewardship both strive to improve healthcare, but are not discussed together often enough as integrated parts of infectious disease care.[30] This may lead to pressure from both sides of the issue on prescribing physicians, which could lead to imbalance in any direction (overuse/underuse).

Without a doubt, first priority should be given to early identification and treatment of individuals with potentially severe infections, considering the diagnostic challenges, the high mortality linked to sepsis and the knowledge that time from presentation to treatment start is a crucial factor for treatment success.[31] Under-treatment of individuals with a potentially severe infection poses a risk of worsening clinical outcomes and can thus never be aligned with antimicrobial stewardship objectives. However, there are challenges regarding how the risks of sepsis and risks of antimicrobial resistance and presented and perceived. Sepsis is often presented in media using emotional triggers with individual narratives. This can be problematic if it leads to a misperception of the risks associated with non-severe illnesses and potentially to altered prescription behaviour on the part of physicians.[32–34] In contrast, antimicrobial resistance is often presented as a vague threat, leading to limited public and physician comprehension, which may be even more problematic if not interpreted in a balanced way.

In short, yes, the sepsis/stewardship dichotomy can be addressed in a balanced way, but this does not happen often enough today. There is a need for ASPs to promote balanced, integrated reporting of risks of sepsis and risks of antimicrobial

resistance, ensuring that treatment of potentially severe infections is given unconditional priority while the threat of non-severe infections is perceived in a balanced way.

6. How do we balance the trade-off between individual and collective risks, patient participation and essentialism?

How do we address the potential conflict between the risk of potential harm for the individual and the future risk of harm for the collective in an ethical framework? This question touches on the discussion in question five. How do we subjectively and objectively quantify the respective risks involved and balance them appropriately? The clinical uncertainty/risk can be separated into several parts: for instance the empirical uncertainty (where a decision has to be made prior to proper diagnostics having been performed), diagnostic uncertainty (where a decision has to be made based on clinical/radiological/aetiological diagnostics that have limited sensitivity and specificity) and definitive uncertainty (where a clear diagnosis has been established or suggested, but it is still unclear what is best practice for this particular patient). Ideally, empirical uncertainty should be minimized *via* quick point-of-care diagnostics, especially for sepsis and respiratory tract infections, where empirical and diagnostic uncertainty is a major challenge,[32] and definitive uncertainty through properly designed clinical research studies. However, until such diagnostic tools are widely available and such studies have been completed, a framework to discuss risk balancing from an ethical perspective is needed.

In ethical terms, antimicrobial resistance has been characterised as a 'super-wicked' problem, defined by a high degree of complexity, the lack of an easy technological solution, a lack of time to respond, the involvement of those trying to solve the problem in its causes, a lack of strong, central authorities and a tendency to discount the future.[35] Increasing attention has been given to the ethical challenges of antimicrobial resistance in general, to intra- and intergenerational fair distribution of resources, but also to stigma and consequences for carriers of resistant bacteria.[36,37] Attention has also been focussed on the ethical dilemma of antimicrobial stewardship specifically.[38,39] Two particular challenges have been identified: how can physician risk perceptions be balanced and less categorical, and how do we

quantify potential risks and benefits (to the individual and to society) of a treatment decision to properly devise guidelines for infections? Despite the complexity, there have been attempts develop a framework for such quantifications.[38]

One specific barrier to rational antimicrobial use is inappropriate problem perception and risk perception. This could mean that treatment decisions are viewed from an essentialist perspective, an unbalanced perception of risk, or both. Even though many treatment choices are made in the face of uncertain diagnostics, treatment guidelines are generally written according to an essentialist perspective and assume a definite diagnosis.[40] In practice, this may lead to a reduced focus on objective risks related to combinations of symptoms in favour of an 'essentialist bias', with a focus on sorting the patient in a specific diagnosis and focusing on treatment for that diagnosis, not on the actual patient. Another potential fallacy is that the type of risk perception that a physician carries into a clinical situation affects levels of use. A large portion of physicians, while acknowledging the general risk of resistance, view changing their own practice as futile or do not see themselves as contributing to the problem of resistance.[32] However, if patient harm from antibiotics is included as a potential risk in the physician's perception, fewer antibiotics are used.[41]

A particular part of the ethical aspect of antimicrobial stewardship is the role of the patient's perception and knowledge of treatment alternatives and potential risks. Patients have the unequivocal right to be informed regarding different treatment alternatives and reasons for suggesting a particular treatment. To what extent is it reasonable to involve the patient in the stewardship discussion and what are the consequences? Using a health belief model to study perceptions of resistance and stewardship in patients, it was demonstrated that patients mirrored most physicians in considering the general problem of resistance as a serious threat, but the risk of it affecting them personally as low. However, it was also clear that few patients discussed treatment choices with their doctors, and more wanted to.[42] Thus, in ASPs, increased discussion with patients regarding antimicrobial stewardship policies should be promoted, including reasons for suggested treatment. In situations where treatment decisions feel difficult to defend and discuss with patients, they should probably be changed.

There is need for improved balancing of individual and collective costs of treatment decisions as well as a balanced risk perception. Moreover, patients should, whenever possible, always be informed on treatment choices/suggestions and the rationale behind them.

7. Should individual dysbiosis from antimicrobials be a part of the antimicrobial stewardship discussion and what role should it play?

One of the lessons learned from risk perception assessment was that if potential harm from antibiotics to the patient was included as a perceived risk, less over-use was demonstrated.[41] Increasing attention has been given to the correlation between gastrointestinal dysbiosis and a number of chronic diseases, including obesity, behavioural disorders, autoimmune disorders and cardiovascular disease.[43] Children seem to be particularly vulnerable to the effects of dysbiosis.[44]

Even though many environmental factors contribute to dysbiosis, antimicrobial treatment is arguably the most prominent among them, potentially altering a number of physiological equilibria.[45,46] Studies have shown that the effect on the abundance of chromosomal resistance elements from antimicrobial therapy is often transient, but the gut microbiota is a potent reservoir of resistance elements and the abundance of resistance genes carried on mobile genetic elements stay high for long periods of time following antimicrobial treatment,[45,47] potentiating further spread and selection. From both an individual and a collective perspective, it is thus reasonable in antimicrobial stewardship to pay more attention to what degree routes of administration and elimination of antibiotics induce dysbiosis and selection of resistance elements. This includes choices of treatment options, such as extended non-systemic use and creation of precision drugs with small collateral effects.[48]

More research is needed on causal effects but, from a precautionary principle, we should increase focus on dysbiosis and subsequent risks as a consequence of antimicrobial use in the context of the antimicrobial stewardship debate. We should also let the increasing body of knowledge on the effect of administration routes, elimination and course duration of antimicrobials on the microbiome inform guidelines.

8. How do we balance the need for uniform methodological evidence with limited evidence for generalizability?

One major challenge for global antimicrobial stewardship is the lack of coordinated implementation. Even though progress has been made, including the definition of global core elements and checklist items by representatives from across the globe,[49] there is concern that such checklists may be difficult to implement in areas where antibiotic use is unregulated, where infectious disease specialists and specially trained pharmcists are few and professional boundaries and hierarchial structures do not empower the work of nurses, pharmacists or stewardship teams.[50,51] Moreover, ASPs are often bottom-up initiatives, and have, from a global perspective, been uncoordinated and fragmented with regards to aim and methodology.[52]

Today, a call for global coordinated action of antimicrobial stewardship is being increasingly championed (and rightfully so).[27,53–55] Where does that leave the different settings from which individual initiatives have been started, and will a common global framework and methodology risk missing objectives locally due to differences in healthcare structures affecting prescription habits? Even if benchmarking prior to start would be identical (which it hardly ever will be), antimicrobial stewardship intervention studies are always likely to be heterogenous, since complete standardisation of interventions is not feasible, making external validity inherently difficult. Experiences from different settings may be rewarding if they are discussed openly with mutual learning as a result.[56] Since there are bound to be local nuances that global core elements cannot tailor to, the solution may be a 'glocalisation' approach with polycentric governance reconciliating the global and the local context.[57] The general agenda should be decided globally, with potential for local policy adaptation of intervention and of priorities. This will also allow for better sense of shared responsibility.

One potential answer is that a uniform best practice is likely not reasonable in the context of antimicrobial stewardship, and that one potential solution is glocalisation, with a global agenda and local tailoring to that agenda, strengthening local engagement and accountability.

9. What are the potential consequences of an effective ASP on the supply of antibiotics?

The need for a stable supply chain has been recognised as an essential empirical part of antimicrobial stewardship, in response to recurrent stock-outs and shortages leading to the need for using broad-spectrum or second-choice antibiotics when they are not warranted.[58,59] There are multiple reasons for the fragility of supply of antimicrobials, and there is ongoing work from multiple stakeholders to improve supply chain stability.

One particular threat is the threat of market failure for antimicrobials. Even if it is assumed that pharmaceutical companies strive to benefit health through the cure and prevention of disease, and even if this is performed in an ethical way including social responsibility, any publicly traded company needs to provide profit, growth and stability for its shareholders. Antibiotics are generally less profitable than other medicines, with low prices and short courses being factors that lead to low margins and low profit. Also, the fact that new antibiotics that enter the market are often used sparsely provides little natural incentives for research and development (R&D).[27] As a consequence, several big pharmaceutical companies have left the antibiotic market.[60] An effective ASP is likely to reduce the demand for antibiotics in general, and for some antibiotics specifically. At the same time, such a program requires access to a variety of antibiotics in different preparations, doses and package sizes in order to optimize treatment courses to reduce unintended consequences from antibiotics. Thus, new business models are needed, not only to facilitate R&D for new antibiotics as suggested by several reports,[27,54] but also in the context of antimicrobial stewardship to ensure a sustained diverse supply of present antibiotics in order to tailor treatment courses optimally.

Thus, without a new business model, adjustments to the old model or cooperation of multiple stakeholders, effective antimicrobial stewardship will likely worsen market failure for antibiotics with reduced supply as a result.

10. Is there a risk of 'crowding out' effects from ASPs?

Financial and human resources within healthcare are limited. Assuming that total resources are unchanged and more of them are allocated to ASPs, some will have to be taken from other, potentially beneficial projects. There is a current call for staffing standards and allocation of resources to prevent infectious diseases and provide antimicrobial stewardship.[61] Working in the field of antimicrobial resistance, it seems self-evident that such resources are needed. But from where should these resources be taken, and what are the potential consequences of such a re-allocation? Is there a risk of 'crowding out' other healthcare initiatives? In this context, crowding out is used in a general sense of a re-allocation of priorities to a pressing issue from things that may suffer as a consequence. The effects of re-allocation of resources in a healthcare system are rarely straightforward or easy to predict,[62] as made evident by the study on the introduction of cancer care pathways on waiting times for cancer patients in Sweden and the study of the effect of a reduction in bed numbers in an emergency ward on the number of cancellations of elective surgery in a British hospital.[63,64]

The issue relates partly to the cost-effectiveness issues and the fact that cost-effectiveness may vary depending on the scale of the antimicrobial resistance issue locally. But cost-effectiveness evaluations alone do not capture the issue in full. It also relates to general health-care priorities and systems dynamics. Some of the antimicrobial stewardship designs with the clearest empirical evidence of effect, such as audit-feedback programs involving infectious disease specialists and/or specially trained pharmacists, are resource-intensive, not mainly in financial terms but in terms of work-hours of infectious disease specialists and/or pharmacists. In contexts where such are in short supply, the consequences may be felt mainly in other areas where this competence is needed. It is, however, important to be aware that any change in healthcare priorities, such as an implementation of an ASP within a system with unchanged total resources, may have unexpected effects. It would therefore be prudent to assess such potential effects, qualitatively or quantitatively, when introducing ASPs.

The answer is that such a risk cannot be excluded, but there is limited evidence, due mainly to the fact that such effects have generally not been studied in the context of antimicrobial stewardship.

Conclusion

Even though most decision-makers recognize and agree that there is a need for immediate action

regarding the global challenge of antimicrobial resistance and suggest such action,[27,54,55] there is considerable uncertainty into exactly what should be done, how this should be done and what such actions lead to. The area of human antimicrobial use and resistance is complex and warrants reflection, discussion, scientific rigor and ethical reflection. In this second part of this narrative review, 10 questions are posed reflecting areas of uncertainty or controversy. This part of the review is meant to stimulate discussion and is by no means exhaustive neither in scope nor in reflection on each issue.

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References

1. Morris AM, Calderwood MS, Fridkin SK, *et al.* Research needs in antibiotic stewardship. *Infect Control Hosp Epidemiol* 2019; 40: 1334–1343.

2. Bassetti M, Giacobbe DR, Vena A, *et al.* Challenges and research priorities to progress the impact of antimicrobial stewardship. *Drugs Context* 2019; 8: 212600.

3. Komp Lindgren P, Marcusson LL, Sandvang D, *et al.* Biological cost of single and multiple norfloxacin resistance mutations in Escherichia coli implicated in urinary tract infections. *Antimicrob Agents Chemother* 2005; 49: 2343–2351.

4. Sander P, Springer B, Prammananan T, *et al.* Fitness cost of chromosomal drug resistance-conferring mutations. *Antimicrob Agents Chemother* 2002; 46: 1204–1211.

5. Levin BR. Minimizing potential resistance: a population dynamics view. *Clin Infect Dis* 2001; 33(Suppl. 3): S161–S169.

6. Kristinsson KG. Effect of antimicrobial use and other risk factors on antimicrobial resistance in pneumococci. *Microb Drug Resist* 1997; 3: 117–1123.

7. Seppala H, Klaukka T, Vuopio-Varkila J, *et al.* The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group a streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. *N Engl J Med* 1997; 337: 441–446.

8. Bergman M, Huikko S, Pihlajamaki M, *et al.* Effect of macrolide consumption on erythromycin resistance in Streptococcus pyogenes in Finland in 1997–2001. *Clin Infect Dis* 2004; 38: 1251–1256.

9. Sundqvist M, Geli P, Andersson DI, *et al.* Little evidence for reversibility of trimethoprim resistance after a drastic reduction in trimethoprim use. *J Antimicrob Chemother* 2010; 65: 350–360.

10. Mahamat A, MacKenzie FM, Brooker K, *et al.* Impact of infection control interventions and antibiotic use on hospital MRSA: a multivariate interrupted time-series analysis. *Int J Antimicrob Agents* 2007; 30: 169–176.

11. Obolski U, Stein GY and Hadany L. Antibiotic restriction might facilitate the emergence of multi-drug resistance. *PLoS Comput Biol* 2015; 11: e1004340.

12. Sundqvist M. Reversibility of antibiotic resistance. *Ups J Med Sci* 2014; 119: 142–148.

13. Andersson DI and Hughes D. Persistence of antibiotic resistance in bacterial populations. *FEMS Microbiol Rev* 2011; 35: 901–911.

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

15. Dyar OJ, Huttner B, Schouten J, *et al.* What is antimicrobial stewardship? *Clin Microbiol Infect* 2017; 23: 793–798.

16. Ibrahim OM and Polk RE. Benchmarking antimicrobial drug use in hospitals. *Expert Rev Anti Infect Ther* 2012; 10: 445–457.

17. ECDC. Proposals for EU guidelines on the prudent use of antimicrobials in humans Stockholm, Sweden 2017. http://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/EU-guidelines-prudent-use-antimicrobials.pdf (accessed 5 January 2020).

18. Laxminarayan R, Sridhar D, Blaser M, *et al.* Achieving global targets for antimicrobial resistance. *Science* 2016; 353: 874–875.

19. D'Atri F, Arthur J, Blix HS, *et al*. Targets for the reduction of antibiotic use in humans in the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) partner countries. *Euro Surveill* 2019; 24: 1800339.

20. Austin DJ, Kristinsson KG and Anderson RM. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proc Natl Acad Sci USA* 1999; 96: 1152–1156.

21. Levin BR, Baquero F and Johnsen PJ. A model-guided analysis and perspective on the evolution and epidemiology of antibiotic resistance and its future. *Curr Opin Microbiol* 2014; 19: 83–89.

22. Lawes T, Lopez-Lozano JM, Nebot C, *et al*. Turning the tide or riding the waves? Impacts of antibiotic stewardship and infection control on MRSA strain dynamics in a Scottish region over 16 years: non-linear time series analysis. *BMJ Open* 2015; 5: e006596.

23. Teixeira Rodrigues A, Roque F, Falcao A, *et al*. Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. *Int J Antimicrob Agents* 2013; 41: 203–212.

24. Blommaert A, Marais C, Hens N, *et al*. Determinants of between-country differences in ambulatory antibiotic use and antibiotic resistance in Europe: a longitudinal observational study. *J Antimicrob Chemother* 2014; 69: 535–547.

25. Klein EY, Van Boeckel TP, Martinez EM, *et al*. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci USA* 2018; 115: E3463–E3470.

26. IPCC. IPCC, 2014: climate change 2014: synthesis report. Contribution of Working Groups I, II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change [Core Writing Team, R.K. Pachauri and L.A. Meyer (eds.)]. http://www.ipcc.ch: 2014 5.

27. O'Neill JM. the review on antimicrobial resistance _ tackling drug-resistant infections globally: final report and recommendations. https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf (2016)

28. Fagerstrom J, Bang M, Wilhelms D, *et al*. LiSep LSTM: a machine learning algorithm for early detection of septic shock. *Sci Rep* 2019; 9: 15132.

29. Marik PE and Farkas JD. The changing paradigm of sepsis: early diagnosis, early antibiotics, early pressors, and early adjuvant treatment. *Crit Care Med* 2018; 46: 1690–1692.

30. Fitzpatrick F, Tarrant C, Hamilton V, *et al*. Sepsis and antimicrobial stewardship: two sides of the same coin. *BMJ Qual Saf* 2019; 28: 758–761.

31. Kumar A, Roberts D, Wood KE, *et al*. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34: 1589–1596.

32. Krockow EM, Colman AM, Chattoe-Brown E, *et al*. Balancing the risks to individual and society: a systematic review and synthesis of qualitative research on antibiotic prescribing behaviour in hospitals. *J Hosp Infect* 2019; 101: 428–439.

33. Livorsi D, Comer A, Matthias MS, *et al*. Factors influencing antibiotic-prescribing decisions among inpatient physicians: a qualitative investigation. *Infect Control Hosp Epidemiol* 2015; 36: 1065–1072.

34. Broom A, Kirby E, Gibson AF, *et al*. Myth, manners, and medical ritual: defensive medicine and the fetish of antibiotics. *Qual Health Res* 2017; 27: 1994–2005.

35. Littmann J. *Antimicrobial resistance and distributive justice* [Dissertation], University College, London, 2014.

36. Littmann J, Buyx A and Cars O. Antibiotic resistance: an ethical challenge. *Int J Antimicrob Agents* 2015; 46: 359–361.

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

38. Littmann J, Rid A and Buyx A. Tackling anti-microbial resistance: ethical framework for rational antibiotic use. *European journal of public health* 2018; 28: 359–363.

39. Oczkowski S. Antimicrobial stewardship programmes: bedside rationing by another name? *J Med Ethics* 2017; 43: 684–687.

40. Jensen UJ. A critique of essentialism in medicine. In: Nordenfelt L and Lindahl BIB (eds) *Health, disease, and causal explanations in medicine philosophy and medicine*. Dordrecht: Springer, 1984.

41. Klein EY, Martinez EM, May L, *et al*. Categorical risk perception drives variability in antibiotic prescribing in the emergency department: a mixed methods observational study. *J Gen Intern Med* 2017; 32: 1083–1089.

42. Heid C, Knobloch MJ, Schulz LT, *et al*. Use of the health belief model to study patient perceptions of antimicrobial stewardship in the

acute care setting. *Infect Control Hosp Epidemiol* 2016; 37: 576–582.

43. Wilkins LJ, Monga M and Miller AW. Defining dysbiosis for a cluster of chronic diseases. *Sci Rep* 2019; 9: 12918.

44. Neuman H, Forsythe P, Uzan A, *et al.* Antibiotics in early life: dysbiosis and the damage done. *FEMS Microbiol Rev* 2018; 42: 489–499.

45. Francino MP. Antibiotics and the human gut microbiome: dysbioses and accumulation of resistances. *Front Microbiol* 2015; 6: 1543.

46. Sun L, Zhang X, Zhang Y, *et al.* Antibiotic-induced disruption of gut microbiota alters local metabolomes and immune responses. *Front Cell Infect Microbiol* 2019; 9: 99.

47. Yassour M, Vatanen T, Siljander H, *et al.* Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability. *Sci Transl Med* 2016; 8: 343ra81.

48. Shahi F, Redeker K and Chong J. Rethinking antimicrobial stewardship paradigms in the context of the gut microbiome. *JAC Antimicrob Resist* 2019; 1: dlz015.

49. Pulcini C, Binda F, Lamkang AS, *et al.* Developing core elements and checklist items for global hospital antimicrobial stewardship programmes: a consensus approach. *Clin Microbiol Infect* 2019; 25: 20–25.

50. Patel PK. Minding the gap: rethinking implementation of antimicrobial stewardship in India. *Infect Control Hosp Epidemiol* 2019; 40: 520–521.

51. Charani E, Smith I, Skodvin B, *et al.* Investigating the cultural and contextual determinants of antimicrobial stewardship programmes across low-, middle- and high-income countries-a qualitative study. *Plos One* 2019; 14: e0209847.

52. Tiong JJ, Loo JS and Mai CW. Global antimicrobial stewardship: a closer look at the formidable implementation challenges. *Front Microbiol* 2016; 7: 1860.

53. Laxminarayan R, Duse A, Wattal C, *et al.* Antibiotic resistance-the need for global solutions. *Lancet Infect Dis* 2013; 13: 1057–1098.

54. WHO. Global action plan on antimicrobial resistance, https://apps.who.int/iris/bitstream/ handle/10665/193736/9789241509763_eng.pdf;jsessionid=705E46A5AB66B5F6C472C89EBEC 1C3B2?sequence=1 (2015, accessed 8 November 2019).

55. (WHO) I. No time to wait: securing the future from drug-resistant infections, http://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_final_report_EN.pdf?ua=1 (2019, accessed 8 November 2019).

56. Goff DA, Kullar R, Goldstein EJC, *et al.* A global call from five countries to collaborate in antibiotic stewardship: united we succeed, divided we might fail. *Lancet Infect Dis* 2017; 17: e56–e63.

57. Rubin O. The glocalization of antimicrobial stewardship. *Global Health* 2019; 15: 54.

58. Malan L, Labuschagne Q, Brechtelsbauer E, *et al.* Sustainable access to antimicrobials; a missing component to antimicrobial stewardship-a tale of two countries. *Front Public Health* 2018; 6: 324.

59. Foundation AtM. Shortages, stockouts and scarcity - the issues facing the security of antibiotics supply and the role for pharmaceutical companies 2018, https://accesstomedicinefoundation.org/publications/shortages-stockouts-and-scarcity-the-issues-facing-the-security-of-antibiotic-supply-and-the-role-for-pharmaceutical-companies (2018, accessed 5 January 2020).

60. Pulcini C, Mohrs S, Beovic B, *et al.* Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia. *Int J Antimicrob Agents* 2017; 49: 98–101.

61. Pulcini C, Morel CM, Tacconelli E, *et al.* Human resources estimates and funding for antibiotic stewardship teams are urgently needed. *Clin Microbiol Infect* 2017; 23: 785–787.

62. Grol R, Wensing M, Eccles M, *et al. Improving patient care the implementation of change in health care.* 2nd ed. Edinburgh: BMJ Books, Wiley Blackwell, 2013, p.374.

63. Smeds M and Poksinska BB. The effects of cancer care pathways on waiting times. *Int J Qual Serv Sci* 2019; 11: 204–216.

64. Lane DC, Monefeldt C and Rosenhead JV. Looking in the wrong place for healthcare improvements: a system dynamics study of an accident and emergency department. *J Oper Res Soc* 2000; 51: 518–531.