Chapter 22
Justifying Antibiotic Resistance Interventions: Uncertainty, Precaution and Ethics

Niels Nijsingh, D. G. Joakim Larsson, Karl de Fine Licht, and Christian Munthe

Abstract This chapter charts and critically analyses the ethical challenge of assessing how much (and what kind of) evidence is required for the justification of interventions in response antibiotic resistance (ABR), as well as other major public health threats. Our ambition here is to identify and briefly discuss main issues, and

N. Nijsingh (✉)
Centre for Antibiotic Resistance Research (CARe), University of Gothenburg, Gothenburg, Sweden

Department of Philosophy, Linguistics and Theory of Science (FLoV), University of Gothenburg, Gothenburg, Sweden

Institute of Ethics, History and Theory of Medicine, Ludwig Maximilians Universität, Munich, Germany
e-mail: niels.nijsingh@med.uni-muenchen.de

D. G. J. Larsson
Centre for Antibiotic Resistance Research (CARe), University of Gothenburg, Gothenburg, Sweden

Department of Infectious Diseases, Institute of Biomedicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
e-mail: joakim.larsson@fysiologi.gu.se

K. de Fine Licht
Centre for Antibiotic Resistance Research (CARe), University of Gothenburg, Gothenburg, Sweden

Department of Technology Management and Economics, Chalmers University of Technology, Gothenburg, Sweden
e-mail: karl.licht@sp.se

C. Munthe
Centre for Antibiotic Resistance Research (CARe), University of Gothenburg, Gothenburg, Sweden

Department of Philosophy, Linguistics and Theory of Science (FLoV), University of Gothenburg, Gothenburg, Sweden
e-mail: christian.munthe@gu.se

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point to ways in which these need to be further advanced in future research. This will result in a tentative map of complications, underlying problems and possible challenges. This map illustrates that the ethical challenges in this area are much more complex and profound than is usually acknowledged, leaving no tentatively plausible intervention package free of downsides. This creates potentially overwhelming theoretical conundrums when trying to justify what to do. We therefore end by pointing out two general features of the complexity we find to be of particular importance, and a tentative suggestion for how to create a theoretical basis for further analysis.

Keywords Antibiotic resistance · Public health ethics · Precautionary principle · Complexity

22.1 Antibiotic Resistance

Antibiotic resistance is emerging as one of our largest global challenges: more and more bacterial infections[1] are becoming increasingly impervious to antibiotics, which increases morbidity, mortality and societal costs around the world.

The evolutionary principle that drives ABR is relatively simple: when populations of bacteria are exposed to an antibiotic, strains that have acquired resistance to the drug (through mutations or through uptake of genetic material) are favoured over the sensitive ones. The emergence of ABR on a macro-scale is, however, notoriously complex.[2] One reason is that ABR is a global phenomenon with a variety of causes on different levels and in different contexts, some of which are poorly understood.

The most obvious cause of ABR is the use of antibiotics in humans, especially when antibiotics are used inappropriately (e.g. when overly broad antibiotics are used, or when a patient has no benefit from antibiotic treatment). The use of antibiotics in animals, both for treatment and prevention of disease and for growth promotion, also contributes to the problem.[3] Some bacteria have the ability to colonize both humans and domestic animals, and mobile genetic elements, such as resistance plasmids, often move across bacterial species. Hence, there are no firm barriers that

[1] We will limit ourselves here to antibiotic resistance. Antibiotic resistance is a sub-category of antimicrobial resistance, which also includes drug resistance in viruses, fungi and other microorganisms than bacteria.

[2] World Health Organization (2014). *The evolving threat of antimicrobial resistance: options for action*. Geneva, Switzerland: World Health Organization.

[3] Anomaly, J. (2020). Antibiotics and Animal Agriculture; The Need for Global Collective Action. In Ethics and Drug Resistance: Collective Responsibility for Global Public Health. Springer, Cham.

separate the microflora of animals from that of humans. The external environment is another source of resistance, both as a transmission route for certain pathogens, for example through faecal contamination of water, and as a source for resistance genes that over time are recruited from harmless bacteria into pathogens, assisted by a selection pressure from antibiotics.[4] The need to take into account the interconnection between humans, animals and the external environment is often referred to as a "One Health perspective".[5]

Clearly, there is an urgent need to address all of these causes of ABR and implement interventions at different sites and different levels of organization. However, as we will see, securing the evidence required to establish both the effectiveness and the risks of such interventions, comes at a moral price. This raises in a straightforward manner the question of what the criteria of evidence should be for the various interventions that aim to fight ABR. This question links the ethical justification of ABR interventions to debates around the ethics of risk and precaution. In other words, all ABR interventions pose the challenge of what quality of evidence for what balance of risks and possible benefits is required for such an intervention to be justified.

22.2 Precaution

The notion of precaution is central to much public health and environmental thinking. Specifically, when faced with complex and potentially extremely threatening phenomena such as a pandemic, global warming or pollution, it makes sense both to act in response to them even if there is a lack of evidence, but also to proceed with caution when enacting precautionary measures to mitigate or prevent damage.

Scholars of the *Precautionary Principle* (PP) have worked to express this intuition more clearly, resulting in a generic criterion of justified decision-making and policy arrangements that can be expressed in the following way:

> *... in the face of an activity that may produce great harm, we (or society) have reason to ensure that the activity is not undertaken, unless it has been shown not to impose too serious risks.*[6]

This criterion expresses three basic things: First, the idea that uncertain major threats may provide reason for action.[7] Second, the contention that whatever such

[4] Bengtsson-Palme, Johan, and DG Joakim Larsson (2015). Antibiotic resistance genes in the environment: prioritizing risks. *Nature Reviews Microbiology* 13.6: 396–396.

[5] Boden, L. & D. Mellor. (2020). Epidemiology and ethics of antimicrobial resistance in animals. In Ethics and Drug Resistance: Collective Responsibility for Global Public Health. Springer, Cham.

[6] Munthe, Christian (2016). Precautionary principle. In: Ten Have (ed.) *Encyclopedia of global bioethics*. Dordrecht: Springer International Publishing.

[7] Compare also: "uncertainty should not be a reason for inaction in the face of serious environmental threats". Daniel Steel calls this idea the ´meta-precautionary principle´. Note that the vagueness of this procedural meta-criterion allows PP to be applied in a large number of different contexts

actions are taken must not themselves impose too serious risks or new uncertain major threats, and, third, that we are required to *demonstrate reasons* both why responses to threats are motivated and why apparent threats may be accepted. The criterion expresses a generic formula, within which more specific PP *versions*, or specific precautionary policy suggestions, must fit in order to be justified. There are thus various ways to flesh out the idea that we have reason to take precautions in the face of major, but uncertain threats. As a version of PP is specified, it further delineates what can properly be considered *responsible* decision-making in such contexts, not least regarding what is required more precisely to satisfy the requirement of demonstrating reasons for whatever precautionary action is suggested.[8]

One basic assumption underlying PP is that there is a moral price to exposing people to risk, as well as to proceed with activities in the face of uncertain risks. However, there is also always a price to any precautionary intervention that aims to clarify uncertainties and to prevent or mitigate risks: these will always claim resources that could have been used for other worthwhile purposes, create risks of their own, and delay or stop possibly valuable activities. For that reason, suggestions for precautionary action need to be subjected to precautionary scrutiny too, and to be justified it needs to be demonstrated that they incur an acceptable price and level of precaution. Particularly in systemically complex situations, the emergence of risks and uncertainties on various levels raises complications concerning how to balance the type and severity of the various harms and uncertainties involved.

A version of PP has to set *standards* concerning when precautionary action is required, and what is required of it in order to be responsible. Daniel Steel has recently explained this in terms of a 'tripod', consisting of a knowledge condition, a harm condition, and a suggested precautionary action.[9] Variations of how this tripod is construed will affect the price of precaution, as well as the level of precaution enacted. A PP version thus needs to specify for (1) any suggested precautionary action, (2) what threat is sufficiently serious for such action to be defensible, and (3) what degree of uncertainty is acceptable for it. For example, in order to, say, justify taking expensive precautionary measures to curb ABR (1), there needs to be a scientifically plausible model (3) in which failure to introduce these measures leads to significant economic or health damage (2). Whether or not in a specific case the model leading to harm is ´plausible´ and the damage is ´significant´ of course requires further elaboration. In any justifiable specification of the 'tripod', it is necessary to balance in a responsible way the need for precautionary action against the price of precaution.

Although details vary among authors, critical debate on what it takes to justify a PP version has led to a reasonably broad consensus on some minimal desiderata. These regard that a sound PP must not balance its required level and price of

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and on different levels of organization. See Steel, Daniel (2014). *Philosophy and the precautionary principle*. Cambridge University Press.

[8] Munthe, Christian (2011). *The price of precaution and the ethics of risk*. Dordrecht: Springer.

[9] Steel (2014).

precaution *arbitrarily* (but according to a general principle that applies equally to all cases), that it needs to avoid so-called *precautionary paradox*, and that principle for responsible balancing of precautionary level and price must be *proportional*.[10]

PP is *arbitrary* when it offers no good, generalizable reasons why a specific course of action is acceptable or not. If an appeal to PP is used to recommend intervention 1, but to prohibit intervention 2, it should be able to meaningfully distinguish between the two measures and show how these are relevantly different. Note that the requirement to avoid arbitrariness also excludes treating the *status quo* with special regard: the fact that things are currently done in certain way is not in itself an argument for doing it that way.[11] It also means that whatever requirements are set by the specification of the tripod in a PP, these apply both to uncertain threats in order to justify precautionary action, *and* to the uncertainties of these actions themselves.

This links to the need to avoid 'precautionary paradox'. PP can lead to paradox in two related ways: Either its requirements are so strong that it tends to ban all options in most situations, thereby undermining any capacity to guide decision-making.[12] Or it issues inconsistent prescriptions by requiring and banning one and the same option.[13] It has been a theme among critics to point out how simplistic versions of PP may easily become paradoxical in any or both of these ways.[14]

The desideratum of proportionality follows from both of these requirements. In order to avoid paradox and arbitrariness, a justified version of PP must present a principle of responsible balancing of what level of precaution is required and what price of precaution is acceptable to pay that applies equally to all situations, as well as to all options in such situations. Any plausible version of PP will thus offer principled grounds for comparing suggested precautionary interventions, or the acceptance of an uncertainty or a threat, to alternative options in a unified manner. Such a version will express an allegedly morally responsible way of balancing the required level and price of precaution. To justify a specific precautionary action in a situation, it is therefore necessary to point how such a PP version supports it. As different situations vary with regard to what options are available, what stakes in terms of threats and prospects these actualise, and what knowledge is available with regard to these factors, one and the same precautionary intervention may therefore be

[10] Munthe, 2011, 2016; Munthe, C. (2017). *Precaution and Ethics: Handling risks, uncertainties and knowledge gaps in the regulation of new biotechnologies*. Berne: Swiss Federal Office for Buildings and Publications and Logistics (FOBL); Steel, (2014).

[11] However, there may be good instrumental reasons to be cautious when implementing change in a situation of great uncertainty. We will return to that point later.

[12] What Munthe (2011, ch. 2) has called *decisional paralysis*.

[13] What Steel (2014) terms *inconsistency*.

[14] Holm, Søren, and John Harris (1999). "Precautionary principle stifles discovery." Nature 400.6743: 398–398. Sunstein, Cass R (2005). *Laws of fear: Beyond the precautionary principle*. Cambridge University Press. McKinney, WJ, & Hill, HH (2000). Of sustainability and precaution: The logical, epistemological, and moral problems of the precautionary principle and their implications for sustainable development. *Ethics and the Environment*, 5: 77–87.

justifiable in some situations, but not in others. This regards also what quality and type of information about risks and effectiveness we require, and how much of further investigation to mitigate uncertainties is needed in the light of that. Precautionary requirements will therefore be gradual rather than absolute, and context-dependent rather than rigid. Different situations will justify different levels of precaution, and different prices of precaution to attain such levels.[15]

This regards not least the option of postponing a specific intervention in order to gather more evidence to ensure its effectiveness and responsibility. Possibly, this is the most common type of precautionary measure, familiar from standard regulation of drugs and the introduction of novel biotechnology.[16] It is also easy to see how this type of precautionary action may often be justified on the basis of a defensible version of PP. However, knowledge is never perfect, and the option to further update the basis of information for assessing the effectiveness and riskiness of an intervention is ever present. So, when do we know enough? How much time and resources should we spend on making sure that what we do in order to invoke responsible precautionary response to dangers and uncertainties will not in fact worsen the situation from a precautionary standpoint by invoking an unjustifiable price of precaution? This is a distinct ethical issue that becomes a particular challenge in the face of complex and drastic public health threats, such as ABR, where the price of delaying interventions is obvious, and costs and new risks of conducting research are salient. If we wait, the ABR problem continues to grow and increasingly threatens to overwhelm us, and if we experiment with interventions this will usually create new uncertainties and risks of harm. At the same time, unproven interventions may both escalate the ABR problem, and expand it to include severe policy failures. This takes us to the question of how these stakes, and options of collecting (or not collecting) evidence, should be assessed and evaluated.

22.3 Evidence

Traditionally, guidelines for evidence basing and research in the area of medicine confine themselves to clinical trials of biomedical interventions, focusing mostly on the immediate somatic effects on individual patients.[17] At the same time, as mentioned, ABR (and most other public health) interventions greatly surpass that area, and mostly occur outside of immediate therapeutic action (although sometimes intended to affect it, e.g., those interventions that regard antibiotic prescription practices). However, the recently revised guidelines by the Council for International Organizations of Medical Sciences (CIOMS) allow for a broader conception of

[15] Munthe, (2017).

[16] Munthe (2011), p. 97. See also Munthe, (2017).

[17] World Medical Association (2014). "World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects." *The Journal of the American College of Dentists* 81.3: 14

'health research', including the study of any intervention that aims to change health-related behaviour on both individual and institutional levels.[18] This more inclusive conception clearly and significantly leaves room for the gauging of the proper amount of evidence for public health interventions.

A starting point for this type of assessment is the recognition of the fact that all health research – not only on biomedical interventions – imposes risks on research subjects, while the projected aim is to gather more knowledge in the interest of science or society.[19] A central tenet of research ethics therefore is that health research either has to plausibly benefit the research subject, or the societal benefit needs to be very large. In the new CIOMS guidelines, the latter is explicitly recognized in terms of the "social value" that may be attained by an intervention.[20] Furthermore, considerations of promoting trust towards health professionals and the complexity of the ethical issues involved provide arguments to treat health research with a certain amount of caution.[21] To this, we may add the precautionary considerations related in the preceding section: while a public health threat may be major and acute, any intervention meant to mitigate or prevent it may instead make it worse, or produce structural side effects that undermine other types of social goods. Therefore, the CIOMS frame is helpful to understand the question of evidence in public health interventions, such as the interventions aimed at fighting ABR.[22] To establish whether the evidence is sufficient, we have to chart the types of harm and uncertainty for various interventions in order to determine whether the expected (social) value of the intervention outweighs the value of postponing the use of a new intervention to collect more solid information about it.

This challenge is well illustrated by debates over suggested interventions in public health emergencies, such as Ebola.[23] When, in 2014, the West African Ebola epidemic was finally recognized as a global threat, it was suggested to prevent

[18] Council for International Organizations of Medical Sciences (CIOMS) (2016). International Ethical Guidelines for Health-Related Research Involving Humans. Geneva, Switzerland: Council for International Organizations of Medical Sciences. http://www.cioms.ch (accessed July 28, 2017). Munthe, C., Nijsingh, N., de Fine Licht, K., & Joakim Larsson, D. G. (2019). Health-related Research Ethics and Social Value: Antibiotic Resistance Intervention Research and Pragmatic Risks. Bioethics, 33(3), 335–342.

[19] Wilson, James, and David Hunter (2010). "Research exceptionalism." *American Journal of Bioethics* 10.8: 45–54.

[20] CIOMS (2016).

[21] Wilson and Hunter (2010).

[22] Attena, Francesco (2014). "Complexity and indeterminism of evidence-based public health: an analytical framework." *Medicine, Health Care and Philosophy* 17.3: 459–465.

[23] National Academies of Sciences, Engineering, and Medicine (2017). *Integrating Clinical Research into Epidemic Response: The Ebola Experience*. National Academies Press. An even more recent example is the Zika epidemic. See Edwards, Sarah JL (2016). "The precautionary paradox and Zika." *Research Ethics*: 178–181.

and Glenza, J. "Zika virus: Floridians fear 'Pandora's box' of genetically altered mosquitos." *The Guardian*, August 14, 2016: https://www.theguardian.com/us- news/2016/aug/14/florida-keys-zika-virus-genetically-modified-mosquitoes (accessed July 25, 2017).

further harm by 'fast tracking' new vaccines and experimental drugs, thus relaxing the demands of evidence required to introduce new medication.[24] This suggestion was countered by public health officials, who argued that the epidemic should rather be controlled by means of proven public health policies, such as proper hygiene, surveillance and quarantine.[25] Another issue that was debated was whether randomized clinical trials could be justified in the context of an epidemic and the extent to which genuine equipoise could be presumed. In part, the answers to these questions depend on the relative risk to which the affected communities were exposed, in another part it depends on how we assess the gravity of uncertainties underlying the assessment of these risks and how we value the importance of acting on good evidence in view of those uncertainties. While the question on the evidence of interventions to counter ABR is similar to such debates, the issue of ABR also raises a new set of worries and topics for discussion. Specifically, whereas the Ebola crisis was unexpected and presented an acute emergency, ABR is – for now – slowly emerging, albeit foreseen, but nevertheless posing a major and growing public health threat. Already a substantial amount of morbidity and mortality is attributed to ABR, but this number is likely to keep growing in a way well known to us.

22.4 Justifying Interventions

Since the causes are varied, the fight against ABR takes place in different arenas. In this section, we distinguish between various groups of interventions. The first set concerns the development of new types of (or alternatives for) antibiotics. Second, we consider interventions that target the access to antibiotics by individuals. Third, various interventions aim to establish a larger degree of surveillance. Last, we bring together various institutional measures to attack the environmental health side of the ABR problem, such as the use of antibiotics in animals, as well as emissions of antibiotics. In accordance with the broad notion of 'health research' introduced in the former section, these interventions span a wide array of different actions and policies. As a consequence, we will consider many different levels and types of intervention; both on the scale of an individual patient–doctor interaction, as well as on the level of macro-economic interventions, institutional regulation and global health treaties. Varied though these interventions may be, they all share the characteristic of aiming to help curbing – or otherwise fighting – ABR. To what extent it can be demonstrated that they are effective in that regard, and to what extent they pose risks of their own, determines whether they can be responsibly introduced.

Not all interventions in the fight against ABR are new. In fact, a number of important interventions intended to counter ABR belong to the classic public health

[24] Geisbert, Thomas W. (2015). "Emergency treatment for exposure to Ebola virus: the need to fast-track promising vaccines." Jama 313.12: 1221–1222.

[25] Rid, Annette, and Ezekiel J. Emanuel. (2014). "Ethical considerations of experimental interventions in the Ebola outbreak." *The Lancet* 384.9957: 1896–1899.

repertoire: screening, surveillance, quarantine, hygiene, and so on. Although they are not always uncontroversial, these interventions have been thoroughly tested and proven effective. Unfortunately, however, they will not suffice in addressing the problem of ABR.[26] New methods will need to be explored, which raises the question how to determine which intervention is preferable; which offers greater relative benefit, and which poses fewer relative risks? The answer to that question depends on the evidence available to assess the various interventions. We have no ambition here to be complete in listing the possible, but aim to illustrate and map some major complexities that arise when balancing the level of precaution against the price of precaution.

22.4.1 Biomedical Interventions

A fundamental problem in managing and fighting ABR is the lack of appropriate biomedical interventions. One aspect of this is *the lack of truly new antibiotics*. Although there is some progress in the development of novel antibiotics that affect Gram-positive bacteria (bacteria with a single outer cell wall),[27] innovation for Gram-negative bacteria that has reached the market has for decades consisted only in variations of the same.[28] In part, this can be attributed to the fact that developing new antibiotics is relatively unappealing from a business point of view. Therefore there is a widely recognized and urgent need to encourage academia and pharmaceutical companies to develop new antibiotics, and to facilitate their introduction.[29]

So-called *expedited programs* to this effect have been launched, for example by the US Food and Drug Administration (FDA).[30] Interventions included in such programs are priority review, accelerated approval, and fast track (which can be combined).[31] By promising a swifter, simplified and/or more relaxed process for licencing new therapies, such options both offer incentives to industry to invest in

[26] O'Neill, Jim (2014). Antimicrobial resistance: tackling a crisis for the health and wealth of nations. Review on antimicrobial resistance.

[27] Wright, Gerard. (2015). "Antibiotics: An irresistible newcomer." *Nature* 517.7535: 442–444.

[28] See, e.g., University of Illinois at Urbana-Champaign. "Antibiotic breakthrough: How to overcome gram-negative bacterial defenses." *ScienceDaily*. www.sciencedaily.com/releases/2017/05/170510132012.htm (accessed July 6, 2017); WHO 2015.

[29] World Health Organization, WHO. *Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics*. Geneva: World Health Organization, 2017. Online access: http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en (accessed July 28, 2017)

[30] U.S. Department of Health and Human Services. *Guidance for Industry. Expedited Programs for Serious Conditions – Drugs and Biologics*. Washington: USDHHS, 2014. Online access: https://www.fda.gov/downloads/drugs/.../ucm358301.pdf *(accessed July 7, 2017).* See for a more elaborate discussion: Munthe, C., & Nijsingh, N. (2019). Cutting red tape to manage public health threats: An ethical dilemma of expediting antibiotic drug innovation. Bioethics, 33(7), 785–791.

[31] https://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm (accessed July 28, 2017)

the development of new antibiotics, and speed up the introduction of successful fruits of such endeavours. Interventions of this sort appear attractive, considering the potential damage that lack of development and delay could cause, motivating a lower acceptable price of precaution than in the case a "normal" drug development context. At the same time, entirely new classes of antibiotics imply elevated uncertainties regarding effect and side effects, pointing to a need for *more* caution, and motivating a higher price of precaution. In addition, problems with regards to the control of prescription, use and transmission imply further uncertainties regarding the benefits of "expediting" new antibiotics. In particular, it creates a stark tension between the overall aim of ABR research and the needs of patients burdened by resistant infections. If a new compound is introduced in a setting where the mentioned problems have not been mastered, resistance, though inevitable, can be expected to develop faster. As a result, there is a relative public health benefit to delay the discovery and introduction of new antibiotics while addressing the problems of ensuring responsible use, and mitigating transmission of resistance. Still, earlier introduction may save lives and reduce morbidity of individuals. Therefore, it is less clear whether expedited programs for the introduction of new antibiotics should be at the top of the priority list. Unless they are combined with effective measures to control usage and transmission, they introduce graver uncertainties of both negative side effects for patients, and of having the overall aim of managing the ABR problem undermined. Below, we will comment on interventions to manage this complexity of the ABR challenge.

Another aspect of this challenge is that, if resources are concentrated to this effect, it may be possible to develop drugs to take in order to mitigate plasmid-mediated transmission of resistant bacteria from one patient to others. These could be taken by patients with resistant infections, but also patients who take antibiotics where this treatment may otherwise give rise to local resistance. This is a possible intervention that is still in a very early stage of exploration,[32] which means there will be a long and expensive path to any possible actual treatment. At the same time, there is an obvious risk that no such success awaits at the other end – creating a severe uncertainty with regard to the actual worth of incentive schemes aimed at effecting such focused research and development endeavours. In addition, any successful treatment of this sort will create an ethical challenge in terms of exposing patients to the risk of side effects of the treatment without any sort of potential somatic benefit for these same patients. If it is successful, it will have an important general primary preventive effect of great public health value in the face of the ABR problem. If the introduction of such a drug would be "expedited", this will at the same time increase the risk and uncertainty regarding negative side effects concentrated only to those people taking the drug. Weighing these stakes has to be a part of striking the balance between what the acceptable price of precaution is to be when comparing incentive schemes.

[32] See, e.g., Buckner, Michelle, Maria Laura Ciusa, and Laura JV Piddock. (2018). "Strategies to combat antimicrobial resistance: anti-plasmid and plasmid curing." *FEMS microbiology reviews*.

Controlling use and transmission is less essential regarding therapeutic interventions where resistance development is not an apparent threat. Phage therapy (the therapeutic use of viral strains to attack bacteria) might fall into that category.[33] The efficacy and safety of phage therapy has not been proven to the stage where it would fulfil current guidelines in Europe and the USA. However, it might be that these guidelines do not quite suffice in assessing the responsible introduction of phage therapy, e.g. since individually designed cocktails may be required for each patient, creating an impediment for designing controlled trials. Thus, phage therapy, or other innovative solutions that do not (as new antibiotic compounds) feed immediately into the ABR development problem, may be a better target for "expedited programs" from an ABR standpoint – at least while we lack effective means to control use and transmission. On the other hand, accepting the higher degree of uncertainty, means lowering the level of required precaution, which may harm patients severely if experimental treatments turn out to be unsuccessful.

A more general challenge posed by all types of expediting program interventions, is that they may inadvertently create incentives that give rise to negative dynamics regarding drug development. The basic problem is that any expedited program creates an incentive for industry to re-direct their research efforts in a way that shapes studies to be less stringent and clinically relevant than what they would otherwise have been. A well-known example of this is the acceptance of surrogate outcome variables (an essential part of accelerated approval interventions), which makes it economically attractive for companies to run studies measuring only these, meaning that there will be a structural dynamic change of clinical research efforts into paths with less potential or without demonstrating actual clinical value. Similarly, so-called compassionate use programs have recently come under fire for creating a structural incentive for industry to move more and more drug development out of the default review process, thus creating a generally decreasing level of safety and elevated uncertainty regarding effect. To be sure, expediting programs partly aim at having industry thus allocate their efforts and resources, however, if there is a structural negative dynamic on the general effectiveness of new drugs, this must be viewed as a relevant downside. For that reason, policy makers may want to consider other solutions to the issue of drug development, such as rewarding pharmaceutical companies for developing new antibiotics, for example with exclusivity extensions, buyouts and entry prizes.[34] Each of these interventions has the potential to offer incentives to the pharmaceutical companies, but also to pose risks to society

[33] De Vos, Daniel & Pirnay, Jean-Paul (2015). "Could viruses help resolve the worldwide antibiotic crisis?" *AMR Control*, 110.

[34] Seth Seabury Neeraj Sood (2017, May 18). Toward A New Model For Promoting The Development Of Antimicrobial Drugs. *Health Affairs Blog*: http://healthaffairs.org/blog/2017/05/18/toward-a-new-model-for-promoting-the-development-of-antimicrobial-drugs/(accessed July 28, 2017); Morel, Chantal M., and Elias Mossialos. "Stoking the antibiotic pipeline." *BMJ: British Medical Journal (Online)* 340. Jim O'Neill (2014) has also suggested a ´pay or play´ principle, where pharmaceutical companies are required to either contribute or pay a fine.

and individuals, for instance a risk of social backlash.[35] There are, of course, also large uncertainties regarding whether or not such actions would be money well spent.

Returning to our main question concerning the evidence required for justifying various interventions that aim to offer incentives to develop new medicine, we see that a trade-off has to be made not just between individual and public interest, but also between various levels of uncertainty, and risks of structural negative dynamic effects. If faster development of antibiotics comes at the price of faster emergence of ABR for those same drugs, this raises the question on how to appreciate the urgency of the matter. In particular, it demands that we weigh current ABR against possible future ABR and the likelihood of developing alternatives for which ABR development is not an issue. There is both a danger of being retrospectively overly restrictive in the use of antibiotics when an alternative to the current drugs is found, as well as a danger of complacency based on the false reliance on such an alternative. At the same time, we need to weigh into the balance the apparent but uncertain risk of incentive schemes being structurally counterproductive.

22.4.2 Prescription Practices

Since the individual use of antibiotics is an important driver of ABR, interventions aiming to control the distribution of antibiotic drugs to individual patients are an important part of ABR policy. The proposed interventions include mandating prescription policies (in those countries where this is not already the case), various limitations to the type of antibiotics that are made available and improved access where antibiotics are currently lacking.

It is a received wisdom that the prescription system is an effective way of controlling the use of drugs. At the same time, the effectiveness on the system may vary, depending on numerous factors. For instance, antibiotic prescription practices across European regions vary considerably, linked to varying levels of institutional corruption.[36] Such structural challenges can be assumed to multiply in countries where there is no system or culture of effective prescription for antibiotics. Given the widespread acceptance of the over-the-counter availability of antibiotics in such societies, not only among citizens, but also medical professionals, and sometimes policy makers, there is a recognised uncertainty as to the real impact of trying to create or toughen up such regulation.[37]

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[35] Munthe et al. (2019).

[36] Rönnerstrand, Björn, and Victor Lapuente. (2017). "Corruption and use of antibiotics in regions of Europe." Health Policy 121.3: 250–256.

[37] Radyowijati, Aryanti, and Hilbrand Haak (2003). "Improving antibiotic use in low-income countries: an overview of evidence on determinants." *Social science & medicine* 57.4 (2003): 733–744. Dreser, Anahí, et al. (2012). "Regulation of antibiotic sales in Mexico: an analysis of printed media coverage and stakeholder participation." BMC public health 12.1: 1051.

We meet here with a type of uncertainty that is entirely about how societies may react to attempted institutional change.[38] Weighing into the mix economic, cultural and institutional factors of relevance, a more incremental change seems preferable. It provides opportunity to attend to the interests of various stakeholders, as well as taking the time for a society to adjust, in order to ease both the passing of regulation, and its effective implementation. However, that requires quite a bit of knowledge of such mechanics of overarching social change, and also uses time itself as a factor. This raises the question of how long is long enough to attempt establishing social change, and how much effort should be spent on securing the understanding of how to make such attempts work. Facing the ABR challenge, how high should the price of precaution due to delaying prescription regulative action be allowed to rise while attending to such uncertainties?

For countries where a reasonably effective prescription practice is in place, unless a patient is critically ill, the first choice of antibiotics is often not the latest, most potent formula (with still limited resistance problems). Therefore, antibiotics prescribed usually bring a greater risk that the treatment will not cure the infection due to resistance. At the same time, this practice serves to protect the future integrity of "last line antibiotics" by minimising their use and thereby inhibiting the evolutionary drive towards resistance to them. Most commentators describe the payoff of these interventions in terms of *public good*, whereas risks of implementing them are considered to be carried by single *individuals*.[39] However, matters are slightly more complex than that. First, although there is agreement that this intervention does delay resistance for broad-spectrum compounds, the magnitude of the effect is still uncertain. Second, since broad-spectrum antibiotics are more likely to drive resistance in the individual patient's own gut flora,[40] there is also a chance of individual benefit linked to prescription practice.

We thus face a complex trade-off situation, where individual risks of suffering untreated infections must be balanced against the uncertain prospect that patients are protected against being infected by resistant bacteria, at the same time as the question remains whether this mix of risk and uncertain benefit for some individuals can be justified by a social benefit of uncertain magnitude. This also raises the question how much effort should be spent on making sure that the right balance is struck, for example by straightening out some of the important uncertainties.

In any case, agreeing that such a practice is indeed justified does not end the problem. We must also ask what intervention would actually effectively address it.

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[38] The risk of incentive schemes for drug creation to produce unintended negative dynamics via their effect on industry in the former section also belongs to this type.

[39] Littmann, Jasper, and A. M. Viens. (2015). "The ethical significance of antimicrobial resistance." *Public health ethics* 8.3: 209–224.

[40] This is phenomenon can be observed in urinary tract infections, for example. As the normal non-resistant invading bacteria of this flora are exterminated by the treatment, a very fertile living space is created for bacteria that are resistant against the drug used. Costelloe, Ceire, et al. (2010). "Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis." Bmj 340: c2096.

One idea, of course, is to make professional prescription guidelines for doctors to use. However, this introduces the uncertainty that doctors may fail to apply them, e.g., due to patient pressure, economic counter-incentives, or the mere inertness of habit. To address that, there is the option of allowing professionals less choice, for example by requiring application to a higher instance and proof of due cause for having a prescription green lighted. Such an intervention could consist of several levels of requirements, and for some antibiotics regular doctors may be stripped of all prescription rights. At the same time, being able to leave professional discretion to doctors in individual cases also has its value, and the more of rigid restriction is built into an intervention, the bigger the risk that individuals are harmed due to lack of (timely) access to treatment. However, rigid regulatory interventions clearly avoid the uncertainty with regard to the overall aims of delaying resistance development, as well as avoiding harmful individual prescriptions. To make this trade-off, it would be of great value to know more about the social dynamics creating the uncertainty around the effectiveness of prescription interventions, as well as how these might be complemented by additional institutional changes to mitigate the pressure on doctors from patients, and to remove economic counter-incentives.[41] On the other hand, as we delay action, or apply overly cautious interventions with uncertain effectiveness while making sure what more exact variant would be best, the price of precaution is allowed to go up in terms present prescription practices being allowed to continue.

This precautionary challenge is further complicated by the fact that there is an instrumental value to fine-tune prescription interventions so that treatment of infection is optimized also under a restrictive prescription practice. The reason for this is that increased persistent infection can be expected to increase the future demand and consumption of antibiotics, thereby accelerating rather than mitigating resistance development in the long run.[42] Depending on what current prescription practices look like in specific societies, this may mean that an optimal prescription intervention should not only decrease prescription, but in some cases leave it as it is, and in yet other even *improve* the access to antibiotics. Considerations of fairness may add further reasons to a similar effect, and also the need of securing the legitimacy of any policy in this area. After all, of what interest is the issue of ABR to anyone who is barred from accessing appropriate antibiotics in the first place? This further complicates the uncertainty about what exact intervention would be most effective. But it also adds a basic source of uncertainty with regard to how the moral stakes should be balanced in a measure of effectiveness. A sound precautionary solution therefore needs to acknowledge the latter point when striking the balance between ensuring a desired level of precaution at an acceptable price of precaution, and allow both considerations of health promotion and fair distribution of the population health.

[41] As such changes may involve drastic reform to entire health care and health insurance systems, the knowledge required is quite advanced and complicated to collect.

[42] Daulaire, N., et al. (2015). "Universal access to effective antimicrobials: an essential feature of global collective action against antimicrobial resistance." *Journal of Law, Medicine & Ethics* 43.2.

22.4.3 Surveillance

The fight against ABR also requires enhanced possibilities of diagnosis and surveillance of resistant bacteria. Better diagnostic methods are in themselves unobjectionable as increased speed, precision and readiness in determining the cause of an infection limits the danger of squandering antibiotics. However, there will be trade-offs between increasing speed, increasing precision and financial costs and possibly the intrusiveness of the sample taking. Because of this, as well as the general uncertainties befalling any new measurement tool, there is once again a challenge to decide how much support for the reliability and validity of a new diagnostic tool has to be secured in order to start implementing it. The balance here, as before, includes assessing the value of more firm knowledge against the price of precaution in terms of delaying tools that may also offer opportunities for better surveillance in the face of the ABR threat. But it also includes the complications as more speedy introduction will tend to increase one or the other of well-known downsides to such interventions.

These complications become especially challenging as resistant infections or even carriership may often actualise restrictive communicable disease management measures, such as compulsory isolation, quarantine or mandatory life-style restrictions. The implied tension between individual interest and collective good is particularly salient when this involves asymptomatic carriers, who have nothing to benefit from being institutionalized.[43] The issue is further complicated when we consider the possibility of false positives, where patients are wrongly identified as carrying resistant bacteria. As in the former section, this also links to a risk of undermining the legitimacy of ABR policies. Thus, while speedy introduction of diagnostic methods certainly has its potential upsides, it will increase uncertainties of a sort that in other areas are often taken to undermine health surveillance programs.

Attempting to strike these several balances, we face the general problem of having the right idea concerning the moral stakes involved and a sound notion of what price of precaution to allow. In addition, increased complexities of how to assess the quality of available and attainable evidence for ambitious and complex public health interventions add another layer of uncertainty.[44]

[43] Weinstein, Robert A., Daniel J. Diekema, and Michael B. Edmond. (2007). "Look before you leap: active surveillance for multidrug-resistant organisms." Clinical Infectious Diseases 44.8: 1101–1107. Nijsingh, N., Juth, N., Munthe, C., "The Ethics of Screening", in: Quah, Stella R. International encyclopedia of public health. Academic Press, 2016. Nijsingh, N., Munthe, C., Lindblom, A., & Åhrén, C. (2020). Screening for multi-drug-resistant Gram-negative bacteria: what is effective and justifiable?. Monash bioethics review.

[44] Attena, (2014).

22.4.4 Environment and Animals

A wide variety of ABR interventions relate to attempts to curb the emission of antibiotics in the environment[45] and their use in animals. We have grouped these together because of the potential risks of the interventions, which seem mostly economical. For example, attempts to enhance transparency of pharmaceutical companies[46]or banning of the use of antibiotics as a growth enhancer,[47] or taxing consumer products emanating from ABR driving practices, such as meat production,[48] do not have direct health risks for humans. Compared to the possible economic damage of such interventions, the health risks of ABR may seem to clearly win out. However, there is still much uncertainty concerning the role of non-human use and pollution in the establishing of ABR and economic cost of interventions carry their own set of secondary risks and uncertainties, which might be substantial indeed as the incurred costs become more significant.

One obvious uncertainty regards the effectiveness of systems of surveillance and control of emission rates in production or compound use in farming. These will include uncertainties and imprecisions of technical methods, but even more institutional uncertainties of the sort we have already discussed related to prescription and surveillance interventions. As already observed, straightening these uncertainties out includes coming to grips with very complex social circumstances, and may require quite a lot of time and resources.

On top of this, macro-economic ABR interventions targeting environmental emission may have adverse effects in themselves, both socially and economically, for instance, by discouraging pharmaceutical business and thereby restricting access to drugs generally. Consequently, we may legitimately ask which interventions are necessary, or reasonable, and which are disproportional, given the uncertain effects of current practices. Should, for instance, pharmaceutical companies be required to monitor and make sure antibiotics emission from manufacturing are very low?[49] Or should regulation rather target the pricing of products, adding tax or extra cost in the procurement of drugs by public national health services? Or should some other

[45] Pruden, Amy, et al. "Management options for reducing the release of antibiotics and antibiotic resistance genes to the environment." *Environmental health perspectives* 121.8 (2013): 878.

[46] Larsson, DG Joakim, and Jerker Fick. "Transparency throughout the production chain—a way to reduce pollution from the manufacturing of pharmaceuticals?." *Regulatory Toxicology and Pharmacology* 53.3 (2009): 161–163. Nijsingh, N., Munthe, C., & Larsson, D. J. (2019). Managing pollution from antibiotics manufacturing: charting actors, incentives and disincentives. Environmental Health, 18(1), 95.

[47] Laxminarayan, Ramanan, Thomas Van Boeckel, and Aude Teillant. (2015). "The economic costs of withdrawing antimicrobial growth promoters from the livestock sector.".

[48] Giubilini, Alberto, et al. (2017). "Taxing Meat: Taking Responsibility for One's Contribution to Antibiotic Resistance." *Journal of Agricultural and Environmental Ethics* 30.2: 179–198.

[49] Bengtsson-Palme, Johan, and DG Joakim Larsson. (2016). "Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation." *Environment International* 86: 140–149.

institutional intervention to similar effect be chosen, for example having high emissions in production reduce the calculated health benefit in the context of health technology assessment? In all these cases, should the link between detected emission rates and such incentives be proportionally or more rigidly designed? If the former, according to what formula or proportionality, if the latter, on what grounds should thresholds be set? And what institutional arrangement would be effective to have whatever intervention is chosen to be effectively implemented? Similar questions appear with regard to interventions aimed at creating incentives to reduce the use of antibiotics in farming.[50]

All of this makes for a considerable difficulty in assessing the proper balancing of the level of precaution and its acceptable price. Surely, the urgency of mitigating major environmental practices that fuel antibiotic resistance development is a priority. However, to find the right way of doing this requires quite a bit of very complex knowledge, and behind this need lurks the very real risk that a more speedy introduction of interventions is not only sub-optimal, but actually makes the problem worse. For instance, implementing any of the regulative interventions mentioned may mainly have the effect of having pharmaceutical and food production relocating to areas where the regulative situation is even worse. Or secondary effects, e.g., in the form of drastically increased food prices may both undermine the legitimacy of ABR policies and create a public health threat of its own. On the other hand, it is well known that it takes considerable time to have large-scale operations such as drug production and farming change their longstanding ways, and in the light of that, applying interventions to address the environmental side of the ABR challenge is paramount.

22.5 Discussion

We have assessed interventions with regard to how much and what kind of evidence is needed when evaluating and implementing interventions in response to antibiotic resistance, a public health threat of immense proportions. The notion of responsible precautionary decision-making provides a basic and strong reason to act in response to this threat. However, determining *what* response to go for introduces complex problems of balancing what level of precaution to aim for and what price of precaution to pay, actualising much more difficult ethical challenges than what is often acknowledged.

We end this exploration by briefly addressing two issues that emerge when we consider the evidence for interventions that aim to fight antibiotic resistance, leading into a final broad suggestion for future analyses to build on.

[50] Silley, Peter, and Bernd Stephan. (2017). "Prudent use and regulatory guidelines for veterinary antibiotics—politics or science?." *Journal of applied microbiology* 123.6: 1373–1380.

First, there is the sheer size of the possible consequences of increased ABR. For example, there is a real question whether standards of treatment and diagnosis in research ethics and clinical ethics may need revision in light of a public health threat as significant to global wellbeing as ABR. Although one should be wary to discard too easily the frameworks that have proven to be of value throughout the years, the possible disruptive effects of ABR raise the issue to what extent these standards can be maintained, given the range of difficult choices we might face. At the same time, we have seen that many of the uncertainties posed by ABR interventions are not so much about having risks of undesirable side effects as such are typically conceived of when evaluating pharmaceuticals. Rather, the important uncertainties are about risks of outright counterproductivity due to social psychological and institutional dynamics, where apparently promising attempts to counter ABR may instead lure us into political, economic or psychological dead ends from which we are unable to get out. Social processes are typically slow, variably inert and intractable, which means also that they may be very difficult to reverse, and that doing so may require a lot of time. Given that interventions on all of the mentioned levels are probably necessary to reduce the risk of emerging resistance and that they are to a large extent interrelated, the standards of evidence should be set from an integrated, One Health perspective.

This connects to the general observation that methods in response to ABR have to intervene on a variety of different levels, from the everyday practice of physicians to those affecting global structures. Interventions worthy of consideration therefore involve a myriad of different types and degrees of uncertainty and risks, which are also unevenly distributed across people, societies and time. Assessment of the evidence thus needs to consider a multi-layered mosaic of uncertainties and ethical dilemmas regarding the short- and long-term trade-off between individual interests and public health aims. This regards especially the issue of how much and what evidence to collect regarding the effectiveness of interventions, and their potential long-term legitimacy.

These considerations may drive one to despair whether a responsible, measured approach to the issues at play here is at all feasible. One way of moving forward in the light of these considerations is to acknowledge that there are good – moral *and* precautionary – reasons to cut the Gordian knot: just as there is a question of how much to amass and ponder evidence and the proper resolution of ethical dilemmas, we must not get stuck forever in the precautionary conundrum. Moving along such a path, one primary consideration is then to assess the relative importance of avoiding harm and risk of harm that result from otherwise apparently effective intervention packages, while avoiding the pull of the enormity of the ABR challenge to lure us into policy deadlocks. In doing so, the complexity and close connections of the various risks offer strong grounds for putting the reversibility of potential adverse consequences at centre stage. Related to debates on the ethics of precaution, this links to different proposals on how to limit the scope of a precautionary principle,

e.g., in terms of *de minimis* risk, and, more specifically, to the importance of avoiding irreversible negative outcomes. This is not to say that this is a generally plausible solution for all precautionary decision-making, but the peculiar complex challenges of assessing evidence for ABR interventions seem to add reasons for the fittingness of an approach that prioritises reversibility.[51]

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