This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

Cutting red tape to manage public health threats: An ethical dilemma of expediting antibiotic drug innovation

Christian Munthe
Department of philosophy, linguistics and theory of science, and the Centre for antibiotic resistance research, CARe, University of Gothenburg.
Christian.munthe@gu.se

Niels Nijsingh
Department of philosophy, linguistics and theory of science, and the Centre for antibiotic resistance research, CARe, University of Gothenburg.

Abstract

Antibiotic resistance, arising when bacteria develop defences against antibiotics, creates a public health threat of massive proportions. This raises challenging questions for standard notions in bioethics when suitable policy is to be characterised and justified. We examine the particular proposal of *expediting innovation* of new antibiotics by cutting various forms of regulatory "red tape" in the standard system for the clinical introduction of new drugs. We find strong principled reasons in favour of such lowering of the ethical standards of research and clinical introduction of new antibiotic formulas. However, this support is undermined by pragmatic challenges due to expected responses from stakeholders, creating uncertainty about what policy could actually be effectively implemented. We describe an underlying dilemma on how to rationally justify compromises between ideal ethical justification and pragmatic risks that needs to be further addressed in this light. We suggest a solution to this dilemma related to proposals of expediting antibiotic drug innovation.

Keywords

Antimicrobial resistance, health policy, legitimacy, pharmacological policy, research ethics, risk and uncertainty

Acknowledgements

This research was supported by the UGOT Challenges Initiative of the University of Gothenburg, and by Riksbankens Jubileumsfond, RJ (application F17-1078:1), for the project *Ethics and Value Challenges in Antibiotic Resistance Management, Policy and Research*.

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

Introduction

Antibiotic resistance[1], arising when bacteria develop defences against antibiotic drugs, creates a public health threat of massive proportions that is particularly difficult to manage well. The main reason for this is that the threat results from a complex interaction of different causes that jointly lead to a gradual accumulation of the problem, which are difficult to counter effectively in a coordinated way. The threat is massive for well-known reasons. If pathogens continue to develop defences against drugs, this could potentially render the medication used against common infections worthless. Not only will this raise the risk of widespread epidemics, it will also endanger current medical practice in several ways. Hospital infections will make inpatient care very dangerous, while the prophylactic use of antibiotics in, for example, surgery, cancer and neonatal care will become futile[2].

Given such dire prospects, the antibiotic resistance challenge raises specific ethical issues about how proportional reactions should be characterised and justified, and what that implies for standard notions in bioethics[3]. One such issue regards to what extent the extraordinary character of the antibiotic resistance threat justifies extraordinary measures, otherwise ruled out on ethical grounds: Should we suspend, abandon or relax 'normal' requirements and standards in medicine, research and health policy? If so, why? And to what extent? In this paper, we focus on one particular idea to

[1] Resistance to other kind of drugs than antibiotics may also pose challenges. Some have therefore advocated the more inclusive term "antimicrobial resistance", or the more unspecific but easily understood term "drug resistance", see Mendelson, M., Balasegaram, M., Jinks, T., et al. (2017). Antibiotic resistance has a language problem. Nature. 545(7652), 23-25. As not all drug resistance gives rise to the public health challenges we focus on in the present context, we have nevertheless chosen to restrict ourselves to antibiotic resistance.

[2] World Health Organization, WHO (2014). The Evolving Threat of Antimicrobial Resistance: Options for Action. Geneva, Switzerland: WHO; World Health Organization, WHO (2015). Global action plan on antimicrobial resistance. Geneva, Switzerland: WHO.

[3] Littmann, J. & Viens A.M. (2015). The Ethical Significance of Antimicrobial Resistance**.** Public Health Ethics. 8(3), 209–224.

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

this effect, namely the notion of *expediting* innovation[4] of new antibiotics by cutting various forms of regulatory "red tape" that are part of the standard system for the development, testing and clinical introduction of new drugs.

One recognised aspect of the drug resistance challenge is the lack of new antibiotic formulas. The consequences of biological resistance development could be handled much better if there was a regular supply of new drugs to replace the ones made inefficient through resistance[5]. However, neither the pharmaceutical industry, nor biomedical research currently prioritize such work, which has led to calls for policy incentives to change this course and stimulate innovation with a strong potential to limit the threat of antibiotic resistance[6]. One group of such incentives is the idea of "expediting" the innovation process by relaxing regulatory requirements and procedures in various stages of the innovation process[7]. Each such stage will present ethical issues, including what level of safety is required to move from preclinical to clinical research, what research ethical requirements are applied in such clinical research, and what standards of proof of effectiveness and

[4] In line with the FDA standard understanding, we use the term (drug) "innovation" to signify all science-based development of new products (in this case antibiotics). This development occurs at several stages, which we explain later in the article. See: https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm592464.htm . There exists extensive general research on the economics and policy of biomedical innovation, posing questions that we do not currently engage with. See, e.g., Karlsson, C. (ed.) (2008). *Handbook on research on innovation and clusters: Cases and policies*. Cheltenham, UK: Edward Elgar Publishing.

[5] As is generally recognized (see for example WHO (2015), op. cit. note 3, innovation would on its own be only partially helpful. In addition, reform is needed to promote antibiotic stewardship, as well as efficient systems for optimal access to antibiotics. However, without innovation, such actions will have only a temporary and limited effect on the challenges resulting from antibiotic resistance.

[6] WHO (2015), op. cit. note 3; Theuretzbacher, U (2017). Antibiotic innovation for future public health needs. Clinical Microbiology and Infection. 23(10), 713-717.

[7] There are also other ideas about how to stimulate industry action in this respect, such as various forms of direct monetary incentives. See, for instance, Nijsingh, N., Larsson, D.G. J., Persson de Fine-Licht, K., Munthe, C. (2019). Justifying Antibiotic Resistance Interventions: Uncertainty, Precaution and Ethics. In Jamrozik, E. & Selgelid, M. (Eds.). Ethics and Antimicrobial Resistance: Collective Responsibility for Global Public Health. Cham: Springer, in press; Seabury, S., Sood, N. (2017). 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, C.M., Mossialos, E. (2010). Stoking the antibiotic pipeline. BMJ: British Medical Journal 340, c2115. Doi: 10.1136/bmj.c2115. In the present context, we are, however, limiting ourselves to the expediting strategy.

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

safety are required for clinical introduction.[8] In this paper, we present a special group of pragmatic challenges and an underlying ethical dilemma of relevance to the analysis of these ethical issues.

We will, first, present in more detail different forms of expediting antibiotic innovation, and formulate the ethical case in favour of such reform. Accepting that this case is strong in principle, we then review a particular type of complicating factor, namely what in other contexts have been termed *pragmatic risks*[9]: how stakeholders and key actors may respond negatively or otherwise suboptimal to the reforms. We argue that such risks create a problematic situation for the justification of the idea of expediting antibiotic innovation by cutting red tape, as adjustments to accommodate for these risks tend to undermine the initial justificatory reasons. We then describe a more general ethical dilemma of how to balance ethical reasons and pragmatic risks when evaluating policy proposals, and suggest an answer to how this dilemma should be resolved with regard to proposals of expediting antibiotic innovation.

Forms of expediting innovation and the case for cutting red tape

The innovation of a new drug has a long path, from basic research to actual clinical introduction. Along this path, a number of regulatory frameworks are in effect to structure how a candidate is reviewed and assessed in different stages of the journey. Examples of importance include rules on patenting, criteria for assessing proof of effect and risks in research, ethical review of drug trials and requirements applied in such settings, the licensing of a new drug based on effect and safety standards based on trial outcomes, and decisions to include a new licensed drug in clinical guidelines and/or subsidy systems. Part of these frameworks may differ in detail and form between

[8] Fast track options, such as priority review, are not obviously riskier, but do involve taking resources away from other type of drugs that are being developed, and may raise issues of systemic bias against more promising candidates for new pharmaceutical treatments related to serious conditions.

[9] Nijsingh et al. (2019) op. cit. note 8; Munthe C., Nijsingh N., Persson de Fine Licht K., Larsson D.G.J. Health-related research and social value: Drug resistance intervention research and pragmatic risks, *in review*.

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

states (sometimes significantly so), while others (such as those of licensing, or common scientific standards) are increasingly harmonized across the world. But each of them offers options of *what* requirements to apply and *how* to apply them. Authorities (or, when the regulation is informal, the parties controlling the issue, such as a branch of the biomedical research community deciding proof and effect-risk standards in research) may thus opt to relax some of the standards and procedures for candidates for new antibiotic candidates, in order to ease and speed up the innovation process, as has been done in so-called orphan areas of pharmaceutical innovation, for instance in the USA[10].

In the following, we will include potential expediting reforms targeting all stages of the innovation process, from the initiation of clinically relevant basic research to pre-clinical and clinical research evaluating candidates, to decisions to license and include a new drug in clinical recommendations. All of these stages are of importance for the actual emergence of new antibiotics available for clinicians, and are therefore necessary to address in order to accomplish an enhanced innovation that could have a real impact on the antibiotic resistance challenge. We are excluding any regulatory frameworks or considerations beyond this stage, for example regarding systems of procurement by health systems, or the clinical ethics used by medical practitioners when deciding what (among licensed and recommended) drugs to actually use, and how to use them, in single cases.

While some have argued that, in situations of extreme hazard and threatening chaos, ethical considerations have no place in justifying actions[11], we consider all potentially justifying reasons brought to bear on such actions ethical. At the same time, it is widely recognized that extreme circumstances may present reasons to overstep standards accepted in normal situations. In the case

[10] U.S. Department of Health and Human Services. (2014). Guidance for Industry. Expedited Programs for Serious Conditions – Drugs and Biologics. Washington: USDHHS. Retrieved July 7, 2017 from https://www.fda.gov/downloads/drugs/guidances/ucm358301.pdf

[11] Orend, B. (2001). Just and Lawful Conduct in War: Reflections on Michael Walzer. Law and Philosophy, 20(1), 1-30.

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

at hand, then, the idea is that the extreme stakes presented by the antibiotic resistance threat, and the role of drug innovation to curb it, such innovation need not be scrutinized as strictly as otherwise required: the normal "red tape" does not apply or, at least, should be partially cut[12]. In the case of the antibiotic resistance challenge, we find five grounds to accept this sort of reasoning, besides simply appealing to a benefit-harm style calculus and the massive stakes:

1. *Innovation speed is crucial*: the antibiotic resistance challenge links to specific need of speedier development of new compounds to "win the race" against resistant pathogens. The notion of expedited antibiotic drug innovation targets exactly that need. Other strategies to respond to the challenge cannot compensate if speedier innovation cannot be effected. This argument supports not only expedited innovation, but also other kinds of interventions to speed up drug development, such as financial incentives.

2. *Inapplicability of research ethical exceptionalism*: Standard ideas of benefit-safety relationships, proof standards, et cetera, for testing and introducing new drugs assume the presence of a decently working health system that offers solidly grounded treatments that can be applied while awaiting the next better thing. This is the motivation of what has been called research ethical exceptionalism[13] and why, for instance, clinical equipoise is normally thought to be required to justify experimentation with new therapies on patients[14]. However, the nature of how antibiotic resistance threatens to undermine (and to already be damaging)

[12] This line of reasoning is common in theories of 'supreme emergency', such as found primarily in war ethics (see however Sandin, P. (2009). Supreme Emergencies Without the Bad Guys. Philosophia, 37(1), 153-167.) When in 2014-2015 the Ebola epidemic struck, similar arguments were heard. See Geisbert, T.W. (2015). Emergency treatment for exposure to Ebola virus: the need to fast-track promising vaccines. Jama. 313(12), 1221-1222; Rid, A. & Emanuel, E.J. (2014). Ethical considerations of experimental interventions in the Ebola outbreak. The Lancet, 384(9957), 1896-1899.
[13] Wilson, J. & Hunter, D. (2010). Research Exceptionalism. American Journal of Bioethics, 10(8):45-54.
[14] London, A.J. (2017). Equipoise in Research: Integrating Ethics and Science in Human Research. JAMA, 317(5): 525-526.

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

large segments of healthcare means that this assumption cannot be upheld. An exception to the "exceptionalist" stance of standard research ethical norms may thus be justified.

3. *Sustainability threats require special ethical consideration*: The above reason can be generalised into a 'sustainability argument', applicable to ordinary biomedical research ethics. It may be argued to hold for any institution meant to ensure some important good, that if this the norms governing this institution serve to undermine its future ability to deliver this good, it is permissible (if not imperative) to set aside the norms normally governing it. It is obvious how this kind of reason may be applied to the antibiotic resistance threat in light of how it undermines the effectiveness of healthcare. Moreover, together with the drastically increased risks of epidemic outbreaks, this will in practice mean that the prospect of future biomedical innovation is undermined (as medical research and development is much more difficult in a chaotic societal situation, and resources are usually reserved for managing acute problems)[15].

4. *The antibiotic resistance threat activates public health ethical norms*: Standard biomedical research ethics rests on an individualistic paradigm, where protection against harm and violation of rights of research subjects and patients is a paramount consideration. However, the reasons 2 and 3, together with the nature of the long-term consequences if the threat is not adequately addressed, means that the values at stake need to be considered in more collectivist terms, moving the issue from the ordinary sector of biomedical research ethics to a public health ethical domain[16]. In that context, innovation regulation must build on the

[15] Angus Dawson has elaborated on the basis of sustainability arguments related to drug resistance in a recent conference presentation, available on video: https://play.gu.se/media/Sustainability+and+antibiotics/0_e6qn6zsu.

[16] Coggon, J. (2010). Does Public Health Have a Personality (and If So, Does It Matter If You Don't Like It)? Cambridge Quarterly of Healthcare Ethics. 19(2): 235–248. Dawson, A. (ed.) (2011). Public Health Ethics: Key Concepts and Issues in Policy and Practice. Cambridge: Cambridge University Press. Munthe, C. (2008). The Goals of

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

need for coordinated political action across time, as well as the public good of having access to effective antibiotics. In that context, harm and infringements to individuals becomes easier to justify, as long as the public health ethical aim is effectively promoted.

5. *Precautionary ethics justifies the imposition of higher risks than normal when ethically important uncertainties need to be settled*. This type of argument has evolved in the area of the ethics of risk and uncertainty of technology and the environment[17], but more recently been applied to bioethical issues and the antibiotic resistance challenge[18]. It builds on the recognition of acting on good reason and evidence as an ethically important consideration, and therefore links immediately to the ethics of regulating research and development in areas of great ethical significance, where there is a serious lack of knowledge and the relevant technology is under development. The antibiotic resistance challenge and its need for drug innovation fits perfectly into this type of reasoning.

We do not claim any of these arguments to be decisive on their own, and note that they may all attract criticism. Nevertheless, we will in the following assume that they jointly offer significant and principled support for expediting antibiotic drug innovation, even if the implied cutting of red tape comes at a cost in terms of more uncertain benefits and elevated risk for research subjects and patients. We do not deny that such reform will actualise many detailed questions regarding design

Public Health: An Integrated, Multi-dimensional Model. Public Health Ethics. 1(1), 39-52; Verweij, M., Dawson, A. (2009). Public Health Research Ethics: A Research Agenda. Public Health Ethics. 2 (1), 1-6.

[17] Munthe, C. (2011). The Price of Precaution and the Ethics of Risk. Dordrecht: Springer.; Steel, D. (2014). Philosophy and the Precautionary Principle: Science, Evidence, and Environmental Policy. Cambridge: Cambridge University Press.

[18] Munthe, C. (2016). Precautionary principle. In ten Have, H. (Ed.), Encyclopedia of Global Bioethics (pp. 2257-2265). Cham: Springer; Nijsingh et al. op. cit. note 8.

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

and implementation[19], and that these will need to be addressed in further ethical assessment. However, we do not provide such details here. We also leave open exactly how far the principled justification that we assume leads, thus leaving for others to pursue further typical bioethical analysis, where different ethical principles and stances are brought to bear on the issue. Instead, we will proceed from our general assumption and address a number of pragmatic challenges that complicate the justification of expediting antibiotic drug innovation, even in light of a strong principled reason in its favour.

Pragmatic challenge 1: Strategical adaption from industry

No matter how lines are drawn in the research ethical argument that we leave for others to work out, relaxing the criteria for antibiotic drug innovation involves accepting greater risk and more uncertain benefits. At the same time, interventions that aim to diminish complex public health threats may backfire due to responses and adapted behaviour of stakeholders[20]. One central stakeholder in the case of cutting red tape to stimulate antibiotic drug innovation is, of course, the pharmaceutical industry. Although it is the point of any kind of expediting reform to have industry adapt its business decisions, they may lead to a situation where, although there are more antibiotics on the market, the public health gain might actually be negative, due to the increase of ineffective or harmful drugs[21]. As we have seen in programs for expediting innovation for orphan drugs and diseases, when industry is rewarded for increasing its innovative flow in one particular domain, it becomes rational to make as much of the innovation to fit that domain, regardless of how well this expanded innovation fits the rationale that originally justified the cutting of the red tape. For instance, many orphan disease programs designed for rare diseases are now being increasingly filled

[19] For instance, issues about damage or risk compensation, as well as global health justice, of the sort discussed by Anomaly and Savulescu, Krockow and colleagues, as well as Millar, in their respective contributions to this special issue.
[20] Nijsingh,et al. op. cit. note 8.
[21] Floyd, J.S. and Psaty, B.M. (2014). The Potential Risks of Expedited Approval of Drugs for Acute Bacterial Infections. JAMA internal medicine. 174(9), 1436-1437.

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

with candidates coming out of recent "personalized medicine" or "precision medicine" efforts for common disease areas (such as cancer). These harvest the benefits of laxer requirements while offering uncertain benefits in terms of the rationale of the original programs[22]. The process also creates opportunity costs in terms of alternative treatments, or treatments in other areas, that are never developed due to the rechannelling of both public and private resources stimulated by the expedited innovation program. Procedures and extra regulation put into place to counter these kinds of developments add extra costs and disincentivise companies from being baited, thus undermining the principled argument for expedited antibiotic drug innovation reform.

None of this is, of course, a result of companies being intentionally malicious, it is a result of companies being companies. From the point of view of business, if the state makes it attractive to launch operations in area *x*, it makes sense for a company to transform more and more of business operations to fit into area *x*. But this transformation may then corrupt the original reason for a state to bait companies into area *x*. Furthermore, it is sound strategical business behaviour to adapt the response in such a way that maximizes the attractiveness of the bait, relative to the cost of the innovation for the company. Such logic can force an expedited reform to cut more red tape in order to have industry respond as desired. In both of these ways, any reform to expedite antibiotic drug innovation may thus be undermined by quite ordinary business rationality. The result is a pragmatic risk that more red tape is being cut for less benefits and at higher costs than assumed in the principled argument in favour of expediting antibiotic innovation.

Pragmatic challenge 2: Negative professional response

[22] Rodriguez-Monguio, R., Spargo, T., Seoane-Vazquez, E. (2017). Ethical imperatives of timely access to orphan drugs: is possible to reconcile economic incentives and patients' health needs? Orphanet Journal of Rare Diseases. 12, 1. Doi: 10.1186/s13023-016-0551-7

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

Other obvious and important stakeholders in the case of the antibiotic resistance challenge are biomedical researchers and health professionals. Just as any reform to expedite antibiotic drug innovation depends on appropriate response from the pharmaceutical industry to serve its purpose, it and its consequences for research and clinical practice need to enjoy sufficient support among involved professionals in order for this reform to be implemented and work as intended. But if researchers and clinicians find these consequences unacceptable, they are likely not to act as they need to act for the reform to produce the desired outcome. They may, for instance, decline to participate in trials they find unethical due to elevated risk levels and more uncertain prospects for future benefits. Similarly, clinical professionals may refuse to recommend a new drug coming out of an expedited process due to the similar reasons. This, of course, holds entirely independent of if such opinions are justified or not (we are presently assuming they are not): professional legitimacy is a key feature of any feasible antibiotic resistance intervention.

This prospect has led some commentators to argue in favour of revisions of the ethics underlying clinical guidelines, so that higher risks and more uncertain benefits for patients are judged more acceptable if they come out of actions to effectively manage the antibiotic resistance challenge[23], and such notions may be extended also to the realm of research ethics[24]. However, while such proposals may be supported by sound theoretical argument[25], it is likely that such changes to clinical and research ethical orthodoxy will be resisted, if only because the individualist stance of these well-established frameworks are strongly entrenched in the training of researchers and clinicians, as well as systems set up to monitor and review activities in this light. Contrary to this,

[23] Littmann, J., Rid, A., Buyx, A. (2018). Tackling anti-microbial resistance: ethical framework for rational antibiotic use. European Journal of Public Health. 28(2), 359–363.
[24] See the contribution of Anomaly & Savulescu to the present special issue for one example.
[25] This, to our mind, remains to be shown, as it may very well be thought to be of great importance that clinical researchers and practitioners continue to prioritise the needs of their individual patients before other considerations, even in the light of the good reasons for expediting antimicrobial innovation.

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

some recent developments have indeed introduced changes to central policy documents that seem to give room for less individualist considerations, such as the notion of "social value" as the ultimate goal of health-related research in the revised CIOMS guidelines for research ethical review[26]. But individualism nevertheless still holds its grip over traditional clinical ethics and the central research ethical document of biomedical research, *The Declaration of Helsinki*[27].

A way out of this challenge would be if the reasons to cut research ethical red tape, and thereby expedite antibiotic drug innovation, could be plausibly formulated in terms of the traditional individualist (biomedical research and clinical) ethos. While not ruling this possibility out entirely, we harbour serious doubt about the feasibility of this way forward. Expediting antibiotic drug innovation unavoidably elevates risks and uncertainties for identifiable and existing individuals. The balancing act of trading off these risks against benefits is not only about a trade-off between individual and collective outcomes, but also about the long-term securing of public goods and the sustainability of health systems, and the latter may be plausibly argued to be about the good of individuals as well. However, these potential benefits of expediting antibiotic drug innovation by exposing current research subjects and patients to elevated risk and uncertainty all lie in an uncertain future, where the (possible) beneficiaries are currently non-existing and unidentifiable. This means that those arguing in favour of cutting red tape will have to accept both instrumentalisation of present patients and research subjects, where these are sacrificed to the benefit of an unclear mass of future people – as well for collective goods – and a particular and controversial type of view on the ethics of future generations, where the possible aggregated needs

[26] Council for International Organizations of Medical Sciences, CIOMS. (2016). International Ethical Guidelines for Health-related Research involving Humans. Geneva: CIOMS.
[27] World Medical Association, WMA. (2013). WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Ferney-Voltaire: WMA.

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

of the future are put before the actual needs of patients today[28]. While normative ethical arguments to this effect may indeed be formulated, we doubt that these arguments can easily be fitted into current individualist orthodoxy of the ethics of biomedical research and clinical practice.

Pragmatic challenge 3: Adverse popular and political response

Expediting antibiotic drug innovation may not only be strategically counterproductive and professionally illegitimate but may also set off destructive dynamics among the broadest group of stakeholders, people in general (and, indirectly, political decision-makers). First, there is an inherent paradox in the message that risks and uncertainties of antibiotic drug development and therapy need to increase in order to protect future antibiotic efficiency, as the reasons that people and policy makers will see for the latter aim are thereby weakened: the public good that is supposed to be protected by cutting research ethical red tape is being devaluated by the very same reform. Second, just as professionals may be unwilling to participate in the implementation of reforms to expedite antibiotic drug innovation, patients and potential research subjects may rationally respond with reduced clinical adherence and research participation, both of which will work against the aim of cutting the red tape. While reduced research enrolment is straightforward and easily understood, reduced clinical adherence may take various forms. One is elevated consumption of prescribed antibiotics where the effect is seen as more uncertain. Another is reduced consumption of prescribed drugs due to perceived elevated risks, so that the therapy becomes inefficient, necessitating repeated treatment and, in the end, elevated antibiotic consumption (as well as sustained ill-health). A third is that patients turn to alternative sources, such as online clinics and pharmacies, to get their hands on what they believe are more safe and efficient antibiotic drugs, leading to risks of elevated consumption that drives resistance (as the drugs acquired may be ones

[28] This aspect may be argued not to regard patients in life threatening circumstances and where there are no feasible treatment options. However, such patients are a rarity, and effective enhancement of innovation will have to include many more patients than this exclusive group.

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

that need to be heavily rationed to manage the resistance threat), inefficient treatment (due to the lack of control of products sold on the shade side of the global drug market), and/or undermined motivation to innovate from industry (as the demand for their novel antibiotic products declines).

On top of this, people in general, just as professionals, may, of course, find the costs of cutting research ethical red tape unacceptable, creating political pressure on policy makers not to go forward with reforms to expedite antibiotic drug innovation. Attitudes of distrust towards the motives of pharmaceutical companies may further fuel such resistance. Depending on the force of such popular response, the resulting political backlash may very well be substantial, and may threaten the political feasibility of effective action to manage the antibiotic resistance challenge for a long time. In addition, the uncertainty created by the strategy to cut the red tape of drug innovation means that there is a risk of creating a false sense of security: believing in the effect of the expedited program to provide a continuous supply of new antibiotic formulas that can keep the resistance threat at bay, we can be expected to discount both the reduced effectiveness of these drugs and the need to work on the resistance challenge from different angles. This dynamic will likely occur to a greater extent when the promise of a new therapy is elevated, such as in the case of 'golden ticket' solutions, such as phage therapy[29]. When the actual outcome is then disappointing, this could lead to further dismay, feeding the negative policy pragmatics created by all of the challenges 1-3.

Pragmatic challenge 4: Rhetorical negative feedback

[29] This is one of several *high risk* (in terms of very uncertain prospect for a useful product at the end of the innovation process), *high gain* antimicrobial innovation options that has been used to strongly advocate expedited innovation reform. See Thiel, K. (2004). Old Dogma, New Tricks—21st Century Phage Therapy. Nature Biotechnology. 22(1): 31-36, as well as the petition at https://www.change.org/p/janet-woodcock-m-d-urge-the-fda-to-loosen-restrictions-on-bacteriophage-therapies-as-antibiotics

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

An obvious way for policy makers to respond to the challenges 2 and 3, is to add to the expedited innovation reform itself a rhetorical narrative that aims to create a support that compensate for the risk of lost legitimacy. We have expressed some doubt about this prospect with regard to challenge 2, and convincing members of the public to support a system that will provide them with less safe and less effective healthcare is a challenge that needs recognition. In both cases, what seems to be required is a distinctly moral tale of what the drug resistance challenge is about and the implied need for speedier antibiotic drug innovation that can make them change their present priorities.

But this rhetorical add-on to the expedited innovation reform also adds a further layer of pragmatic risk. For what if the public and professionals don't buy the story, but on the contrary find it repugnant? If, for example, the rhetoric endeavour is viewed by the public as an attempt to coax them into accepting increased risks to patients and research subjects for the benefit of large corporations, not only may political backlash be reinforced, basic trust in state institutions may be undermined. It does not take much imagination to see how a rhetorical move in favour of cutting research ethical red tape may create a breeding ground for a toxic relationship between key stakeholders and the state that can require a long time to repair.

Conclusion: a further dilemma and a suggestion

There are strong principled reasons in favour of expediting antibiotic drug innovation, and thus to accept a lowering of ethical standards of research and clinical introduction of new antibiotic formulas. However, this support is weakened by the four pragmatic challenges we have described. It is, of course, at this point an open question just how likely to occur the scenarios we have sketched are[30]. Whether or not all or any of them arises as a response to the relaxing of specific

[30] Perhaps with exception for the first challenge of strategic adapted industry response. As this phenomenon has been observed in relation to expedited programs for orphan disease treatments, there some empirical support of such response to be expected also in the antibiotic case.

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

standards with regard to the various stages of antibiotic drug development, depends on a lot of factors, not the least of which is how extensive the expediting measures are. Their uncertainty, however, is no reason to simply disregard them[31]. In the worst case, these challenges threaten us with costly counterproductive reforms that lack the legitimacy necessary to be implementable or politically feasible. This may create long-term political backlash against policies in response to the antibiotic resistance challenge, as well as undermining basic trust in institutions necessary for any such policy to be effective. Such stakes create a reason to adapt reform proposals to appease key stakeholders in order to create legitimacy and institutional effectiveness.

However, this conclusion leaves us to face a new dilemma, which is of a more general nature, illustrated by image 1:

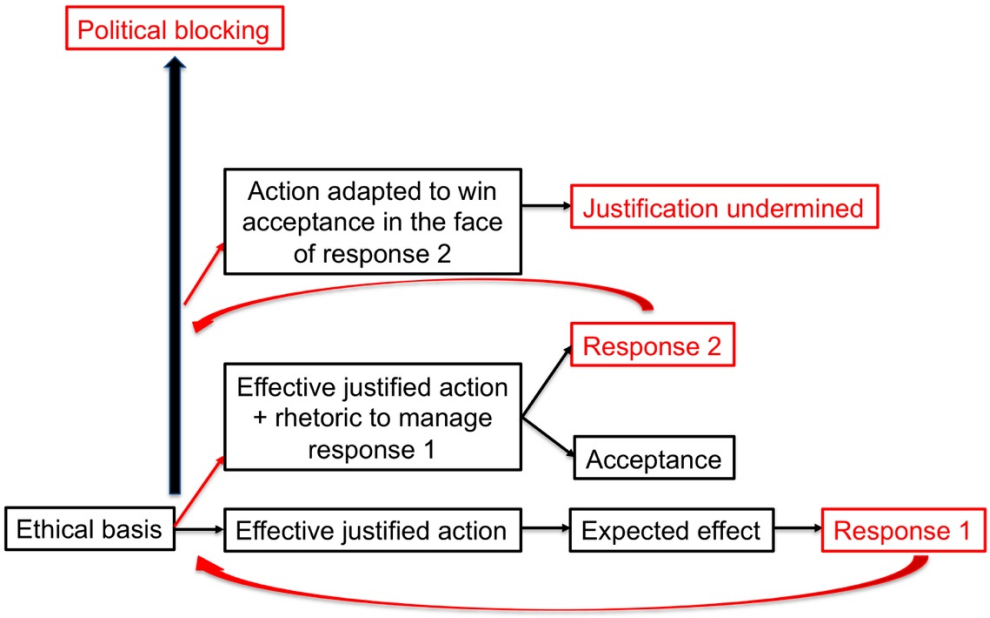

Image 1

[31] Nijsingh et al. op. cit. note 8.

This is a "preprint", the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

As an effective justified action, assessed to be so on a valid ethical basis, becomes infeasible due to negative stakeholder response (marked in red) policy makers are forced to reconsider (red feedback arrow). They first create a rhetoric for having stakeholders view the action in a more favourable light[32]. If luck wins the day, this will resolve the pragmatic challenge, but if not (as we have argued is not an unlikely outcome in the case of reform to expedite antibiotic drug innovation), the negative response will accumulate, again forcing reconsideration. This process will then have policy makers adapt by weakening the force of the action (to have less of the objectionable effect) in order to finally win acceptance, but at the cost of simultaneously weakening the original ethical justification of the action. Alternatively, they may resist adaption and pressing on to have the action implemented (typically, using force), in which case the risks of severe political blocking of effective policy increases. This type of dilemma is relevant for many serious public health threats, one of which is that of antibitic resistance, as these usually require drastic action and controversial revisions of public policy and practice. Recently, the ethical dimension of such 'wicked problems' of health policy implementation have been lifted as a major gap in biomedical research ethics[33].

We suggest that the importance of securing the functionality of basic institutions and of avoiding long-term blocking of political action in response to the antibiotic resistance challenge means that policy avenues actualising this secondary dilemma should often be abandoned. They should be pursued only if they can be made to win necessary stakeholder acceptance at a fair distance from the point where they are either having their original justification undermined, or where real political blocking becomes a viable possibility. We are not certain where this leaves the notion of expediting antibiotic drug innovation in response to the antibiotic resistance threat. However, we do believe

[32] It is also possible to consider further actions to secure acceptance, such as stakeholder or community engagement programs. See King, K.F., Kolopack, P., Merritt, M.W., Lavery, J.V. (2014). Community engagement and the human infrastructure of global health research. *BMC Medical Ethics* 15, 84. Doi: 10.1186/1472-6939-15-84.
[33] Lavery, J.V. (2016). 'Wicked problems', community engagement and the need for an implementation science for research ethics. *Journal of Medical Ethics* 44(3): 163-164.

This is a ”preprint”, the authors manuscript of an article after peer review but before the final editorial changes, published in the scientific journal *Bioethics*, Early view, doi: 10.1111/bioe.12605. Citation should refer to the published version, available here: https://onlinelibrary.wiley.com/doi/10.1111/bioe.12605

that this is not the only action exposed to this kind of complication among the many policies in the quickly growing toolbox of suggested responses to fight the threat of resistance to antibiotics.