

Health-related Research Ethics and Social Value: Antibiotic Resistance Intervention Research and Pragmatic Risks

Christian Munthe

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

Niels Nijsingh

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

Karl de Fine Licht

RISE – Research institutes of Sweden; the Royal Institute of Technology; and Chalmers Institute of Technology.

D.G. Joakim Larsson

Institute for Biomedicine, Department of infectious diseases, and the Centre for antibiotic resistance research, CARE, University of Gothenburg.

Keywords:

Antimicrobial resistance, CIOMS, Drug resistance, Evidence based practice, Health policy, Research ethics

Abstract

We consider implications for research ethical evaluation of two fundamental changes in the revised research ethical guideline of the Council for International Organizations Of Medical Sciences (CIOMS): An extension of scope follows from exchanging 'biomedical' for 'health-related' research, and the new evaluative basis of 'social value' implies new ethical requirements on research. We use the example of antibiotic resistance interventions to explore the need to consider serious instances of what we term 'pragmatic risks' of such interventions in research ethical review to evaluate the social value of certain health-related research. These (pragmatic) risks severely threaten the social value of interventions in all areas where human and social responses significantly impact their effectiveness. Thus, the social value of health-related research needed to demonstrate such effectiveness depends on the extent and the successful management of such risks. Research designed to take the management of pragmatic risks into account thereby also gives rise to similar types of risks, and the potential for social value in light of those risks needs consideration in ethical review based on the new guidelines. We argue that, to handle this new expanded task, the international system of research ethical review addressed by the guidelines needs institutional development.

Acknowledgement:

This research was supported by the UGOT Challenges Initiative at the University of Gothenburg; by the Swedish Research Council (VR) and the Swedish Research Council for Health, Working Life and Welfare (FORTE), contract no. 2014–4024, for the project *Addressing Ethical Obstacles to Person Centred Care*; and by VR, contract no. 2014-40, for the *Lund-Gothenburg Responsibility Project*. We are grateful to Kristian Kvint for linguistic advice.

1. Introduction

In the revised 2016 research ethical guidelines, published by the Council for International Organizations of Medical Sciences (CIOMS)¹, there is an extended scope to all 'health-related research', and the inclusion of 'social value' as a new basis for research ethical assessment. In this article we analyze the implications if these revisions for research ethical evaluation, by analyzing how they would apply to research for evaluating interventions in response to antibiotic resistance. An analysis of other ethical aspects of antibiotic resistance research and management is not within scope². Our aim is more restricted, namely to trace interesting research ethical implications of the mentioned changes in the new CIOMS guidelines with the help of the case of research on antibiotic resistance interventions.

We argue, first, that the case of antibiotic resistance illustrates and underscores the value and potential usefulness of both mentioned changes of the new CIOMS guidelines. We then probe a particular challenge for assessing the social value of health-related research made salient by antibiotic resistance intervention research, one we call *pragmatic risks*. Such risks are actualized when health-related interventions depend on certain human and social responses to be effective. If the role of such responses is sufficiently decisive for the effectiveness of an intervention, while the stakes of the problem addressed by the intervention are significant, the pragmatic risks become a major challenge for the social value of the intervention. We use the case of antibiotic resistance interventions to illustrate how the expansion of the scope from biomedical to health-related research may create such a challenge that needs to be considered in research ethical review. For instance, health policy changes aimed at reducing antibiotic

¹ Council for International Organizations of Medical Sciences, CIOMS (2016). *International Ethical Guidelines for Health-related Research involving Humans*. Geneva: CIOMS.

² For a useful overview of this area, see Littmann, J. & Viens A.M. (2015). The Ethical Significance of Antimicrobial Resistance. *Public Health Ethics* 8(3), 209–224.

use may bring about more sick leave, employment insecurity and more expensive food, leading to social reactions that politically block effective antibiotic resistance reform for a long time (thus undermining the social value of such intervention attempts)³. Briefly, we also trace how a similar challenge may appear in other areas of health-related research, pointing to some generic features playing a role for that. On this basis, we argue that assessment and management of major pragmatic risks are crucial for the evaluation of the social value of this type of health-related research, but that existing institutional frameworks of research ethical review present challenges for this particular task. This highlights a need for improved institutional structures for research ethical assessment in light of the revised CIOMS guidelines. While we sketch one possible direction for such improvements, we acknowledge that more work is needed to find feasible solutions to this effect.

We start by briefly describing how we interpret the introduction of the concepts of health-related research and social value in the revised CIOMS guidelines. In section 3, we then describe how the nature of antibiotic resistance research fits and supports this expanded scope and value base of these guidelines. In section 4, we introduce the notion of pragmatic risks in more detail and describe how such risks of antibiotic resistance intervention are crucial for the social value of such interventions, then continuing, in section 5, to demonstrate how this creates particular challenges for the evaluation of the social value of health-related research on such interventions. We also sketch how this upshot of the expanded scope and broadened value base creates new requirements for the research ethical review institutions addressed by the revised CIOMS guidelines. In section 6, we summarize the argument and our conclusions, also making some pointers to what other areas of health-related research may face similar challenges to demonstrate social value as the antibiotic resistance intervention area due to

³ These and other types of interventions are extensively described and discussed in sections 3 and 4.

pragmatic risks. Finally, we outline some crucial issues regarding possible reform of current research ethical review institutions in need of further work in light of our observations of the implications of the new CIOMS guidelines.

2. Health-related Research and Social Value

The revised 2016 CIOMS guidelines for research ethical assessment present two fundamental changes to earlier versions. First, the scope of the types of research to which the guidelines apply has widened considerably. While previously limited to biomedical research, thus following its research ethical sibling, the Declaration of Helsinki⁴, the guidelines now address a variety of 'health-related' research. Second, while previously, also similar to the Declaration of Helsinki, the CIOMS guidelines held out health and wellbeing as the primary value that may motivate research, it now presents a more inclusive value-base, summed up by the term 'social value'.

In the Guidelines, "health-related research" is defined as follows:

... activities designed to develop or contribute to generalizable health knowledge within the more classic realm of research with humans, such as observational research, clinical trials, biobanking and epidemiological studies.⁵

And the CIOMS working group goes on to explain:

⁴ World Medical Association, WMA (2013). WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Ferney-Voltaire: WMA. The two guidelines complement each other in addressing different primary audiences. While the Helsinki Declaration foremost addresses medical researchers and research organizations, the CIOMS guidelines are meant to enhance and underpin the assessments made by research ethical review bodies, such as institutional review boards. Nevertheless, as will be addressed in section 5, they also link to each other in various ways.

⁵ CIOMS (2016), op. cit. note 1, p.xii.

Generalizable health knowledge consists of theories, principles or relationships, or the accumulation of information on which they are based related to health, which can be corroborated by accepted scientific methods of observation and inference.⁶

The term 'generalizable health knowledge' thus indicates the use of a systematic method from any of the sciences. This characterization excludes the execution of actual institutional and social policy, even if these are made with human health in mind, such as in the case of a public health intervention. At the same time, the working group is keen to stress that a broad selection of research undertaken *in relation to* such policy will be included:

The Working Group considered biomedical research too narrow since that term would not cover research with health-related data, for example. At the same time, the Working Group acknowledged that this new scope also had limits. [...] The Working Group also acknowledged that there is no clear distinction between the ethics of social science research, behavioral studies, public health surveillance and the ethics of other research activities.⁷

Therefore, we will understand 'health-related research' to include any proper research (using methods from any scientific realm) related to policy developments made with human health in mind. This would include, for instance, research to evaluate not only biomedical interventions (such as trials of medical treatments), but also institutional ways of organizing such interventions (e.g., comparing different public health responses to an epidemic), as well as

⁶ Ibid.

⁷ Ibid: ix.

observational studies to figure out how such organizational solutions work on their own, or the amassing of behavioral data to better predict health-related behavioral responses to institutional change.

The concept of 'social value' is introduced and explained in the following way⁸:

In order to be ethically permissible, health-related research with humans, including research with samples of human tissue or data, must have social value. [...] social value of research can be difficult to quantify, but it is generally grounded in three factors: the quality of the information to be produced, its relevance to significant health problems, and its contribution to the creation or evaluation of interventions, policies, or practices that promote individual or public health.⁹

A first observation is that the notion of social value in the guidelines is not about restricting factors that may speak against otherwise desirable research¹⁰, but about what can make a research study desirable in the first place. One immediately visible novelty in this regard, compared to earlier versions of the CIOMS guidelines (as well as the Declaration of Helsinki), is the promotion of *public* health to be as important as *individual* health for evaluating the desirability of health-related research. As public health is intertwined with general structural societal concerns about economy, institutional function and social stability¹¹, this signals a considerable broadening of the base of values underlying this element of

⁸ The notion of social value of research has already attracted some critical attention in the bioethics literature, see for instance the special issue Rid, A., Shah, S.K. (eds.) (2017). Substantiating the social value requirement for research. *Bioethics* 31(2): 71-152. The aspects we lift in the present article have not been extensively discussed in that context.

⁹ CIOMS (2016) op. cit. note 1, p. 9.

¹⁰ These are addressed by other parts of the guidelines, not in focus in the present context.

¹¹ 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 Public Health: An Integrated, Multi-dimensional Model. *Public Health Ethics*. 1(1), 39-52.

research ethical assessment. Within this broader base, there is a much larger span of possible conflicts not only between individual and collective concerns, but also between different collective concerns (such as the values governing different public institutions). Therefore, it is a complex task to demonstrate that some piece of research is desirable in terms of social value.

The CIOMS working group then goes on to explain what it takes for some health-related research to actually have social value:

Social value refers to the importance of the information that a study is likely to produce. Information can be important because of its direct relevance for understanding or intervening on a significant health problem or because of its expected contribution to research likely to promote individual or public health. The importance of such information can vary depending on the significance of the health need, the novelty and expected merits of the approach, the merits of alternative means of addressing the problem, and other considerations. For example, a well-designed, late phase clinical trial could lack social value if its endpoints are unrelated to clinical decision-making so that clinicians and policy-makers are unlikely to alter their practices based on the study's findings.¹²

Here, there is a salient focus on having research *actually* promoting individual and public health, and not only under ideal circumstances. This, in turn, highlights the *pragmatic*¹³ side of health interventions, i.e. how human and social responses to implementation of an

¹² CIOMS (2016), op. cit. note 1, p. 1.

¹³ This use of the expression "pragmatic" is inspired by usual way of talking about the pragmatics of social practices and arrangements, e.g., language or politics. The pragmatics of such areas, in the form of (expected) human and social responses to them, may influence what is practical or feasible to do, or change otherwise expected outcomes of actions or practices.

intervention influence the prospect of actual health effects found in studies where circumstances are *ideally controlled* and where the institutional, social and psychological complications of clinical reality therefore are largely ignored.

A well-known example is provided by medication adherence. It has been observed that, once the strict trial protocol is not enforced and the extra resources made available by the study are no longer present, this leads to a drop in adherence to treatment which may severely undermine or even erase the benefits of a drug as proven in clinical trials.¹⁴ Thus, assessing social value will include also considerations about such barriers, and the possibility of changing intervention and trial designs to improve the prospect of having a real impact on individual or public health.

When viewed together with the broadening of the scope of the guidelines, this significant broadening of their value base also signals an ambition of the new guidelines to be a first sketch of an ethics of research aimed for evidence-based health policy. That is, while the guidelines do limit themselves to presenting a basis for evaluating health-related *research*, they at the same time provide an implicit case for more such research to demonstrate the social value of *health policy interventions*. When linked to the observation about the necessary considerations of the pragmatics of health-related research on interventions in order to evaluate their social value, this significantly increases the stakes and complications to be considered in comparison to when the guidelines addressed only biomedical research and had a value base restricted to (health-)scientific potential. We elaborate further on this significance of the new guidelines in section 4.

¹⁴ See, e.g., Brown, M.T., Bussell, J.K. (2011). Medication Adherence: WHO Cares? *Mayo Clinic Proceedings*. 86(4), 304-314.

3. Antibiotic Resistance Intervention Research

The changes in scope and value basis make the revised CIOMS guidelines into a fitting framework for the ethical assessment of research on complex interventions to address the challenge of antibiotic resistance. Antibiotic resistance not only threatens to undermine global public health and the effectiveness of modern health systems¹⁵, it is also very difficult to manage and respond to. This since a combination of natural and complex social factors drive a slowly accumulating, systemic and relentless undermining of the effectiveness of antibiotics. This combination of features is shared with some other vast global health challenges, such as climate change and mass refugee migration.

The basic mechanism of antibiotic resistance is simple: when bacteria are exposed to antibiotics, strains that have developed resistance (through mutations of pre-existing DNA or through uptake of genetic material) are favored by evolutionary selection. In contrast, the global health challenge created by antibiotic resistance has become overwhelmingly complex.¹⁶ One factor that contributes to this challenge is, of course, how antibiotics are used in humans, especially when they are used in excess (e.g. when overly broad antibiotics are used, or when a patient is taking an antibiotic for an indication where the health benefits are non-existing or highly questionable). However, already this factor links immediately to many-layered facts about the organization of healthcare, the regulation of antibiotic prescription, and existing cultural expectations related to, e.g., sick leave, hygiene practices, and healthcare consumption. Moreover, the use of antibiotics in animals (i.e. for treatment and prevention of

¹⁵ World Health Organization (2014). *The Evolving Threat of Antimicrobial Resistance: Options for Action*. Geneva, Switzerland: World Health Organization.

¹⁶ Ibid.; Littmann, J., Viens, A.M. (2015). Is Antimicrobial Resistance a Slowly Emerging Disaster? *Public Health Ethics*. 8(3), 255-265.

disease and for growth promotion) raises issues of similar complexity from a political, institutional and cultural perspective. Certain bacteria may infect humans as well as domestic animals, and genetic resistance traits may be transferred across bacterial species as well as biospheres¹⁷. The external environment thus acts as a transmission route for pathogens, and as a source for resistance genes that move from harmless bacteria into pathogens, assisted by a selection pressure from antibiotics.¹⁸ Here too there is an interplay with institutional, cultural and, not least, economic factors, e.g., influencing the level of emission control from industrial production of antibiotics.¹⁹ To have effect on the antibiotic resistance challenge, interventions that address any of these areas will thus have to consist of complex "packages" of biomedical and institutional actions²⁰.

As the system that drives the antibiotic resistance challenge is so difficult to understand, it becomes equally difficult to understand how and if proposed interventions to respond to the problem would in fact work. As the stakes are so high in terms of social value – antibiotic resistance threatens to undermine large parts of current public health, and to set the potential of broad segments of ordinary healthcare back almost a century – this means that all interventions under non-ideal circumstances also carry significant uncertainties and risks in

¹⁷ Anomaly, J. (2019). Antibiotics and Animal Agriculture; The Need for Global Collective Action. In Jamrozik, E. & Selgelid, M. (eds.). *Ethics and Drug Resistance: Collective Responsibility for Global Public Health*. Cham: Springer, in press; Boden, L. & Mellor, D.

(2019). Epidemiology and ethics of antimicrobial resistance in animals. In Jamrozik, E. & Selgelid, M. (eds.). *Ethics and Drug Resistance: Collective Responsibility for Global Public Health*. Cham: Springer, in press; Parsonage, B., Hagglund, P.K., Keogh, L., Wheelhouse, N., Brown, R.E., Dancer, S.J. (2017). Control of Antimicrobial Resistance Requires an Ethical Approach. *Frontiers in Microbiology* 8: 2124. Doi: 10.3389/fmicb.2017.02124

¹⁸ Bengtsson-Palme, J., Kristiansson, E., Larsson, D.G.J. (2017). Environmental factors influencing the development and spread of antibiotic resistance. *FEMS Microbiology Reviews*. Epub ahead of print, doi: 10.1093/femsre/fox053.

¹⁹ Larsson, D.G.J., Andremont, A., Bengtsson-Palme, J. et al. (2018). Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic resistance. *Environment International* 117: 132-138. Doi: 10.1016/j.envint.2018.04.041

²⁰ Nijssingh, 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.

terms of social value.

In a recent overview, it is described how different kinds of antibiotic resistance interventions may have a number of downsides that need to be carefully considered²¹. They may be ineffective, thus wasting important (often massive) resources, as they will often consist in far-reaching policy changes, such as revised regulation, or economic incentive schemes. The interventions may also be outright counterproductive, worsening rather than mitigating the antibiotic resistance problem, for instance, surveillance programs that deter carriers of resistant pathogens from seeking healthcare through stigma effects²². They may introduce new serious risks of their own, such as incentive programs to industry that steers innovation away from other important areas of public health, or economic models that favors the most inexpensive way of production, thereby increasing risks for severe environmental antibiotic pollution²³. Finally, some interventions may bring complex conflicts of interest that from different perspectives create motivations to oppose the same interventions and undermine their effectiveness, for instance, reduced antibiotic use that would cause increase of paid sick leave, or more expensive food.

The resulting complexity of justifying health policy interventions in response to antibiotic resistance constitutes a strong reason to both ascertain the justification of antibiotic resistance interventions, and for ethical assessment of research to that effect. The revised core of the CIOMS guidelines seems to provide an excellent framework for answering such a call.

Antibiotic resistance intervention research cannot be limited to the biomedical realm, since

²¹ Ibid.

²² Battin, M.P., Francis, L.P., Jacobson, J.A., Smith, C.B. (2009). *The Patient as Victim and Vector: Ethics and Infectious Disease*. Oxford: Oxford University Press; Munthe, C., Juth, N. (2012). *The Ethics of Screening in Health Care and Medicine: Serving Society or Serving the Patient?* Dordrecht: Springer; Rump, B., Timen, A., Hulscher, M., Verweij, M. (2018). Ethics of Infection Control Measures for Carriers of Antimicrobial Drug-Resistant Organisms. *Emerging Infectious Diseases*. 24(9), 1609-1616.

²³ Bengtsson-Palme, J., Gunnarsson, L., Larsson, D.G.J. (2018). Can branding and price of pharmaceuticals guide informed choices towards improved pollution control during manufacturing? *Journal of Cleaner Production*. 171, 137-146.

this does not tell us all we need to know to get interventions that actually work, making the expanded scope of the guidelines to regard all health-related research very fitting. These interventions will regard the biomedical effect targets together with a complex range of human and societal considerations, thus fitting well to the expanded value base of the guidelines in terms of social value. In addition, the case of antibiotic resistance can serve as an example for how to use the guidelines in this respect in relation to other types of global health challenges where interventions need to target similarly complex combinations of factors.

In the following, we will address one peculiar aspect of the problem of the ethical assessment and justification of antibiotic resistance interventions, and then use this as a platform for some concluding suggestions on how the CIOMS guidelines should be discharged in this area, as well as to interventions in response to relevantly similar health challenges.

4. Pragmatic Risks of Antibiotic Resistance Interventions

As mentioned, effective interventions in response to the antibiotic resistance challenge have to be of a social and institutional nature, although making use of existing biomedical and technical tools, and they may include attempts to stimulate biomedical innovation. Such interventions may concern the introduction of various forms of so-called "expediting" policies of innovation. Other examples include reforming regulation in areas such as antibiotic production and prescription, animal farming and food systems, screening and surveillance of (potential) patients and farming animals. But interventions may also consider overarching social arrangements, changing policies that direct trade, pricing and priority-setting of drugs

as well as food²⁴.

Interventions of this sort differ from biomedical ones (say, a pharmacological treatment or a surgical procedure) in that they primarily address human behavior, motivation, and the institutional handling of such. This means, however, that they will also produce human and social reactions and responses that impact on the actual outcome of the intervention. To handle this, antibiotic resistance interventions will have to attend to this pragmatic side of health interventions not only to ascertain that they *designed* so that people, groups and institutions do their respective parts in them as intended, but also to *present them rhetorically* in ways to attract acceptance in light of immediate as well as downstream consequences. However, also this latter type of action may produce adverse responses, thereby adding to the pragmatic risk while attempting to manage it²⁵.

For instance, schemes to expedite innovation may easily become politically unpopular if perceived as providing undeserved favors (e.g. to particular commercial actors), allowing too risky innovations to be introduced, or provide unintended incentives that counteract public health. Moreover, to function institutionally, the design needs to consider tensions and conflicts between different sectors of society, and also these solutions need to be "sold to the public". Plans to monitor the presence of resistant bacteria in potential patients, antibiotic emissions from farming and pharmaceutical production will, for instance, need to be traded off against the right to privacy, the freedom of business, and the access to affordable medication and food.

²⁴ Nijsingh et al. (2019), op.cit note 22.

²⁵ In the literature on policy reform and implementation research, this type of challenge has been lifted as a "wicked problem" since the 1970's. However, it is only recently that it has started to attract attention as an ethical challenge for health policy and related research. See 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.

Importantly, our point here is *not* about the obvious normative ethical issues that need to be resolved. Rather, we are holding out that no matter how the normative ethical inquiries end up, this need not change the actual behavior and attitudes of people in a way necessary for the intervention to be effective. Therefore, when evaluating the social value of interventions, as well as health-related research into such interventions, major pragmatic risk factors need consideration. If a health-related research project to this effect does not consider such risk factors and study them, this is a reason against its social value. If it does, it will itself imply the same sort of pragmatic risks, which need consideration in ethical review. These risks would not have been on the map for ethical review based on the old guidelines (since social value was not a criterion in those), and the broadening of the scope of the guidelines means that much more complex and severe such risks need considerations (i.e. political opposition rather than mere non-adherence to medication regimens).

There are different types of major pragmatic risk factors involved in such considerations related to antibiotic resistance interventions and health-related research that aims to demonstrate their social value. Expediting programs are one example of how one may try to stimulate innovation to fight the antibiotic resistance problem (this may regard not only new antibiotics, but also new approaches for diagnostics, surveillance and transmission control). Other measures to the same end include strategically directed public grants, subsidies of new products, prize-competition schemes, accommodation for elevated costs in priority setting schemes, and other financial incentives²⁶. However, all such schemes may easily incentivize companies and researchers to focus *overly* on the exact parameters that will match the

²⁶ Laxminarayan, R., Duse, A., Watal, C. et al. (2013). Antibiotic resistance—the need for global solutions. *The Lancet Infectious Diseases Commission* 13(12), P1057-1098. Doi: 10.1016/S1473-3099(13)70318-9; Simpkin, V.L., Renwick, M.J., Kelly, R., Mossialos, E. (2017). *The Journal of Antibiotics* 70, 1087–1096. Doi: 10.1038/ja.2017.124.

incentive mechanism²⁷, thereby undermining public health in other ways, even if successfully advancing some aspect of the antibiotic resistance problem²⁸. For example, an inexpensive diagnostic tool aimed at diagnosing malaria, could, when applied, lead to increased use of antibiotics without proof for bacterial infections, hence likely contributing to antibiotic resistance.²⁹

Other interventions instead aim to improve antibiotic stewardship, e.g., by restricting antibiotic prescription and farming use. Since such interventions will immediately impact on the living conditions of people (e.g., restricted access to antibiotics, potentially longer sick leave periods, elevated health insurance cost, more expensive food) in ways that are unpopular. Additionally, political changes that are also unpopular may be necessary (e.g., tax increases³⁰, restricted consumer freedom³¹), each aspect creates pragmatic risks threatening the feasibility or effectiveness of interventions.

Similar pragmatic risks link to interventions targeting environmental aspects of the antibiotic resistance challenge, such as production emissions in the pharmaceutical and agricultural area³². Measures to monitor and control such emissions may run contrary to local business and political interests, and also be in conflict with health policy goals in consumer countries

²⁷ The backlash to schemes put in place to handle the problem of orphan diseases is instructive as a case in point. The pharmaceutical industry responded to these schemes by basically changing their business models to try to make all diseases orphaned through various 'precision medicine' approaches which drastically elevated the total cost for drugs in healthcare systems. See, e.g., 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

²⁸ 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; Nijsingh, N. Munthe, C. Cutting red tape to manage public health threats: Should antimicrobial drug innovation be expedited? In review.

²⁹ Hopkins, H., Bruxvoort, K.J., Cairns, M.E., et al. (2017). Impact of introduction of rapid diagnostic tests for malaria on antibiotic prescribing: analysis of observational and randomized studies in public and private healthcare settings. *BMJ*. 356, j1054.

³⁰ Giublini, A., Birkl, P., Douglas, T., Savulescu, J., Maslen, H. (2017). Taxing Meat: Taking Responsibility for One's Contribution to Antibiotic Resistance. *Journal of Agricultural and Environmental Ethics* 30(2): 179-198.

³¹ Parsonage et al. (2017) op. cit. note 17.

³² Bengtsson-Palme, J., Larsson, D.G.J. (2018). Protection goals must guide risk assessment for antibiotics. *Environment international* 111: 352-353. Doi: 10.1016/j.envint.2017.10.019

to reduce the costs of drug procurement in public healthcare systems. However, in this domain there are additional pragmatic risks due to the fluidity of production location, meaning that effective regulation or incentivizing systems to curb such emissions in a certain country or region could lead to production moving to countries or regions with more unregulated jurisdictions, in the end lead to less control than before. At the same time using this risk as an argument for not enforcing, e.g., reasonable environmental standards locally would be highly questionable from an ethical point of view. Therefore, just as in other areas of environmental policy (such as climate change), firmer global institutional and legal frameworks may be desired³³. But such ambitions are bound to create pragmatic risks on the global political level, due to unwillingness to give up national sovereignty or opposition to schemes for distributing the burdens imposed by such arrangements between states³⁴. Of course, several of these pragmatic risk mechanisms may also interact. For instance, if inappropriate handling of the ethical aspects of pragmatic risks is picked up by the public, the reaction may reinforce the mentioned political responses to make these risks even more serious.

Pragmatic risks and uncertainties of antibiotic resistance interventions arise due to their dependency on certain human, social and institutional responses to be effective and defensible. This makes such risks different from risks and uncertainties arising due to the complexity of natural systems. The latter case actualizes the need of understanding the system well enough to be able to identify what causal pathways to manipulate to achieve the desired

³³ Küster, A., Adler, N. (2014). Pharmaceuticals in the environment: scientific evidence of risks and its regulation. *Philosophical Transactions of the Royal Society B*. 369, article 20130587; Milmo, S. (2014). Regulating the Environmental Impact of Pharmaceuticals. *Pharmaceutical Technology*. 38(6), online only. Retrieved from: <http://www.pharmtech.com/regulating-environmental-impact-pharmaceuticals> [Accessed 2017-10-31].

³⁴ This particular challenge is raised by several responses to a recent "roadmap initiative" by the European Commission, entitled Strategic approach to pharmaceuticals in the environment. Retrieved from: https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-2210630_en [Accessed 2017-10-31]

result. The dynamics of human and social responses, however, means that whatever way in which an intervention attempts to manage anticipated responses will *itself* be the object of a new layer of responses, and so on³⁵. For this reason, pragmatic risks create a particular challenge for the evaluation of proposals for antibiotic resistance interventions. While it may be tempting to argue from a precautionary standpoint that the stakes of the antibiotic resistance problem can justify quite rash action³⁶, such rashness will increase pragmatic risks that may impede effective antibiotic resistance efforts. In the worst case, reactions will amount to complete political blockage that remains for decades, thus severely worsening a situation that is already precarious.

5. Implications for Ethical Assessment of Antibiotic Resistance Intervention Research

The pragmatic risks of antibiotic resistance interventions add to the already presented reasons for evaluating such interventions in health-related research before they are rolled out. In effect, they also add to the reasons for ethical assessment of such research that takes pragmatic risks into account. In order to demonstrate social value, such health-related research will have to expose actors of importance in the antibiotic resistance landscape to triggers that produce pragmatic risks. Otherwise, this research will not add to our knowledge of what would be the *actual* outcome of interventions. It is, of course, possible to apply safeguards to the design of such research in order to mitigate pragmatic risks³⁷. Additionally, all research made in order to evaluate an antibiotic resistance intervention does not have to be

³⁵ Kasperson, R.E., Renn, O., Slovic, P., et al. (1988). The social amplification of risk: A conceptual framework. *Risk Analysis*. 8(2), 177-187.

³⁶ Munthe, C. (2016). Precautionary principle. In: ten Have, H. (Ed.), *Encyclopedia of Global Bioethics* (pp. 2257-2265). Cham: Springer.

³⁷ For instance, various types of community engagement measures, 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.

of a "field trial" type (or observational studies of rolled out interventions). However, all such safeguards will then make the research say less determinate things about the actual effectiveness of the intervention itself, and therefore decrease its potential social value³⁸.

Moreover, although research to evaluate antibiotic resistance interventions to ensure their effectiveness is highly desirable, depending on how people and institutions react to the research and the safeguards, adverse human and social responses may ensue, thus creating new pragmatic risks threatening the effective management of the antibiotic resistance problem. Aspects that may produce such reactions are, for example, perceived unacceptable harm coming out of expediting programs to promote technical innovation; allegedly politically unacceptable side-effects of policies aimed at realizing stewardship in the consumption of antibiotics; and lack of acceptance of costs and alleged side-effects of attempts to effect surveillance and control of antibiotic emissions into the environment.

As mentioned, the revised CIOMS guidelines provide both reasons and an intellectual framework to take pragmatic risks into account. Pragmatic risks of the sort actualized by antibiotic resistance interventions, as well as research to evaluate such interventions, are of particular importance for assessing the 'social value' held out by the guidelines as decisive for the justification of health-related research. In particular, it is crucial for getting a grip on the potential of health policy interventions to sufficiently promote individual and public health in the complex of motivational forces surrounding real life application. Ethical review of health-related research to evaluate antibiotic resistance intervention thereby needs to consider major pragmatic risks, as well as the background knowledge in social science³⁹ necessary for appropriately assessing them.

³⁸ If the research is nevertheless accepted, but to the price of various risks and costs, this may in itself produce pragmatic risks of public backlash against not only the intervention evaluated, but the research to evaluate it.

³⁹ We take 'social science' to indicate knowledge of cultural, institutional and political incentives and forces, and individual motivation seen from a behavioural as well as an internal psychological standpoint.

The CIOMS guidelines primarily address research ethics committees, such as institutional review boards (IRB), and do provide these with reason and framework for research ethical review to secure the social value of health-related research on the effectiveness of antibiotic resistance interventions. However, as these institutions have not been built up with such a significantly expanded task in mind, it is less certain whether they are fit for the challenge. First, the typical competence profile of IRBs and similar bodies may be put into question in this respect. While the mix of ethicists, legal experts and scientific scholars usually present in such settings may assess methodological soundness and immediate risks to research subjects, it is much less certain if they are able to reliably assess pragmatic risks of health policy interventions. This connects to the way in which the revised CIOMS guidelines remove the ethical landscape of research it addresses from the one often seen as central to IRB work in the health research area: the Helsinki Declaration. A side-effect is an expansion of what type of competences and priorities need to govern the work of a typical IRB, which makes it less fitting to perform the kind of assessment that the new CIOMS guidelines seem to support in cases like research on antibiotic resistance interventions.

There are three main ways to respond to this situation. First, the IRB system may be reformed so that it becomes better prepared to meet the challenge of reviewing health-related research to test antibiotic resistance interventions (and other health-related research on areas ridden by pragmatic risks). However, as this system is tightly linked to the idea of assessing studies and researchers in light of the Declaration of Helsinki, we somewhat doubt the feasibility of this proposal. At the same time, the idea that IRBs need to be both ethically, legally and methodologically competent does not lose its rationale just because the notions of health-related research and social value require more in terms of what relevant ethical and methodological competence is required. Addition of such competence to facilitate proper quality of reviews, in case it is absent, would therefore seem to be imperative.

Second, we may consider creating a secondary IRB system, exclusively designed to meet the requirements created by the idea of ethical review of health-related research to promote social value in areas where major pragmatic risks are a real issue⁴⁰. Reviews conducted by such IRBs would then need to pay particular attention to policy and social response aspects giving rise to pragmatic risks at the macro level of proposed health policy interventions. For instance, imagine a study aiming to test restrictive antibiotic prescription privileges for physicians in a society where no such restrictions exist; or increased such restrictions that can be predicted to increase paid sick leave in a society. The pragmatic risks actualized by this type of reforms are not only difficult to evaluate, they also plug immediately into real ideological and political controversy that may complicate both effective management and consensus on they are to be assessed and evaluated. For this reason, a body at the administrative level of a typical IRB may be viewed as ill placed to properly manage the challenges implied by the new CIOMS guidelines.

This leads to the third way of responding to the challenge of pragmatic risks of health-related research: Ethical review of health policy interventions of the type actualized by the antibiotic resistance problem would perhaps better take place at a level of government committee work, where actual political and other crucial interests have representation and linked concerns may be addressed.

6. Concluding discussion

We have argued for two main points. First, the extended scope and the broader base of values make the revised 2016 CIOMS guidelines very fitting as a framework both for motivating

⁴⁰ We expand on how to characterize this area in the final discussion.

research to effect evidence-based health policy in important areas, and to ethically review such 'health-related research' on the basis of its 'social value'. Second, we have described how this implication moves the guidelines into a more requiring territory than before, when they restricted themselves to biomedical research evaluated with biomedical scientific advance as the base value. The guidelines now require consideration of what we have called 'pragmatic risks' of a particularly challenging type. We have used the phenomenon of interventions in response to antibiotic resistance to illustrate both of these points.

Due to the complexity of the challenge addressed by such interventions, it is crucial for the evaluation of social value to consider how people at different levels, as well as organizations and institutions, may respond to them. In the worst case, such responses may transform otherwise effective interventions into disastrously counterproductive failures, e.g. due to political paralysis or irresolvable conflicts of interest. Therefore, ethical assessment of research aimed to evaluate such interventions (meant to be performed with the social value of the research in mind) needs to have the consideration of major pragmatic risks in focus.

While the case of research on antibiotic resistance interventions is just one type of health policy research that fit the notion of health-related research to be justified in terms of social value, we have pointed out some generic features giving rise to pragmatic risks of this magnitude that are present also in other areas of relevance from a health-related research standpoint. Health-related climate policy research, as well as research on other major environmental health measures such as the use of gene driving and editing to combat malaria or zika, are obvious examples⁴¹. Another area is major institutional reforms of health systems, where political controversy and conflict is usually at the center of debates. In all these areas,

⁴¹ Thompson, P.B. (2018). The roles of ethics in gene drive research and governance. *Journal of Responsible Innovation* 5(sup1): S159-S179. Doi: 10.1080/23299460.2017.1415587

the need for health-related research to demonstrate social value is clear, while features producing severe and complex pragmatic risks are abundant.

We have ended our analysis by arguing that the current institutional organization of research ethical review may need to be further developed in this light. The review of research made to ensure evidence-based health policy in areas fraught with major pragmatic risks would perhaps be better placed at higher institutional levels, where political stakes and positions can be addressed in a constructive way. The reason for this is that the pragmatic risks posing the more serious threats to effective health interventions, depend closely on large-scale institutional, political and social factors.

At the same time, this idea clearly leads to new questions, which cannot be answered within the scope of the present paper. For instance, how should we demarcate the health-related research in need of the higher-level review of social value from such research where the traditional institution would do? A further worry may be about a higher-level review, as sketched, essentially changes the nature of research ethical oversight, politicizing it in undesirable ways. These and other issues are thus in need of further probing considering the expanded scope and broadened value base of the revised CIOMS guidelines.

References

Anomaly, J. (2019). Antibiotics and Animal Agriculture; The Need for Global Collective Action. In Jamrozik, E. & Selgelid, M. (eds.). *Ethics and Drug Resistance: Collective Responsibility for Global Public Health*. Cham: Springer, in press.

Battin, M.P., Francis, L.P., Jacobson, J.A., Smith, C.B. (2009). *The Patient as Victim and*

Vector: Ethics and Infectious Disease. Oxford: Oxford University Press.

Bengtsson-Palme, J., Gunnarsson, L., Larsson, D.G.J. (2018). Can branding and price of pharmaceuticals guide informed choices towards improved pollution control during manufacturing? *Journal of Cleaner Production*. 171, 137-146.

Bengtsson-Palme, J., Kristiansson, E., Larsson, D.G.J. (2017). Environmental factors influencing the development and spread of antibiotic resistance. *FEMS Microbiology Reviews*. Epub ahead of print, doi: 10.1093/femsre/fux053

Bengtsson-Palme, J., Larsson, D.G.J. (2018). Protection goals must guide risk assessment for antibiotics. *Environment international* 111: 352-353. Doi: 10.1016/j.envint.2017.10.019

Boden, L., Mellor, D. (2019). Epidemiology and ethics of antimicrobial resistance in animals. In Jamrozik, E. & Selgelid, M. (eds.). *Ethics and Drug Resistance: Collective Responsibility for Global Public Health*. Cham: Springer, in press

Brown, M.T., Bussell, J.K. (2011). Medication Adherence: WHO Cares? *Mayo Clinic Proceedings*. 86(4), 304-314.

Council for International Organizations of Medical Sciences, CIOMS (2016). *International Ethical Guidelines for Health-related Research involving Humans*. Geneva: CIOMS

Dawson, A. (ed.) (2011). *Public Health Ethics: Key Concepts and Issues in Policy and Practice*. Cambridge: Cambridge University Press.

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.

Giublini, A., Birkl, P., Douglas, T., Savulescu, J., Maslen, H. (2017). Taxing Meat: Taking Responsibility for One's Contribution to Antibiotic Resistance. *Journal of Agricultural and Environmental Ethics* 30(2): 179-198.

Hopkins, H., Bruxvoort, K.J., Cairns, M.E., et al. (2017). Impact of introduction of rapid diagnostic tests for malaria on antibiotic prescribing: analysis of observational and randomized studies in public and private healthcare settings. *BMJ*. 356, j1054.

Kasperson, R.E., Renn, O., Slovic, P., et al. (1988). The social amplification of risk: A conceptual framework. *Risk Analysis*. 8(2), 177-187.

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

Küster, A., Adler, N. (2014). Pharmaceuticals in the environment: scientific evidence of risks and its regulation. *Philosophical Transactions of the Royal Society B*. 369, article 20130587.

Larsson, D.G.J., Andreumont, A., Bengtsson-Palme, J. et al. (2018). Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic resistance. *Environment International* 117: 132-138. Doi: 10.1016/j.envint.2018.04.041

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.

Laxminarayan, R., Duse, A., Watal, C. et al. (2013). Antibiotic resistance—the need for global solutions. *The Lancet Infectious Diseases Commission* 13(12), P1057-1098. Doi: 10.1016/S1473-3099(13)70318-9

- Littmann, J. & Viens A.M. (2015). The Ethical Significance of Antimicrobial Resistance. *Public Health Ethics* 8(3), 209–224.
- Littmann, J., Viens, A.M. (2015). Is Antimicrobial Resistance a Slowly Emerging Disaster? *Public Health Ethics*. 8(3), 255-265.
- Milmo, S. (2014). Regulating the Environmental Impact of Pharmaceuticals. *Pharmaceutical Technology*. 38(6), online only. Retrieved from: <http://www.pharmtech.com/regulating-environmental-impact-pharmaceuticals>
- Munthe, C. (2008). The Goals of Public Health: An Integrated, Multi-dimensional Model. *Public Health Ethics*. 1(1), 39-52.
- Munthe, C. (2016). Precautionary principle. In: ten Have, H. (Ed.), *Encyclopedia of Global Bioethics* (pp. 2257-2265). Cham: Springer.
- Munthe, C., Juth, N. (2012). *The Ethics of Screening in Health Care and Medicine: Serving Society or Serving the Patient?* Dordrecht: Springer.
- Munthe, C., Nijsingh, N. Cutting red tape to manage public health threats: Should antimicrobial drug innovation be expedited? In review
- 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.
- Parsonage, B., Hagglund, P.K., Keogh, L., Wheelhouse, N., Brown, R.E., Dancer, S.J. (2017). Control of Antimicrobial Resistance Requires an Ethical Approach. *Frontiers in Microbiology*

8: 2124. Doi: 10.3389/fmicb.2017.02124

Rid, A., Shah, S.K. (eds.) (2017). Substantiating the social value requirement for research. *Bioethics* 31(2): 71-152.

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

Rump, B., Timen, A., Hulscher, M., Verweij, M. (2018). Ethics of Infection Control Measures for Carriers of Antimicrobial Drug-Resistant Organisms. *Emerging Infectious Diseases*. 24(9), 1609-1616.

Simpkin, V.L., Renwick, M.J., Kelly, R., Mossialos, E. (2017). *The Journal of Antibiotics* 70, 1087–1096. Doi: 10.1038/ja.2017.124

Thompson, P.B. (2018). The roles of ethics in gene drive research and governance. *Journal of Responsible Innovation* 5(sup1): S159-S179. Doi: 10.1080/23299460.2017.1415587

World Health Organization (2014). *The Evolving Threat of Antimicrobial Resistance: Options for Action*. Geneva, Switzerland: World Health Organization.

World Medical Association, WMA (2013). *WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*. Ferney-Voltaire: WMA