Antimicrobial resistance and biological governance: explanations for policy failure
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Abstract:

The paper reviews the state of policy on antimicrobial use and the growth of antimicrobial resistance (AMR). AMR was anticipated at the time of the first use of antibiotics by their originators. For decades, reports and scientific papers have expressed concern about AMR at global and national policy levels, yet the problem, first exposed a half-century ago, worsened. The paper considers the explanations for this policy failure and the state of arguments about ways forward. These include: a deficit of economic incentivisation; complex interventions in behavioural dynamics; joint and separate shifts in medical and animal health regimes; consumerism; belief in technology; and a narrative that in a 'war on bugs' nature can be beaten by human ingenuity. The paper suggests that these narratives underplay the biological realities of the human-animal-biosphere being in constant flux, an understanding which requires an ecological public health analysis of AMR policy development and failure. The paper suggests that effective policy change requires simultaneous actions across policy levels. No single solution is possible, since AMR is the result of long-term human intervention which has accelerated certain trends in the evolution of a microbial ecosystem shared by humans, animals and other biological organism inhabiting that ecosystem. Viewing the AMR crisis today through an ecological public health lens has the advantage of reuniting the social-ecological and bio-ecological perspectives which have been separated within public health. (227 words)

Keywords: antibiotics; antimicrobial resistance; ecological public health; evidence-based policy; evidence-policy-behaviour gap

Introduction: a question of perspective

The problem of antimicrobial resistance (AMR) has been much documented worldwide. The persistence of the problem suggests that policy responses have been inadequate or at best have not yet worked. This paper considers what those policy responses are, how they have been framed and by whom. It proposes that the language and focus of the policy discourse indicate a deep structural problem not just for public health but also for food system management. AMR thus illustrates the pertinence of the ecological public health approach and obstacles to it being mainstreamed. In this paper we use the term AMR, although much public discourse has used 'antibiotic resistance'. AMR refers to resistance developing to anti-bacterial, anti-viral and other medicines used against pathogenic infections; it is the more accurate term to describe the public health problem. Most of the public focus and attention, however, has been focused on worsening resistance amongst bacteria, and the diminishing effectiveness of antibiotics used to treat infections caused by pathogenic bacteria. In the common vernacular, "antibiotic" resistance is often used synonymously with AMR.

Evidence about AMR has mounted for decades, and concerns about the consequences of antibiotics overuse hastening AMR and rendering antibiotics ineffective were made well over half a century ago.[1, 2] Policy responses to the threat have been varied, ranging from denial to the nigh apocalyptic, from anticipating a world without effective antibiotics and implicitly anticipating a return to a time before the Second World War,[3] to calls for a massive public investment in a new generation of drugs.[4] Since the evidence base for concern about AMR has only strengthened with each passing decade, it is both timely and important to consider why policy makers have been so slow to respond to earlier warnings based upon that evidence, and the calls for more urgent action. The World Health Organization (WHO) among others has puzzled over this slow transition from evidence to action. [5]

To some extent, AMR policy is another example of the gap between evidence, policy and behaviour change that has been all too familiar in the history of public health policy development. The UK's National Institute of Clinical Excellence, for instance, issued its first formal guidance to General Practitioners and health workers on over-use and misuse in August 2015.[6] The paper suggests that policy makers are being offered a narrative of crisis which itself carries some risks. Such a narrative presumes that policymakers and regulators need to reassert control, with policy messages framed by notions of containment, order and authority in contrast to fears about messiness, disorder or anarchy. In our view, part of the complexity for policy-makers has lain in the different management systems for human and animal health, and the segmentation of state institutions responsible for public health and for food and farming.

The reasons for concern about diminishing antibiotic effectiveness are clear and real. The growing seriousness of AMR, and its human impacts, have been documented elsewhere.[5] Antibiotics are in wide use globally on both humans and animals. Countries vary enormously in antibiotic use, especially when adjusted on a per person or per animal basis. Taking animal production, the WHO has reported that Norway uses relatively small amounts, 20mg to produce 1 kg of meat, for example, whereas the Netherlands uses 180 mg to produce one kg, and the USA an estimated 300 mg.[5, 7] In the US, the Food and Drug Administration (FDA) reported that 13.5 million kgs of all US antimicrobials – some 80% of the total – were sold for use in agriculture in 2011.[8] Of US sales of medically important antibiotics – penicillins, macrolides, cephalosporins and other antibiotics of human importance – more than 70% in 2011 were sold for use in livestock and poultry, not for use in medicine; less than 3.3 million kilograms of antibacterials were sold for use in human medicine that same year.[9] By size China is the largest antibiotics producer and consumer in the world. In a 2007 survey, the estimated annual antibiotics production in China was 210 million kg, of which 46.1% were used in livestock industries.[10] With such heavy, routine use, AMR is unsurprising.

AMR is an issue that draws out divergent perspectives on the role of policy. Some call for technical development (new drugs); others for legal change (tougher regulatory controls); others for behaviour change (less and more judicious use). Some focus on AMR risks to humans; others to animal husbandry. Some call for the application of a systems perspective and 'good multilevel governance' as the key to successful containment;[11] others for tighter prescription rules only. Here is where an ecological public health (EPH) perspective helps make sense; it reduces the policy cacophony' – different solutions vying for policy attention.[12]

EPH locates human health problems as the result of interactions between human physiology, context, and the flow of inputs and outputs.[13] Although it has a long history, shaped by mid 19th century Darwinian analysis and subsequent scientific breakthroughs such as germ theory, the isolation of bacteria and viruses, and latterly gene typing, ecological thinking is today mostly associated in public health with the social-ecological perspective.[14-16] The social-ecological perspective, valuable though it has been, has focussed on social environment and dynamics as a determinant of health; the public health importance of the physical and biological environment has been somewhat overlooked. Surely a more full understanding of the dilemma raised by AMR requires both strands of ecological thought: the biological and the social. The strength of the term 'ecological' is its ability to capture the dualistic and interactive relationship of humans and nature. In the biological sciences the notion of ecological research has more closely retained the Darwinian meaning that Haeckel (who coined the word) gave it,[17] where 'ecological' refers to the multi-layered interactions of complex life forms.

Within public health, ecological public health is the term now used to reclaim this broader conception of public health promotion as the task of unravelling bio-human-social connections and reconfiguring them to create the conditions for good rather than poor health.[13] The relevance of EPH thinking is apparent in issues as varied as recognition that climate change requires societal change,[18] to new ways of treating sewage,[19] and cancer.[20] In this sense, ecological thinking is the science of interdisciplinary research stretching across life in its multiple levels and forms and which engages assumptions of complexity, emergence, habit, novelty and system. AMR illustrates the need for the two ecological traditions – the biological and the social –once more to be one, albeit with neither being reducible to the other. This is a complex perspective to translate and 'sell' to policy makers.

Documenting the rise in policy concern

Over their first several decades, what has been referred to as the 'golden age' of antibiotic use, their impact was miraculous.[21] They were remarkably effective in tackling an array of everyday infections, sexually transmitted infections, tuberculosis, pneumonia and more. Yet expert advice now concludes their efficacy is under extreme threat.[5, 22, 23] Half of all antibiotic consumption may be unnecessary, yet sales via the internet are growing.[3] The concern about over-use and misuse is not new. Both Sir Alexander Fleming, the discoverer of penicillin, and René Dubos, the discoverer of gramicidin (an antibacterial agent that inhibits the growth of gram-positive bacteria) predicted AMR in the 1940s. The fact of antimicrobial resistance had been observed in the 1930s.[24] When accepting his Nobel Prize in 1945,Fleming worried that the time might come when penicillin "can be bought by anyone in the shops" and thus inevitably expose microbes to non-lethal quantities of the drug and "make them resistant".[25] Penicillin was initially obtained without medical prescription and penicillin resistant bacterial strains were first isolated in significant numbers in 1946.[26]

Fleming, Dubos and others realised then, as others much more recently had seemingly forgotten, that antimicrobials were likely (perhaps bound) to lose potency due to the intrinsic nature of microbial evolution.[27] These were valuable substances not to be used lightly. Such warnings jarred with the technological impetus of these years, continuing on to today, and as such were denounced as hubristic by ecological writers like Lewis Mumford.[28] In the 1950s, antibiotics as a technology gained a similar allure to nuclear power, with the same warm glow of technological modernity, technical efficiency and problem resolution. Nuclear power (and bombs) came to the fore at roughly the same time yet were regulated and controlled by tight state controls and fiercely bureaucratised access, if with fewer considerations about the long-issue of nuclear waste. The analogy between nuclear power and AMR is found in the framing of early debates around their use as 'use versus abuse' (or use versus misuse), a conventional distinction within mid 20th century science policy, with the technology in each case being depicted as neutral and free of ideological contamination.

Decades later, the applicability of this framing to antibiotics and AMR are open to debate. It is what recent science policy analysts have referred to as one of its 'framing assumptions'.[29, 30] Understandable intentions are built into antimicrobials such as the human desire to protect health by controlling nature, but these also sit alongside other framing assumptions – however incorrect -- such as that life forms are static, or that humans <u>are</u> in control of nature, or that medicines that are effective at one point in time will always be so. As Dubos argued constantly, none of these assumptions, given the dynamism of evolutionary processes, is beyond question and indeed they represent a form of scientific and policy 'utopianism'.[31]

The history of the use of antimicrobials is an important element to build into policy analysis, and it should not be left to historians, if only because antibiotics, as non-renewable resources, leave a long (biological) shadow of their previous pattern of use. If there is to be sound policy on AMR, policy makers must learn why such early warnings were disregarded.[32] Investigations by Dubos[1, 33, 34] and others[35] pointed to the need to treat biological agents with extreme caution. Human health should be located in its wider biological, material, social and cultural context, Dubos argued. More recent thinking in this mould reaffirms Dubos' arguments. Baquero and colleagues, for example, although using the term antibiotic resistance, see this as a consequence of "anthropogenic alterations in different environments, with consequences in human health and possibly in the health of the biosphere".[36] In effect, human health cannot be separated from eco-systems health; indeed even if the focus is on the health of human physiology alone, this requires us to locate the body within a complex interplay of factors and forces, recognising too that past human activity has also changed the environment.

The early warnings from pioneers were almost immediately backed by reputable <u>national</u> bodies in Western countries which normally have considerable influence over global policy, but on AMR there appears to have been slower support at the <u>international</u> and multinational level. Table 1 lists some early reports by high standing national bodies. Table 2 documents AMR warnings at the international level, mostly since 1998. The tables suggest not that there has been no policy but that there has been much; if so, these policies must be judged to have partially or largely unsuccessful, and is why analysts should give more attention to what has stopped follow-up and implementation.

The USA was the first big user of antibiotics in animal rearing. In 1956, the US National Academies of Science and National Research Council hosted the first international conference on antibiotic use in agriculture where concerns about over-use were voiced in evolutionary and ecological terms. At the dinner address of the conference, Dubos stated: "[i]t is extremely difficult, if not impossible, to foresee the ultimate consequences of any intervention even when it consists in the use of a selective drug effective against only one or a very few components of the ecological system."[37] In 1969 the Swann committee published its concerns in the UK,[38] and in 1977 the US Food & Drug Administration (FDA) tried unsuccessfully to regulate or ban routine use of penicillins and tetracyclines in animals feeds.[39, 40]

Table 1 Some national warnings of AMR, 1950s-90s

Date	*Body*	*Country*	*Action*	*Comment*
1956	National Academies of Science	USA	Hosted First International Conference on the Use of Antibiotics in Agriculture	Early concerns about AMR and antibiotic overuse
1969	Swann Report	UK	Report on antibiotic use by veterinary medicines	'landmark' report led to withdrawal of some antimicrobials from list of authorised antibiotic growth promoters in some EU countries (1972-74)
1977	FDA	USA	FDA begins hearings to withdraw routine use of key antibiotics (penicillins, tetracyclines) in animal feeds	Industry strongly resisted the prospect of legal controls
1986	Swedish Agriculture Ministry	Sweden	Ban on antimicrobial growth promoters	A reversal of a 1977 warning that AMR was not a concern! Some follow-up by Denmark and UK
1992	General Accounting Office	USA	Recombinant Growth Hormone	Expressed concern about use of antibiotics in growth hormones
1998	House of Lords	UK	Resistance to Antibiotics	"a major threat to public health"
1998	European Union Chief Medical Officers	EU	Copenhagen Recommendations	"International spread of micro-organisms means that resistance to antimicrobial agents can no longer be regarded as a national problem. It is a European and global problem and requires a common strategy."

Those failed 1977 FDA initiatives are important. Citing the opinion of FDA scientists, that antibiotics in animal feed posed a threat to public health, the Agency promised – and then failed to bring about -- firm action to stop that misuse. Some 35 years later, the issue re-emerged for public review in a legal case brought in 2012 by a US environmental NGO questioning what it regarded as 35 years of FDA inaction.[41] Specifically it asked why the FDA had weakened its proposed policy from one based on legislation to one invoking self-regulation. The use/abuse model of science in policy, in effect, did not apply. In fact, the policy was shifted from reliance on 'hard' to 'soft' policy measures, suggesting – to invoke another theory from political science - that the FDA was suffering from what Bernstein in the 1950s termed 'regulatory capture', the processes by which regulatory bodies become subservient to the industry they were established to regulate.[42 43]

But if this was the case, the FDA would have not come up with tough proposals in the first place. The more plausible explanation is that the FDA's failure to impose a new culture on industry illustrates what might be termed '*de*regulatory capture' (i.e. the inverse of 'regulatory capture'). This is where a business sector exerts strong political pressure to stave off a potential threat to its business logic and seeks to avoid regulation or presses for its elimination. The business logic here is and was the routine addition to animal feed of relatively cheap antibiotics, both to get animals faster to slaughter weight on less feed, as well as to offset the infection risks created by raising animals in modern, intensive systems often marked by crowding, poor hygiene and nutrition and stress. These intensification methods served to raise more animals with less land and labour requirements, albeit with more consumption of antibiotics and energy, and creation of more resistant bacteria, air and water pollution. So long as the short-term costs of the latter could be controlled or avoided, the intensive model appeared to be more efficient and produce lower cost meat for the consumer.

Sweden provides another insight to the pressures on policy. In 1977, its Agricultural Board conducted an inquiry into AMR, concluding that the risks were negligible, only for the farmers in 1984 to ask for antibiotics to be banned from feedstuffs following consumer concerns. In 1986, antibiotics were banned from animal feed use as growth promoters, as further concerns for human health were voiced.[44, 45] The public, rather than industry or science, was the catalyst for policy change and implementation. As a result, Swedish policy pioneered the argument that tight controls would retain antibiotics for more effective human use.

Table 2: Modern Intergovernmental AMR policy development, 1998-2015

Date	*Parent body*	*Report/action*	*Comment*
1998	WHA	World Health Assembly resolution WHA 51.7	Proposes that there is enough evidence to act on AMR
2001	WHO	WHO Global Strategy for Containment of Antimicrobial Resistance	Made eight clusters of actions needed to reduce AMR by different interest groups: prescribers, patients, hospitals, vets, Governments, industry
2001	Codex Alimentarius Commission	Report of Executive Committee meeting June 28-29, 2001	Saw future competition between human and animal use; made request to address AMR as both human and animal problem
2001	European Commission	European Council Recommendation 2002/77/EC	Proposed multidisciplinary Coordination at EU level (following 1998 EU Conference on AMR in Copenhagen)
2003	FAO, OIE, WHO	Joint Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance Scientific assessment	High level co-ordination requires improved data and agreement on classification
2005	WHA	World Health Assembly resolution WHA A58/14	At the WHA, member states expressed concern at lack of progress since 1998
2005	EU	Ban on feeding of all antibiotics and related drugs to livestock for growth-promotion purposes	Took effect January 1, 2006
2007	FAO, WHO, OIE	Report of Joint FAO/WHO/OIE Expert Meeting on Critically	Brought together human and animal perspectives around concept of there

		Important Antimicrobials	being critically important Antimicrobials for both; agreed common classification system
2007	WHA	Resolution WHA 60/16	Follow up by member states to 2005 resolution
2008	WHO	Creation of Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR).	20 person group to advise WHO on implementation of strategy; met four times 2009-12
2009	WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR).	Critically Important Antimicrobials for Human Medicine (2nd revision)	Further expressions of expert concern
2011	Transatlantic Taskforce	Recommendations for future collaboration between the US and EU	Outlines and recommends future collaboration to tackle AMR
2011	European Commission	Action plan against the rising threats from antimicrobial resistance	Outlines a roadmap for EU actions 2011-15
2011	WHO Director-General	World Health Day 2011: Combat drug resistance: no action today means no cure tomorrow, Statement by WHO Director-General	Proposed six clusters of actions: national plans, surveillance, essential medicines supply, regulation for both animals & human use, prevention, innovation
2012	WHO	The evolving threat of antimicrobial resistance: Options for action	Presentation of information and analysis to support WHO strategy.
2014	WHO	Draft global action plan	Both the result of and accelerated global consultation
2014	Antimicrobial Review	International Commission chaired by Jim O'Neill, former Goldman Sachs chief economist	This argues a business-oriented case for investment in new drugs
2015	WHO	Global action plan	Presented to 68th World Health Assembly

The picture that emerges from Tables 1 and 2 is intriguing. With such a weight of official and 'heavyweight' reports calling for action, it is not possible to argue policy has failed due to lack of evidence. A common complaint by scientists that: 'if only the policy-evidence gap was narrowed, policy makers would be convinced about the need for action'. Rather, it is the portrait of a more complex policy battle between positions and interests, not captured by the use/abuse interpretation of events which posits that technologies (in this case antimicrobials) are neutral and that the key policy challenge is how to ensure they used appropriately and not abused. This has been noted by other researchers.[45] Even when powerful evidence is given for change, policy-makers can remain unable or unwilling to implement changes in drug use whether for food production or healthcare. This shift from policy to implementation appears to have been elusive, despite copious warnings. As a result, by the 21st century the ecological web has tightened and the room for policy manoeuvre has narrowed. Given the wealth of early warnings on AMR for both animal and human use, the failure to see that humans and animals co-exist in the same eco-system is all the more remarkable. As a 1992 study by the US General Accounting Office of antibiotic use in recombinant bovine growth hormone (rBGH) showed, the FDA had erroneously divorced animal guidelines from human ones.[46] Even though rBGH raised more problems about animals than for humans, the GAO's verdict is interesting; dispassionately, it recognised the need to link human and animal use in one policy framework. Over 20 years later, the FDA's antibiotic surveillance system is now being criticised for being overly reliant on the regulatory target, the pharmaceutical companies, for its operating funds, thereby opening itself once again to concerns around undue influence on regulations, policy implementation and conflicts of interest.[47] Still today, the US food system facilitates antimicrobial use; the US United Soybean Board, a trade body, for example, promotes antimicrobials in feedstuffs for export.[48]

Making sense of the policy situation: how has AMR been maintained?

Hindsight about the past confers an extraordinary degree of analytic power to later policy analysts. The argument emerged from our account here does not need to invoke hindsight at all. As we saw, the warnings of the consequences of misuse had come from the originators of the biological agents themselves, prior to their industrialised use. What has happened instead is precisely what had been feared: a potential frittering away of the immense benefits of discovered biological agents. For the lessons to be drawn for public policy, different questions arise. Given the source and clarity of such warnings, how could such a situation possibly have occurred? Further, rather than solely focussing on ignored warnings, is it not legitimate to ask what has reinforced the policy refusal to act? How, in other words, has the policy discourse maintained and fuelled rather than slowed down the growth of AMR? We now explore some possible explanations.

Explanation 1: resistance to policy frameworks based on complexity

The message from the originators of antibiotics was founded on an appreciation of the importance of biological complexity and the dynamic character of biological-environment interchange. Policy advisors and makers, however, find complexity problematic. They tend to idealise neat cause and effect explanations and clear impact effects, whereas complexity is hard to 'sell' to decision makers and superiors. As implementers, they face real problems in coordinating multi-level interventions. So the challenges are both at the analytical end, and the implementation end.

AMR, however, is a problem which requires not just multilevel policy interventions sought by Tomson and Vlad,[11] but actions which link biological, material, economic, political and cultural dynamics within one coherent policy framework. This is 'messy' to those who desire policy and 'policy delivery' to have neat, clear linkages between cause and effect. Despite policy documents and calls for coherence growing over time (see Tables 1 and 2 above), the actual responses have remained stubbornly fragmented. Reviews such as the WHO's 2012 outline of policy options suggested that AMR requires multiple actions on multiple levels from multiple actors,[5] but there is little evidence as yet of multi-party, multi-actor, multi-level systemic engagement. Perhaps Sweden has gone the furthest in attempting an integrated policy framework, and that for agricultural use mainly, but in world agricultural terms, it is a tiny actor. Indeed, this might be why it has acted – partly because its farm sector is not sufficiently powerful to be able to maintain a 'right' to routine antimicrobial use, and partly because of its fairly strong modern tradition of consultative ('corporatist') governance.

This exceptionalism suggests that resistance to the development of an integrated position on AMR is more the norm. Across the globe, there have been modifications in this sector or that, to this or that category of usage, such as to 'custom and practice' in poultry use and some medical practice, but nothing that could be deemed co-ordinated policy action, let alone a paradigm shift.

Policy-makers also have not accepted fully the implications for both agriculture and medical practice from the real life complexities of microbial ecology, namely that life-forms are in a slow flux across species. On the contrary, both medical practice and consumer 'demand' have reinforced inappropriate use of antimicrobials, one by seeking satisfied patient-customers who demand pills and the other the pursuit of "cheap" meat from industrial-scale food production systems. This intensification of demand has clear environmental impacts too, such as manure waste from animal production systems. There is thus a policy lock-in restricting the potential of creating an integrated approach across both human medicine and animal husbandry. One exception may be the global response to the threats to public health and global trade from avian and swine flu strains that typically arise on Asian farms and have the potential to break out to human populations far away; but even in this case, there has been little attention to the issue of widespread use of antibiotics in livestock and poultry that intersect with some of the same production practices that contribute to influenza risk and spread.[49]

In this failure to address complexity, some similarities can be noted to what is observed about other large-scale issues in public health such as obesity and climate change. These are issues apparently so large that they dwarf existing institutional capacity in their requirement for engagement of multiple actors around multiple levers. If no single institution or coalition is aware of a public health problem –as was the case for HIV/AIDS, for example, before its aetiology was clarified in 1981 [50, 51]–policy-makers can be forgiven if their actions make an emerging situation worse. Copious amounts of information and evidence have flowed on AMR, however, as they have for obesity and climate change over decades, yet policy-makers have not managed to confront or challenge the environmental conditions of human design and creation, despite these generating and worsening the problems.

Features of the AMR crisis draw particular parallels to the global crisis in obesity. Whereas HIV/AIDS posed a threat of contagion (a specific disease seemingly out of control which might spread) and possessed a fear factor (with its own complications of victim-blaming), with obesity and AMR there is a situation of 'policy cacophony' described above.[12] In addition, for AMR as with obesity, there were and are strong monied forces opposed to systemic change as well as there being divided, competing and divergent strands of policy argument. The net effect of this mix has been to marginalise serious consideration being given to an integrative system perspective with due implications for systemic change.

A key ingredient for robust policy is to have an informed and strong civic pressure on policy makers. This was the case for HIVAIDS, at least in Western states, where a powerful combination of gay activists, medical scientists and public health analysts (across the range from education to economics) set out with urgency to convince policy makers that prevention was needed and worth the investment. In fact, important politicians were convinced and did take action, even in Britain under Mrs Thatcher's premiership.[52] This has not been the case for AMR or obesity.

The combination of inside-science and inside-society pressures has been missing for AMR policy until relatively recently. To advance a future where antibiotics are not overused, and remain effective for longer, what may be required is a mix of patient power demanding drug retention for sound use and consumer power demanding different values across the food system -- rejecting routine drug use in pursuit of mass, cheap meat whatever the cost to ecosystems or human health, for example. Although there are pockets of consumer activism, it is currently the case that this cultural element has not taken off in AMR policy. It deserves more attention.

One sub-feature within the complexity explanation is also worthy of consideration; it concerns food antimicrobial use rather than human use. For many reasons, the food systems of developed economies appear to have created ever longer supply chains. These have been shown to make transparency harder, even in simple industrialised foods such as bread.[53] The inquiry into the European 2013 horsemeat scandal noted how everyday processed meat products had labyrinthine international supply chains and connections, making surveillance and trust harder.[54] This man-made food system compounds biological and scientific complexity. The WHO has noted that, despite some improvements in surveillance, the norm remains a lack of transparency about food chains and poor knowledge of the full biological effects of AMR .[55] In many developing and developed countries, sales and use of drugs are poorly monitored and documented, although some countries such as India have been estimated to have experienced a virtual doubling of antimicrobial use since 2005;[5] it does now claim to have clear AMR policies.[56]

Explanation 2: an inappropriate 'war on bugs' narrative

Antimicrobials were and still are presented as being the 'big guns' in a health war. If Dubos raised a sceptical eye in the initial years of mass antibiotic use, contemporary biologists like Judith Crawford have been rare in questioning the appropriateness of the 'war against germs' metaphor upon which popular compliance so depends.[57] The image that antibiotics are weapons in a war against germs seriously misrepresents how the natural microbial world really works. Indeed, the war analogy undermines the case for integrated and comprehensive AMR policy and interventions. There are more appropriate metaphors than war, such as feedback loops, systems dynamics and resilience.[58] Indeed, these are now informing the current interest in a new wave of investment in drugs, as we discuss later.

If anything of value is to emerge from the collective embrace of the 'war on bugs' metaphor it could be the eventual understanding that the war is being lost, in part because humans are fighting it against themselves and in part because it is fighting an environment changed by humans. With its more than 9 billion farm animals raised for meat production each year, the U.S. also produces massive amounts of manure. And as has been noted, the vast majority of U.S. antibiotics sales are destined for these animals as well. Around 75% of antibiotics fed to animals pass directly through the gut into faecal waste and then is applied back onto the land, becoming a means of environmental entry of both antibiotic residues and gene-based determinants of antibiotic resistance (genes, plasmids, etc.).[59] The 2012 WHO Report on AMR, while attesting to its importance, saw this issue as beyond its scope,[5] despite its importance. This situation potentially suits some protagonists who do not want public trust in the food industry to be harmed, nor the vast sums spent by food companies and their 'front' organisations on public relations to be questioned .[60] Questions about the need to change production and use can be countered by a combination of effective lobbying and arguments about jobs, trade, contribution to GDP, or just doubts being thrown on proof.

The war metaphor and analysis is actually a popularisation of a version of risk analysis, in which advantages and disadvantages of antimicrobial use are presumed to be in a constant trade-off which needs to be carefully managed by humans. The value-neutral outcome of AMR, in this narrative, represents a lack of information or poor risk assessment. It invokes the use/abuse model of science and technology which posits that technologies and scientific developments are intrinsically neutral and rendered 'good' or 'bad' only by human choice, shaped by use or abuse.[61] This is what the recent UK guidance note from NICE cited earlier invokes: sensible antibiotic use by doctors and health workers could be reduced by 25%. This use/abuse approach is actually not helpful. The alternative narrative fits AMR better; this proposes that technologies – antibiotics, here–embed particular values; their use embodies and reflects certain 'framing assumptions'.[62, 63] In the case of antibiotics use, such assumptions include that 'bugs' can be 'beaten', and that humans can and should control life-forms for their own purposes. These assumptions have had considerable appeal to policy makers and industrial agricultural and food business interests, but their usefulness to business interested has thankfully now started to be questioned. The World Economic Forum's 2013 annual Global Risks report, for example, highlighted the risk to business from AMR.[64] The worry is that markets might be compromised by its spread.

Explanation 3: a belief in technological fix

Notable public health successes in recent decades, more often than not, have represented progress as being dependent on technological fixes, from new vaccinations and smokestack scrubbers to the flush toilet. The trick is to distinguish problems amenable to technological fixes from those that are not, and to appreciate that some short-term fixes might only be appropriate as an interim substitute for longer-term, more sustainable or robust measures. In the case of AMR, the routinisation of antibiotic use among humans and animals can be seen as one logical outcome of a broader techno-economic vision for economic development, in effect the conditions of progress being aligned with a succession of incremental technological fixes. In this analysis, technology drives wealth, and wealth generates health. This explanation was much invoked to justify the so-called 'green revolution' in 20th century farming. In that, nature was cast as a block or limit to productivity; these had to be overcome by human ingenuity, i.e. science into practice.[65-67] This logic also was apparent in relation to AMR in the 1950s, for example, when use of routine feed antibiotics was thought to increase the growth rate of US pigs by an average 10-20%, saving labour and other costs; the appeal was obvious.[68] Using the latest comparative data, by 2011, farm use of antimicrobials in the USA was almost four times that of human use, accounting for 29.9 m lbs against 7.7 m lbs for use by sick humans;[69] and even that was beginning to backfire, as CDC notes.[70]

When early doubts about AMR were being voiced by Fleming or Dubos, it was perhaps understandable that to stand in the path of routine use of antibiotics could be depicted as being anti-progress and anti-business. A half century on, business and policy makers surely have more experience of 'unintended consequences', the inevitability of 'trade-offs', and other notes of caution. In the EU, one effect of heightened awareness of risk management has been the introduction of the precautionary principle in policy making.[71] This differs from the US regulatory model, which typically requires scientific evidence to justify restrictions on the use of a particular technology.[72] In effect, the principle is entirely reversed. Fluoroquinolone antibiotics, for example, were FDA-approved for use on poultry flocks via addition to their drinking water supplies, despite warnings that this practice would spur resistance to form to the fluoroquinolones – a critically important class of drugs to human medicine. Almost immediately, such resistance was noted to develop among Campylobacter bacteria, a common contaminant on poultry meat.[73] The FDA fought in court (ultimately successfully) to force the sole remaining company making the poultry product to withdraw it from the market, which took five years in total.[74, 75]

Modern food supply chains are long and have many linkages. Within them knowledge is fragmented, dissipated and frequently restricted. For the business community, and to some extent for policy makers, the temptation to continue to use economic productivity as the preferred measure of the health of these supply chains remains strong, even as it downplays longer terms costs of AMR and other threats to food safety, resilience or sustainability. From that perspective, there is no need for the EU's precautionary principle, which is viewed instead a mask for protectionism. This issue might seem far from public health but a study undertaken for the European Parliament accepted that this principle is now put at risk through the proposed EU-US trade agreement TTIP (Transatlantic Trade and Investment Partnership) noting that "convergence runs the risk of weakening, if not eliminating, (the current European) conception of consumer and environmental protection." [72] The effect, say its critics, is to expand corporate rights to challenge national and local regulations for food and farming systems. Is the TTIP poised to maintain the conditions which will continue the development of AMR?

Explanation 4: different strategies are needed for humans and animals

The technical perspective on effective antibiotics governance (discussed above) is exacerbated by the split of attention between human and animal use; doctors are nominally in control of the former and veterinarians of the latter. Though devised for human use initially, antibiotics were quickly and extensively applied to farm animals, often at a mass, not individual scale, and increasingly as a part of a particular model of industrialised, intensive livestock production system. In the 1940s, the growth-promoting effects of certain pharmaceutical compounds on animals was first observed and the United States Food and Drug Administration (FDA) approved their use as feed additives without veterinary prescription in 1951.[44] In June 2015, the FDA finalised its Veterinary Feed Directive which, by the end of 2016, will require that veterinarians sign off on a directive for all remaining feed additive antibiotics. Until then, while some classes of antibiotics are used only for animals, many – including penicillins, tetracyclines, macrolides, streptogramins and sulfonamides– are both used clinically for ill human patients and routinely to promote weight gain and prevent disease in food animals. Additional antibiotics, such as third generation cephalosporins and gentamicin, have been injected routinely into eggs as an unapproved or 'off label' use, despite their importance to human medicine.

In effect, this mixed market has been precisely the drug-shopping scenario Fleming once warned against. It has contributed to farm environments where reservoirs of resistance to multiple antibiotics exist in water supplies or in soil and among farmers and farm workers. Surveillance of retail meat from many countries also demonstrates reservoirs of multidrug resistant bacteria in the global meat supply, especially in chicken and pork. The US National Antimicrobial Resistance Monitoring System (NARMS) found that supermarket meat samples collected in 2011 harboured significant amounts of salmonella and campylobacter which together caused 3.4 million cases of food poisoning a year. 9% of raw chicken and 10% of raw turkey samples were tainted with the 'superbug' variants of salmonella; 74% of these samples were antibiotic resistant in 2011 compared to 50% in 2002.[76] The split between human and animal use confuses rather than helps policy makers to address AMR.

Explanation 5: economic costs can arbitrate policy action

In the early phase of antimicrobial use on farms and humans (from the mid 20th century), the profitability on pharmaceutical investment was high. According to numerous accounts, this is no longer the case. A central argument of the 2014 Commission chaired by former Goldman Sachs economist Jim O'Neill (made a Minister and put into the House of Lords by the Conservative Government elected in 2015) is that governments need to incentivise pharmaceutical companies to tackle AMR.[4] Gone is the war metaphor. The discourse offered by the O'Neill Commission is that the economic framework needs to be rewritten to encourage global pharmaceutical companies to invest in the development of new, expensive antibiotics.[77-79] Others meanwhile argue that such drugs are intrinsically low-margin products and that only mass scale use warrants such development, and that the pharmaceutical industry is locked into selling antibiotics as farm productivity enhancement products and is unlikely to desist until regulated. It is this last explanation which may help explain why, until 2005 Bayer Corporation was marketing a fluoroquinolone antibiotic product for mass use in poultry flocks long after FDA-compiled evidence had concluded that such use was spurring development and contamination of poultry meat with FQ-resistant campylobacter, a major foodborne pathogen.[73] Meanwhile, Bayer also marketed Ciprofloxacin, the increasingly ineffective human fluoroquinolone that was and is a drug of choice for treating people eating this same chicken meat and contracting resistant campylobacterosis.

An assumption in this explanation is that cost is the ultimate or best arbiter of policy. That public health interventions and policy options are often costed may be true, but this is not the same thing as assuming that cost will determine appropriate policy or action. Indeed, the case of AMR shows this not to be the case. The economic costs of AMR are extremely high, whether the policy focus is on-farm or in human health. One hospital study in Chicago, USA, in 2008, looking at just 188 patients, estimated that the total attributable medical and societal cost of AMR infection in those patients alone was at least $13.35 million.[80] Extrapolated to the entire USA, AMR has been estimated to result in treatment costs in hospitals alone as high as $26 billion, measured in 2000 dollars; in 2012 dollar values, the figure could be nearly $35 billion, and nearly $70 billion if lost work and other societal costs are included.[7, 70] For the European Union, the European Centre for Disease Prevention and Control has estimated that AMR results in 25,000 deaths annually and has related costs of over €1.5 billion in healthcare expenses and productivity losses.[81] With such high costs, are the attributable costs of antibiotic resistance not high enough to justify more assertive policy to reduce antibiotics misuse and overuse, including in livestock production?[82] Costs aside, the health toll is large. The US Centers for Disease Control has estimated that 2 million people sicken in the US with antibiotic-resistant infections and 23,000 die annually.[70] The sad but unpalatable conclusion has to be that, far from cost driving policy reform, high costs have been normalised.

Explanation 6: a behavioural and moral problem

We now examine a cultural explanation for the maintenance of AMR. Could it be that AMR is exacerbated by sloppy or stupid or immoral behaviour by humans in their quest for control over nature? Certainly, the history of public health has included a strong cultural-behavioural element.[13] The understanding of the significance of poor health-related behaviour and the difficulty in changing them are hardly new; one can think of the difficulties Ignaz Semmelweis encountered when arguing for hand-washing procedures by doctors attending childbirth in the mid-19th century.[83] So is AMR being reinforced by poor behaviour, requiring cultural rather than financial incentives and 'corrections'? Certainly, there is more than a hint of morality in AMR guidance invoking cost saving or waste reduction. Even putting such overtones aside, the view that inappropriate prescribing of antibiotics in healthcare settings is in part a behavioural problem seems plausible; appeals are made to this or that actor – now consumers, now doctors - to desist. Calls for adherence to antibiotic stewardship guidelines and voluntary programs have become increasingly strident. If AMR is at root a behavioural issue, then it must be rooted in a particular national context. Some European countries link their own low rates of healthcare associated AMR with low levels of antibiotic prescribing.[80] Attention to behavioural cultures among hospital staff has been seen as a 'success story' with reduction in MRSA bloodstream infections falling 18-fold (from 1.3% to less than 0.1%) since 2006 and a 5-fold reduction in *clostridium difficile* infections (from 2% to 0.4%) over the same period. Even so around 300,000 patients a year in England in 2011 acquire a healthcare-associated infection, a prevalence rate of 6.4%.[84]

But is it a behavioural explanation for AMR to say that it is an outgrowth of consumer pressure? Perhaps. Patients demand antibiotics and consumers demand cheap meat, this line of argument suggests, and therefore lock the health professions or the food supply chain into collusion. This does not, however, fully account for consumers' lack of understanding of the nature or consequences of resistance, or the threat to antibiotic effectiveness.

If consumers do see drugs as 'magic bullets' for all ailments, policy makers should consider how such beliefs were created and sustained, and how they can be managed. In this regard, one interesting development is the creation of new and growing civil society coalitions calling for curtailed antibiotic use.[85, 86] These may open up culture change without this being seen as top-down, moralistic or hectoring. They were effective in Sweden in the 1980s, so why not elsewhere since? International civic or citizen campaigns are, in our judgement, needed but they are hard and expensive to organise; billions of dollars might be estimated by the O'Neill Commission as needed to incentivise Big Pharma to create new categories of antimicrobials but only a tiny fraction is offered for culture change. The EU has been funding AMR media-based campaigns targeting consumers at a member state level since 2009 which it claims to be effective; but these concentrate almost wholly on human use rather than on livestock or veterinarian use. The 2010 EU Eurobarometer survey on AMR showed considerable and intriguing variations in national consumer understanding of direct human health.[87] A repeat survey in 2013 showed some improvement.[88] Why is there such variation? How can new behaviour be instilled into this cultural mix? That behavioural campaigns can make a difference has been shown by integrated efforts in Belgium and France.[89] In the USA, the CDC and others' communication campaigns have been seen to make a difference, but have been constrained by continued antibiotic use in animal husbandry. We see this cultural dimension as intrinsic to any ecological public health strategy. As we have argued above, the AMR challenge requires integrated action to link the societal, the biological, the material and the cultural elements.

Looking ahead: will policy address the complexity?

AMR is a problem of evolutionary complexity. As Baquero and colleagues have argued, because of the feedback loops of complex systems, no single intervention will ever be sufficient and only the use of multiple, wide-ranging associations of interventions might be able to produce an overall positive synergistic effect.[36] Defining and adopting an ecological public health policy perspective, the paper therefore has argued that biological change has to be core to the public health analysis of AMR; such a perspective has been marginal to current policy debates, but the case for it strengthens as more stakeholders accept its premise that systems problems like AMR require multiple policy levers, and multi-level action.

There may be some reversibility to AMR but the more years of activity go into creating ecological reservoirs of resistance, the more difficult and less successful it is likely to be to reverse the damage already done.. The expense and uncertainty of success in finding new novel classes of antibiotics makes this equation particularly troubling, and threatens healthcare let alone national budgets. As with climate change and obesity, there are encouraging signs that policy makers accept the problem has progressed already to the point where only some degree of adaptation to it may ultimately be possible. That is not an excuse for inaction. It is a reminder of the urgency of the task. Public health leadership on AMR is therefore required, as any review of the situation must conclude that the current policy mix is not working; if it was, AMR would be under control. There are signs of some movement by some sections of the meat industry.[90] This needs to be global since supply chains are global. Nor can the public health movement, including the professional leaders within the civil services, generate requisite change on their own; mass citizen (rather than consumerist) concern is needed to put pressure on both medical and veterinarian use. Consumer values surely need to change; they probably need to pay more for better quality meat grown without antibiotic use in intensive food production systems; for nutrition reasons, the rich societies need to contain burgeoning consumption, anyway. There are advantages to health and the environment from keeping meat production in more clearly defined environmental limits. Consumers also need responsive governmental structures, at multiple governance levels, ready and willing to put health, consumer and environmental protection above those of industry lobbies. [91]

To conclude, this paper has agreed with those who argue that the AMR crisis requires a global, unified public health approach, much as has been successfully undertaken for smallpox elimination and curbing tobacco consumption, and ought to be applied to obesity. To confront antibiotic overuse, and overcome policy inertia, campaigns are needed to provide leadership across medical, veterinarian, health education, consumer, farmer and grower bodies. Based on past performance, and for reasons which have been discussed, we do not anticipate early political leadership on this, but the politicians deserve and need better briefing and scrutiny from an ecological public health perspective. All governments and oppositions need to be reminded that the destruction of antibiotics is happening on their watch. This is a problem that cannot be pushed into the future.

Adopting an ecological public health perspective with respect to AMR also means moving beyond the bio-medical model's focus on the individual patient or the individual meat-producer. Patients are not simply consumers of antibiotics, nor farmers simply purveyors of cheap meat, as the market model can often present them. Public health requires population-scale actions. Because there is a public interest in having antimicrobials that work, the use of antimicrobials is more than an individual decision between patients and doctors or veterinarians. A recent paper proposed a tough new international Framework Convention, as for tobacco.[92] This should be debated. It might be one mechanism, among many, which builds pressure for systemic change.

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