Antibiotic resistance is the quintessential One Health issue

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The scale of antimicrobial resistance

In May this year, the long-awaited final report from the *Review on Antimicrobial Resistance* was published.[1] The report estimates that the 700 000 annual deaths currently attributable to infections by drug-resistant pathogens will increase, if unchecked, to 10 million by 2050, running up a bill of US$100 trillion in terms of lost global production between now and then. The reported numbers are somewhat apocalyptic, as they are based on crude projections of current trends and presume the failure of anti-malarial drugs and antiretroviral therapy as well as antibiotics. Nor do they account for the possible entry of new drugs onto the market. There is huge uncertainty associated with the human burden of antimicrobial resistance (AMR) in general and antibiotic resistance in particular (for the purpose of this article the widely used term antimicrobial resistance [AMR] is retained, though the emphasis here is on antibiotic resistance). The precision of the estimates does not really matter much: the point is that the problem is already immense and is growing rapidly. We have been squandering our antibiotic resources for far too long and immediate action is needed on a very large scale if we are to reverse current trends.

AMR as a One Health issue

It is difficult to imagine an issue that epitomises the principles of One Health more than AMR does. The One Health approach, defined as '…the collaborative effort of multiple disciplines – working locally, nationally, and globally – to attain optimal health for people, animals and our environment…',[2] recognises that the health of people is connected to the health of animals and the environment. AMR has clear links to each of these three domains. The contribution of animal production, both terrestrial livestock and aquaculture, to the global AMR crises is questioned by some on the grounds that we don't see so many animal-associated infections in humans.[3] While this may be true, because of the way that many antibiotics are used in animal production, in sub-therapeutic doses and with long exposure periods, these production systems create ideal conditions for bacteria to fix genes that confer resistance. These genes can subsequently be transmitted to human-adapted pathogens or to human gut microbiota via people, contaminated food or the environment. They also provide ideal conditions for the amplification of genes that may have arisen in people or the environment. The fact that the antibiotics used in human and animal health largely comprise the same or very similar molecules would be expected to drive the transmission of resistance between animals and people, either directly or via the environment.

Of the three domains, human health takes the spotlight, with multidrug-resistance genes now highly prevalent in many important and common pathogens like *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus*. Quite apart from the many infectious diseases for which we rely on antibiotics to combat, these drugs underpin modern medicine by allowing us to carry

out common surgical procedures and treatments that depress the immune system, such as chemotherapy to treat cancer. The global burden of AMR on the population has been estimated,[1,4] and more specific studies have also been carried out; for example, the estimated 214 000 neonatal deaths attributable to resistant sepsis infections globally in 2013; 111 523 occurring in the five countries with the highest numbers of neonatal deaths in the world: India, Pakistan, Nigeria, Democratic Republic of Congo and China.[5]

Such estimates of the burden of AMR have not been attempted for livestock or aquaculture, perhaps due to a perceived lower importance. Resistance to antibiotics among mastitis pathogens, for example, is well documented though it is not considered to be an emerging or a progressing problem.[6] Recent estimates of the amount of antibiotics consumed in livestock production conservatively place this at 63 151 tonnes in 2010.[7] The situation is less clear in aquaculture.[8] Although actual figures are currently unavailable, the published estimates of the proportion of antibiotics consumed in animal agriculture—84% (for 36 antibiotics) in China[9] and 70% in USA[10]—suggest global agricultural consumption probably exceeds that of humans. A large part of this use is justified and valid on veterinary grounds,[6] but there is much misuse in the agricultural sector. With such large consumption levels it seems likely that agricultural use contributes significantly to AMR. A recent review suggested that misuse of antimicrobials in animal production is a clear and substantial driver of AMR,[11] and there is a growing body of evidence linking antibiotic consumption in livestock to AMR in the clinic.[12] Many infections in people are endogenous; derived from the human gut flora. An important gap in knowledge relates to the possible extent and mechanisms of transmission of antibiotic resistance genes between the normal gut flora of animals and that of humans.

The third One Health pillar, environmental health, including that of crops where antimicrobials are also used in plant protection,[13] is the least well understood in this tangled web of antibiotic gene evolution, transmission and persistence. Environmental bacteria, being quantitatively the most prevalent organisms, serve as sources for AMR genes that can become incorporated, over time, into pathogens of people and animals. This naturally occurring phenomenon is exacerbated by the influx to the environment of AMR genes from livestock and human waste[14] and by the vast quantities of antibiotic residues that enter the environment from the pharmaceutical industry,[15] from intensive livestock farms[16] and from hospitals.[17] Because of this, it has been proposed that these activities represent effective hotspots for the development and spread of AMR genes.[18] The impact of such factors is likely to be more pronounced in developing countries with lax environmental legislation and enforcement. Soil and water microflora play complex and critical roles in ecosystem functions such as the recycling of carbon and nutrients. Disrupting these vital processes by creating an imbalance may threaten planetary health,[19] potentially pushing ecosystems beyond critical environmental thresholds.[20]

The relative roles of these three domains in the development, transmission and persistence of AMR genes is poorly understood. A truly One Health approach to dealing with AMR, embracing all three domains, will depend on a sound grasp of the relative importance of each in the evolution of AMR bacteria and genetic determinants, the ways in which they interact, and the transmission routes and mechanisms involved.

AMR is also a One World issue

As well as being a One Health issue, AMR is a One World issue. The globalisation of the food system, with increasing movement of livestock and agricultural produce, combined with increasing human travel, facilitates the rapid spread and mixing of AMR genes that emerge. A worrying example is the emergence of a plasmid-mediated resistance gene (mcr-1) to colistin, a last-resort antibiotic, identified in people and pigs in China last year.[21] This was followed by its rapid spread across Europe and Canada to the USA, where it has recently been identified.[22] A similar case is the spread of New Delhi metallobeta-lactamase 1 (NDM-1), a transmissible genetic element encoding resistance genes against most known beta-lactam antibiotics, from its point of emergence in New Delhi, India, in 2008.[23] Likened in this regard to carbon emissions,[24] no matter how good a country's programme of antimicrobial stewardship in health and agriculture, they are laid bare to the importation of AMR genes that have emerged and spread from other parts of the world. Such rapid spread of resistance must surely create a disincentive for the pharmaceutical industry, with an eye on profits from high income countries (HICs), to develop new antimicrobials against which AMR genes may be rapidly acquired through abuse in low- and middle-income countries (LMICs).

The other factor making AMR a One World issue is that dealing with AMR is central to the long-term economic development of countries and to our global well-being.[1] LMICs face the greatest burden of AMR because of their disease-prone environments, poorer sanitary standards and, for the poorest, much reduced access to effective antibiotics.[5] Poor access to competent veterinary and extension services leaves farmers in LMICs with antibiotics as their only resource to tackle endemic bacterial animal infections. Interventions must be based on an understanding of and respect for the different social and socio-economic contexts in which they are to be implemented. AMR is a global problem calling for global solutions: but the solutions will not be the same in every country, or among different socio-economic groups. Some use antimicrobials too much, some too little and many use them unwisely: understanding patterns of use and incentives for changing these, and exploring alternative options, must underpin any reduction efforts.

Increasing recognition of AMR

The *Review on Antimicrobial Resistance* comes at an important time and has no-doubt already been influential in bringing this critical topic into the arena of global public debate among stakeholders who would normally have not paid attention to this problem. The commitment by G7 countries in Berlin in 2015, to promote the AMR agenda, was cemented at this year's G7 Ise-Shima Summit in Japan, at which it was proposed to 'promote the One Health Approach to tackle cross-cutting issues of AMR in human and animal health, agriculture food and the environment, and take actions involving multiple sectors, such as by integrating collaboration between the responsible ministries, in line with the 2015 WHO Global Action Plan on AMR adopted and relevant resolutions of FAO and OIE.'[25] In May 2015, the 68th World Health Assembly endorsed a resolution making it

mandatory for member countries to align national action plans with the global standard by May 2017, and WHO subsequently published the *Global Action Plan on Antimicrobial Resistance*[26] to guide Member States in developing their plans. It is expected that a resolution will be adopted at the 71st Session of the United Nations General Assembly in September 2016, which, if effective, could place national governments under pressure to take action towards reducing consumption of antibiotics in both human medicine and agriculture.

Call for interdisciplinary research in support of appropriate action

Whatever action we take will only be sustainable if it is based on a sound understanding of the relative roles of people, animals and the environment in the emergence, spread and persistence of AMR genes. This is not a problem that HICs will be able to solve alone. The important role that animal agriculture plays in livelihoods in LMICs is unknown or underestimated by many in HICs and needs to be an integral part of the thinking and negotiation if we want to avoid the pitfalls seen in climate negotiations, with LMICs often reluctant to take measures that may compromise their short-term economic development. The One Health science seems to fall short when it comes to understanding the economic forces behind many emerging infectious diseases; there is a further gap to be bridged between the biomedical, environmental and animal sciences, and the social sciences.

Integrated approaches to reduce selection pressure and disrupt AMR transmission cycles on a global scale must be sought that are founded not only on sound One Health principles, but also based on economic evidence and on principles of social equity and global access to effective healthcare for people and their animals.

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