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Editorial

A Global Antimicrobial Conservation Fund for Low- and Middle-Income Countries

On 21st September 2016, for only the 4th time in history, a health topic will take centre stage at a United Nations General Assembly (UNGA) high-level meeting where heads of state are present. A day-long session has been convened to discuss the global threat from the lack of access to antimicrobials and from increasing antimicrobial resistance (AMR). The main focus will be on antibiotic resistance. The involvement of the UN underlines the significance of this threat to public health, food security, global economic growth, and progress towards the 2030 Sustainable Development Goals.[1]

Like climate change, AMR depends on effectively managing global public goods and common resources, in this case antimicrobials, whose use drives resistance, and thereby deprives others of their benefits. Such management requires interdependent action in three areas: conservation, access and innovation (figure 1).

Akin to the reduction in use of fossil fuels to curb pollution levels that impact on climate, conserving antimicrobials to limit development of resistant microbes, thereby ensuring the continuation of their efficacy for all in need, is a critical strategic response. This must occur in parallel with existing efforts to promote greater, appropriate access to antimicrobials for the millions of people who currently, unfairly face disease without them. Simultaneously, re-igniting a dormant antimicrobial research and development (R&D) pipeline to produce new classes of antimicrobials is equally important to renew this crucial man-made resource. The formation of DNDi/WHO's drug accelerator program, the Global Antibiotic Research and Development (GARD) Partnership[2], as well as new funding streams like Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)[3] and the nascent Global Antimicrobial Resistance Innovation Fund (GAMRIF)[4] are welcome and timely initiatives. However, if we are to ultimately reverse or indeed decelerate our new reality of the post-antibiotic era, then antibiotic conservation is going to need to take centre stage in an overarching strategy for AMR control, while we wait for new products to be developed, and even once we have them. This will be an ever-lasting battle, which will require strong conservation policies to be put in place permanently.

Much of the global overuse of antimicrobials occurs in low- and middle-income countries (LMICs), topped by the BRICS nations (Brazil, Russia, India, China and South Africa) driving consumption in both animal and human sectors.[5] In general, an increased demand for animal protein accompanies the transition from low to higher incomes[6] and is currently met by more intensive farming practices. Historically, these practices rely on sub-therapeutic doses of antibiotics for animal growth promotion (AGP), a practice banned in the European Union since 2006, as well as wide scale treatment of healthy animals to prevent them getting sick (metaphylaxis), and hence avoiding reduced productivity. Veterinarian prescribing controls a comparatively small percentage of total use in animals.

Although not confined to LMICs, the drivers of antimicrobial overuse and misuse in human health are multifactorial and magnified in these settings by the still massive burden of infectious diseases, high poverty levels leading to lack of access to clean water, sanitation and hygiene, unregulated access to antimicrobials over-the-counter and from street-sellers without prescription, cultural perceptions of antimicrobials (antibiotics in particular) as confirmation of illness and vindication of being unwell, and lack of education of healthcare professionals and the public in terms of the adverse effects that inappropriate antimicrobial use exacts on the public health. In addition, aggressive marketing and a limited regulatory and enforcement capacity of pharmaceutical company practice can drive overuse in some settings.

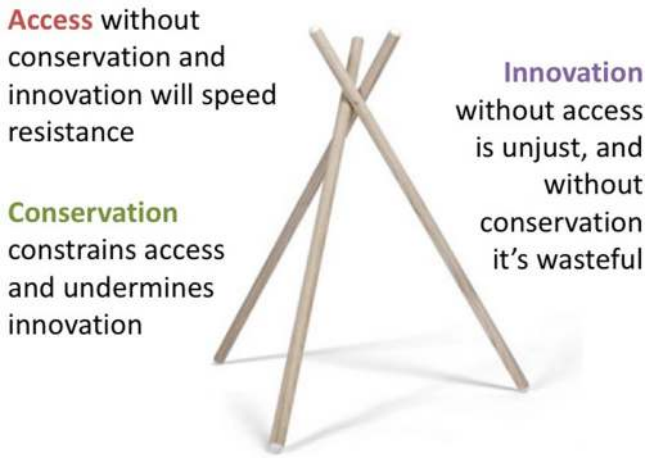

Figure 1. Policy Tripod for Addressing Antimicrobial Resistance.[19]
Reproduced from Hoffman, S. J. and Outterson, K. (2015), What Will It Take to Address the Global Threat of Antibiotic Resistance? *Journal of Law, Medicine & Ethics* 43(S3): 6–11. doi:10.1111/jlme.12267.

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It is in the developing world that over 90% of the estimated 10 million AMR-related deaths per year will occur by 2050.[7] The catch-22 is that these are the countries that generally need improved access to antimicrobials and are the least able to finance conservation efforts due to resource limitations and weaker health systems.

The final O'Neill Report on Antimicrobial Resistance highlights 10 interventions that are needed to address the global antimicrobial resistance crisis.[8] Its recommendation of a global innovation fund to drive R&D for new antimicrobials, vaccines and diagnostics has been a focus of attention in the run up to UNGA, and is an important initiative. However, for many LMICs, it is clear that government budgets will only go so far in supporting each stage of the process towards antimicrobial conservation, and serious consideration must be given to how low income, and lower-middle income countries are going to translate their national action plans into practice without international financial and technical assistance? Furthermore, how will countries that receive such aid be held accountable for delivering on commitments made? How will countries conserve new antimicrobials with the current challenges they face that have contributed to the AMR crisis?

We recommend the formation of a Global Antimicrobial Conservation Fund to complement the tranche of innovation funds that have recently been announced. Rather than this being a permanent flow of funds, which is unsustainable, a conservation fund would provide transitional financial and technical support to build capacities and programs within the poorest countries, which would then be taken over domestically as possible. Such a fund would not diminish the responsibility of national governments in the development of their national AMR plans nor for delivering meaningful outputs. Rather, it would confer support for accelerated action, to conserve a rapidly dwindling resource and could be linked to a formal resource conservation agreement. For those wealthier countries already spending considerably on AMR, financially contributing to such a global conservation fund protects their domestic investments and is one of the most cost-effective ways of mitigating risk posed by the transnational migration of resistant microbes.

Surveillance of antimicrobial resistance and consumption forms a critical pillar of all AMR national action plans. Countries have been encouraged to join the Global Antimicrobial Resistance Surveillance System (GLASS)[9], yet few LMICs in Africa, Asia and South America have the laboratory infrastructure and reporting mechanisms in place to provide meaningful input or to qualify for inclusion. Transitional financial and technical support to individual countries to stimulate growth and build human resource capacity in surveillance is crucial, but forming or strengthening regional collaborative networks also needs consideration by funding mechanisms such as the Fleming Fund.[10] A 'hub-and-spoke' model where a country or countries with greater laboratory and surveillance infrastructure in place supports regional neighbors is an attractive one. However, additional funding mechanisms to the £250 million Fleming Fund will be needed to make significant inroads into the lack of surveillance infrastructure across the vast majority of developing countries. LMICs will equally need to be supported in the area of documenting consumption and the types of antimicrobials in their markets under the whole surveillance umbrella.

Three other important conservation strategies that require international funding are highlighted in the O'Neill report; public awareness campaigns, building human resources, and infection prevention interventions. A sustained, global, public awareness campaign on antimicrobial resistance and conservation is estimated to require USD $40-100 million per annum. The Indian red line campaign, which identifies antibiotics or products containing them, is the first attempt to make antimicrobials easily identifiable to the public, and could be rolled out internationally possibly combined with regulating antimicrobials as a separate class of medicines.[11] Yet a more diverse approach may be needed, which takes into account how different societies in LMICs deliver health information. This may be as diverse as oral story telling around the village fireplace and other traditional community-based teaching methods, all the way up to the use of comparatively high technology social media campaigns.

This issue also speaks to how we are to finance the building of human resources to undertake communication and all the other facets of a stewardship response in resource poor settings. A lack of remuneration for doctors working in the field of Infection compared to most other clinical specialties has been identified.[8] While it is important to stimulate the global growth of clinical and laboratory specialists in Infection, it is far more important to broaden the discussion to consider which cadres of health care professionals (HCPs) are best placed to steward antimicrobials towards their optimal use and how we are going to finance growth across many human resources needs. There will not be a 'one size fits all' model for all countries; rather, flexibility in the model or framework will be required. Indeed, studies from LMICs of stewardship programs run by doctors[12], pharmacists[13], nurses[14], and community health workers[15] have already highlighted the diversity of programs that can lead to significant reduction in antimicrobial consumption and the optimization of their use in public and private sectors. The barrier is frequently not just the number of HCPs available, but that time is not apportioned to their working day to enact stewardship. There is often so little leeway in the system, that asking HCPs to take on extra tasks or reduce some of their existing workload to accommodate stewardship activities is often impractical. Extra finances and a harmonization across donor-driven vertical health programmes that often compete for the time and attention of a limited number of health staff will be needed on a transitional basis for LMICs to address this shortfall.

The third and perhaps most fundamental intervention for antimicrobial conservation that will require additional funding in LMICs is delivery of basic infection prevention measures for communicable diseases. LMICs continue to face the challenge of unsafe water and poor sanitation, which drives diarrhoeal diseases. Basic necessities like running water and sanitizing agents are often lacking in health facilities outside of the major cities. Others do not have the finances to deliver essential vaccination programs to protect children against pneumonia and other vaccine preventable infections. In food production, infection prevention i.e., increasing biosafety and biosecurity are core components to change that would be necessary to assure food security if AGPs are to be rapidly phased out and metaphylaxis for healthy animals either banned or limited.[16,17] Without external financial aid, many LMICs are unlikely to be able to put in place the public health interventions that have formed the bedrock of antimicrobial conservation in high-income countries.

Calls for the formation of a high-level coordinating mechanism to oversee the next phase of the global response to AMR are being made in the run up to the UNGA high level meeting.[18] One function of such a body could be to coordinate how funds from governments and foundations should be spent. A rapid scaling up of funding for low- and lower-middle income developing countries to support antimicrobial conservation in the form of a Global Antimicrobial Conservation Fund should be a critical component of the deliberations to come.

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