Introduction

There is a need to escalate the global public health response to the growing threat of antimicrobial resistance.

Antimicrobials – including antibiotics – are used to treat infections caused by bacteria, as well as by other microbes, such as viruses, parasites and fungi. Globally, millions of people are infected with antibiotic-resistant bacteria each year; hundreds of thousands lose their lives. More and more strains of bacteria are resistant to an ever-rising number of antibiotics, and pathogenic species that have become resistant cause infections that can no longer be treated with antibiotics. This seriously jeopardizes not only our ability to treat common infections but also to perform complex medical procedures such as organ transplants and cancer treatments.

Although resistance is a natural process the use of antibiotics causes it to emerge. The extensive misuse and overuse of antimicrobials both in humans and animals have accelerated the emergence and spread of resistance. Without a radical change in the current practices and rates of antibiotic usage, antimicrobial resistance will become one of the greatest threats to humankind; to public health and to the global economy.

This is aggravated by the fact that no new classes of antibiotics have been developed since 1987. There is some progress being made but not significantly or rapidly enough. A new antibiotic substance was found in the human nose, which could potentially be used to treat antibiotic resistant pathogens such as methicillin-resistant S. aureus (MRSA). However, for this new antibiotic substance to be ready for human use, many more tests and clinical trials will need to take place which means that we are still years away from being able to use it. Meanwhile, the lack of effective antibiotics against resistant infections can affect us all – patients and doctors, farmers and consumers, humans and animals – without regard for international borders.

Accordingly, a broad global commitment was made among countries on a new global plan to combat antimicrobial resistance (AMR). The World Health Assembly in May 2015 adopted the Global Action Plan on Antimicrobial Resistance (GAP).

Summary

On 21 September 2016 at the sides of the United Nations General Assembly, there will be a High Level Meeting that will deliver a political declaration to strengthen coordinated global action to tackle antimicrobial resistance (AMR). There is enough evidence demonstrating that AMR is already causing untreatable infections all over the world. For developing countries, AMR is both a public health challenge and a development challenge. Tackling AMR in developing countries requires deep understanding of the particular context and needs of the rural and urban populations. In this note, we examine four critical issues for developing countries to design an effective public health response to AMR, and for which international support is needed, in the form of public financing, investment and policy space for implementation.
The plan outlines the following five objectives that are meant to support the actions needed to address antimicrobial resistance:

- Improve awareness and understanding of antimicrobial resistance through effective communication, education and training;
- Strengthen the knowledge and evidence base through surveillance and research;
- Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;
- Optimize the use of antimicrobial agents in human and animal health;
- Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

Now it is a question of implementation. On 21 September 2016 at the sides of the United Nations General Assembly there will be a High Level Meeting on AMR that will deliver a political declaration and hopefully pave the way for coordinated actions on AMR with a higher political commitment.

There is enough evidence to demonstrate that AMR is already causing untreatable infections all over the world. For developing countries, AMR is both a public health challenge and a development challenge. Tackling AMR in developing countries requires deep understanding of the particular context and needs of the rural and urban populations. In this note, we examine four critical issues for developing countries to design an effective public health response to AMR, and for which international support is needed, in the form of public financing, investment and policy space for implementation.

1. Access

For developing countries the challenges that AMR poses adds to the already existing ones, particularly when it comes to access to medicines, vaccines and diagnostics. A 2012 report by UNICEF found that diarrhea and pneumonia are the leading causes of child death globally and that “less than a third of children with suspected pneumonia received antibiotics in developing countries, with South Asia averaging 18 per cent.” These figures resonate with a Lancet study from early 2016 which found that more than a million children worldwide die each year because of untreated infections such as pneumonia and sepsis.

The case of pneumonia provides an important example of the current challenges on access since pneumonia infections can be prevented with the pneumococcal conjugate vaccine (PCV). Countries that are able to provide immunization for children have seen important decreases of infection and therefore there is less need to use antibiotics. However, today the price of such a vaccine is out of reach for many children in developing countries prompting Médecins Sans Frontières (MSF) to launch a campaign directed at Pfizer and GlaxoSmithKline (GSK) for the reduction of prices. According to MSF data PCV alone accounts for about 45 per cent of the total cost to vaccinate a child in the poorest countries. If we are to tackle resistance it is important that we make sure preventive measures such as vaccines are affordable, without which the challenge is an even bigger one for developing countries.

Another example is the rapid increase of resistance in tuberculosis (TB). Today there are more and more cases of extensive drug resistance TB (XDR TB) and the majority of these cases are in developing countries. The increase in resistance is threatening the possibility to provide adequate treatment for this infection and even estimates by the Review on Antimicrobial Resistance emphasized that from “the 10 million deaths that might be associated with drug resistance each year by 2050, around a quarter will come from drug-resistant strains of TB.” This means that efforts to step up adequate treatment for TB need to take into account the particular needs of developing countries.

The access challenges also include the need for laboratory and diagnostic capacity that is necessary for detecting pathogens that will help health workers to determine the best course of treatment. For developing countries access to vaccines
and diagnostics are key tools to prevent infections but this alone is not enough. It is also necessary to step up important public health improvements in sanitation, hygiene and safe water initiatives. Access to current and new antibiotics will be necessary to ensure not only the health of the population but to design strategies that will allow countries to improve the use of existing antibiotics and the conservation of new ones. Thus, access to affordable antibiotics, vaccines and diagnostics tools constitutes an urgent priority for developing countries and it is important that price is not used as an incentive to curbed misuse, especially in resource poor settings.

2. Research and Development

One of the aggravating factors for the rise in AMR is that there are few prospects for medical products such as vaccines, medicines and diagnostics. In the face of drug-resistant bacteria, the dry pipeline for new antibiotics is particularly troubling. The impact in developing countries is severe. About 95 per cent of the cases of tuberculosis (TB) infection occur in low and middle-income countries, where cases of multidrug-resistant tuberculosis are on the rise.9 Adding to this burden, the high price for the few new TB drugs, i.e. bedaquiline and delamanid, is prohibitive for developing countries.

Accelerating research and development (R&D) to bring about new affordable products must be a global policy priority. These efforts need to target expanding the pipeline of R&D projects, increase R&D efficiency with enhanced collaboration and knowledge sharing, adequate target product profiling based on priority health needs and the context of the end users; and greater transparency on R&D costs. New medical products must be effective and accessible and affordable to reach all who need them. There is little social value if new products are developed but they are not accessible in countries and areas where the diseases burden is high.

There is substantial evidence that the current incentive model for research and development (R&D) fails to drive private pharmaceutical firms to produce new medical products to treat a number of diseases that do not offer profitable commercial returns. Thus, increasing R&D to meet health needs is not necessarily in line with the private sector goal of profit maximization. For many diseases that lack private R&D efforts, such as neglected diseases, it is largely due to low purchasing power. Antimicrobials are of more general use across populations and low purchasing power is not the major factor deterring private investment efforts. There are many other factors that reduce prospects of revenues for private firms in new antimicrobials. These include the short dosing regimen of patient intake in their lifetime and scientific challenges that increase risks if R&D efforts fail.

Public sector support for R&D is necessary and commitments should be relative to the financial capacity of the country concerned.

Two policy perspectives can be taken to address the gap in R&D efforts for new antimicrobial products. One way is to focus on mobilizing private sector R&D, within the realm of the dominant market-driven, intellectual property-led innovation model. Countries can make efforts to address the mismatch of incentives for the private sector to invest in R&D. The big challenge here is designing incentives that will create R&D while at the same time ensure affordability and access to new products, and ensuring the cost-effectiveness of governments’ limited resources. In this area, a consortium of large pharmaceutical firms has declared interest in increasing investment in R&D in antibiotics but call on governments to help create a “sustainable business model.”10 Governments are requested to allocate more funds, – the magnitude is unclear due to lack of transparency in industry costs of R&D – to “create a sustainable and predictable market” for new antibiotics, diagnostics and vaccines. No one knows with certainty how much funds are required. The report of Lord Jim O’Neill estimates that such costs would entail about USD 0.8 to 1.3 billion in the form of upfront large payments called “market entry rewards” for antibiotics, and proposes the establishment of a Global Innovation Fund for AMR, endowed with USD 2 billion over five years. There is also a call for additional incentives, such as facilitating regulatory approvals or extending time during
which the product is not subject to any competition.

The assumption is that if there are significant funds available to ensure profitable compensation for R&D, private firms will populate the antimicrobial pipeline. However, it would be misguided to assume that if the cost of R&D is largely met by public funds, high prices and enforcement of patents and other legal monopoly rights against potential competitors and other competition reducing strategies would not be practiced by private firms. Evidence to date shows that this is not the case. Public funding support for basic and translational research is already substantial and this has not deterred regular industry strategies at the cost of access to adequate and affordable treatment.

Another approach is to encourage supplementary models to the market-driven, IP-centric R&D model. Innovative approaches to R&D that delink costs of R&D from prices and sales volumes have been tried and identified. To some extent private sector firms are engaged in some efforts such as public-private partnerships for the development of products for neglected diseases for which commercial markets are non-existent. One new related initiative, the Global Antibiotic Research and Development Partnership (GARDP), has surfaced for R&D in antibiotics, building on the experience of the product development partnership, Drugs for Neglected Diseases Initiative (DNDi). Other approaches include open collaborative R&D models and prizes. In such an approach, the R&D process is coordinated by a public-interest organization that may involve multiple actors that bring in different core strengths; the financing of R&D is mainly through public-sector and donor funds; intellectual property is managed by the initiative in the public interest as opposed to an incentive for R&D; which in principle provides for a set up to allow for new products to meet health needs and be made accessible at affordable prices. That said, the sustainability of these private initiatives is in question and there is need for a broader framework of accountability and transparency. This has been highlighted by the recent United Nations Secretary General High Level Report on Access to Medicines.11

A set of principles can assist in prioritizing the type of initiatives or mechanisms for de-linkage of costs of R&D from prices and sales volumes, that developing countries may choose to support for promoting R&D in antimicrobials, at the national level or as part of a regional or global initiative. These principles may include that R&D priorities should be needs-driven and evidence-based, guided by agreed priorities set by governments and by principles of shared responsibility, affordability, effectiveness, efficiency and equity, as agreed under the WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPOA) and the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG), and that will also be reinforce by the UN High Level Declaration on AMR. Other important principles to include are government oversight for increased accountability of any supported R&D initiative, be it solely public, public-private partnership or solely private involving public investment and transparency in defining product target profiles that should be based on health needs and the costs of R&D activities. Developing countries should also give special consideration to supporting de-linkage mechanisms in disease areas where problems of antibiotic resistance are more acute, and those that can involve domestic academia, labs and companies to strengthen the domestic R&D capabilities, technology transfer and knowledge diffusion.

3. Regulation on Use of Antimicrobials

Use in animals

One of the many drivers of the overuse of antibiotics and its contribution to resistance is the use of antibiotics for animal husbandry and aquaculture. While many of these treatments are necessary, the problem is intensified by the use of antibiotics as growth promoters or other non-therapeutic uses in animals.

Improving regulation of antibiotics in animal husbandry, including limiting and eventually phasing out use for growth promotion, is an important measure to reduce rates of antibiotic resistance in humans. Because a lot of the same drugs that are used to treat infections in humans
are also used for animals, selection of the resistant bacteria has resulted from either type of usage.

There is increasing evidence that shows infections in humans that are resistant to the same bacteria as in animals and animal food products. An increasing number of studies indicate that a major proportion of resistant E. coli that cause extra-bowel infections in humans may have originated in food animals. Another example is Campylobacter infections that have increased markedly in both developed and developing countries and more antibiotic resistance strains suggest that the use of fluoroquinolones as growth promoters is accelerating this trend. The 2014 WHO surveillance report points out that “the classes of antibiotics used in food-producing animals and in human drugs are mostly the same, thereby increasing the risk of emergence and spread of resistant bacteria, including those capable of causing infections in both animals and humans.”

Moreover, new data is emerging that point to the disproportionately high amount of antibiotic use in animals, particularly in the industrial production of food animals, which is generating resistant genes, such as the MCR-1. This situation is reducing options for treating infections in humans. Accordingly, antibiotics should only be used for treating animals when indicated by a genuine therapeutic need and based on antibiotic therapeutic guidelines.

To add to the existing evidence of resistance, the case of colistin is an important example. This antibiotic has been used to treat gastrointestinal infections in livestock and was rarely used in humans because of the toxicity to the nervous system and kidneys but with the emergence of resistance to all other antimicrobials colistin has begun to be used as a last resort. Even though colistin had hardly been used to treat infections in humans, scientists have found the gene MCR-1, that is resistant to colistin, and that today has spread to a number of countries around the world which means that even this last resort antibiotic will no longer be effective.

Thus there is more and more scientific evidence that shows that resistant bacteria can be transferred to humans from animals and one of the ways in which this occurs is through the food chain. The discovery of the resistance to colistin has prompted the Pan-American Health Organization (PAHO) to issue an epidemiological alert urging its Member States to take measures leading to prohibiting the use of colistin for prophylaxis and as growth promoters in animals. This call for a ban on particular a class of antibiotics or for growth promotion purposes is not new; in fact the WHO in the Global Action Plan on Antimicrobial Resistance has called for “phasing out of use of antibiotics for animal growth promotion and crop protection and reduction in nontherapeutic use of antimicrobial medicines in animal health.”

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The increase in resistance due to the use of antibiotics in animals represents a bigger challenge for developing countries. In many settings there is little surveillance and the use of antibiotics follows animal production practices that will require very costly investments to move away from. The economic impact that changing current animal husbandry practices will have might not be so significant in high-income industrialized countries but estimates from the OECD point out that “countries with less optimized production systems could observe larger productivity and economic effects.”

The investment needed for transition to alternative production methods, that would not require the extensive use of antimicrobials, will be of high cost and will definitely have an impact for producers in developing countries and small farmers. In order for these countries to make the necessary transitions to more sustainable production practices, resources, technology and technical assistance will need to be mobilized for this transition to be possible in the developing world.
Promotion of antibiotics

Another issue that will need to be addressed is the promotion and advertising of antibiotics, including the marketing of inappropriate uses or incentivizing medical and veterinary personnel to overuse or inappropriately prescribe antibiotics. In many countries healthcare professionals are influenced by profit gains when prescribing certain antibiotics. Economic incentives that encourage inappropriate use as well as marketing and promotion for non-therapeutic use in animals should be prohibited.

Prescriptions

In many places around the world antibiotics are sold without prescription and there has been considerable debate on how this situation increases resistance since there is little control over what medicines are sold, and whether people are taking antibiotics in the most appropriate manner. Even though this is a very important and serious concern it is equally important to look at the fact that if a ‘prescription only’ status is enforced, poor and rural populations will not be able to access lifesaving treatments and this in turn would increase existing health inequities. Such regulations cannot take place without acknowledging the different levels of development and the context of each country. It is therefore necessary that these regulations examined at the national level and that countries have enough policy space to adequately decide on the best course of action. Also, strategies need to be crafted that will improve prescription by using surveillance data that will guide healthcare professionals into providing more adequate treatments.

4. Human and Infrastructure Capacity

The WHO has highlighted that countries with weak and poorly resourced health systems will have the greatest problems in managing drug resistance. Key policies that need to be pursued include strengthening overall health systems, enhancing infection prevention and control, and strengthening surveillance and laboratory capacity. International resources need to be deployed to support national implementation in developing countries.

Developing countries bear the greatest burden of infectious diseases and in many settings access to adequate sanitation and safe water is a challenge that increases the risk of transmission of infections. Moreover, many countries face shortage of health care personnel, which in turn affects the adequate supply of health care needs. Furthermore, the medical costs of health treatments are also a significant challenge and patients that have to pay medical costs of out pocket are less likely to seek appropriate care and therefore might delay treatment or just directly buy medicines. Poor patients may not have the resources to pay for a full prescription of antibiotics and may just consume partial amounts that may be sold at a cheaper price than a full course.

Infection and control protocols are key in reducing infections but in order to effectively establish them in health care settings, it is necessary to have enough health personnel who can be trained and to assist in the control of infections. However, this might not be the case in many settings. Other risk factors that increase the likelihood of acquiring drug resistant infections in hospitals settings, particularly in developing countries, include poor hand washing practices and isolation facilities, patient overcrowding and frequent patient and staff transfers.

Strengthening laboratory and human resources capacity is particularly important to carry out surveillance that will help inform decision makers and health-care professionals on the best courses of treatment. The 2015 report from WHO on the country situation analysis found that: “countries cited a lack of laboratories with sufficient competent technical staff, weak infrastructure, poor data management and lack of standards as impediments to effective laboratory surveillance”. The lack of proper laboratory infrastructure not only impacts on proper surveillance systems, it also affects the possibility to provide accurate diagnosis and in many cases infections are diagnosed empirically due to the lack of laboratory capacity and affordable and efficient diagnostic tests. Therefore there is a clear need for investment in laboratory capacity and also in diagnostic tests that are suitable for resource poor settings.
5. Policy Recommendations

- Development and implementation of National Action Plans to address AMR, in which affordable and timely access to new and old antibiotics, vaccines and diagnostics is at the forefront of the strategy for the containment of AMR.

- Financial and technical assistance for developing countries to formulate and implement National Action Plans to address AMR.

- Regulations for drug companies on ethical promotion and marketing of their medical products and prohibition of sales promotion that target doctors or veterinarians.

- Strengthen investment for surveillance system.

- Strategies for prescriptions of antibiotics that take into account the national context and realities.

- Phase out of antibiotics that are not used for therapeutic purposes or ban the use of particular classes of antibiotics in animals.

- Financial and technical assistance for developing countries to make the transition into more sustainable animal husbandry models and practices.

- Support initiatives to promote R&D in new antimicrobials that effectively de-link R&D costs from price and volume, and ensure access and affordability.

- Educate the public on using antibiotics properly, including when they should not be used.

Note*

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Endnotes


Tackling Antimicrobial Resistance: Challenges for Developing Countries


24 Antimicrobial Resistance in Developing Countries, ed. by Iruka N J. Sosa, Anibal; Byarugaba, Denis K; Amabile-Cuevas, Carlos F; Po-Ren, Hsueh; Kariakuri, Samuel; Okeke, Antimicrobial Resistance in Developing Countries (Springer, 2009).


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