SOUTH CENTRE

POLICY BRIEF

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Tackling Antimicrobial Resistance: Challenges for Developing Countries

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Introduction

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

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 inappropriate use of antibiotics causes it to accelerate. 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 medical practices to reduce infection and rates of inappropriate 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 are very few effective, safe options to switch to once resistance develops to existing antibiotics, as the antibiotic development pipeline is nearly dry, particularly for gram negative pathogens. In 1990, 18 pharmaceutical corporations had active programs to address antimicrobial resistance. By 2010, only four remained in this space. 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).[1] However, for this new antibiotic substance to be ready for human use, many more tests and clinical trials will need to take place to prove it is safe and effective to use. There is also hope for effective alternative treatment for bacterial infections, such as the use of peptide polymers

Summary

On 21 September 2016, a High Level Meeting was held on antimicrobial resistance at the sides of the United Nations General Assembly. It was followed by the adoption of a political declaration. This declaration paves the way for new coordinated actions on antimicrobial resistance backed by higher political commitment, on the basis of the Global Action Plan on Antimicrobial Resistance (GAP) of the World Health Organization (WHO).

There is enough evidence demonstrating that antimicrobial resistance is already causing untreatable infections all over the world. For developing countries, addressing antimicrobial resistance is both a public health challenge and a development challenge. Tackling antimicrobial resistance 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 antimicrobial resistance, and for which international support is needed, in the form of public financing, investment and policy space for implementation.

to kill superbugs without antibiotics.[2] We are still years away from new antibiotics and alternative treatments.

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.

Recognizing the dire need for action, a broad global commitment was made among countries on a new global plan to combat AMR. The World Health Assembly of the 194 Members of the WHO in May 2015 adopted the Global Action Plan on Antimicrobial Resistance. 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. In 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 but for developing countries, being 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 heath 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 pose add to 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."[3] 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.[4]

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.[5] According to MSF data, PCV alone accounts for about 45 per cent of the total cost to vaccinate a child in the poorest countries.[6] Moreover, even at the lowest subsidized GAVI prices, the cost of fully vaccinating a child increased 68-fold from 2001 to 2014 and many middle income countries are paying higher prices.[7] 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) and the low access to treatment. 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[8] 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."[9] This means that efforts to step up adequate treatment for TB need to

take into account the particular needs of developing countries. The prices of new drugs, where they do exist as well as delays in their registration in developing countries are also creating barriers in dealing with AMR. The pricing and availability of new TB drugs such as bedaquiline and delamanid, remains a huge challenge in high TB burden countries. MSF estimates that two years after these two drugs have come to the market, less than 2 per cent of those who need these treatments can access them, and at current prices they are out of reach for most governments and patients.

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.[10] 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 of **new** 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 lack of innovation on TB is also particularly concerning for developing countries as about 95 per cent of the cases of tuberculosis infection occur in low and middle-income countries, where cases of multidrug-resistant tuberculosis are on the rise.[11]

Accelerating research and development efforts to bring about new products must be a priority. These efforts must ensure that new medical products are able to adequately meet health needs and they must be accessible and affordable to all who need them. If new products are developed but they are not affordable or accessible in countries and areas where the diseases burden is high, these will be out of reach for people who need them.

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. Private firms will bring to market the products that are more profitable. Thus, increasing R&D to meet health needs, which are a global need and integral to the public health goal, is not necessarily in line with the private sector goal of profit and sales maximization. For many diseases that lack private R&D efforts, such as neglected diseases, it is due to the low purchasing power of the countries and populations most affected. 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 fact that companies cannot rely on high level of sales to recover profits and investments due to short dosing regimen of patient intake in their lifetime and government policies to discourage unnecessary use of antibiotics.

Considerations of access, affordability and stewardship must be at the centre of any initiative to increase R&D efforts for new antimicrobials. This is particularly pertinent as discussions are ongoing with regard to the global pooling of resources towards R&D.

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. 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, 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."[12] 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 profit-maximizing strategies, to the detriment of access to affordable medicines and treatment.

Another approach to promote R&D and innovation is to consider complementary models to the industry-led R&D model. Various innovative approaches to R&D 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 undertaken by a public-interest organization; the financing of R&D is mainly through public-sector or donor funds, alternative incentive models are used to delink cost of R&D from volume-based sales and prices of antibiotics – which support conservation of and access to new antibiotics – and to ensure that products will be accessible through prices that are as low as possible. This requires measures such as removing barriers to follow on innovation and competition, including patents and other forms of intellectual property protection.

A set of principles can assist in prioritizing the type of initiatives or mechanisms 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 have been developed 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).[13] Mechanisms should delink (separate) the cost of R&D from the price of medical products and sales to ensure that these will be available and affordable in a sustainable manner to the populations that need them. Any measure that can promote R&D but that can have the effect of limiting access or allowing for high prices and inappropriate promotion/sales is not an effective mechanism for the purposes of public health.

Moreover, special considerations should be given to mechanisms that build on open knowledge approaches to allow knowledge to be shared and to ensure that access to R&D outputs is not restricted, including access and sharing of information from clinical trials. Developing countries should also consider mechanisms that can contribute to strengthen the R&D capacity of and/or technology transfer to these country. Pooling funds and collaborative R&D are means to support cost-effective and collaborative interventions. Public sector support for R&D is necessary and commitments should be relative to the financial capacity of the country concerned, while ensuring a public return in terms of affordability and priority setting on this public investment.

Any global initiative that developing countries support should effectively promote de-linkage of the costs of R&D from prices and sales volumes, be needs-driven and evidence-based, guided by agreed priorities set by governments and by principles of shared responsibility, affordability, effectiveness, efficiency and equity.

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 and other non-therapeutic uses in animals.

Improving regulation of antibiotics in animal husbandry, including limiting and eventually phasing out their 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.

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.[14] Another example is Campylobacter infections that have markedly increased in both developed and developing countries and more antibiotic resistance strains suggest that the use of fluoroquinolones as growth promoters is accelerating this trend.[15] 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."[16] There is little separation of the types of antibiotics that are being used in human beings and animals, and the vast amount of antibiotics that is being used at the moment in animals is a contributing factor of resistance, and must be addressed in order to help curb resistance spreading further.

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.[17] 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.[18]

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.[19] 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 a growth promoter in animals.[20] The call for a ban on a particular 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."[21]

Moreover, new data is emerging that points 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.[22] 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.

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 established 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."[23]

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.[24] 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 in-

appropriately prescribe antibiotics. In many countries health-care professionals are influenced by profit gains when prescribing certain antibiotics.[25] Economic incentives that encourage inappropriate use as well as marketing and promotion for non-therapeutic use in animals should be prohibited.[26]

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.[27] 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 are 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 health-care professionals into providing more adequate treatments.[28]

4. Human and Infrastructure Capacity

The World Health Organization 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 who have to pay medical costs out pocket are less likely to seek appropriate care and therefore might delay getting medical care 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 hospital settings, particularly in developing countries, include poor hand washing practices and isolation facilities, patient overcrowding and frequent patient and staff transfers.[29]

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".[30] 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.[31] 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 systems.
- 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 fully delink R&D costs from price and volume; and ensure access, affordability and stewardship, and do not rely on intellectual property rights as an incentive mechanism.
- Educate the public and health workers on using/prescription of antibiotics properly, including when they should not be used.

Note*

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