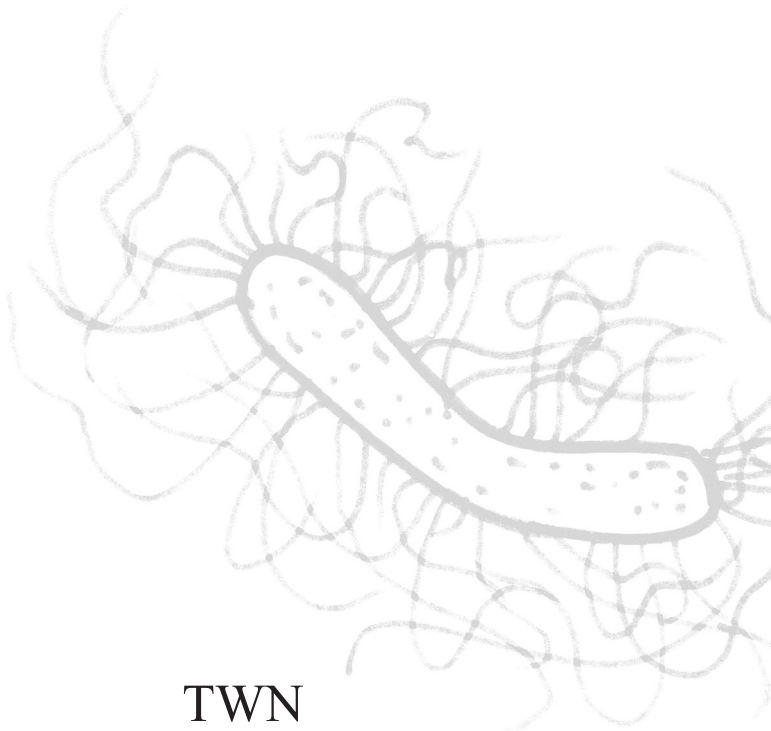


The Global Threat of Antimicrobial Resistance and the Challenges and Needs of Developing Countries

MARTIN KHOR



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Note

This is a revised and updated version of a background paper used as speaking notes by the author in a panel discussion during the United Nations General Assembly high-level event on antimicrobial resistance at the UN in New York on 21 September 2016, which was convened at the level of heads of state and government.

This revised paper was also presented at the Asian Regional Workshop on Antimicrobial Resistance (organised by the Third World Network and the South Centre and supported by the Fleming Fund) held in Penang, Malaysia, on 26-28 March 2018.

Chapter 1

A Major Global Health Crisis

ANTIMICROBIAL resistance (AMR) is a major and serious problem. It represents possibly the greatest global crisis in public health today, akin to climate change as the top environmental problem.

Antimicrobial resistance is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it. Resistant microorganisms (including bacteria, fungi, viruses and parasites) are able to withstand attack by antimicrobial drugs, such as antibacterial drugs (e.g., antibiotics), antifungals, antivirals and antimalarials, so that standard treatments become ineffective and infections persist, increasing the risk of spread to others.¹

Resistance by bacteria and other microbes to antibiotics and other medicines may be a natural process, as the disease-causing microbes evolve through time in response to the medicines. However, the rate of resistance is accelerated and the scope of resistance broadened by several factors: the inappropriate use of antibiotics, due to inappropriate prescribing and dispensing; inappropriate marketing methods and sales promotion; lack of awareness among patients; the inappropriate and widespread use of antibiotics in the animal husbandry and agriculture sector, which passes on resistant microbes to humans; the spread of resistance through the environment; and the existence of certain genes that specialise in accelerating and spreading resistance among bacteria, thus greatly increasing the rate and spread of resistance to many species of bacteria that cause diseases.

¹ World Health Organisation (WHO), 2015. Fact Sheet on Antimicrobial Resistance.

AMR is now a global crisis, with many pathogens becoming resistant to many antibiotics. As leading public health officials and senior scientists have warned, we are now entering a post-antibiotic world, in which it is increasingly difficult to treat simple ailments and dangerous diseases. The incidence of multidrug resistance has risen significantly, and for a few diseases there is almost no cure left. In 2012, then World Health Organisation (WHO) Director-General Dr Margaret Chan warned that every antibiotic ever developed was at risk of becoming useless. “A post-antibiotic era means in effect an end to modern medicine as we know it. Things as common as strep throat or a child’s scratched knee could once again kill.” The Chief Medical Officer of the United Kingdom, Dame Sally Davies, warned in 2013 of a “catastrophe” of AMR being so widespread that we would be back to a 19th-century situation of a pre-antibiotic era when many diseases could not be treated.

Recent information on the extent of resistance

A good description of the extent of the AMR crisis has been given by WHO in its Fact Sheets on AMR. The following is a summary of the WHO findings as at January 2018:²

- Antimicrobial resistance threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi.
- Patients with infections caused by drug-resistant bacteria are at increased risk of worse clinical outcomes and death compared with patients infected with non-resistant strains of the same bacteria. They also consume more healthcare resources than patients having non-resistant strains of the same bacteria.
- There are high proportions of antibiotic resistance in bacteria that cause common infections (e.g., urinary tract infections, pneumonia, bloodstream infections) in all regions of the world.
- Resistance of *Klebsiella pneumoniae* (common intestinal bacterium that can cause life-threatening infections) to a last-resort treatment (carbapenem antibiotics) has spread to all regions. In some countries, because of resistance, carbapenem antibiotics do not work in more

² WHO, 2018. Fact Sheet on Antimicrobial Resistance, January 2018.

than half the people treated for *K. pneumoniae* infections. *K. pneumoniae* is a major cause of hospital-acquired infections such as pneumonia, bloodstream infections, and infections in newborns and intensive care unit patients.

- Resistance in *Escherichia coli* to a widely used medicine for treating urinary tract infections (fluoroquinolone antibiotics) is very widespread. This treatment is now ineffective in over half of patients in countries in many parts of the world.
- A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant Gram-negative bacteria. People with MRSA are 64% more likely to die than those with a non-resistant form of *S. aureus*, which is a common cause of severe infections in the community and hospitals.
- In 2016, there were 490,000 new cases of multidrug-resistant tuberculosis (MDR-TB). Only a quarter of these were detected and reported. Extensively drug-resistant tuberculosis (XDR-TB) has been identified in 121 countries. MDR-TB requires treatment courses that are much longer and less effective than those for non-resistant TB. Among new TB cases in 2016, 4.1% were MDR-TB (19% for those previously treated for TB). About 6.2% of people with MDR-TB have XDR-TB.
- As of July 2016, resistance to first-line treatment for *P. falciparum* malaria (artemisinin-based combination therapies or ACTs) was confirmed in five countries (Cambodia, Laos, Myanmar, Thailand, Vietnam) of the Greater Mekong subregion. Patients with artemisinin-resistant infections recover if they are treated with an ACT containing an effective partner drug. However, along the Cambodia-Thailand border, *P. falciparum* has become resistant to almost all available antimalarial medicines. The spread or emergence of multidrug resistance, including resistance to ACTs, in other regions could jeopardise important recent gains in malaria control.
- Treatment failures due to resistance to treatments of last resort for gonorrhoea (third-generation cephalosporin antibiotics) have been confirmed in at least 10 countries. The new updated WHO guidelines for gonorrhoea do not recommend quinolones (a class of antibiotic) due to widespread high levels of resistance. Gonorrhoea may soon become untreatable as no vaccines or new drugs are in development.

- In 2012, WHO reported a gradual increase in resistance to HIV drugs, albeit not reaching critical levels. Since then, further increases in resistance to first-line treatment drugs have been reported. In 2010, 7% of people starting antiretroviral therapy (ART) in developing countries and 10-20% in developed countries had drug-resistant HIV. In some countries, resistance of 15% or more is reported for those starting HIV treatment, and up to 40% among those restarting treatment. Those who have HIV resistant to first-line treatment require second- and third-line regimens but these are three and 18 times more expensive respectively than first-line drugs.

Chapter 2

The Global Response

The WHA Global Action Plan and other developments

WHO's World Health Assembly (WHA) in May 2015 adopted the Global Action Plan (GAP) on Antimicrobial Resistance. It has five objectives: (i) to use medicines properly in human and animal health; (ii) reduce infection by sanitation, hygiene and infection prevention measures; (iii) strengthen surveillance and research; (iv) educate the public as well as doctors, veterinarians and farmers on proper use of antibiotics; and (v) increase investment in developing new medicines, diagnostic tools and vaccines.

Implementation of the GAP at global and national levels will be a good start in the long battle against AMR. It is important to recognise the conditions and challenges faced by developing countries and assist them to address these challenges in order to facilitate their implementation of the plan.

The WHA resolution (WHA68.7) adopting the GAP requested WHO member states to submit national action plans (NAPs) within two years, i.e., by May 2017. WHO, the UN Food and Agriculture Organisation (FAO) and the World Organisation for Animal Health (OIE) have produced a manual for preparing the NAPs.³

³ WHO, FAO, OIE, 2016. Antimicrobial resistance: a manual for preparing national action plans.

As of April 2017, 67 countries had completed their national action plans and 62 others were in the process of doing so, according to a WHO secretariat report.⁴ Almost all the NAPs reflect the One Health approach, with a multisectoral coordination group and actions planned across health, agriculture and other sectors. According to WHO: “The challenge now is to implement plans, sustain action and ensure that essential priority actions are incorporated into relevant plans and budgets.”

WHO has also carried out the following: (i) established the Global Antimicrobial Surveillance System (GLASS), with 43 countries enrolled or in the process of doing so; (ii) developed a list of critically important antimicrobials for human medicine (WHO CIA List), with the latest version in 2016; (iii) published in November 2017 a set of guidelines on the use in food-producing animals of the antimicrobials included in the list, aimed at preserving their effectiveness and protecting public health; (iv) published in 2017 a set of guidelines on infection prevention and control at the national and acute healthcare facility level; (v) published in 2016 global guidelines on the prevention of surgical site infection; (vi) published an updated version of the WHO model list of essential medicines in 2017, with an antibiotic chapter offering guidance on management of major infective syndromes; and (vii) issued a list of priority antibiotic-resistant bacterial pathogens where new medicines are most urgently needed, to guide the priority for research and development (R&D) of new antibiotics.

Pursuant to a decision in resolution WHA68.7, WHO is also developing, in consultation with member states and relevant partners, “options for establishing a global development and stewardship framework to support the development, control, distribution and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines and other interventions, while preserving existing antimicrobial medicines and promoting affordable access to existing and new antimicrobial medicines and diagnostic tools, taking into account the needs of all countries, and

⁴ WHO, 2017. Antimicrobial resistance: Report by the Secretariat (Document A70/12, dated 10 April 2017).

in line with the global action plan on AMR.” The document is still under preparation.⁵ A draft of the framework has been prepared by the WHO secretariat. It is important for developing countries to take an active role in the consultations with WHO to develop this framework.

The UN General Assembly high-level event and political declaration on AMR

Another landmark development at the global level on AMR was the adoption on 21 September 2016 of a political declaration by heads of state and government at a high-level event on AMR. It was subsequently formally adopted by the United Nations General Assembly.

Many political leaders and ministers spoke at the event on the need to fight the AMR crisis. The political declaration recognised that antibiotic resistance is the “greatest and most urgent global risk” and that “due to AMR many 20th century achievements are being gravely challenged, particularly the reduction in illness and death from infectious diseases...” This is the first ever statement by the heads of all the countries that recognise the AMR crisis and in which they pledge to take action.

The then UN Secretary-General Ban Ki-moon said that AMR has become one of the biggest threats to global health. “All around the world, many common infections are becoming resistant to the antimicrobial medicines used to treat them, resulting in longer illnesses and more deaths. At the same time, not enough new antimicrobial drugs, especially antibiotics, are being developed to replace older and increasingly ineffective ones.”

The heads of three international agencies, WHO, FAO and the OIE, made speeches and also issued a joint statement signifying their joint efforts to address AMR. The WHO Director-General Margaret Chan warned that “AMR poses a fundamental threat to human health, development and security”. Referring to the declaration, she said “the commitments made today must now be translated into swift, effective actions ... We are running out of time.”

⁵ See WHO, 2017. Antibiotic resistance: Report by the Secretariat (Document A70/12, 10 April 2017), paragraph 18 for a report on the progress of the framework.

The declaration stressed the need for developing countries to obtain financial resources. It also stressed that “affordability and access to existing and new antimicrobial medicines, vaccines and diagnostics should be a global priority.”

On the need for innovation, the declaration recognised the importance of delinking the cost of investment in R&D from the price and volume of sales so as to facilitate equitable and affordable access to new medicines, diagnostic tools and vaccines.

The declaration established a task force of agencies (co-chaired by WHO and the UN Secretary-General’s office) which would provide guidance for global action on AMR, and requested the UN Secretary-General to report on progress of implementation of the declaration and to make further recommendations.

In 2017, the Inter Agency Coordinating Group (IACG) was established by the UN Secretary-General to follow up on the declaration. It is made up of individual experts (many drawn from health ministries) and representatives of UN and other international organisations. The IACG has a plan of action, and has held three meetings to date. It also established six sub-groups to come up with analysis and recommendations. The report of the IACG will be submitted to the UN Secretary-General, who will present his own report to the UN General Assembly in 2019. The IACG will be holding more consultations with member states and with public interest groups. It is important for developing countries’ policymakers and non-governmental organisations (NGOs) to engage with the IACG.

Chapter 3

The Need for Developing-Country Involvement

It is to be expected that the developed countries will take the lead in the global fight against AMR. This is due to the greater availability of financial resources, and higher levels of scientific knowledge, research capability and technology as well as institutional and organisational capabilities including in the healthcare sector. Thus much of the global progress in the fight against AMR, in science, technology, surveillance, regulations and discovery of new antimicrobials, is expected to take place first in the developed countries.

However, the developing countries will also have to play a central role in the global battle against AMR, since it is in these countries that the majority of the world population reside, that there is the highest number (and in some cases highest incidence) of people suffering from drug-resistant diseases, and that pathogens with the genes specialising in spreading resistance have mainly been found in patients. Moreover, in an increasingly globalised world with a high degree of travel and trade, there can be the easy spread of drug-resistant bacteria and diseases.

Therefore, the special needs and interests of the developing countries have to be given the highest priority in the global fight against AMR if we are to make adequate progress.

Developing-country awareness of the AMR crisis

Political leaders and public health officials in developing countries are becoming more aware of the AMR crisis.

At the summit meeting of the Group of 77 and China, which has 130 developing-country member states, held in Santa Cruz (Bolivia) in May 2014, the political leaders of the Group adopted a declaration which included the following paragraph 66:

“We are concerned about the increasing problem of antimicrobial resistance to existing drugs, including those against TB and malaria. As a result, increasing numbers of patients, especially in developing countries, face the prospect of dying from preventable and/or treatable diseases. We urge the international health authorities and organisations, especially WHO, to take urgent action and to work together upon request with developing countries that do not have adequate resources to address this problem.”

In May 2017, the Non-Aligned Movement (NAM)’s health ministers and senior officials met on the sidelines of the World Health Assembly. The NAM ministerial declaration they issued referred to AMR as follows: “We express great concern on the spread of antimicrobial drug resistance and its potential massive threats to global public health achievements and the urgent need for global action to address this threat and, welcoming the political declaration of the high-level meeting of the UN General Assembly on antimicrobial resistance and progress made in implementing resolution WHA68.7 on Global Action Plan on Antimicrobial Resistance; and the crucial need to support Member States with technical assistance to develop their national plan on antimicrobial resistance in response to the Global Action Plan.”⁶ NAM is a movement of more than 100 non-aligned countries, most of them developing countries, which works mainly within the UN. It is significant that such an umbrella organisation of so many developing countries called for urgent global action to address AMR and expressed the crucial need to support its member states with technical assistance to develop their national AMR plans.

⁶ See South Centre News on AMR No. 4, 6 September 2017.

The health ministers of WHO's South-East Asia Region, at a WHO regional workshop in Jaipur (India) in September 2011, adopted the Jaipur Declaration on AMR, which included the following: "We the Health Ministers of SEAsia Region ... recognise it is imperative that national governments accord utmost priority to this neglected problem, to preserve efficacy of anti-microbial agents in our fight against microbial diseases." It was followed by 18 action points.

And as mentioned above, in May 2015, the World Health Assembly, of which the majority of members are from developing countries, adopted the Global Action Plan on AMR, with a commitment that national action plans would be drawn up by all countries within two years. However, in most developing countries, the public is still lacking knowledge and awareness of the threat of AMR, while coordinated and systematic action is also at only a beginning stage. Therefore, much more has to be done.

Chapter 4

Impact of AMR in Developing Countries

PEOPLE in developing countries will be most affected by the AMR crisis. AMR is estimated by the UK-sponsored Review on Antimicrobial Resistance, in a 2014 report, to globally cause 700,000 deaths annually at present (and this is a low estimate).⁷ The number of annual deaths attributable to AMR is projected to rise to 10 million in 2050. Of these deaths, it is projected that 390,000 will be in Europe, 317,000 in North America, 22,000 in Oceania, 4.7 million in Asia, 4.2 million in Africa and 392,000 in Latin America.

For most diseases the majority of people affected by AMR are in developing countries. The Review on Antimicrobial Resistance concludes that “countries that already have high malaria, HIV or TB rates are likely to particularly suffer as resistance to current treatments increases.”⁸ Particular countries at risk include India, Nigeria and Indonesia (malaria) and Russia (TB), and Africa will suffer greatly as the HIV and TB co-morbidity is likely to get worse.

The Review also estimates that 300 million people are expected to die prematurely because of drug resistance over the next 35 years (i.e., 2015 to 2050) and world GDP will be 2% to 3.5% lower than it otherwise would be in 2050. Between now and 2050 the world can expect to lose \$60-100 trillion of economic output if AMR is not tackled. (By 2030, world GDP will be 1.4% smaller, with over 100 million people having died prematurely). Countries from the Organisation for Economic Cooperation and Development (OECD, the club of rich nations) are

⁷ Review on Antimicrobial Resistance, 2014. Antimicrobial resistance: Tackling a crisis for the health and wealth of nations, pages 5, 13.

⁸ Ibid., page 9.

expected to have \$20-35 trillion in cumulative loss of output by 2050; which means that about \$40-65 trillion or two-thirds of the losses will be borne by non-OECD countries.

The case of tuberculosis is illustrative. In a 2016 report, the Review on Antimicrobial Resistance found that of “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 Most of these anticipated cases and deaths from resistant TB will be from developing countries, although TB is also affecting several developed countries.

The majority of people affected by increasing resistance to drugs treating malaria and to the first-line treatments for HIV/AIDS are also from developing countries. Pathogens that are increasingly resistant to powerful antibiotics (*E. coli*, *K. pneumoniae*, *S. aureus*, *Salmonella*, *Shigella*, gonorrhoea) are prevalent in developing countries.

Policymakers and the public in developing countries should therefore recognise that the AMR crisis is mainly taking place in their countries and that they have to give the highest priority to addressing it. At the same time, the international community has to pay special attention to the needs of developing countries and to assist them in addressing the AMR crisis.

⁹ Review on Antimicrobial Resistance, 2016. Tackling drug-resistant infections globally: Final report and recommendations.

Chapter 5

Genes Accelerating Resistance Found in Developing Countries

IN recent years, there has been the discovery of at least two types of genes (NDM-1 and MCR-1) that have the characteristic of being able to make bacteria highly resistant to known drugs and to also spread from one species of bacteria to other species through horizontal gene transfer. Bacteria containing these genes were first found in developing countries, and their presence is now confirmed in many other countries. The discoveries of NDM-1 and MCR-1 add urgency to the task of addressing antimicrobial resistance.

The NDM-1 gene has the ability to alter bacteria and make them highly resistant to drugs. In 2010, two types of bacteria (*E. coli* and *K. pneumoniae*) were found to host this gene. Most of the initial cases were found in South Asian countries. It has since spread to many countries. The gene has been found to jump among various species of bacteria at superfast speed, making more species of bacteria drug-resistant. NDM-1 has now been found in over 20 species of bacteria. The gene makes the bacteria highly resistant to all known drugs except two, including colistin.

In 2015, scientists found another gene, MCR-1, which creates resistance to colistin, a powerful antibiotic used as a last resort to treat infections when other medicines do not work. The gene also has the characteristic of being able to move easily from one strain of bacteria to other species of bacteria. Yi-Yun Liu and colleagues published a paper in *The Lancet Infectious Diseases* journal in 2016¹⁰ revealing they found the MCR-1 gene in pigs at slaughter that they tested, chicken and pork being retailed

¹⁰ Yi-Yun Liu et al., 2016. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study, *The Lancet Infectious Diseases*, 2016, 16: 161-168.

and hospital patients. The scientists found the gene in 166 out of 804 pigs at slaughter that they tested, 78 of 523 samples of chicken and pork being retailed, and in 16 of 1,322 hospital patients. The study indicates there is a chain in the spread of resistance from the use of colistin in livestock feed to colistin resistance in slaughtered animals, in food and in human beings. Colistin is part of a category of antibiotics known as polymyxins. Previously they had not been widely used in humans due to their toxic side-effects, but they have recently become a last-resort treatment when other antibiotics do not work because of resistance.

One of the authors of the study, Prof. Jian-Hua Liu from South China Agricultural University, was quoted by *The Guardian* as saying these are extremely worrying results, which reveal the emergence of the first polymyxin resistance gene that is readily passed between common bacteria such as *E. coli* and *K. pneumoniae*. This suggests that “the progression from extensive drug resistance to pan-drug resistance is inevitable”, added Liu. Extensive resistance is when a bacterium is resistant to many drugs, while pan-drug resistance indicates resistance to all drugs.

Another of the paper’s co-authors, Prof. Timothy Walsh from the University of Cardiff, told the BBC: “All key players are now in place to make the post-antibiotic world a reality. If MCR-1 becomes global, which is a case of when and not if, and the gene aligns itself with other antibiotic resistance genes, which is inevitable, then we will have very likely reached the start of the post-antibiotic era. At that point, if a patient is seriously ill, say with *E. coli*, then there is virtually nothing you can do.”

A major reason for the emergence and spread of the gene is suspected to be the heavy use of colistin to feed livestock to promote their growth. In February 2016, *The Lancet* published a comment from scientists that “we must take the call to curtail the use of polymyxins (including colistin) in agriculture to the highest levels of government or face more patients for whom we need to say, ‘Sorry there is nothing I can do to cure your infection.’” Other antibiotics that are used by human beings should also be prohibited or heavily restricted in the livestock sector, especially if they are used as growth promoters.

The 2016 paper mentioned that besides China, the MCR-1 gene had also been found in Malaysia and Denmark. Since then, the gene has also been discovered in bacterial samples in many other countries, including Thailand, Laos, Brazil, Egypt, Italy, Spain, England and Wales, the Netherlands, Algeria, Portugal and Canada.

Chapter 6

Challenges Faced and Actions Required

DEVELOPING countries face many challenges in addressing AMR. There is a lack of awareness, expertise, funds, technical equipment, personnel and political will to take the range of actions required. These are serious obstacles to the implementation of AMR action plans.

Another issue is that AMR is a problem that involves several sectors and thus the mandates of different government ministries or departments. The sources of the problem are in health, agriculture and livestock, and the environment. In addition, to educate the public, the education and information departments need to be involved. The involvement and commitment of all these agencies are required in the multifaceted fight against AMR. Obtaining the commitment and coordination of the various sectors requires great effort and the commitment of political leaders at the highest level. It is not easy to achieve this.

The developing countries also have other problems that compete with AMR for attention and resources. Although it is a very major problem, AMR is a silent killer rather than an obviously critical issue compared with other issues within and outside the health sector (such as malnutrition, infection outbreaks and epidemics; conflict and terrorism; floods, drought, water scarcity and climate change; unemployment, poverty, migration and refugees).

In the competition for scarce funds and personnel, it is difficult for AMR to obtain the resources and attention it deserves.

Actions to address AMR at national level

Boosting the capacity of developing countries to take required actions is of key importance. The actions that need to be taken at national level include:

- Research in science, including analysis of bacteria mutation, gene transfer, rates and ways of the spread of resistance, and AMR in the food chain
- Vastly improving surveillance and data collection on resistance in various pathogens to various drugs, and resistance of bacteria in food-related animals, in food and in the environment
- Improving and upgrading laboratory equipment, especially diagnostic tools, to enable better diagnosis, to distinguish between bacteria and viruses, and between resistant and non-resistant pathogens, so as to enable appropriate treatment
- Infection control in hospitals, including hygiene, upgrading of rooms and theatres, equipment, air-flow systems etc.
- Infection control through provision of safe water, proper sanitation and habitat and a clean environment
- Formulating and implementing a national policy for rational and appropriate use of antibiotics and other antimicrobials
- Regulation and enforcement in the sale, prescription and dispensing of antimicrobials
- Guidelines or regulations for medical personnel, hospitals and clinics on the appropriate use of antibiotics, and on relations with industry sales representatives
- Regulating the marketing practices of drug companies to improve their role in appropriate drug use, and addressing the effects of incentives to sales personnel and to medical and veterinary personnel that are linked to the volume of antibiotic sales
- Regulation of the agriculture and livestock sector to phase out the non-therapeutic use of antibiotics, as this inappropriate use is a major factor in the AMR crisis. As a first step, antibiotics that are used for treatment of life-threatening diseases in humans should be prohibited for use in animals as growth promoters
- Addressing the contamination of the environment by residues of antibiotics, including those emitted by drug factories and medical facilities

- Educating the consumer and community on the appropriate use of antibiotics
- Formulating policies enabling affordable access for the public to existing and new antibiotics and other antimicrobials
- Establishing a national action plan on AMR and the institutional framework for implementation, including coordination within the health sector and with other ministries including ministries of agriculture, education and information
- Boosting the capacity of health-related NGOs, the media and educational institutions to take on AMR issues as a priority
- Mobilising domestic and external funds to enable implementation of the national AMR plan and activities.

Chapter 7

Making Resources Available for Developing Countries

IN order to implement the necessary actions, the developing countries require international cooperation for the following:

- Obtaining adequate financial resources for addressing AMR. Developing countries will have to mobilise domestic resources to carry out activities to address AMR. However, some of them, especially lower-income countries, will require international funding to augment the domestic resources, due to the high cost involved and competing issues that also require financing. Countries should prepare their comprehensive AMR action plans together with cost estimates and a budget with estimates of the resources that can be mobilised nationally and resources sought from international cooperation.
- Obtaining equipment and technology needed to address AMR. These would include equipment for diagnosis, for making hospitals and clinics AMR-proof, scientific research and innovation.
- Upgrading hospital facilities to improve infection control, surveillance and diagnosis, the ward and surgical environment, to minimise the spread of infections (especially resistant infections) within the hospitals and to provide an appropriate environment for patients with resistant infections.
- Obtaining antibiotics and other antimicrobials to treat patients, including those with ailments caused by drug-resistant pathogens.
- Phasing out the non-therapeutic use of antibiotics in the animal husbandry sector.
- Addressing the environmental aspects of AMR.
- Recruitment and training of adequate numbers of personnel including for management and coordination of the AMR action plan, surveillance, administration and enforcement of guidelines and regulations.

- Boosting the capacity of communities, civil society organisations, educational institutions and the media to raise public awareness and take other actions relating to AMR.

An international fund, or a number of funds, should be established to assist developing countries to meet the costs of the above actions to address AMR. Part of the fund(s) should be used for making available technical equipment that may be required for surveillance, diagnosis and treatment.

The case of drug-resistant tuberculosis

The urgent need for financial and other resources to tackle AMR is illustrated by the efforts to respond to drug-resistant tuberculosis. Tuberculosis is expected to account for a quarter of AMR-related deaths by 2050, according to the Review on Antimicrobial Resistance. According to a 2014 WHO report, there were 480,000 new cases of multidrug-resistant TB in 2013 and 210,000 deaths from MDR-TB. The report states that the health service capacity to treat patients has not kept up with the pace of diagnosis, creating “waiting lists” for MDR-TB treatment. The report also makes the following points:

- “Without political commitment, financing and action by stakeholders, the MDR-TB crisis cannot be effectively addressed...”
- “The MDR-TB response needs to be fully financed for current interventions and research for new tools.”
- “Key challenges in MDR-TB response include ... insufficient funding including for research.”
- \$8 billion per year is required to respond to the TB epidemic, of which one-fifth (\$1.6 billion) is for MDR-TB detection and treatment. There is an annual funding gap of \$2 billion, plus another \$2 billion is needed for R&D.

Similarly, significant financial resources are also required to take actions to respond to resistance in other diseases.

According to several reports, new treatments for treating resistant TB are too expensive for most patients in low-income countries to purchase and for their governments to supply for free or at subsidised rates.

Chapter 8

Affordable Access to Antibiotics and Other Antimicrobials

ONE major issue of concern to developing countries is their need for affordable access to antimicrobials, both existing and future ones. Even when the medicines are not patented and there is competition from generics, many poor patients cannot afford treatment. If the antimicrobials are patented, the prices escalate and pose a big barrier to access. As resistance builds, second- and third-line drugs are needed to treat existing diseases; these new drugs are likely to be patented and expensive.

The following are examples of the barrier to access caused by the high cost of new antimicrobials:

- Two new drugs for treating drug-resistant TB which have been recommended by WHO have been on the market for four years, but only 4,800 people with DR-TB in 2016 were treated with them, according to the medical humanitarian group Medecins Sans Frontieres (MSF) in a statement released in 2017.¹¹ Only 469 people received delamanid and just over 4,300 received bedaquiline. Thus, fewer than 5% of people needing the drugs received them while others continued to be treated with older and more toxic regimens that have a cure rate of only 50% and cause severe side-effects. More than half a million people were infected with DR-TB in 2015. In an earlier statement in 2016, MSF said the price of a single course of delamanid in developing countries was \$1,700 per person, and it called for a 98% price reduction.¹² Delamanid has to be taken with several other drugs to effectively treat DR-TB, and the regimens, without

¹¹ Medecins Sans Frontieres, 2017. Tuberculosis: Fewer than five per cent of people in need are treated with new drugs (Statement, 23 March 2017).

¹² Medecins Sans Frontieres, 2016. Access: Developing countries hit with high price for important new TB drug (Statement, 26 February 2016).

delamanid, already cost \$1,000-4,500 per treatment course at the lowest prices available in developing countries, which is unaffordable for governments. MSF is advocating a target price of \$500 per treatment course for DR-TB.

- The prices of second- and third-line HIV medicines are much higher than those of first-line medicines. Patients who no longer respond to first-line treatment (due to resistance) have to switch to the newer medicines but face cost and access problems. According to MSF, in 2015 the lowest available price of a first-line one-pill-a-day combination (tenofovir+emtricitabine+efavirenz) was \$100 per person per year. But the lowest price of newer drugs (or “salvage” treatments) needed by people who have run out of other treatment options was \$1,859 per person per year (raltegravir+darunavir+etravirine). This is 18 times the price of first-line therapy and over six times the price of a second-line combination. The MSF report finds that “prices of older HIV drugs continue to decline while newer drugs remain largely priced out of reach. This is in large part because pharmaceutical corporations maintain monopolies that block price-lowering generic competition.”
- A new drug for hepatitis C, sofosbuvir, was introduced in the US market at \$80,000 for a course of treatment. In middle-income developing countries that were not offered a voluntary licence by the drug company Gilead, the price varied from about \$10,000 to \$40,000. Sofosbuvir, usually taken in combination with another drug, has a much higher efficacy rate (95%) and less side-effects compared with older regimens. But the price of sofosbuvir is out of reach to most people and governments in developing countries (and developed countries too). The high prices are maintained due to a patent owned by Gilead. In 2017, Malaysia issued a compulsory licence for sofosbuvir. A local firm is now importing generic sofosbuvir from Egypt. The lowest price offered by Gilead to the Malaysian government for sofosbuvir was RM50,000, according to the Health Minister.¹³ The government has now negotiated to obtain a generic version of sofosbuvir at RM1,000 a patient. The government is now offering the combination of sofosbuvir and daclastavir at government

¹³ As reported in Loh Foon Fong and Clarissa Chung, 2018. Free Hepatitis C treatment for all, *The Star* (Malaysia), 20 March. The information in the rest of this paragraph is from this report.

hospitals for free; it will bear the cost of treating patients. Previously, some patients had to pay RM300,000 for a treatment course. Malaysia has 400,000 people with hepatitis C. According to a news report, 23,000 patients in the Health Ministry's list will be treated in stages, with 2,000 treated in 2018.

The above three examples illustrate that access to new antimicrobials being developed will be a major issue. With regard to antibiotics, the new antibiotics should be considered international public goods accessible to people especially in developing countries which otherwise cannot afford them if they are sold at monopoly prices.

Developing countries also need affordable access to vaccines as well as laboratory and diagnostic equipment.

Affordable and reliable access is required not only for new antimicrobials but also for existing ones. Many people in developing countries still do not have access to the existing medicines, either because they are not available in the market or the public hospitals, or because they are unable to afford them. According to leading experts representing key stakeholder groups including ReAct – Action on Antibiotic Resistance, Global Antibiotic Research and Development Partnership and the European Society of Clinical Microbiology and Infectious Diseases, in a commentary in *The Lancet Infectious Diseases* journal, unsustainable production and supply of old antibiotics is becoming a serious global problem that further limits the treatment options for common bacterial infections and this is adding to the worldwide crisis of antimicrobial resistance. “Shortages and sudden price increases of antibiotics have been reported, indicating a fragile supply system. Consequences might include worse clinical outcome, accelerated resistance development and increased costs for the individual and society at large,” according to one of the authors, Thomas Tangden, Medical Director at ReAct.¹⁴

When patents become a barrier to access, countries have the policy option of making use of the flexibilities in the World Trade Organisation (WTO)'s Agreement on Trade-Related Aspects of Intellectual Property

¹⁴ ReAct, 2018. Unavailability of old antibiotics is threatening effective treatment of common bacterial infections. Statement dated 22 February 2018.

Rights (TRIPS), such as establishing patent criteria that improve the quality of patents by awarding patents only for genuine inventions; and issuing compulsory licences or government-use orders to increase market competition by enabling the production and importation of generics. However, countries that exercise their right to make use of these flexibilities often encounter strong opposition from originator drug companies and their home-country governments. The legitimate use of flexibilities should not be opposed.

It is important that the principle of access is given priority when evaluating and developing models for research and development of new antimicrobials.

The political declaration on AMR adopted at the UN General Assembly high-level event places great emphasis on access. In many parts, the declaration mentions affordable access to existing and new antimicrobials as an important principle and objective.

Chapter 9

Taking Up the Issues of Access and Financing

THE issue of affordable access to antimicrobials was taken up in the discussions and negotiations at the WHA leading up to the adoption of the Global Action Plan on AMR. During the WHA session in May 2014 that had adopted a resolution mandating the formulation of the GAP, several developing countries stressed the need for access to medicines.

For example, India made a statement that included the following points:

- Ways to ensure financial accessibility to new antibiotics have to be better addressed in the GAP. Otherwise prices will be prohibitive for developing countries.
- New ways are needed to fund R&D based on the delinkage principle.
- There is a need to support transfer of technology to low-income countries for laboratory work, surveillance etc.
- There is a need to mobilise financial and technical resources to support developing countries.

Ghana, speaking for African countries, also underscored the need for the global plan to consider specific needs of developing countries, as well as access to new antibiotics and diagnostics.

Responding to the statement by India, the UK delegation said it recognised the legitimate concerns of developing countries on access to antibiotics and that technical capacities as well as affordable drugs must be supported.

The Antibiotic Resistance Coalition of NGOs said at the WHA that the global plan should give a clear leadership role to WHO and member states should provide resources to WHO for this. The plan must also include delinking the costs of R&D from the price of medicines.

At the closing of the session on AMR which adopted the resolution, WHO Assistant Director-General Keiji Fukuda stated: “To have a successful global action plan, the specific needs of developing countries such as capacity building have to be considered.”

The issues of financial resources, technology transfer and access were also highlighted by various delegations in the discussions on AMR at the WHA sessions in 2015, 2016 and 2017.

The political declaration of the UN General Assembly on AMR is very strong on capacity building, access to medicines, technology transfer and financial support to developing countries. It says (in paragraph 10(d)) that the heads of state and government “underline further that affordability and access to existing and new antimicrobial medicines, vaccines and diagnostics should be a global priority”. Paragraph 10(f) says the heads of state and government want to “enhance capacity building, technology transfer on mutually agreed terms and technical assistance and cooperation for controlling and preventing antimicrobial resistance, as well as international cooperation and funding to support the development and implementation of national action plans, including surveillance and monitoring, the strengthening of health systems and research and regulatory capacity, without jeopardising, in particular in the case of low- and middle-income countries, health or posing barriers for access to care.”

At the WHA in May 2017, several developing countries, including Brazil and India, stressed the need to place access to affordable existing and new antibiotics and diagnostic tools as priority issues, as it was not enough to take action on the control and distribution of antibiotics.¹⁵ They also highlighted the need to use innovation models based on the delinkage principle (see Chapter 10), to ensure affordable medicines. These two issues of access and delinkage were prominent in the UN General Assembly political declaration, but were not given due recognition in the development and stewardship framework document, complained Brazil.

¹⁵ See Mirza Alas, 2017. State of discussion on AMR action, two years after the WHA Global Plan. South Centre News on AMR, 22 August 2017.

Chapter 10

The Need for an Innovation Model Consistent with Access to New Antibiotics

It is imperative to develop new antimicrobial medicines, diagnostic tools, vaccines and other products as a major part of addressing the AMR crisis. There are deep-rooted problems with R&D in relation to antibiotics. One is that there have been few or no new categories of antibiotics discovered in the past two to three decades, and there are few promising new products in the present pipeline. A reason for this may be that there is less profit to be made from antibiotics compared with drugs for diseases which require long-term treatment.

The second problem is that the dominant R&D model links medicine prices to the cost of R&D by means of patents for the company, which results in high prices for new drugs which are unaffordable to most people in developing countries. There is thus a need for an R&D model that is compatible with access to medicines, one which delinks the cost of innovation from the price of new medicines as well as from sales volume. This is often referred to as innovation models based on the delinkage principle.

There are at least two main strands of thinking on what R&D model to encourage. The first is to continue with the dominant model but provide more R&D grants to companies and allow an extended patent term for new antibiotics in the hope that this will provide more incentives to the major drug companies and result in new products. The downside is that this increases the period of monopoly and high prices, and worsens the problem of access.

The second is to establish public funding by governments and donations by charities, so that the cost of innovation is not borne by the companies. The proprietary rights to the new products would belong to the public fund or charity, which has the option of providing licences freely to

companies or institutions, at least to those from developing countries; or licences granted to companies would be linked to conditions that favour access. This would delink the cost of innovation from the prices of the new products, which can be set at affordable levels. WHO has been exploring options for new partnerships for open collaborative models of R&D. It has partnered with the Drugs for Neglected Diseases initiative to set up a non-profit Global Antibiotic Research and Development Partnership to develop new affordable antibiotics that will also be subjected to a conservation scheme.¹⁶ Another example of this new approach to R&D is the 3P Project, an initiative of MSF with other organisations involved in TB that aims to conduct collaborative research to develop new treatment regimes for TB by sharing data and intellectual property, and by paying for research using a novel combination of grants and prizes.¹⁷

Another idea, championed by the Review on Antimicrobial Resistance, is to establish an innovation fund to provide large payments or “market entry rewards” to companies that have succeeded in producing new antibiotics. This would provide incentives by enabling the companies to recover their innovation cost. However, it is not clear whether this will result in affordable prices being set by the recipient companies, which may be allowed to obtain patents or even extended terms for patents, or whether they will use their monopoly to set high prices, in which case the objective of access would not be met. For it to be viable socially and not only commercially, the market entry reward scheme should be matched with the access objective.

The political declaration on AMR adopted by political leaders at the UN is clearly in favour of R&D activities that are closely linked to access to medicines and that are in line with the delinkage model. It has a lengthy paragraph (10(c)) dealing with R&D, which states that the heads of state and government “underline also that all research and development efforts should be needs-driven, evidence-based and guided by the

¹⁶ WHO, 2016. Global action plan on AMR: Options for establishing a global development and stewardship framework (Document A69/24 Add.1, 13 May 2016).

¹⁷ Medecins Sans Frontieres, 2016. (i) Lives on the Edge; (ii) Issue Brief on Time to Align Medical Research with People’s Health Needs; and (iii) Press Release on medical research policies (14 September 2016).

principles of affordability, effectiveness and efficiency and equity, and should be considered a shared responsibility: in this regard, we acknowledge the importance of delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales so as to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines and other results to be gained through research and development.”

The UN Secretary-General’s High-Level Panel on Access to Medicines has emphasised that “market-based models of innovation for AMR are unsustainable. Funding for R&D to address AMR and related challenges must be operationalised through delinkage models. Indeed, the challenge of AMR represents an important and incontestable context in which the viability of delinkage innovation models can be fully explored.”¹⁸

¹⁸ Report of the UN Secretary-General’s High-Level Panel on Access to Medicines, September 2016, page 31.

Chapter 11

Ground View of Status of AMR and Actions from an Asian Workshop

A GOOD glimpse of the reality of and problems in implementing action on AMR in developing countries was provided at the Asian Regional Workshop on Antimicrobial Resistance held on 26-28 March 2018 in Penang, Malaysia. It was co-organised by the Third World Network and the South Centre with support from the Fleming Fund of the United Kingdom Department of Health.

The picture arising from the workshop was that the AMR crisis is affecting many Asian countries seriously. There has been progress in the last few years in recognising this crisis. But for most countries the battle is only at the beginning stage, much more needs to be done, and several problems of implementing national plans need to be overcome if real progress on the ground is to be made.

The workshop was attended by 55 participants, including policymakers from 10 countries, as well as representatives of civil society, scientists and regional AMR focal points of WHO and FAO. The policymakers were from Indonesia, Thailand, Malaysia, the Philippines, Myanmar, Vietnam, Cambodia, Laos, China and India. NGOs from most of these countries, as well as Australia, also attended.

The workshop had the following landmark features:

- High-level policy and technical experts, most of them being focal points or coordinators of their national AMR committees, took part. They presented on the status of the AMR situation and the actions, including national AMR plans, being taken.

- The government officials were AMR experts from both the human health and animal sectors, which is quite rare as usually international AMR meetings involve officials from only one sector or the other. The workshop thus lived up to the concept of a One Health approach.
- Civil society groups involved in AMR or general health issues were also represented, enabling dialogues to take place between the governmental and non-governmental sectors. It was recognised that actions by both are crucial to generate public awareness and mobilise public support for AMR actions.
- The workshop provided the most up-to-date information on global and regional developments (including from WHO and FAO experts) as well as the state of policies and actions at national level.

From the presentations and discussions at the workshop, the following main points can be drawn:

- There has been quite a lot of progress in making a start in combatting AMR, with countries already formulating their national action plans and having national AMR committees. However, while some countries have incorporated both the health and agriculture/animal sectors in their national AMR committees, others have only the health ministry in the committees.
- While the health ministries have embarked on a number of activities such as surveillance and infection control, the agriculture/livestock sector in many countries has still to catch up with regard to actions.
- One encouraging sign is that Indonesia has banned the use of antibiotics as growth promoters in livestock since January 2018, whereas Vietnam imposed a similar ban a few years ago and in Thailand there has been a ban on antibiotic use as growth promoters in chickens since 2006.
- In most countries, little work has been done on the environmental component of the spread of AMR. This is an area requiring much more work.
- While plans and guidelines have been formulated in a number of areas, implementation in most countries is still inadequate. This is because of various factors, depending on the country concerned.

- Among the problems of implementing action are:
 - (a) Lack of priority and lack of political interest or will;
 - (b) Lack of financial resources in the country or in the ministry concerned to carry out activities at an effective level;
 - (c) Inadequate quantity and quality of human resources in the relevant government ministries or agencies to sufficiently work on AMR issues;
 - (d) Difficulties in coordinating within and especially between the various relevant ministries and departments, especially between the health and animal sectors. Perspectives and priorities often differ. The inclusion of other sectors, for example environment and education, may make the coordination task more complex.
 - (e) Too little equipment available for diagnostic work;
 - (f) Lack of champions and of a systematic stewardship programme at national or local level. It was observed that when a country has a national champion or champions, the progress in actions is more advanced.
- There is still inadequate understanding of the AMR issue in the animal sector in many countries. The WHO guidelines on antibiotic use in animals are a useful and important reference as they take a human health perspective. This should be supplemented by guidelines jointly issued by WHO, FAO and the OIE, so as to involve all the relevant international organisations.
- To increase the speed of implementation and of progress, international cooperation and support is very important. For example, there should be a fund or funds with sufficient resources to help developing countries to coordinate their AMR actions and to build their technical and organisational capacity.

Chapter 12

Summary of Key Points on Meeting the Needs of Developing Countries

PROGRAMMES dealing with implementing actions on AMR should include the following points:

- Fully take into account the challenges and needs of developing countries.
- Strong international cooperation for building capacity of developing countries to address AMR.
- Mobilising of financial resources to support capacity building and implementation of AMR action plans in developing countries.
- Establish a global fund for capacity building in developing countries on AMR issues, to be based in the UN, and linked to implementing the Global Action Plan on AMR. Meanwhile, governments should be encouraged to establish their own funds or allocate part of their development aid to assist developing countries to address AMR.
- Technology transfer and the provision of technical equipment including diagnostics and knowhow to developing countries on grant or concessional terms.
- Ensuring affordable access to existing and new antimicrobials, vaccines and diagnostics, especially to people in developing countries.
- Developing and encouraging R&D models which delink the price of antimicrobials and other products from the cost of R&D; including where the innovation costs are financed through public funds and charities, and the licence to produce the new products is available at low cost, at least to companies and institutions in developing countries.
- Support to developing countries for capacity building and financing of the comprehensive range of activities in addressing AMR at

national level, including prevention of infections, appropriate use of antibiotics, new regulations including on marketing, prescription and dispensing of drugs and their enforcement, reform of antibiotic use in agriculture, improvement of practices in hospitals and clinics, educating the public, etc.

The Global Threat of Antimicrobial Resistance and the Challenges and Needs of Developing Countries

ANTIMICROBIAL resistance (AMR) — in which a microorganism (such as a bacterium, virus, fungus or parasite) becomes resistant to an antimicrobial drug used to treat infections caused by it — is possibly the most serious public health threat of our time. Recognising the gravity of the problem, the international community has moved to address a phenomenon that could undermine prevention and treatment of an increasing range of diseases and lead to millions of deaths.

This global response, stresses this paper, must centrally involve the developing countries, where the impact of the AMR crisis would be greatest. Strengthening the capacity of developing countries to tackle AMR in turn requires international support in the way of financial and technological resources. Such support should, crucially, also include means to ensure affordable access to antimicrobials, both existing ones as well as new drugs developed to counter the AMR threat.

This paper is a revised and updated version of a background paper used as speaking notes by the author in a panel discussion during the United Nations General Assembly high-level event on antimicrobial resistance at the UN in New York on 21 September 2016, which was convened at the level of heads of state and government. It was also presented at the Asian Regional Workshop on Antimicrobial Resistance (organised by the Third World Network and the South Centre and supported by the Fleming Fund) held in Penang, Malaysia, on 26-28 March 2018.

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