

POLICY BRIEF

ANTI-MICROBIAL RESISTANCE – AN URGENT GLOBAL CONCERN^{1,2}

HOW SHOULD THE WORLD RESPOND TO THE GROWING CRISIS OF ANTIMICROBIAL RESISTANCE?

Recognition of antimicrobial resistance³ (AMR) has been around almost as long as antimicrobials themselves⁴. But the world has been slow to recognize the scale of the problem and to act on it as drug after drug encounters resistance and too few alternative treatments come forward.

Bacteria continue to develop resistance while the flow of new antibiotics has diminished; international travel and cross-border migration spread resistant bacteria within and between regions; and there are growing concerns about indiscriminate use of antibiotics in the production of food, livestock and marine products, with potential for increasing susceptibility to resistance in humans. Currently, in both the human health and agricultural sectors, regulations on access to and use of antibiotics are weak. This allows antibiotics to be overused and misused through self-prescribing, over-the-counter access and health practitioners and hospitals prescribing for inappropriate indications.

Amidst deepening concern⁵⁻⁷, a draft resolution⁸ on AMR was presented to the WHO Executive Board (EB) in January 2014 and will be debated

by the World Health Assembly (WHA) in May 2014. It urges Member States to take actions to contain AMR, accelerate efforts to secure access to effective antimicrobials and use them responsibly. It also requests the WHO Director-General to take a number of steps, including strengthening WHO's tripartite collaboration with the Food and Agriculture Organization (FAO) and World Organisation for Animal Health (OIE); exploring options for a high-level UN initiative; and developing a Global Action Plan to combat AMR.

To help clarify issues and concerns in advance of the 2014 WHA, the Global Health Programme at the Graduate Institute of International and Development Studies, Geneva and the Centre for Global Health Security, at Chatham House in London, organized a public event on 21 March 2014. This Policy Brief highlights the main lessons and key issues for debate emerging from this event.

PUBLIC EVENT: THE GROWING CRISIS OF ANTIMICROBIAL RESISTANCE

Ilona Kickbusch (Director, Global Health Programme, GIIDS) welcomed participants to the event, which typified the role of the Programme in providing a Geneva platform for discussion and debate on critical global health issues.

In his welcoming remarks, **David Heymann** (Head and Senior Fellow, Centre on Global Health Security, Chatham House, UK) observed that, while it had been relatively easy to mobilise world action during the SARS outbreak, it was proving more difficult to gain commensurate international attention for AMR and to ensure that there was adequate diagnosis and treatment available for infectious diseases. He hoped the WHA Resolution on AMR would strengthen the international response and acknowledged the important role that sponsors of the Resolution, including the UK and



Sweden, were playing in gathering support.

In her Keynote address, Dame **Sally Davies** (Chief Medical Officer and Chief Scientific Advisor, Department of Health, UK) recalled how reliant the world had become on antimicrobials, which had massively reduced serious illness and mortality from infectious diseases. But we now had a broken market model with no new classes

of antibiotics being discovered since 1987 and we were now at the dawn of a post-antibiotic era in which resistance to available drugs was already a deadly reality. There were promising signs of new science that could deliver new drugs as well as much-needed tools for rapid diagnosis of AMR-resistant strains, and encouraging evidence that proper management and control of infections and better regulation of the use of antimicrobials could greatly limit the spread of AMR. One major challenge in limiting the development of AMR was the role played by the use of antibiotics in farm animals, not just to control disease but also as a growth promoters. It was striking that – seemingly uniquely in this area – the pressure was on the medical profession to provide evidence for damaging impact on human health, rather than apply the precautionary principle and challenge the veterinary community to demonstrate that their use of antibiotics was safe for human health. Dame Sally highlighted the challenges on multiple fronts – conservation, hygiene, R&D pipeline, geography and surveillance of AMR, science and research, economics – that needed to be overcome and the importance of strengthening international collaboration, working with a wide range of governmental and non-governmental organisations, international regulatory bodies and others to mobilise action to deliver the scale of change needed globally. The UK and Sweden had secured a Resolution on antimicrobial resistance at the January 2014 WHO EB, which received co-sponsorship from over fifty countries covering all six regional groups of WHO. This marked an important first step in developing a Global Action Plan, which would bring together the key sectors. The Resolution now went to the 194 member countries of WHA in May 2014 for approval.

The first Panel discussion, moderated by **Ilona Kickbusch**, involved **Sylvie Briand** (Director, Pandemic and Epidemic Disease Department, WHO), **Marc Sprenger** (Director, European Centre for Disease Prevention and Control), **Otto Cars** (Director, ReAct) and **Manica Balasegaram** (Executive Director, MSF Access Campaign).

SCALE AND SCOPE OF THE AMR PROBLEM

AMR is a global problem: infections and resistance to the drugs used to prevent and treat them readily spread across geographical borders and all countries are affected.

The growing AMR problem represents a global failure in public policy, global governance, research prioritization and the market system. While the impact of AMR is on health, many of the key solutions do not lie in the health sector: a cross-sectoral response is essential.

- 25,000 deaths per year in Europe and 23,000 in the USA result from sepsis caused by resistant bacteria. One child every five minutes dies of infection caused by resistant bacteria in South East Asia.
- The practice of modern medicine is not possible without effective antibiotics. Most surgery makes use of prophylactic antibiotics.
- Positive and negative trends can coincide: e.g. decrease in MRSA in many European countries currently parallels an increase in carbapenem-resistant *Klebsiella*.
- Faced with the rising tide of AMR there has been a tendency towards increased use of broad-spectrum and last-line antibiotics. This is not

KEY ASPECTS OF THE GLOBAL RESPONSE TO AMR

CONSUMPTION OF ANTIBIOTICS

Antibiotics are frequently used inappropriately, both in human health and in veterinary health. Levels of antibiotic consumption vary greatly between and within countries, indicating a lack of consistency in regulatory and prescribing practices. Overall, this tends to be reflected in a relationship between use levels and AMR in countries. The problem is further compounded by the widespread availability, especially in LMICs, of sub-standard drugs, some of which have low doses of antibiotics that contribute to the selection of resistant strains of organisms.



In his Keynote Address, **Abdul Ghafur** (Coordinator 'Chennai Declaration', Apollo Honorary Associate Professor, Apollo Specialty Hospital, Chennai, India) referred to the spread of methicillin-resistant staphylococcus aureus (MRSA) and a range of 'Gram-negative superbugs' around the world. He described the growth of the problem in India, including the rapid emergence of resistant strains of pathogenic organisms such as *Klebsiella* and India's efforts to

introduce a national policy for the containment of AMR and the learning that had resulted from difficulties in its implementation, which had preceded the 2012 'Chennai Declaration', a roadmap to tackle the challenge of AMR. This advocated a step-by-step approach to an 'implementable policy' rather than a 'perfect policy' and had enabled the government of India to move forward on regulating and controlling the use of antibiotics.

The second Panel discussion, moderated by **David Heymann**, involved **Martha Gyansa-Lutterodt** (Director of Pharmaceutical Services and Chief Pharmacist, Ministry of Health, Ghana), **Visanu Thamlikitkul** (Professor of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok) and **Koen Van Dyck** (Head of Unit, Veterinary Directorate, DG SANCO, European Union).

In concluding the public event, **David Heymann** observed that AMR is 'a wicked public health problem, requiring a complex solution', due to the multiple dimensions of the problem and the diversity of actors in government and outside that needed to be involved in finding a solution.

sustainable and the emergence of widespread resistance to these agents is just a matter of time.

- AMR is particularly difficult to address in low- and middle-income countries (LMICs) and in countries in conflict. LMICs are potentially an important source of emerging AMR, owing to the often unregulated use of antibiotics; and may also suffer disproportionately from its impacts on health and the economy owing to weaknesses in health systems, poor availability of affordable drugs; and the presence of sub-standard products in circulation. It is therefore essential to address health and regulatory systems that ensure access to treatment while reducing misuse.
- LMICs face a greater burden of infection than high-income countries and need systemic improvements in water and sanitation and other interventions (e.g. vaccines) which reduce the need for antibiotic use.
- Lack of affordable, rapid diagnostic tests that can be used at or near the point of care or in the field to recognize AMR organisms impairs responsible use. The challenge is especially acute in LMICs which have limited laboratory facilities.

Some initiatives to limit AMR have been successful, but are fragmented. There is need for much more cooperation and collaboration, including on surveillance and on international support to efforts to collect and store national information.

THE 'ONE HEALTH' APPROACH

'One Health', first promoted in 2004 by the Wildlife Conservation Society and subsequently endorsed by many agencies including WHO, the EU and US-CDC, recognizes the intimate connections between human and

animal health. Among other areas, it advocates a single, integrated approach to AMR, including the prudent use of antibiotics in both human beings and animals. EU legislation on animal nutrition banned the use of antibiotics for growth promotion in animal feed from January 2006⁹. There is a need globally to ensure that antibiotics are not used for animal growth promotion and that key antibiotics are exclusively reserved for human use – which, beyond legislation, may require new incentives and alternative animal nutrition schemes to be implemented.



WHO

WHO's response has included the establishment in 2013 of a Technical and Strategic Advisory Group; development of a tripartite approach with the FAO and OIE; coordination of all relevant internal departments; and development of a WHA resolution requiring a Global Action Plan to be submitted to the 2015 WHA.

EUROPE

The European Centre for Disease Prevention and Control (ECDC) undertakes coordination of surveillance involving three networks.

European Antibiotic Awareness Day¹⁰ was established in 2008 and is marked on 18 November each year, when a number of initiatives take place across Europe to spread the messages on the risks associated with inappropriate use of antibiotics.

The European Commission has substantial investments in the field, with more than 50 research programmes related to AMR. It also sees a role in surveying the AMR research being conducted by EU member states and trying to avoid unnecessary overlap.

The Innovative Medicines Initiative¹¹ is Europe's largest public-private initiative, aiming to accelerate development of better and safer medicines, including in the field of AMR.

LOW- AND MIDDLE-INCOME COUNTRIES (LMICS)

LMICs have key roles to play in combatting AMR and it is important that they be supported to develop their capacities in areas such as surveillance and information management. While some have yet to join the fight and ways need to be found to encourage them, a number of countries are already increasing their efforts to respond. For example:

- After the 2012 Chennai Declaration, India introduced new national guidelines for antibiotic use in 2013 and has begun implementing these, which aim to progressively reduce antibiotic over-use by halting over-the-counter sales of specified antibiotics, expanding record keeping of antibiotic prescriptions and expanding the Indian Council of Medical Research's surveillance network.
- China's National Antibiotic Restraining Policy, drafted in 2011 and introduced in 2012, is already significantly reducing antibiotic consumption in the country.
- Ghana introduced a new infection control policy and manual in 2011, aiming to reduce healthcare-associated infections; and requires that at least 2% of resources from funding agencies be directed to monitoring antibiotic use.
- Thailand has committed to AMR containment, introducing a Policy for Rational Drug Use (2011) and a National Strategy for Emerging Infectious Diseases, including AMR (2012). A committee on AMR containment was appointed in 2012, which established goals and

processes, proposed a roadmap and identified gaps to be addressed. The Thailand AMR Containment Package 2013-16 includes five systems: Surveillance, Infection Prevention and Control; Rational Use of Antibiotics; Public Awareness; and R&D of New Therapy and Control Measures. Implementation is being supported by a National Alliance for AMR Prevention and Control and linkages developed with international programmes, including the Asian Network for Surveillance of Resistant Pathogens (ANSORP).

LIMITING THE SPREAD OF INFECTIONS

Efforts to limit the spread of infections and AMR must begin with better personal and institutional hygiene. Hand-washing (e.g. after visits to the toilet and between contacts of health personnel with patients) is vital to limit the transfer of AMR. Systematic use should be made of alcohol-based antiseptic hand rubs.

CIVIL SOCIETY RESPONSES

Civil society organisations (CSOs) have played a key role in raising awareness and galvanizing the response to AMR. Examples include initiatives such as the Chennai Declaration; action by patient safety groups; and the work of ReAct (an independent global network for concerted action on antibiotic resistance) and Médecins Sans Frontières.

CSOs and the media help raise public awareness and educate the public on issues such as misuse of antibiotics, sub-standard drugs and the importance of personal hygiene measures. But field evidence suggests that CSOs and the media often have limited or erroneous understanding of key facts regarding infectious diseases and AMR and have a need for capacity building to fulfil their roles effectively.

Political pressure is needed from the public and media, to bring governments to the tipping point where effective action on AMR becomes imperative.

DEVELOPMENT OF NEW ANTIMICROBIAL AGENTS

New antibiotics: The pharmaceutical industry has traditionally been the source of new antibiotics and during the 'golden period' (1940s-80s) discovered and developed many new classes of antimicrobial agents. A combination of factors, including scientific challenges, low prices and the reservation of new products for 'last line' defence against the growing problem of AMR, reduced the incentives for industry investment in R&D. This has resulted in drying up of the pipeline of antibiotic development.

There has been some attention to 'fixing' the failed business model through devising better commercial incentives such as, for instance, in the recent GAIN Act in the USA, but these have so far been largely ineffective. However, there are also arguments that the traditional

business model is intrinsically unsuited to future development of critical agents that should be regarded as global public goods and that it is better to seek models that dissociate the costs of R&D from the pricing of the products/return on investment. Funding for the essential R&D then needs to come from public sector support as well as from the private and philanthropic sectors; with financing mechanisms (whether, e.g., in the form of up-front funding, advance market commitments or prizes) that would ensure a fair level of contribution by each country, since every country in the world would benefit. The delivery mechanisms for the new antibiotics should not be based on a business model which generates pressure to increase sales, but must rather encourage rational use.

Other antimicrobial agents: While much emphasis has been placed on the need for refreshing the antibiotic pipeline to deliver new drugs, other scientific approaches must also play a role in treatment and control. For example:

- Vaccination has made a major contribution to preventing infections. The potential for vaccination to play a role in controlling AMR needs to be explored and the Global Vaccine Action Plan¹² linked with the Global Action Plan on AMR.
- The use of bacteriophages (viruses of bacteria that can kill and lyse the bacteria they infect; already extensively used in veterinary medicine) to control and treat infections in humans, including those caused by AMR organisms, warrants detailed investigation.

SURVEILLANCE

Strengthening and harmonizing national, regional and global surveillance of AMR is essential to control and treatment. Many countries have insufficient capacity in their national surveillance systems. The problem is often compounded at local levels by hospitals failing to institute infection monitoring and control systems and to have identified individuals with overall responsibility for them.

Harmonization of the monitoring of bacteria from human, animal and food sources is very important to ensure that comparable data are available on

CONCLUSIONS

AMR is a high priority global public health problem requiring solutions at all levels of governance. The problem has many dimensions, encompassing the conservation of available drugs, the development of new ones, and measures to prevent the spread of resistant organisms locally and globally. Failures in varying degrees in existing systems (including market mechanisms for drug discovery and development; access systems for drugs; public health measures; veterinary and food systems) have contributed to the emergence and spread of AMR.

Effective response must be multi-sectoral in character and requires comprehensive and integrated measures that include human and animal health and food production and supply chains; public, private and civil society actors; governmental and non-governmental players in low- and middle-income as well as high-income countries. The proposed WHO Resolution and action plan is a step in this direction but is only a beginning. The UN and the international system as a whole needs to work together to address the problem.

In view of the critical importance to health globally, there is a strong case for including targets and indicators related to combating AMR in the

these closely connected domains and that a comprehensive picture can be developed of the 'burden of resistance'.

LEARNING FROM OTHER HEALTH-RELATED INITIATIVES

While AMR has many unique features, it also shares a number of characteristics with other global health-related challenges and there are lessons to be learned from the experiences of international attempts to deal with these. Examples include the global responses to HIV/AIDS; to SAARS and Avian Flu; to the rising tide of non-communicable diseases; to the control of alcohol and tobacco use; to the lack of drugs for neglected diseases; and to the challenges of climate change.

REFRAMING THE PROBLEM

The problem of AMR needs to be reframed as "access to effective treatment for bacterial infections" and placed in a health systems perspective. To ensure products are available that are sustainable, equitable and affordable, access to effective treatment for bacterial infections must be achieved through needs-driven R&D; controlled distribution; conservation policies; and prevention of infections.

As a problem with transnational dimensions requiring concerted, collective action, AMR seems to meet the criteria for consideration of the need for a new international law. International governance must provide the basis for global agreements, targets and accountability.

Different political venues can be used to make the case for action on AMR. These can include the UN, WEF, G7/8, G20, OECD, South Centre, International Conference of Drug Regulatory Authorities.

Entry points to international action may include initiatives related to universal health coverage, health systems strengthening, health security, ethics and 'One Health'. A significant opportunity was seen to be connecting the global challenge of AMR with the evolving post-2015 Development Agenda and in particular seeking the inclusion of indicators and targets related to combatting AMR.

post-2015 Sustainable Development Goals. Development agencies must include action on AMR in their portfolios and disease-based global health initiatives must work together to address this common challenge.

Critical elements of the response include preventing the development of AMR and the spread of infection; better surveillance to monitor the problem; new diagnostics to enable cheap, rapid and reliable diagnosis at the point of care so that it is understood whether antibiotics are needed, and for helping medical workers to determine the right antibiotics to use; new business models to incentivise a continuing pipeline of new antibiotics; and other measures to reduce the inappropriate use of antibiotics in both human beings and animals. New approaches to ensure antibiotics as a global public good are vital if the world is to avoid a long gap when there will be no effective antibiotics available for a range of life-threatening infections.

While a global challenge requires a global response, the solutions must be tailored to local circumstances and resources. The diverse sectors involved must avoid blaming one another for the emergence of the problem, but focus on collaborating in developing solutions.

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3. Antimicrobial resistance (AMR) refers to the loss of effectiveness of any anti-infective medicine, including antiviral, antifungal, antibacterial and antiparasitic medicines. In this text it is understood to include the term 'antibiotic resistance', which refers only to resistance to medicines in bacteria. While this Policy Brief mainly discusses examples of ABR, it is clearly desirable that any new global approach would include the potential to address emergence of resistance to antifungal, antiparasitic and antiviral compounds and the recommendations and conclusions are equally relevant to all these aspects of AMR.