

Briefing Series on Trilateral Cooperation



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WHO, WIPO, WTO Joint Technical Symposium on *Antimicrobial Resistance: How to Foster Innovation, Access and Appropriate Use of Antibiotics?*

Key Issues

- The issues surrounding AMR cut across diverse policy fields and call for global action. The costs of addressing AMR are unavoidable at the global level.
- Affordability of, and access to, quality antibiotics remain key challenges. In developing countries, the lack of access to antimicrobial medicines remains a priority public health concern. AMR is not only a challenge, but also an opportunity for strengthening health systems.
- Antimicrobial stewardship means appropriate use to improve patient outcomes while minimizing the development and spread of resistance.
- The R&D environment must be predictable and sustainable because the innovation cycle is long and there are challenges to delivering antibiotic innovation. Alternative innovation models are needed and should de-link R&D costs from product prices and sales volumes.
- Healthy livestock is important as a source of income and for food security. AMR developed in animals

may easily spread throughout the global food supply chain and lead to foodborne human infections.

- WTO trade rules can support access to medicines and facilitate good practices for antibiotic use. They permit members to take scientific, evidence-based trade measures to protect public health.

The World Health Organization (WHO), the World Intellectual Property Organization (WIPO) and the World Trade Organization (WTO) Joint Technical Symposia provide a platform for participants to exchange information and experiences and to discuss current issues. The sixth Joint Technical Symposium, held in Geneva on October 25, 2016, reviewed issues related to antimicrobial resistance (AMR). AMR occurs when bacteria, parasites, viruses and fungi become resistant to the drugs which are used to treat infections caused by these organisms. AMR affects all areas of health, involves many sectors and has an impact on the whole of society.

Introduction

WIPO Director General Francis Gurry emphasized that antimicrobial resistance (AMR) crosses the areas of health, human welfare, economics and political coordination. The current private, market-based innovation model has failed to effectively stimulate adequate antimicrobial innovation. In discussing this failure, it is important to keep in mind that intellectual property (IP), a key component of the innovation system, is part of the solution. IP encourages creation of knowledge by incentivizing investment in the production of new knowledge and serves as the passageway between science and the market. Several studies have identified goals for action, including raising awareness of the global AMR threat and the complexity of an effective response. Collaboration between organizations and governments is needed to develop ideas for action and solutions.

WTO Director-General Roberto Azevêdo noted strong political will for a constructive response to the AMR challenge. Trade could help face the challenge. Firstly, trade could support better access to medicines through the elimination of trade barriers. Recent reforms of the global trading system include the 2013 WTO Trade Facilitation Agreement that tackled red tape and cumbersome border procedures and the amendment to the TRIPS Agreement giving legal certainty that generic medicines can be produced and exported to countries with no or limited pharmaceutical production capacity. Secondly, trade could help by supporting good practices for antibiotic use. While the “right to regulate” is well-established in trade law, WTO Agreements encourage governments to base any restrictive measures on international standards, guidelines or recommendations where applicable. Thus, WTO trade law could help support the implementation of international standards and good practices for the appropriate use of antibiotics.

WHO Special Representative for AMR, Keiji Fukuda, identified AMR as a fundamental social threat, like climate change. The 2016 UN General Assembly High-Level Meeting on AMR and the recent communiqué by G20 health ministers demonstrate the growing attention being paid to AMR. Many people lack understanding of AMR which hampers implementation of the requisite fundamental changes in how society uses antimicrobials. Mr. Fukuda highlighted financing as a cross-cutting issue for action. The WHO Global Action Plan on AMR should be implemented by national action plans which can only be tackled by cross-sectoral collaboration through a “one health” approach. A key challenge is the creation of a stewardship framework for the appropriate use of antibiotics in health and agriculture. Affordability and broader access remain key priorities. For example, pneumonia accounted for 15 percent of all deaths of children under five years old. Only one-third of affected children received the antibiotics they need. Access should be ensured for needed new diagnostics and medicines. Models for innovation, procurement, delivery and financing of treatments established for HIV/AIDS, malaria and tuberculosis, could serve as a blueprint for improving access to antibiotics. Strengthening health and agricultural systems is the most sustainable approach to addressing AMR.

Keynote address: The UK Review on AMR

Hala Audi, Head of the Review Team of the United Kingdom Review on AMR, explained that the Review involved policymakers, economists, microbiologists and external organizations. The report illustrates the potential future burden of AMR, with an estimated impact by 2050 of 10 million deaths annually and of 100 trillion US dollars in losses to the global gross domestic product, threatening development and prosperity. In light of the thin pipeline of new antibiotics, global action must reduce unnecessary demand for antimicrobials and stimulate the supply of new ones. Novel push and pull funding mechanisms that incentivize research and

development (R&D) while de-linking the profitability of an antibiotic from volumes sold should be used to correct the antibiotics market. This includes promoting new, rapid diagnostics and preventive measures, including vaccines, to reduce the volumes of antibiotics prescribed unnecessarily. Infrastructure investment and infection prevention reduce the need for antibiotics. The report estimates costs of up to four billion US dollars per year over the next 10 years to effectively address the most urgent AMR needs, including tuberculosis. This amount is affordable and cost-effective at the global level given that estimates of the economic impact of AMR today are already much higher and that the costs of AMR for governments are inevitable. The needed funds could be reallocated from other resources or levied through new funding streams, for example, by levying charges and taxes for the pharmaceutical sector.

Panel 1 – Fostering access and appropriate use

Evelina Tacconelli, Professor of Infectious Diseases, University of Tübingen, Germany, noted that every AMR response strategy inevitably involves decisions with ethical implications. Every prescription of antibiotics has an impact on the community as a whole and its individual members—whether infected or not. Mortality is significantly higher for patients hospitalized in low- and middle-income countries when compared with high-income countries and it is higher for patients with resistant infections compared with non-resistant ones. Patients with a resistant infection stay in hospital up to 10 days longer. A systematic literature review has shown that inappropriate antibiotic use is reported in up to 70 percent of published cohort studies on severe infections in hospitalized patients, leading to an increased mortality rate of 30 percent. There is evidence for inappropriate prescribing in communities. For example, women were prescribed antibiotics at a higher rate than men without apparent reason for that practice. There is sufficient evidence to associate the prescription of antibiotics with the development of AMR. The risk of a hospitalized patient receiving antibiotics being colonized with antibiotic resistant bacteria is three times higher than the risk to a hospitalized patient not receiving antibiotics. Stewardship, introducing measures for responsible and rational use, is essential. It is estimated that if hospital guidelines on antimicrobial use are applied, mortality may be reduced by 35 percent and resistance rates reduced by 52 percent.

Eveline Wesangula, National AMR Focal Point in the Ministry of Health and Coordinator of the Global Antibiotic Resistance Partnership (GARP), Kenya, stressed the importance of well-functioning national healthcare systems to ensure and monitor appropriate use of antibiotics. In Kenya, infectious diseases are responsible for 50 percent of all deaths. There is a visibly growing trend of antibiotic resistance. Diagnostics are inadequate, with widespread inappropriate use of antibiotics in humans and animals. Many people die because they cannot afford medicines. Regulatory systems and health systems should be strengthened,

namely through rational selection and use of medicines, affordable prices, sustained financing, reliable health supply systems and robust regulation systems. Improvements should be implemented by national governments according to national needs. Kenya developed its National Action Plan on AMR in collaboration with the ministries of health, agriculture and fisheries, and has undertaken efforts to increase awareness among the general public, health workers and farmers. Improved health outcomes enable society to sustain demand for innovation. Those improvements would diminish AMR, and strengthen the Kenyan health care system as a whole. Thus, the AMR issue presents not only a challenge, but also an opportunity for strengthening health systems.

Robert Ahern, Leader of Agricultural Health and Food Safety, Inter-American Institute for Cooperation in Agriculture (IICA), Costa Rica, explained that his agency focuses on two areas: encouraging appropriate use of veterinary drugs and helping countries establish AMR surveillance programs. Countries' differing levels of development and access to antibiotic drugs creates complexity. Where antimicrobial drugs are not available, there is little exposure to AMR and associated risks. However, once resistance has developed, it can easily spread throughout the global supply chain. The ideal would be to provide affordable access to medicines, coupled with the education and expertise needed to guide appropriate use. A harmonized message by the international community, including the private sector, should be customized to different stakeholder interests, needs and realities. It could say: "Use products only when prescribed by a veterinarian and use them according to the label." Every reasonable economic opportunity should be taken to reduce the use of antibiotics based on clear, adequate and well-developed guidelines for raising healthy animals in a cost-effective manner.

Panel 2 – Business models for antibiotic innovation

Jean-Pierre Paccaud, Director of Business Development & Legal, Drugs for Neglected Diseases *initiative* (DNDi), Switzerland, reported that DNDi and WHO had launched the Global Antibiotic Research and Development Partnership (GARDP) in May 2016. GARDP is a not-for-profit product development partnership (PDP) aimed at developing new antibiotic treatments, promoting sustainable and equitable access to these treatments and their responsible use and stewardship. The strategy is to identify global health needs that are less likely to attract the private sector and explore how to overcome drug-resistant bacteria, through the repurposing (or reformulation) of existing drugs, alone or in combination, and looking at innovating approaches when available. GARDP aims to build a robust pipeline and develop four to five new treatments by 2023. The initiative seeks to explore alternative business models since the market has failed to sufficiently support the development of new antibiotics. Such models must be sustainable. Using IP is considered, but always for the benefit of patients.

Viviana Muñoz Tellez, Coordinator of the Development, Innovation and Intellectual Property Program, South Centre, Switzerland, stated that the lack of innovation in medicines, diagnostics, vaccines and alternative treatments is due to systemic problems of the current innovation model. The largely private-sector led model of profit-based innovation, backed by IP rights, is ineffective. New models need to drive innovation from a public health perspective and deter misuse and over-use of antimicrobials. IP rights, patents and market exclusivity are inadequate incentives for R&D, can pose barriers to availability and affordability of products and can delay generic competition. New models to promote R&D should be needs-driven, evidence-based and guided by principles of affordability, effectiveness, efficiency and equity, and should be considered a shared responsibility. New models should de-link the cost of investment in R&D from the price of products and volume of sales in order to facilitate equitable and affordable access. That requires the creation of incentives to enable stakeholder participation. Such agreement is embodied in the UN High-Level Declaration on AMR of October 5, 2016. Current and new models of innovation for AMR should be evaluated against these principles.

Brian Woolhouse, Head of Hospital and Acute Care Business, MSD, United States, asked all stakeholders to take collective action to accelerate antimicrobial innovation, delay the emergence of resistance and apply a "one health" approach that considers human, animal and environmental issues. Ongoing investment in antimicrobial R&D faces major scientific, regulatory, and economic challenges. MSD continues investing in R&D for antibiotics and vaccines. Bacteria are constantly evolving, the R&D and regulatory environments are complex, targeted infections are sometimes rare and the expected returns remain limited. Reimbursement schemes do not recognize the value that novel antibiotics bring to society. The R&D environment should be predictable and sustainable because the innovation cycle is long and there are challenges to delivering antibiotic innovation. Novel incentive models could reward innovation earlier in the product life cycle and decrease the proportion of manufacturer revenue resulting from sales volumes and could include market-entry rewards in key markets and transferable exclusivity rights. The January 2016 Davos Declaration and the September 2016 Roadmap on AMR demonstrate private sector commitment to exploring opportunities for collaboration between the public and private sectors to promote innovation, improve appropriate use and stewardship, and expand global access.

Panel 3 – Trade policy in support of antimicrobial access and stewardship

Monique Eloit, Director General, World Organization for Animal Health (OIE), France, recalled that more than 80 percent of the world population is engaged in production and commercialization of animal-based food. Healthy livestock is an important source of income and provides food security for all. Global consensus exists to phase out the use of antimicrobials for animal growth promotion. Nonetheless, access to effective antibiotics

to be used under veterinary supervision to control animal diseases is vital for protecting animal and human health. OIE has developed standards for responsible and restrictive use of antimicrobials, a list of important veterinary antibiotics, and standard certificates for safe animal trade to avoid spread of diseases. OIE, together with WHO, the Food and Agriculture Organization of the United Nations (FAO) and the World Customs Organization (WCO) supports countries in strengthening veterinary services and legal frameworks to monitor use of antimicrobials in animals. OIE has worked with its partners on a global database on antimicrobial use. With academia and the private sector, OIE is engaged in supporting research for alternatives to antibiotics, including vaccines.

Lucas Vinícius Sversut, Second Secretary, Permanent Mission of Brazil to the UN Office and Other International Organizations in Geneva, said that WHO, FAO and OIE should continue working within their respective mandates, framing the human, animal and phytosanitary dimensions of AMR according to their specificities. A global stewardship and development framework should balance monitoring, control and conservation with access and affordability where antibiotics are needed. Unnecessarily restrictive policies should be avoided since they may increase barriers to access, undermine the flexibilities provided for public health objectives in international agreements, violate the right to health and jeopardize food security and nutrition. AMR must be grounded on scientific evidence and risk analysis. Awareness campaigns and prevention of infections are relevant to communicate AMR as an international public health challenge and not as a security threat. AMR can leverage systemic responses to the problem of access to medicines for all persons and all illnesses disproportionately affecting the population, and revisit the innovation system where it is deficient. The public sector could play a greater role in R&D. Generics are a part of the solution and TRIPS flexibilities should be reaffirmed. The UN could work towards a common definition of R&D costs, subtracting disbursements disconnected from the production chain as well as direct and indirect subsidies. AMR must be accountable to the social-equity dimensions of the 2030 Agenda for Sustainable Development. Further discussion on balances and safeguards for human rights and development are needed.

Jørgen Schlundt, Professor of Food Science and Technology, Nanyang Technological University, Singapore, stressed the urgent need to reduce antibiotic use in animals. According to US estimates, 15 to 25 percent of antibiotics treat sick humans and sick animals respectively whereas 50 to 70 percent make healthy animals grow faster. Such use is unwise and must end. Animal production in Denmark has been increased without using antibiotic growth promoters. Data show a close association between antibiotic use in animals and AMR, and between AMR in the food supply and in foodborne human infections. Simple steps to improve the situation include: documentation of antibiotic use and occurrence of resistance,

regulation of antibiotic use for health reasons in animals and humans, and removing the right of veterinarians and medical doctors to make profit from distributing drugs. Total antimicrobial consumption may be reduced without compromising quality. The European Union banned antimicrobials for growth promotion. In the future, more countries may follow suit and consequently ban the import of food products produced with antibiotics or products with a high prevalence of AMR bacteria. Such trade restrictions could adversely affect countries, specifically food-exporting developing countries. WTO rules allowed blocking imports of products if scientific evidence demonstrates a significantly increased health risk. Trade limitations and import controls ensure that producing countries reduce antibiotic usage in animals.

Closing

Assistant Director General Minelik Alemu Getahun of WIPO summarized the challenge: making antibiotics available to all and, if available, using them appropriately to avoid resistance. Medicines must remain effective for the future. The discussion on innovation, access and stewardship illustrates the complexity of the issue. Possible solutions were suggested and some of the proposed measures are not expensive. They include awareness-raising, improvements in the patient-doctor relationship to promote appropriate use of antibiotics, capacity-building and addressing issues related to animal health and agriculture. More changes are required in innovation, production and trade-related regulations and mechanisms. A range of possible models to incentivize and support innovation were discussed, as well as innovative partnerships like GARDP and the importance of well-functioning health systems. The inspiring discussions provided valuable insights for future deliberations among all relevant stakeholders.

Further information

Symposium webpage with links to event presentations, videos and a background paper: http://www.wipo.int/meetings/en/2016/wipo_wto_who_technical_symposium.html

Citation: WHO/WIPO/WTO Briefing Series on Trilateral Cooperation, WIPO, WHO, WTO Joint Technical Symposium on Antimicrobial Resistance: How to Foster Innovation, Access and Appropriate Use of Antibiotics?

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