Preparing better for the Next Pandemic: Drug-Resistant Infections and Access to Antibiotics

Among the updates from the WHO Secretariat that delegates will receive at the 74th World Health Assembly is one on antimicrobial resistance. This update comes five years after the World Health Assembly adopted the World Health Organization's Global Action Plan on Antimicrobial Resistance and nearly two years after the UN Secretary General received recommendations from the UN Inter-Agency Coordination Group on AMR.

Despite several calls to action between 2016, 2017, 2018, and 2021, the global response to AMR still needs to be supported not just by words, but with financing. Five years now into the WHO Global Plan of Action, the Tripartite Multi-Partner Trust Fund on AMR has mobilized less than $15 million in support, barely a rounding error in what has been spent on COVID-19. **As COVID-19 has shown, we can either tackle emerging infectious diseases by paying now or paying much more later.**

Briefing Document Overview

Antimicrobial resistance intersects with several topics of discussion at the 74th World Health Assembly. This document is organized into two sections: 1) Making antimicrobial resistance (AMR) into pandemic preparedness and response and 2) Innovation and Access to Health Technologies, lessons from COVID-19 and AMR. **Throughout the document, we have used arrows (➡) to highlight key concerns for Country Delegations attending the World Health Assembly.**

WHA Agenda

Pillar 1: One billion more people benefitting from universal health coverage

- Item 13.3 Expanding access to effective treatments for cancer and rare and orphan diseases, including medicines, vaccines, medical devices, diagnostics, assistive products, cell- and gene-based therapies and other health technologies; and **improving the transparency of markets for medicines, vaccines, and other health products**
- Item 13.4 Global Strategy and plan of action on public health, innovation and intellectual property ➡ WHA resolution on "Strengthening Local Production of Medicines and Other Health Technologies to Improve Access"
- **Item 13.5 Antimicrobial Resistance** (A74/10 Rev.1)

Pillar 2: One billion more people better protected from health emergencies

- Items 17.1 to 17.4 Public health emergencies: preparedness and response
- Item 21 Poliomyelitis eradication (A74/19)

Pillar 4: More effective and efficient WHO providing better support to countries

- Item 26.4 Global strategies and plans of action that are scheduled to expire within one year (HIV, viral hepatitis, and sexually transmitted infections for the period 2016—2021 and EB148(13)
- Item 33 Updates and future reporting on Rheumatic fever and rheumatic heart disease (A74/40)

Antimicrobial Resistance: The tide is rising

Globally, the UK Review on AMR puts the human toll from drug-resistant infections today at 700,000. However, **up to 5.7 million people die from treatable infections each year, most in low- and middle-income countries, many because they lack access to antibiotics.** In the 2017 World Health Organization's Essential Medicines List, antibiotics were the most common drug class. However, the World Bank projects that if we do invest to contain AMR, **low-income countries will "see substantial economic payoffs," but the greatest absolute and per capita gains would "flow to upper middle-income and high-income countries."** This finding reaffirms why higher-income countries, even from a self-interested perspective, should invest in a global response to tackle AMR.

Stronger, coordinated global AMR governance is needed

I. Progress on curbing use of antimicrobials for food animal production has been glacial. Today more than 40 countries voluntarily report that they continue to use antibiotics for growth promotion in livestock.

In 2017, the WHO issued Guidelines on the Use of Medically Important Antimicrobials in Food-Producing Animals. These included several strong recommendations, including the call for an overall reduction in use of all classes of antimicrobials in food-producing animals and complete restriction of use of all classes of medically important antimicrobials in food-producing animals for growth promotion. However, OIE and FAO have not been able to endorse these recommendations, nor make significant progress to advance them. In 2021, OIE's voluntary reporting system indicated that a quarter of countries, or 42 countries, continue to use antimicrobials for growth promotion in food animal production, but to ensure continued cooperation in the voluntary reporting of these data, the agency has not been able to make transparent the identity of these countries. More must also be done to finance the transition of these production practices away from the use of antibiotic growth promoters in resource-limited settings.

II. Five years into the Global Action Plan, we still have no review on our progress under the Tripartite Agencies' Joint Secretariat on AMR. Where is the Five-Year Review of the Global Action Plan on AMR?

The Monitoring and Evaluation of the Global Action Plan on Antimicrobial Resistance committed to a five-year review where: "An independent assessment will take place within the first five years of the GAP implementation, concentrating on the lessons learned at the country, regional and global levels. It should inform revisions to the GAP. From the fifth year, an independent evaluation will assess the impact and value for money and identify opportunities to increase impact." This review could not be timelier to carry out, but the WHO's update does not mention this review.

Where is the Five-Year Review of the Global Action Plan on AMR? What are the plans for taking stock of what has been accomplished, how the AMR work can have greater impact, what should be prioritized, and what milestones have been missed? [Relevant to the discussion of WHA Agenda Item 13.5 on "Antimicrobial Resistance" (document A74/10 Rev.1)]

III. The Global Leaders Group had terms of reference to put forward Key Performance Indicators, so that progress on AMR could be benchmarked. However, the process for shaping these has not been transparent, nor has it yet resulted in any announcement of such measures.

A One Health Global Leaders Group on AMR was constituted earlier this year. Importantly, the terms of reference for the GLG call for developing key performance indicators by which the Tripartite Agencies might benchmark progress on tackling AMR.

The WHO Secretariat is in the process of releasing an AMR NAP costing and budgeting tool. Such a tool needs to assist Member States in identifying and prioritizing affordable and effective interventions and mobilize financing to support NAP implementation as only one in five countries have funded NAPs. How much countries spend on tackling AMR is unknown, though countries do provide estimated costs through the Joint External Evaluations. **Funding for AMR NAPs is a key performance indicator to watch.**

Furthermore, country participation is also down in this last Tripartite AMR Country Self-Assessment Survey, falling from 82% (159/194) to 70% (136/194) in 2019-2020. Further analysis should be done to explore this drop off in response rate. More than half the countries (19/36) that dropped from the 2019-2020 TrACSS had not yet developed a NAP on AMR.

A One Health perspective might also be brought to these Key Performance Indicators. For example, even if countries adopt the AWaRe criteria for managing antibiotics in the Access, Watch and Reserve categories, countries can continue to use in even greater volumes the same medically important antimicrobials in food animal production. Will this end up offsetting the benefits of better stewardship in the healthcare delivery system?

Another lesson that we might gain from the TrACSS Country Self-Report Questionnaire is that some self-reported data on progress is best benchmarked against external measures. Using data from a WHO-UNICEF survey, the TrACSS survey already flagged that countries overestimated the proportion of healthcare facilities with basic water supplies, basic hand hygiene and functional sanitation facilities.

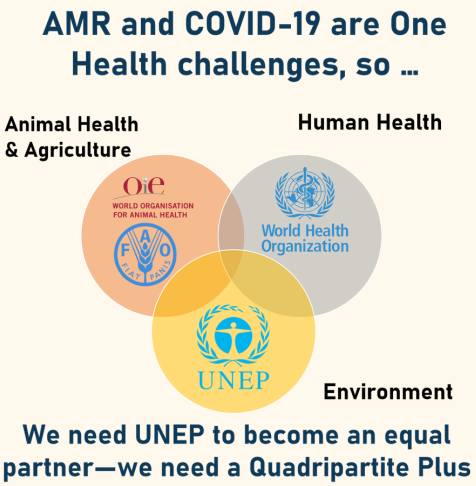
How is the Global Leaders Group coming up with these Key Performance Indicators? What public consultation with governments and civil society are they undertaking? And how will these Key Performance Indicators hold accountable the Tripartite Agencies to the goals of the Global Action Plan, not just countries implementing their NAPs? [Relevant to the discussion of WHA Agenda Item 13.5 on "Antimicrobial Resistance" (document A74/10 Rev.1)]

1. Countries were classified as having developed a NAP if they answered C, D, or E on TrACSS item 5.1.

IV. Global AMR Governance should move from Tripartite to Quadripartite Plus to address AMR as a One Health challenge.

As COVID-19 has shown, infectious diseases require a One Health approach for prevention and response. Global AMR governance would be enhanced if we could bring a truly One Health approach to tackling this global health challenge. Making the Tripartite (WHO/FAO/OIE) into a Quadripartite Plus, by adding the UN Environment Program plus engaging other UN agencies, would be an important step in this direction.

Up to 80% of antibiotics consumed by humans and animals are excreted and end up in the environment. Responding to these concerns, the UN Environment Program has embarked on a major report on AMR and the environment (see IV. Antimicrobial Resistance, Para. 34).



Member States might ask why the UN Environment Program is not yet a full-fledged member in the Joint Secretariat on AMR. There is also a need to engage other UN agencies, from UNICEF to UNDP, as well in these intersectoral efforts. [Relevant to the discussion of WHA Agenda Item 13.5 on "Antimicrobial Resistance" (Document A74/10 Rev.1)]

V. Mobilizing the financing of National Action Plans on AMR needs a jumpstart.

Only one in five countries participating in the Tripartite AMR Country Self-Assessment Survey (TrACSS) had identified funding sources to implement its National Action Plan on AMR. Between this survey and the last, seven countries joined these ranks, but six slid backwards from having identified funding sources. Since the start of the TrACSS surveys, ten countries have slid backwards from having financed their NAPs, and none have restored this funding to date. **We need AMR financing to match the commitments for implementing the change promised in NAPs on AMR.**

The Tripartite Joint Secretariat on AMR (WHO/FAO/OIE) has been establishing the Multi-Partner Trust Fund for AMR, but has only raised less than $15 million. Alongside spending on COVID-19, this is barely a rounding error in resource mobilization. **Countries can make investments in AMR that will pay themselves off in little time, and these investments can do "double-duty" in supporting pandemic preparedness.** The OECD found that a public health package of antimicrobial stewardship, environmental hygiene, media campaigns and rapid diagnostics, for US$2 per person could pay for itself within just one year and end up saving USD 4.8 billion per year in OECD countries.

In laying out the economic impact of AMR, the World Bank has found that more than 80% of the benefits from AMR investment would be to high-income countries and upper middle-income countries—a fact that might be used to motivate such countries to contribute.

Tackling Antimicrobial Resistance as Part of Pandemic Preparedness

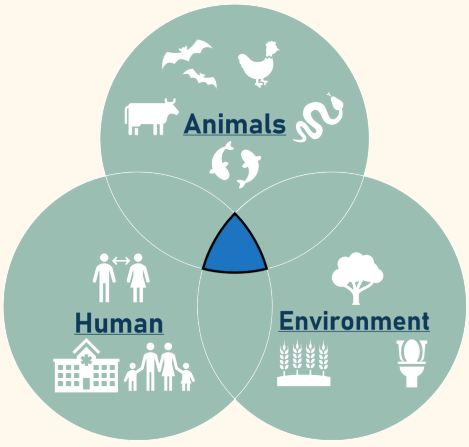
The pandemic highlights several opportunities to turn the corner on financing AMR through the pandemic response and recovery.

Across a spectrum of activities, well-planned investments into COVID-19 pandemic response can also positively impact AMR. **A One Health approach is vitally important** as diseases that spread between human and animals, also called "zoonoses," account for more than 60% of known human infectious pathogens.

AMR is central to pandemic preparedness and response. The Joint External Evaluations—the technical framework for monitoring and evaluating the International Health Regulations—and WHO benchmarks for International Health Regulations (IHR) capacities track, in part, aspects of the implementation of AMR NAPs, infection prevention and control, emergency preparedness and medical countermeasures and personnel deployment capacity. If the enhanced infection prevention and control efforts against COVID-19 can be sustained, health systems will see some spillover benefits for drug-resistant bacteria and other respiratory viruses. The Draft resolution on strengthening WHO preparedness and response to health emergencies urges Member States to improve efforts to strengthen capacities relating to IHR (2005), several intersect with AMR. For instance, when tracking AMR capacity, the Joint External Evaluation looks at four different domains: 1) effective coordination on AMR, including NAPs; 2) AMR surveillance; 3) infection prevention and control; and 4) One Health stewardship of antimicrobial use.

A cornerstone to future pandemic preparedness will be to build an effective global, integrated surveillance system.

COVID-19 has heightened the value of integrated surveillance, which uses samples from humans, animals, and the environment. Resultantly, it can detect across the One Health spectrum where new outbreaks occur, or variants may emerge. Already sewage surveillance for COVID-19 has helped predict resurgence in places. Infrastructure developed by the existing poliovirus surveillance system provides a start for analyzing samples. In fact, as the WHA report on poliovirus eradication indicates, this infrastructure has already been enlisted to support COVID-19 surveillance. Genomic laboratory capacity would prove useful during COVID-19 and set countries up to tackle foodborne diseases and AMR.



One Health

Integrated Surveillance

Transition of the Global Polio Laboratory Network and opportunities for emerging infectious diseases

To work towards the polio eradication, the Global Polio Laboratory Network (GPLN), a network of more than 140 laboratories in 92 countries, was established. As polio has been locally eradicated, environmental surveillance for poliovirus (i.e., sewage surveillance) has been important for rapidly responding to outbreaks. Environmental surveillance has been increasingly used for COVID-19 and there are calls for public health authorities to use low-cost sewage surveillance for antimicrobial resistance.

The GPLN has developed in-country lab capacity that has expanded to other diseases. GPLN staff report spending 30% of time providing surveillance for other diseases. These staff have overlapping technical expertise for surveillance of viruses such as measles, rubella, rotavirus, yellow fever, and Japanese encephalitis. **A cornerstone to future pandemic preparedness will be to build on existing infrastructure to support an effective global, integrated surveillance system.**

Antibiotic use in food animals accounts for more than 70% of global consumption. The FAO has acknowledged that "food is likely to be quantitatively the most important potential transmission pathway from livestock to humans," and low-income countries face the largest burden of foodborne illnesses. **Therefore, investments are needed to improve biosecurity and animal welfare in economies that are dependent on agriculture, ensure food security and address disparities in the burden of foodborne illnesses.**

How can the WHO support an integrated surveillance system to include AMR, one that builds upon efforts to improve pandemic preparedness and the existing poliovirus surveillance system [Relevant to discussions of WHA Agenda Items 17.1 to 17.4 COVID-19 response and the draft resolution on "strengthening WHO preparedness and response to health emergencies" and Item 21 "Poliomyelitis eradication" (Document A74/19)]?

Tackling Antimicrobial Resistance also presents unique challenges, such as stewardship

Importantly, AMR is a different challenge as antibiotics must be conserved. The more antibiotics we use, the greater the drive for resistance to these medicines. Unlike treatments for other pandemic threats, **we will need to steward the use of these potentially life-saving resources, both in our healthcare delivery system and also in our food system**. This will require specific infrastructure, training and technical assistance, and regulatory follow-through.

During the pandemic, more than 70% of COVID-19 patients received antibiotic therapy. However, only 8% of COVID-19 patients had documented bacterial co-infections. The intensive use of antibiotics for COVID-19 patients has been seen the world over from Mexico City, United States, Indonesia to China. COVID-19 has also disrupted access to healthcare. Preliminary U.S. data suggest that outpatient antibiotic prescribing decreased during April and May 2020 compared with the same time period in 2019. **Access to antibiotics has played a crucial role during the pandemic and has also highlighted how countries need to take greater action to promote antimicrobial stewardship in healthcare.**

The need for innovation in the antibiotic R&D pipeline

The more of antibiotics we use, the greater the drive for resistance to such drugs. So unlike some pandemic threats, we need to steward and reserve the use of these potentially life-saving resources, both in our healthcare delivery system and also in our food system. This also means that the market size for treatments of drug-resistant infections should remain low in volume, and if priced affordably to those in need, is potentially low in returns. By contrast, the demand for COVID-19 vaccines is a high-volume market and lucrative. For instance, Pfizer's vaccine returned US$3.5 billion in first-quarter revenues for 2021. AMR requires building a different kind of innovation ecosystem.

What is in the antibiotic R&D pipeline is NOT enough to replenish the diminishing number of effective antibiotics. Looking at the current clinical pipeline, the WHO has found that of 43 antibiotics under development, only 60% of these are active against WHO priority pathogens, significantly fewer fulfilling one or more of the innovation criteria, and only 2 antibiotics active against multi-drug resistant, Gram-negative bacteria. Over 40% of systemic antibiotics were withdrawn from the market between 1980—2009, and the vast majority were not for safety reasons. This suggests that these antibiotics were likely of little commercial or clinical value. In the long-term, patients, hospitals, and health systems need novel antibiotics that address drug-resistant infections. R&D incentives and reimbursements need to align public health need and groundbreaking innovation while ensuring new antibiotics are made available to patients in low-resource settings.

Old antibiotic in shortage even for large number of rheumatic heart disease patients

Shortages of antibiotics have occurred not only for low-volume markets like second-line antibiotics or old antibiotics being brought back into use, but also for high-volume markets. Rheumatic heart disease resulting from a group A streptococcal bacterial infection afflicts 40 million people. Patients with rheumatic heart disease require monthly injections of benzathine penicillin G. Despite the large number of rheumatic heart disease patients, a 2017 survey of 95 countries found that over 40% reported a benzathine penicillin shortage. A shortage of this antibiotic, used to treat pregnant women with syphilis, was also later seen to be associated with a more than two-fold increase in the incidence rate of congenital syphilis in Rio de Janeiro between 2013 and 2017. This was a period when there was a shortage of this drug.

How can efforts to advance local production also address sustainable access for key antibiotics (WHA Agenda item 13.4 and and proposed WHA resolution "Strengthening Local Production of Medicines and Other Health Technologies to Improve Access")? Benzathine penicillin G used to treat the 40 million patients with rheumatic heart disease as well as pregnant women with syphilis has had a history of shortages in recent years.

Strategies for ensuring sustainable access to existing and new antibiotics

There are numerous interventions across the pharmaceutical value chain that could enable more sustainable access.

I. Enabling innovation: Target Product Profiles and Intellectual Property Pooling

The public sector can help create an enabling environment for innovation, from setting target product profiles that define the product characteristics for a desired drug, including an affordable price point, and to ensure access to the building blocks of knowledge. There are many reasons to pool intellectual property, even in non-pandemic times. Innovation often requires putting together various components (e.g., antigens and adjuvants in a vaccine or the components of a diagnostic test). The Medicines Patent Pool is a noteworthy pooling effort. Over the past ten years, the Medicines Patent Pool has enabled licensing from originator companies to generic manufacturers in low- and middle-income countries. It began with cross-licensing HIV/AIDS medicines, but the portfolio has grown to include other antimicrobial medicines to treat hepatitis C and TB. **These examples demonstrate that countries have the tools to enable sustainable access whether a product is in its earliest stages or already on the market.**

II. Establishing access conditions for publicly supported antibiotics

New medicines in low- and middle-income countries are often introduced late: the average time between a new drug or vaccine's first registration anywhere in the world and its last registration in Sub-Saharan Africa was between 4 and 7 years. Furthermore, only 60% of new antibiotics launched between 1999 and 2014 had registered sales in more than 10 countries, many of which were high-income countries. Public-private partnerships and funders like GARDP and CARB-X have tried to incorporate conditionalities for funded partners, but their efforts are early stage at this point. And we do not have full transparency of the contracts signed, nor do we know how the firms will be held accountable. The Drugs for Neglected Diseases Initiative, a product development partnership for neglected diseases treatments, has put into practice several access conditions. Their licensing commits to the final product being available at-cost, plus a minimal margin, as demonstrated when a child-adapted formulation of benznidazole reached market.

III. Strategies for achieving delinkage of price and quantity

The traditional business model incentivizes companies to sell more antibiotics to earn greater revenues. Volume-based sales model risks driving greater drug resistance. Recently, the AMR Action Fund launched with $1 billion in private sector financing for investing in late-stage antibiotic development. By picking off the best of what largely has been financed by the public sector, it hopes to bridge the last mile to market for promising antibiotics. It remains unclear what access and stewardship conditions apply, or whether efforts will be made to delink volume-based sales from revenues. Yet public and philanthropic funding from the Wellcome Trust and the European Investment Bank contributes to this fund, supplanting an earlier public sector-driven effort that WHO and the European Investment Bank had planned. The AMR Action Fund also serves as a platform for advocating for higher reimbursement and returns on novel antibiotics.

By contrast, delinkage divorces the returns on a drug company's R&D investment from volume-based sales revenue, or in other words, price and quantity. Achieving this through reimbursement reform has not proven easily workable. **But we might be able to work towards delinkage conditions through more end-to-end approaches, such as pooled procurement and public sector manufacturing**. This is timely to raise given the potential value of these approaches for scaling up COVID-19 vaccines.

Through pooled procurement, *countries can work together to buy antibiotics. By so doing, they can ensure manufacturers a guaranteed forecasted demand for their product, and for those needing the product, secure a fairer price reflecting this volume buy*. We can build upon the lessons of the Global Drug Facility, which has become a one-stop shop for TB commodities. The Global Drug Facility is playing a key part in procuring medicines for drug-resistant TB (e.g., bedaquiline and delamanid) and Xpert system cartridges for diagnosing TB.

WHO Member States may also wish to follow closely and inquire about SECURE, an unfolding initiative to foster access to essential antibiotics, build sustainable global supply chains and create viable markets for new and existing antibiotics. This initiative is organized by WHO, GARDP, the Clinton Health Access Initiative and UNICEF. The tentative timeframe is to pilot a small portfolio of antibiotics between 2022 to 2025. Hopefully, it will bring in the experience of the Global Drug Facility, which is not at this point a part of this initiative.

Public sector manufacturing also can help ensure a secure and affordable supply of antibiotics. From Oswaldo Cruz Foundation and Farmaguinhos in Brazil to state-owned production in China, the public sector in some countries has also played a role in manufacturing drugs or vaccines. Even before the pandemic, CivicaRx demonstrated how a non-profit generic company could take on the manufacture of drugs for the healthcare delivery system. CivicaRx was created out of the need in the U.S. healthcare system to supply drugs that faced shortages, stockouts, or significant price hikes. Over 40 healthcare organizations and several foundations became shareholders in this non-profit generic manufacturer, and the first two products they contracted for manufacture were, in fact, two important antibiotics—daptomycin and vancomycin. What is striking about this model is that it aligns the demands of the healthcare delivery system with the supply provided by the manufacturer by vertically integrating both. Health systems that represent over a third of U.S. hospitals bed are part of CivicaRx.

What has WHO done to ensure greater transparency and access conditions in AMR initiatives, including the industry-led AMR Action Fund, GARDP, and other initiatives like CARB-X? How are such principles going to be followed through in the SECURE initiative, proposed by WHO with GARDP, UNICEF and the Clinton Health Access Initiative? And will the SECURE Initiative build upon lessons from the Global Drug Facility? [Relevant to WHA Agenda Item 13.5 Antimicrobial Resistance (A74/10 Rev.1) and earlier WHA72.8 resolution on "Improving the transparency of markets for medicines, vaccines, and other health products"]

Antibiotic Resistance Coalition

Launched in May of 2014 at the World Health Assembly, the Antibiotic Resistance Coalition (ARC) is comprised of 30 members. ARC includes networks of consumer groups, like Health Action International, social movements like the People's Health Movement, and policy networks that provide thought leadership across development issues such as the Third World Network. Members of ARC range from Health Care Without Harm, which represents over 36,000 health centers, to U.S. PIRG, which has a Health Professional Action Network with 50,000 members. ReAct's Strategic Policy Program serves as the Secretariat of the Antibiotic Resistance Coalition. **Find out more at ignitetheidea.org/about-arc and subscribe to the ARC Newsletter to receive monthly updates on AMR Policy and Science.**

For further information on this briefing document, please contact: Professor Anthony So (aso5@jhu.edu) or Prateek Sharma (psharm32@jhu.edu).