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The Journal of Global Antimicrobial Resistance meets the World Health Organization (WHO)☆

Antimicrobial resistance (AMR) represents a significant challenge. The first report from the World Health Organization's (WHO) Global Antimicrobial Surveillance System (GLASS) recently revealed that there is widespread occurrence of antibiotic resistance among 500 000 people with 8 suspected bacterial infections across 22 countries [1].

In order to explore and enhance understanding of how infectious disease experts and healthcare professionals are meeting the challenge of the global spread of antibiotic-resistant pathogens, the Journal of Global Antimicrobial Resistance interviewed Dr Marc Sprenger (MS), Director of the Secretariat for Antimicrobial Resistance at the World Health Organization (WHO).

JGAR: Why does the AMR crisis need to be managed with great urgency?

MS: Modern medicine is dependent upon effective antibiotics. Our main concern with antimicrobial resistance (AMR) is that it is increasingly restricting our power to treat serious infections. We know, for example, that resistance levels of *Klebsiella pneumoniae* against carbapenems, the last-line antibiotics, are very high. Thus, to effectively treat this infection we increasingly need to use colistin, which is a very toxic and old-fashioned antibiotic; and, even against colistin, we are seeing resistance. This means that, in some parts of the world, we are no longer able to treat these kinds of infections. This is not only related to pneumonia or urinary tract infections. We potentially may not be able to protect cancer patients and people with compromised immune systems: a child who is being treated for acute leukaemia could survive cancer but could die from an opportunistic infection. This is all very serious.

JGAR: Antibiotic consumption is a primary driver of antibiotic resistance. Do you agree?

MS: Yes, the rise in resistance is mainly due to antibiotic overuse. There is overuse in the human sector, but there is also overuse in agriculture, which accounts for 70% of the total global consumption of antimicrobials. In the human sector, we know that antibiotics are being used to treat viral infections or for a sore throat: and often there is really no need to treat these self-limiting infections with an antibiotic. A lot of patients put pressure on doctors, dentists or nurses to get antibiotics. That's why we need to raise awareness among the general public that it is unnecessary to take antimicrobials for flu. Of course, we also need to train doctors (Box 1 and Fig. 1).

JGAR: Regarding education at different levels. Is the WHO addressing the need to improve awareness and understanding of AMR at different levels in different ways?

MS: Doctors and general healthcare professionals play a very important role. One of our priorities is to work with medical and veterinary schools to make sure that there is appropriate attention given to AMR and antimicrobials in the curricula. A very effective way of helping doctors perceive whether they are over- or under-prescribing antibiotics is through comparison with other colleagues ("benchmarking"). Raising awareness among the general public is rather more difficult. We have rolled out several AMR awareness campaigns and are seeking the guidance of a group of experts on behaviour change. But of course, any campaign needs to consider the cultural context. One of the key messages is that we should only get antibiotics on prescription. That sounds reasonable, but in practice it is much more complex. If you are in a developing country, for example, and you don't have access to a family doctor, your only choice may be to go to the market and buy some antibiotics without prescription. That is why WHO advocates to strengthen national health systems and is supporting countries to improve their health systems, as a prerequisite to being able to fight AMR (Box 2).

JGAR: Looking at the global data we can see many differences between LMICs, MICs and HICs, regarding both the intrinsic characteristics of AMR (e.g., onset, epidemiology, antibiotic consumption) and the possible valid solutions to solve it. Why does this require a global approach and what are the strategies?

MS: We are very much aware of this diversity. There is a striking difference in the levels of consumption of antibiotics across different countries. This is not happening because one country's population is less 'healthy' than another's. This is purely a cultural phenomenon, and that is why we need to change it. And sometimes, low consumption levels are indicative of limited access to and availability of antibiotics.

The overall target of all these strategies is to reduce untreatable infections. In LMICs where, despite the high levels of antibiotic consumption, inequalities in drug access and high rates of infectious disease related mortality, we need to make sure that everyone has access to the right antibiotic and that the basic elements are in place like an efficient sewage system and safe drinking water. I have seen very good examples. I went to a village in Thailand, where they have a very simple philosophy: for diarrhoea, upper respiratory infections and bleeding, you don't need antibiotics; the only thing you do need is to follow-up and check whether there is a severe infection. They have trained children, adults, health practitioners and community leaders and have managed to reduce antibiotic consumption by 50%.

☆ Interview with Marc Sprenger, Director of the Secretariat for Antimicrobial Resistance.

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Box 1. Global antibiotic consumption.

A study (published in 2018) conducted by the Centre for Disease Dynamics, Economics and Policy analysed the global antibiotic consumption (AC), expressed in defined daily doses (DDD) between 2000 and 2015. Data highlight that the overall AC has increased by 65% and the AC rates, expressed per 1000 inhabitants/day increased by 39%. Is important to highlight two aspects: (i) although AC rates in low-income and middle-income countries (LMICs) remain lower, the overall AC increase is driven by LMICs; (ii) the usage of last-line antibiotics has intensified in both LMICs and high-income countries. Finally, 2030 estimations of worldwide AC are up to 200% higher than DDDs, which were calculated in 2015 [2].

Box 2. Antibiotic prescription education.

A 2013 cross-sectional survey in 13 European countries (Belgium, Croatia, Denmark, France, Germany, Italy, Netherlands, Norway, Serbia, Slovenia, Spain, Switzerland, United Kingdom) questioned 37 medical schools regarding teaching prudent antibiotic prescribing. Results showed that prudent antibiotic use was taught in all but one medical school. In particular, teaching was mandatory for 53% of the courses. However, some important topics, such as the significance of duration of antibiotic therapy, were poorly taught. The main reported issue for more extended programmes was lack of time [3].

There is one other thing to bear in mind: if we develop new antibiotics, which we hope to do, they must be affordable for everyone. That is why we established a few years ago, together with the Drugs for Neglected Diseases Initiative, a new initiative called the Global Antibiotic Research & Development Partnership (GARDP) (Box 3). Through this initiative WHO, which provides support in setting the priorities and addressing specific needs of LMICs and MICs, is advocating for approved access to new antibiotics. If a new antibiotic is in the pipeline, we work to ensure that once the antibiotic reaches the market, it will be available for free or at very low cost in low-resource countries, and at a regular price in HICs. We have also developed a priority pathogens list (PPL) to encourage research and development where the needs are greatest (Box 3).

It is important that patients have access to the appropriate antimicrobials when needed. WHO has recently updated the Model List of Essential Medicines (EML) (Box 3) with new advice on the use of antibiotics, presented as an 'aware index' of three groups of antibiotics: (1) the ACCESS group, which is a basket of first-line antibiotics that should always be available in all countries at an affordable price and recommended as empiric; (2) the WATCH group, which includes antibiotics to be prescribed as first or second choice treatments but only when there is a clear indication as they a have higher resistance potential; and (3) the RESERVE group, which should only be used as last-resort options when there is no alternative. Some countries are using the third, RESERVE, category of antibiotics to treat a simple infection: in these cases, antibiotics are not being used appropriately (Box 4).

JGAR: Going back to surveillance, how important is it to have harmonization across national surveillance systems?

MS: It is crucial to have harmony, especially among the larger countries, and we hope that governments and national surveillance centres will work together to achieve this. The good news is that the Fleming Fund of the UK, supports LMICs in developing and improving laboratory and diagnostic capacity, and is working to challenge AMR [4]. WHO is undertaking analysis in all countries to see what is needed to build up 'basic microbiology' capacities. Moreover, we are trying to get data out through the GLASS system (Box 3), but there is a long way to go (Box 5).

JGAR: Many countries are making serious efforts to collect surveillance data. What needs to be in place in order to standardise the reporting system and build the global approach we are taking about?

MS: It is very difficult, as there are big discrepancies between countries. To minimise this and the problem of bias, we have discussed and agreed upon eight pathogens to be included in the GLASS system (Box 5). In 10 years' time we should have much better insight. Right now we are hesitant to compare results from different countries because of selection bias. It is very interesting to look at and compare GLASS to the European Antimicrobial Resistance Surveillance Network (EARS-Net), which is a system that has now been going for 20 years. The difference between

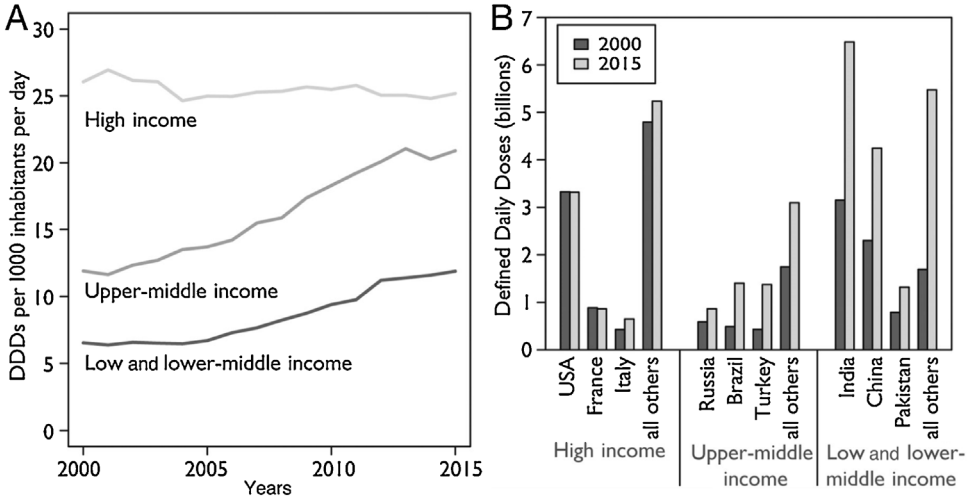

Fig. 1. (A) Antibiotic consumption rate in defined daily doses per 1000 inhabitants per day. (B) Greater total antibiotic consumption (defined daily doses) in LMICs mainly due to the larger populations [2].
Data source: IQVIA MIDAS, 2000–2015, IQVIA Inc. (https://www.iqvia.com/solutions/commercialization/geographies/midas).
Abbreviations: DDDs, defined daily doses; LIMCs, low-income and middle-income countries.

Box 3. WHO documents and projects to support appropriate usage and development of antibiotics and AMR surveillance.

	Description	Objectives
Global Action Plan (GAP)	A GAP to tackle AMR was endorsed at the 68th World Health Assembly in May 2015: http://www.who.int/antimicrobial-resistance/global-action-plan/en/	•to improve awareness and understanding of AMR •to strengthen knowledge through surveillance and research • to optimise the use of antimicrobial agents •to develop an economic case for sustainable investment, which considers the needs of all countries, and increases investment in new medicines, diagnostic tools, vaccines, and other interventions
Global Antibiotic Research & Development Partnership (GARDP)	Founded in 2016, this is a not-for-profit research and development (R&D) joint project by the WHO and Drugs for Neglected Diseases initiative (DNDi): https://www.dndi.org/diseases-projects/gardp/	•to target products that industry will not develop due to lack of profitability •to pilot the use of alternative incentives to delink the cost of R&D from volume-based sales and prices of antibiotics, which support access to new antibiotics •to ensure that new antibiotics are affordable to all who need
Model Lists of Essential Medicines	Launched in 1977 and coinciding with the endorsement by governments at the World Health Assembly of 'Health for all' as the guiding principle for WHO and countries' health policies: http://www.who.int/medicines/publications/essentialmedicines/en/	•to advise on which medicines are needed to address the most important public health needs •to list antibiotics that can be used for common infections and which to preserve for the more serious circumstances
Global Antimicrobial Resistance Surveillance System (GLASS)	Launched on the 22 October 2015, it is the first global collaborative effort to standardise AMR surveillance: http://www.who.int/glass/resources/publications/early-implementation-report/en/	•to provide a standardised approach to the collection, analysis, and sharing of AMR data by countries •to document the status of existing or new national AMR surveillance systems •to foster national AMR surveillance systems and ensure production of reliable information
Global priority pathogens list (global PPL)	A list of antibiotic-resistant bacteria, as requested by Member States: http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf	•to help align R&D priorities with public health needs •to identify the most important resistant bacteria at a global level for which there is an urgent need for new treatments
Guidelines on the use of medically important antimicrobials in food-producing animals	New guidelines on the use of medically important antimicrobials in food-producing animals, recommending that farmers and the food industry stop routinely using antibiotics to promote growth and prevent disease in healthy animals: http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia_guidelines/en/	•to help preserve the effectiveness of antibiotics that are important for human medicine by reducing their use in animals

EARS-Net and GLASS is that EARSNet looks at the percentage of resistant bacteria in cases where they have an isolate of that bacteria, while GLASS looks at various metrics such as the frequency of patients with growth of non-susceptible bacteria per specimen type, species and the incidence of non-susceptible infections per syndrome per organism under surveillance. For example, for all urine samples we look to see if there is there a resistant pathogen and its percentage. If you look at the difference between the samples from a community-care setting vs. a nosocomial setting, this approach could provide very useful information.

Box 4. RESERVE group antibiotics.

Eight antibiotics are in the RESERVE group and need careful management in order to preserve their effectiveness: aztreonam, fosfomycin (IV), fourth generation cephalosporins (e.g., cefepime), oxazolidinones (e.g., linezolid), fifth generation cephalosporins (e.g., ceftaroline), tigecycline, polymyxins (e.g., polymyxin B), colistin and daptomycin. http://www.who.int/medicines/publications/essentialmedicines/en/.

Box 5. GLASS collects data on eight pathogens from urine, faeces, blood, and urethral/cervical swabs.

1. *Acinetobacter baumannii*
2. *Escherichia coli*
3. *Klebsiella pneumoniae*
4. *Neisseria gonorrhoeae*
5. *Salmonella spp.*
6. *Shigella spp.*
7. *Staphylococcus aureus*
8. *Streptococcus pneumoniae*

http://www.who.int/glass/resources/publications/early-implementation-report/en/.

JGAR: What are the costs of implementing this global approach versus the costs of AMR increasing in prevalence? And, who is paying?

MS: If you look at the GAP (Box 3), you need an initial investment to kick-start the process. But then the countries should develop their own national action plans and that requires political leadership from the outset. The question then becomes, how will these plans be implemented? The answer is that we need to have someone who will take responsibility and provide investment, as this will require money. For example, if we can prevent prolonged lengths of stay in hospitals, this will prove less expensive in the long run. In general, it is very difficult to say how much we need to invest.

JGAR: Let's talk about the 'One Health' approach. In response to the need to engage public health, veterinary, food and agriculture sectors, WHO is currently being supported in a tripartite initiative by the United Nations Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE) in implementing the Global Action Plan. Do you think that, at this time, there is a high level of awareness about the danger of misusing antibiotics to grow animals and food – and of the consequences of the spread of antimicrobial-resistant pathogens – among farmers, vets and food workers?

MS: Yes, at least in the European Union because there are robust regulations controlling the use of antibiotics either as growth promoters or as preventive measures. In the United States, there is awareness about 'antibiotic-free meat' and there is a real movement coming from consumers, in line with WHO guidelines which we are very happy about. However, much more regulation is needed in several countries to reduce the use of antibiotics in animal husbandry.

JGAR: It is widely known that human well-being is inextricably tied to that of animals and the environment, and hundreds of studies provide evidence to support limiting the use of antibiotics in the environment. However, we still need integratedepidemiologic/genomic analyses which prove that pathogens isolated from animals and the environment have a causal link with antibiotic-resistant infections in humans. What needs to be done to reduce unnecessary antibiotic use in agriculture and animals?

MS: We know from all our investigations that there is clear evidence of a relation between what is found in animals and humans. For this reason, the 'precautionary principle' has been introduced: if you do not have full evidence but the harm is evident, you should be very careful. A new guideline called 'Guidelines on use of medically important antimicrobials in food-producing animals' has been developed and was released in November 2017. It aims to help preserve the effectiveness of antibiotics that are important for human medicine by reducing their unnecessary use in animals. We all need to change things. So, it should be a shared responsibility across different players from governments, institutions, citizens, doctors, vets, policymakers, and so on. And only if we do that, recognizing that to not act is risking a very dangerous situation, will we be able to stop the spread of resistant pathogens.

JGAR: Who do you think has the most significant role in raising awareness and spreading knowledge about AMR? And, finally, how do you envisage the future and what are your hopes?

MS: Members of the general public are largely unaware that antimicrobial resistance can cause substantial mortality. The most recent data from the European Centre for Disease Prevention and Control indicates that more than 33,000 deaths each year in the EU are attributable to AMR. Patients go to hospital for a hip replacement but there is a risk that they could die; and yet, it will not be known that this was due to infection from a resistant form of Klebsiella or MRSA. We need to increase this awareness and try to bring about a change in the behaviour of all players. This will take a long time. However, I am quite enthusiastic, as we are mobilising everyone, from governments to consumers, but there is much more to do. Overall, I am quite optimistic because change is occurring, there is much greater awareness, political involvement and, last but not least, good examples that show results both in the human health sector and in animal husbandry. And if I was not optimistic, I couldn't do this work.

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