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## **Global action plan on antimicrobial resistance**

### **Options for establishing a global development and stewardship framework to support the development, control, distribution and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines and other interventions**

#### **Report by the Secretariat**

1. In resolution WHA68.7 (2015) the Health Assembly adopted the global action plan on antimicrobial resistance. Among other things, it requested the Director-General “to develop, in consultation with Member States<sup>1</sup> and relevant partners, options for establishing a global development and stewardship framework to support the development, control, distribution and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines and other interventions, while preserving existing antimicrobial medicines, and promoting affordable access to existing and new antimicrobial medicines and diagnostic tools, taking into account the needs of all countries, and in line with the global action plan on antimicrobial resistance, and to report to the Sixty-ninth World Health Assembly”.
2. The task as framed in resolution WHA68.7 is ambitious and will need further discussion among Member States and relevant stakeholders on the way forward. Steps in that regard began with consultation with Member States and relevant partners, including a one-day meeting (Geneva, 29 February 2016) that brought together Member States, relevant international organizations, notably the Food and Agricultural Organization (FAO), the World Organisation for Animal Health (OIE), South Centre, the World Intellectual Property Organization (WIPO) and the World Trade Organization (WTO), and nongovernmental organizations in official relations with WHO. The Secretariat prepared a background paper for this consultation that formed the basis of the discussions.<sup>2</sup> At the request of the participating Member States, an additional opportunity was provided to submit comments in writing in the following two-week period. Six Member States, FAO and OIE provided comments in writing.
3. This report aims to facilitate discussion at the Sixty-ninth World Health Assembly and attempts to provide a balanced perspective on the major options identified to date. It does not focus on individual elements of a possible framework.

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<sup>1</sup> And, where applicable, regional economic integration organizations.

<sup>2</sup> Consultation on options for establishing a global development and stewardship framework:  
[http://www.who.int/phi/news/consultation\\_stewardship-framework/en/](http://www.who.int/phi/news/consultation_stewardship-framework/en/) (accessed 6 April 2016).

## OBJECTIVE AND SCOPE

4. On the basis of resolution WHA68.7, the objectives of a possible global development and stewardship framework can be summarized as follows:

- preservation of antimicrobial medicines through a stewardship framework covering control, distribution and appropriate use
- development of new health technologies for preventing and controlling antimicrobial resistance
- promotion of affordable access to existing and new antimicrobial medicines and diagnostic tools.

## WHAT COULD CONSTITUTE A FRAMEWORK?

5. As exemplified in the Figure, a framework could take the form of one of several different types of instruments. Such instruments all fall under the rubric of normative mechanisms foreseen in Articles 19–23 of WHO’s Constitution. Such a framework might therefore be adopted in various ways – for example, through a non-legally-binding recommendation constituted as, or approved through, a resolution of the World Health Assembly, as with the Pandemic Influenza Preparedness Framework, through regulations<sup>1</sup> such as the International Health Regulations (2005), or through a convention such as the WHO Framework Convention on Tobacco Control. As a general rule, the form and method of adoption should reflect the intended purpose and content of the framework.

**Figure. Examples of a global framework**

Types of instrument	Examples
<b>Frameworks, strategies, plans of action, and codes</b>	<p><i>Frameworks</i> WHO Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits</p> <p><i>Strategies and action plans</i> Global action plan for prevention and control of noncommunicable diseases 2013–2020</p> <p>Global Technical Strategy for Malaria 2016–2030</p> <p><i>Codes</i> International Code of Marketing of Breast-milk Substitutes</p> <p>WHO Global Code of Practice on the International Recruitment of Health Personnel</p>
<b>Regulations</b>	International Health Regulations (2005)
<b>Conventions</b>	WHO Framework Convention on Tobacco Control

<sup>1</sup> Article 21 of WHO’s Constitution.

## **Relationship with the global action plan on antimicrobial resistance**

6. The global action plan on antimicrobial resistance<sup>1</sup> provides a blueprint, with the strategic objectives and technical actions that are needed to comprehensively address antimicrobial resistance. Resolution WHA68.7 points out that any new framework must be in line with the global action plan, and thus the framework is best seen as an agreement among Member States to achieve some of the strategic objectives. The framework would not cover other important elements such as awareness raising, education, training and professional codes of conduct (Objective 1), infection prevention and control (Objective 3) and monitoring and surveillance of resistance (Objective 2).

7. Furthermore, the framework will help Member States and other stakeholders to take forward the three elements of stewardship, development and access. This report reflects the perspective that a framework would provide a specific mechanism for attainment of certain key objectives of the global action plan.

## **PRESERVING ANTIMICROBIAL MEDICINES THROUGH A GLOBAL STEWARDSHIP FRAMEWORK**

8. Stewardship describes the careful and responsible management of something entrusted to one's care. With respect to antimicrobials, careful management means their appropriate use to improve patient outcomes while minimizing the development and spread of resistance. Any stewardship framework should balance the issues of access to antimicrobial medicines, their appropriate use, scientific knowledge, and the elements of the one-health approach, namely human, veterinary, agricultural, environmental and possibly other aspects.

9. Achieving a balanced approach to stewardship will require involvement of all stakeholders besides Member States, including the pharmaceutical industry, regulatory agencies, and medical and veterinary professionals. Specifically, it will need close collaboration with FAO and OIE. FAO is the leading intergovernmental agency with the mandate to improve agriculture, forestry, fisheries and management of natural resources and to achieve global food security and nutrition, for which efficacious antimicrobial uses play a key role. OIE promotes the responsible and prudent use of antimicrobial agents in animals, so as to preserve their therapeutic efficacy and prolong their use in both animals and human beings. Its 180 Member Countries have adopted intergovernmental standards and guidelines, related to antimicrobial resistance, including monitoring of quantities of antimicrobial agents used in animals and the OIE list of veterinary important antimicrobials.<sup>2</sup>

## **WHICH MEDICAL PRODUCTS SHOULD BE SUBJECT TO A POSSIBLE GLOBAL STEWARDSHIP FRAMEWORK?**

10. Any global stewardship framework will have to define the products it encompasses and the rules applying to those products. Resolution WHA68.7 uses the term "antimicrobial medicines", which subsumes antibiotics and other medicines, including antiviral, antifungal and antiparasitic agents. All such medicines can be subject to the emergence of resistance in organisms. An important issue is

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<sup>1</sup> [http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1) (accessed 7 April 2016).

<sup>2</sup> <http://www.oie.int/en/our-scientific-expertise/veterinary-products/antimicrobials/> (accessed 7 April 2016).

whether the framework should cover all such medicines or focus on antibiotic medicines. For some conditions and diseases, such as HIV/AIDS and malaria, special programmes and organizations exist that work on the development of new treatments, access to existing treatments and, in part, issues surrounding resistance. Inclusion of all such medicines would create a broad framework that would unify approaches to stewardship of all classes of antimicrobial medicines, but it would also, potentially, be more complex to negotiate. Another option would be to use a stepwise approach, starting with existing antibiotics, which are subject to both increasingly rapid emergence of resistance and a lack of investment in research and development, and then expanding coverage to new antibiotics and other medicines.

11. Regardless of approach, it will be necessary to clarify which antimicrobial medicines should be subject to the framework. The Secretariat intends to revise WHO's list of critically important antimicrobials for human medicine<sup>1</sup> and is currently identifying which antibiotics should be included in the WHO Model List of Essential Medicines. The comprehensive review of the antibiotic chapter in the latter will expand the list to include all potentially relevant antibiotics that should be subject to different degrees of monitoring and levels of appropriate use. The objective of the revision of the WHO Model List of Essential Medicines is to summarize the evidence supporting antibiotic use for the most common and relevant infections, define a subset of antibiotics that should always be available, and define the antibiotics that should be reserved for targeted uses. A review of the evidence supporting key messages to increase responsible use will also be undertaken to support the policy recommendations of the Expert Committee on Selection and Use of Essential Medicines. OIE's International Committee has adopted a list of antimicrobial agents of veterinary importance that addresses the needs to treat animal diseases with a global perspective.<sup>2</sup> Recommendations on the use of specific molecules critically important for both human and animal health (Cephalosporines 3rd and 4th generation and Fluoroquinolones) have been endorsed and adopted recently. One option could be to start developing a common list of antibiotics of global priority that would be subject to a new global stewardship framework.

## **DEFINING APPROPRIATE USE**

12. A stewardship framework will require agreement as to what constitutes "appropriate use". The answer may vary from one region to another; relevant considerations can include availability of medicines, professional medical guidance and practice, local patterns of infection, performance of the national health system and diagnostic capacity.

13. Implementing appropriate use practices will involve many different actors including manufacturers of antimicrobial agents for human, veterinary and agricultural use; distributors, such as wholesalers and pharmacies; and users, including ambulatory and hospital settings, clinics and homes, prescribers, patients, veterinarians and farmers.

14. There is a need for more research, evidence and sharing of experience about what practical measures promote appropriate use while delaying emergence of resistance and not impeding access to antimicrobial treatments. The Secretariat has commissioned an overview of systematic reviews to

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<sup>1</sup> WHO. Critically important antimicrobials for human medicine – 3rd revision. Geneva: World Health Organization; 2011 ([http://apps.who.int/iris/bitstream/10665/77376/1/9789241504485\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/77376/1/9789241504485_eng.pdf), accessed 7 April 2016).

<sup>2</sup> [http://www.oie.int/fileadmin/Home/eng/Our\\_scientific\\_expertise/docs/pdf/Eng\\_OIE\\_List\\_antimicrobials\\_May2015.pdf](http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/Eng_OIE_List_antimicrobials_May2015.pdf) (accessed 7 April 2016).

identify interventions that improve the use of antibiotics in human beings, with a focus on low- and middle-income countries. This analysis will allow a more evidence-based selection of options.

15. One issue to consider is whether to reserve for human use exclusively certain existing antibiotics and others in development, recognizing that some antibiotics are also used for animal health and taking into account the precautionary approach in line with the global action plan on antimicrobial resistance.<sup>1</sup> Another issue concerns the ways in which antimicrobial medicines reach the end user. For example, companies, wholesalers, distributors, pharmacies, hospitals, clinicians and others can market and sell antimicrobial medicines. In some instances, professional bodies have an important role in oversight or establishing guidance but in some instances and settings there is little oversight or control over practices. The role of prescribers is important in preserving the usefulness of antimicrobials.

16. Certain distribution routes – for example, through internet sales – can facilitate inappropriate use. In addition, some practices provide or are based on economic incentives to sell more antibiotics. The size of packs and how they are sold by pharmacies can also influence treatment adherence and thus formation of resistance.

17. Antibiotics and active pharmaceutical ingredients can increase the development of antimicrobial resistance in other ways, for example, through release into the environment during manufacturing processes and into wastewater treatment. These concerns could be covered by a framework.

18. Antibiotics are used in the veterinary sector for multiple reasons, for instance to treat ill animals in farms, veterinary clinics, private households and zoos, to provide prophylaxis for healthy animals against disease, and sometimes as growth promoters. Antibiotics are also used in the plant sector, for example streptomycin to treat fire blight in fruit trees. Antifungal and antiparasitical agents are used in both humans, and agriculture and the veterinary sector. Close collaboration with FAO and OIE will be needed to address stewardship in these areas and identify further steps beyond those already taken by these organizations.

## **PROMOTING APPROPRIATE USE**

19. A global framework would have to go beyond defining appropriate use of antimicrobial medicines in order to strengthen measures that can help to achieve such practices taking into account existing international standards and guidelines. The global action plan on antimicrobial resistance already includes several areas of action and measures under Objective 4, including the distribution, prescription and dispensing of antimicrobials, criteria for selection and use (including treatment guidelines that promote appropriate use of essential antibiotics), and effective and enforceable regulation. There are, however, other possible measures, including: steps to ensure that promoting and marketing approaches reduce suboptimal use of antimicrobials; steps to ensure that priority antibiotics are only used when they are required for essential health care purposes; and electronic prescription for all antibiotics.

20. Some measures in the veterinary and agricultural sectors are already included in the global action plan under Objective 4, including enactment and implementation of policies on use of

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<sup>1</sup> Paragraph 10 of the global action plan.

antimicrobial agents in terrestrial and aquatic animals and agriculture and the phasing out of use of antibiotics for animal growth promotion and crop protection in the absence of risk analysis.

21. As a general principle, any global framework would have to take into account the capacity of different health systems, countries, cities and rural areas to adopt new measures, and ensure that any new measures do not impede access to treatment, including access in the veterinary sector. Access to effective antimicrobials is also a prerequisite for productive and sustainable agriculture, particularly animal husbandry and aquaculture and safe food,<sup>1</sup> but they need to be used appropriately. In this context, the FAO/WHO Codex Alimentarius Commission and its standards and related texts on the minimizing and containing of antimicrobial resistance, the risk analysis of foodborne antimicrobial resistance, good animal feeding and the maximum residue limits of veterinary drugs in food,<sup>2</sup> as well as existing OIE standards and guidelines already provide some methodologies to reduce appropriately the risk of the emergence of resistance or spread of resistant bacteria that result from the use of antimicrobial agents in food-producing animals.<sup>3</sup> The Codex Alimentarius Commission's maximum residue limits, Code of Practice and Guidelines are not legally binding, but they do have a legal status under WTO agreements similar to OIE standards that increases their effectiveness in promoting appropriate use of antimicrobials in animals and ensuring food safety. The respective part of a possible framework dealing with the veterinary and the agricultural aspects would have to be developed in close collaboration with OIE and FAO. The Codex Alimentarius Commission is expected to discuss the need for further work on antimicrobial resistance in its next session in June 2016. It is also crucial that the framework does support the implementation of national plans on antimicrobial resistance that are created in response to the global action plan. The framework would have to leave sufficient leeway for countries to reflect local health care needs and the particularities of their national or regional systems.

## **DEVELOPMENT OF NEW ANTIMICROBIAL MEDICINES, DIAGNOSTIC TOOLS, VACCINES AND OTHER INTERVENTIONS**

22. The scope of resolution WHA68.7 includes diseases for which there seems to be sufficient investment into research and development, for example, hepatitis C, as well as areas where there is not enough investment, for example, neglected diseases and antibiotics. The current market-driven system does not provide enough incentives for the private sector to invest into the needed research and development of new antibiotics, vaccines and rapid point-of-care diagnostic tools. The global action plan points out that too few antibacterial agents are in development and states that “new concepts are needed for providing incentives for innovation and promoting cooperation between policy-makers, academia and the pharmaceutical industry to ensure that new technologies are available globally”.

23. Although antibiotics are still a commercial market, parallels can be drawn to the area of neglected diseases and emerging pathogens with pandemic potential, where similarly the market does

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<sup>1</sup> See Conference of FAO Resolution 4/2015, Antimicrobial resistance (<http://www.fao.org/3/a-mo153e.pdf>, accessed 7 April 2016).

<sup>2</sup> Maximum residue limits for 22 antimicrobials in a variety of species and tissues for food use have been recommended. The Commission also adopted a Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC/RCP 61-2005) and Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (CAC/GL 77-2011) (see, respectively [http://www.codexalimentarius.org/download/standards/10213/CXP\\_061e.pdf](http://www.codexalimentarius.org/download/standards/10213/CXP_061e.pdf) and [http://www.codexalimentarius.org/download/standards/11776/CXG\\_077e.pdf](http://www.codexalimentarius.org/download/standards/11776/CXG_077e.pdf), accessed 7 April 2016).

<sup>3</sup> <http://www.oie.int/en/our-scientific-expertise/veterinary-products/antimicrobials/> (accessed 7 April 2016).

not provide enough incentives for the massive investment in research and development that is needed to tackle these global health threats appropriately. The Consultative Expert Working Group on Research and Development has provided a detailed assessment of the gap in research and development and assessed different strategies for bridging it.<sup>1</sup> In line with the latter report, the global action plan emphasizes the principle of de-linking the cost of investment in research and development from price and sales volume. If implemented, this principle would remove pressure on pharmaceutical companies to maximize prices and sales volumes, thereby facilitating the implementation of policies to expand access and ensure conservation. However, application of the principle of de-linkage would require a sustainable financing mechanism that at present does not exist and more deliberations among Member States. Different political initiatives are currently being explored that should be taken into account in these discussions.<sup>2</sup>

24. Several national and regional initiatives have already been implemented, including the Biomedical Advanced Research and Development Authority in the United States of America; the Innovative Medicines Initiative in Europe; the Joint Programming Initiative on Antimicrobial Resistance; and various prize funds for diagnostics, such as the Longitude Prize.

25. Under Objective 5 of the global action plan, the Secretariat is urged to explore the options for the establishment of new partnerships to establish open collaborative models of research and development. WHO, in partnership with the Drugs for Neglected Diseases initiative, is engaged in setting up a new, not-for-profit product development partnership, the Global Antibiotic Research and Development Facility, to develop new affordable antibiotics that will be subjected to a conservation scheme.<sup>3</sup> This partnership will provide a cost-effective platform for the development of needs-based new treatments according to identified priorities and could play a central role in any future research and development mechanism.

26. One issue is whether any new products developed under a global development framework would be submitted to the stewardship framework. This issue touches on questions of ownership. Different models for resolving ownership questions have been discussed; for example, market-entry rewards to provide incentives for the development of new antibiotics, including the use of public health-oriented licensing agreements following the model of the Medicines Patent Pool<sup>4</sup> or the use of not-for-profit entities such as the partnership between WHO and the Drugs for Neglected Diseases initiative.

27. The identification of research and development needs will require a quantitative and qualitative analysis of the research and development pipeline to identify all products in preclinical and clinical development. Priority products, based on global public health needs, must also be identified, as well as the products needed to fill identified gaps, for example through the definition of target product

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<sup>1</sup> WHO. Research and development to meet health needs in developing countries: strengthening global financing and coordination. Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination. Geneva: World Health Organization, 2012 ( [http://www.who.int/phi/cewg\\_report/en/](http://www.who.int/phi/cewg_report/en/) (accessed 7 April 2016).

<sup>2</sup> For an analysis of existing proposals, see Renwick MJ, Brogan DM, Mossialos E. A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. *The Journal of Antibiotics* (2015):1-16 ([http://eprints.lse.ac.uk/64852/1/Mossialos\\_systematic\\_review\\_and\\_critical\\_assessment1.pdf](http://eprints.lse.ac.uk/64852/1/Mossialos_systematic_review_and_critical_assessment1.pdf), accessed 7 April 2016).

<sup>3</sup> See for further details: [http://www.who.int/phi/implementation/consultation\\_imnadp/en/](http://www.who.int/phi/implementation/consultation_imnadp/en/) (accessed 7 April 2016).

<sup>4</sup> See for example the Review on Antimicrobial Resistance chaired by Jim O'Neill.

profiles.<sup>1</sup> For vaccines and antibiotics – as well as for alternatives to antibiotics – analyses of products in the pipeline have been published, and WHO is planning to undertake a more comprehensive assessment of the research and development pipeline and needs within the implementation framework of the global action plan. The outcome of this assessment will feed into WHO's Global Health Research and Development Observatory. Based on this analysis of gaps, a scientific committee drawing experts from different fields and all WHO regions could identify priority areas and products that should be developed. Another area requiring further discussion is whether the framework would cover research and development for the human and the veterinary sector, for example vaccines in the veterinary sector.

## **PROMOTING AFFORDABLE ACCESS**

28. Resolution WHA68.7 also specifies that the framework promote affordable access to existing and new antimicrobial medicines and diagnostic tools. Lack of access remains a huge problem in many countries. Pneumonia accounts for 15% of all deaths of children under 5 years old, killing an estimated 922 000 children in 2015. Only one-third of children with bacterial pneumonia receive the antibiotics they need.<sup>2</sup> In the long run, building strong health systems is the most sustainable approach to ensuring affordable access to good-quality essential medicines, including antimicrobial medicines and vaccines, as well as diagnostics and other vital interventions. High prices of originator and generic medicines are one barrier to access to medicines. One option to overcome this challenge is de-linkage (see paragraph 23). Where patents are still in force and high prices obstruct access, another option is voluntary licensing agreements; these have emerged as a tool to provide access to affordable essential medicines. A further option is for countries to use the flexibilities contained in the Agreement on Trade-Related Aspects of Intellectual Property Rights in line with WHO's global strategy and plan of action on public health, innovation and intellectual property.

29. New models for procurement, delivery and financing of treatments have been established for HIV/AIDS, malaria and tuberculosis and could serve to expand access to antibiotics. Another option is to consider a global mechanism for procurement of some antibiotics that facilitates access. In this context, there are potential lessons to learn from the example of medicines against multidrug-resistant tuberculosis and experiences in expanding access and use of quality-assured, artemisinin-based, combination therapies for malaria to reduce emergence of resistance. Broadening access to early and rapid diagnostic testing can contribute to appropriate use. Other measures include identifying essential antimicrobial treatments as the WHO Model List of Essential Medicines currently does and streamlining of procurement and regulatory mechanisms.

30. The quality of antimicrobials that are sold is an important consideration both in the human as well as in the veterinary sector. This type of medicine is the most frequently reported category of falsified and substandard medicines and vaccines which are tracked in the WHO medical products

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<sup>1</sup> Resolution WHA68.7 does not specify whether development should include treatments for animals, but veterinary vaccines make an important contribution to reducing antibiotic use in animal husbandry and fish farming. The OIE has already worked on prioritisation of diseases for which vaccines could have the potential to reduce the use of antimicrobials in animals.

<sup>2</sup> <http://www.who.int/mediacentre/factsheets/fs331/en/> (accessed 8 April 2016).

database.<sup>1</sup> Any global procurement mechanism would have to consider how to ensure quality control. Potentially, the WHO Prequalification Programme could play a role.

31. Other measures that could contribute to promoting affordable access include streamlining guidance for treatment; identifying essential antimicrobial treatments as currently done for the WHO Model List of Essential Medicines; and streamlining procurement and regulatory mechanisms. Developing options for the establishment of a possible global framework will also require taking account of the outcomes of the United Nations Secretary-General's High-Level Panel on Access to Medicines.

## **CONCLUSION**

32. Further work is needed to formulate more concrete options for a global framework. One useful course of action could be to develop a global prioritize list of antibiotics that would be subject to a global stewardship framework and to identify research and development needs.

## **ACTION BY THE HEALTH ASSEMBLY**

33. The Health Assembly is invited to note the report and to provide further guidance on future strategic directions and activities.

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<sup>1</sup> See the statistics: <http://www.who.int/medicines/regulation/ssffc/surveillance/en/>.