




Food and Agriculture  
Organization of the  
United Nations



World Health  
Organization



# Global Framework for Development & Stewardship to Combat Antimicrobial Resistance

## Draft Roadmap

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## ABBREVIATIONS

<b>ATLASS</b>	Assessment Tool for Laboratory and Surveillance Systems
<b>BARDA</b>	Biomedical Advanced Research and Development Authority
<b>CAC</b>	Codex Alimentarius Commission
<b>CARB-X</b>	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
<b>CEPI</b>	Coalition for Epidemic Preparedness Innovations
<b>CEWG</b>	Consultative Expert Working Group
<b>DND<i>i</i></b>	Drugs for Neglected Diseases <i>initiative</i>
<b>EC</b>	European Commission
<b>EML</b>	Essential Medicines List
<b>FAO</b>	Food and Agriculture Organization of the United Nations
<b>FIND</b>	Foundation for Innovative New Diagnostics
<b>HIC</b>	high income country
<b>G20</b>	Group of 20
<b>GARDP</b>	Global Antibiotic Research and Development Partnership
<b>GHIT</b>	Global Health Innovative Technology Fund
<b>GRABTB</b>	Global Research Alliance for Bovine Tuberculosis
<b>GSMS</b>	Global Surveillance and Monitoring System
<b>IACG</b>	Interagency Collaboration Group
<b>IAVI</b>	International AIDS Vaccine Initiative
<b>IMI</b>	Innovative Medicines Initiative
<b>IPM</b>	International Partnership of Microbicides
<b>LMIC</b>	low-and middle-income country
<b>LMT</b>	Laboratory Mapping Tool
<b>MMV</b>	Medicines for Malaria Venture
<b>MVI</b>	Malaria Vaccine Initiative
<b>NGO</b>	nongovernmental Organization
<b>OFFLU</b>	OIE/FAO Network of expertise on animal influenza
<b>OIE</b>	World Organisation for Animal Health
<b>OTC</b>	over-the-counter
<b>PDP</b>	product development partnership
<b>PVS</b>	performance of veterinary services
<b>R&amp;D</b>	research and development
<b>SF</b>	substandard and falsified
<b>STAG</b>	Scientific and Technical Advisory Group
<b>STAR IDAZ</b>	Global Strategic Alliances for Coordination of Research on Major Infectious Diseases of Animals and Zoonoses
<b>STAR IDAZ IRC</b>	STAR IDAZ International Research Consortium on Animal Health
<b>TB</b>	tuberculosis
<b>TDR</b>	Special Programme for Research and Training in Tropical Diseases
<b>TFAMR</b>	Task Force for Antimicrobial Resistance
<b>TPP</b>	target product profile
<b>UNGA</b>	United Nations General Assembly
<b>VICH</b>	Veterinary Medicinal Products
<b>VOF</b>	VICH Outreach Forum
<b>WHO</b>	World Health Organization
<b>WTO</b>	World Trade Organization

**This updated version of the draft Roadmap describes the current situation and the proposed way forward with respect to the establishment of a global framework for development and stewardship to combat antimicrobial resistance.**

**The draft Roadmap was updated after the discussion at the Seventieth World Health Assembly (2017) taking into account the statements made during the Fourth Meeting of Committee A.<sup>1</sup> WHO solicited comments from Member States through the Circular Letter to Member States for the Consultation on the framework, taking place 9-10 November 2017 . The comments received were also taken into account in the updating of this document.<sup>1</sup>**

**The draft Roadmap was developed in close collaboration with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE).**

## **1. SCOPE AND OBJECTIVE**

### **1.1 CONTEXT**

In September 2016, the United Nations General Assembly in its “Political declaration of the high-level meeting of the General Assembly on antimicrobial resistance” called upon the WHO, together with FAO and OIE, to finalize a global development and stewardship framework.<sup>2</sup> As mandated in WHA68.7, the framework will 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.<sup>3,4</sup> The WHO Director-General submitted options for establishing such a global development and stewardship framework to the Sixty-ninth World Health Assembly.<sup>5</sup>

### **1.2 OBJECTIVES**

On the basis of resolution WHA68.7<sup>3</sup> and as described in A69/24.Add. 1<sup>5</sup>, the objectives of a global development and stewardship framework can be described as the following:

- Research & Development (R&D): support the development of new affordable antimicrobial medicines, diagnostic tools, vaccines and other interventions for detecting, preventing and controlling antimicrobial resistance;
- Access: promote affordable access to existing and new antimicrobial medicines, vaccines and diagnostic tools of assured quality;
- Stewardship: preserve antimicrobial medicines by taking measures to promote their control, appropriate distribution as well as appropriate use.

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<sup>1</sup> <http://www.who.int/antimicrobial-resistance/en/>

### 1.3 WHAT DO WE UNDERSTAND BY ‘FRAMEWORK’?

At the outset, one of the key questions is how to reach a common understanding of the character and function of a framework. In drafting resolution WHA68.7, the World Health Assembly deliberately chose the term ‘framework’ to provide flexibility with respect to the selection of the most appropriate instrument(s). The term ‘framework,’ in general, refers to a basic conceptual structure. The future framework thus will provide an overarching structure for various tools and instruments aimed at addressing three key objectives: 1) fostering research and development (R&D), 2) access, and 3) stewardship. In doing so, the framework will build on existing standards, guidelines and tools that are currently being implemented by FAO, OIE, and WHO.<sup>6-17</sup> Where gaps remain, new tools need to be developed. While WHO is the lead agency for human health and related issues, animal health and welfare related standards fall within the mandate of the OIE, and sustainable agriculture (animal and plant production), feed and food security fall within the competence of FAO. The joint FAO/WHO Codex Alimentarius Commission develops food standards with the dual objective of protecting consumer safety and health and ensuring fair trade practices. These existing instruments will be taken into account and can be used to further the objectives of the framework. In general, elements of the framework that have repercussions for human, animal, plant and environmental health sectors could be endorsed by the constituencies of the three organizations.

This Roadmap proposes a modular approach through which the framework can be developed and built over time. The framework is envisaged to form an “umbrella” uniting different instruments. Ultimately, there may be a need for an overarching instrument that defines overall objectives, principles, governance, and possible accountability and financing mechanisms. The fact that the framework will unite different instruments also means that different elements of the framework could take different forms as exemplified in Figure 1.

Type of instrument	Examples
1. Frameworks, strategies, plans of action, voluntary guidelines and codes	<p><i>Frameworks:</i></p> <ul style="list-style-type: none"> <li>- WHO Pandemic Influenza Preparedness</li> <li>- Framework for the sharing of influenza viruses and access to vaccines and other benefits</li> </ul> <p><i>Strategies and action plans:</i></p> <ul style="list-style-type: none"> <li>- WHO Global Action Plan for prevention and control of noncommunicable diseases 2013–2020</li> <li>- FAO Global Plan of Action for Animal Genetic Resources</li> <li>- WHO Global Technical Strategy for Malaria 2016–2030</li> <li>- Tripartite Rabies strategy (2017)</li> </ul> <p><i>Voluntary Guidelines:</i></p> <ul style="list-style-type: none"> <li>- FAO Voluntary Guidelines to support the progressive realization of the right to adequate food in the context of national food security (2005)</li> <li>- FAO Voluntary Guidelines for Securing Sustainable Small-Scale Fisheries in the Context of Food Security and Poverty Eradication (2015)</li> </ul> <p><i>Codes:</i></p> <ul style="list-style-type: none"> <li>- WHO International Code of Marketing of Breast-milk Substitutes</li> </ul>

	<ul style="list-style-type: none"> <li>- WHO Global Code of Practice on the International Recruitment of Health Personnel</li> <li>- OIE PVS Pathway</li> <li>- OIE Terrestrial and Aquatic Code chapters on responsible and prudent use of antimicrobial agents in animals.</li> <li>- FAO International Code of Conduct on Pesticide Management</li> <li>- Codex Alimentarius Code of Practice to Contain and Minimise Antimicrobial Resistance</li> </ul>
2. Regulations	<ul style="list-style-type: none"> <li>- WHO International Health Regulations (2005)</li> <li>- OIE Standards for Quality of Veterinary Services</li> </ul>
3. Conventions and Treaties	<ul style="list-style-type: none"> <li>- WHO Framework Convention on Tobacco Control</li> <li>- FAO International Plant Protection Convention</li> <li>- FAO International Treaty on Plant Genetic Resources for Food and Agriculture</li> </ul>

**Figure 1. Examples of a global framework<sup>3</sup>**

Such instruments all fall under the rubric of normative mechanisms foreseen in Articles 19 – 23 of WHO’s Constitution, articles VI and XIV of FAO’s constitution and OIE’s Basic Texts. 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; the International Code of Conduct on Pesticides Management or the standards, codes of practice, guidelines and other recommendations approved by the Codex Alimentarius Commission, which are voluntary by nature and do not have a binding effect on national legislation, but which are specifically identified in the WTO Agreement on the Application of Sanitary and Phytosanitary Measures as the international benchmark texts for food safety.
- through regulations<sup>2</sup> such as the WHO International Health Regulations (2005); or
- through a convention such as the WHO Framework Convention on Tobacco Control , the FAO International Plant Protection Convention or the International Treaty on Plant Genetic Resources for Food and Agriculture

As a general rule, the form and method of adoption should reflect the intended purpose and content of the framework.

Specific elements of the framework will require endorsement by the three organizations governing bodies and Member Countries following each organisations rules and endorsement processes.

To develop the framework, WHO is undertaking a study that will provide options for the content and form of the “umbrella” framework. The Secretariat will seek input on this during the consultation on 9-10 November 2017.

<sup>2</sup> Article 21 of WHO’s Constitution.

Independent activities within the three organizations contribute to and complement the work of the tripartite collaboration on AMR. For example, in 2016, the FAO governing body adopted the FAO Action Plan on Antimicrobial Resistance.<sup>18</sup> In addition, taking into account the Global Action Plan on Antimicrobial Resistance endorsed by OIE Member Countries in 2015, the World Assembly of Delegates adopted Resolution No. 36 at the 84<sup>th</sup> OIE General Session in May 2016 requesting the development of an OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials that was then published in November 2016.<sup>19</sup>

#### **1.4 HOW DOES THE FRAMEWORK RELATE TO THE GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE?**

A key question is how the framework relates to the Global Action Plan on Antimicrobial Resistance. As stated in WHA68.7, the global framework aims to create an environment conducive for developing new antimicrobial products, conserving them, and ensuring affordable access. This framework, therefore, directly addresses objectives 4 and 5 of the Global Action Plan:

- optimize the use of antimicrobial medicines in human and animal sectors, develop the economic case for sustainable investment that takes account of the needs of all countries;
- increase investment in new medicines, diagnostic tools, vaccines and other interventions.

Within this context, it is important to highlight that the framework is not intended to replace the Global Action Plan. The fact that the framework should focus on some elements of the Global Action Plan is not a prioritization of these elements, rather, it will provide focus for work under objectives 4 and 5 with full understanding that some overlap exists between the five objectives of the plan; for example, appropriate use of antibiotics relies heavily upon the availability of data on resistance and data on the use of antimicrobial agents.

Based on this understanding, the framework will not address improving awareness and understanding of antimicrobial resistance through effective communication, education and training (objective 1), strengthening the knowledge and evidence base through surveillance and research (objective 2) or reducing the incidence of infection through effective sanitation, hygiene and infection prevention measures (objective 3) of the Global Action Plan. Activities to address objectives 1-3 are already at various stages of implementation under the Global Action Plan.

The framework is meant to be a global framework. It will support but not interfere with or replace the national action plans that will remain the primary tool of implementation at the country level of the Global Action Plan.

#### **1.5 SCOPE OF THE FRAMEWORK**

Resolution WHA68.7 takes a very broad approach, encompassing new antimicrobial medicines, diagnostic tools, vaccines and other interventions. The term ‘antimicrobial medicines,’ which subsumes antibiotics and other medicines, includes antiviral, antifungal,

antibacterial and anti-parasitic agents. In principle, it also includes therapies for viral infections such as influenza or HIV. All such medicines are susceptible to the emergence of resistance.

Special programmes and initiatives have been established over the past few years to address some, but not all, of the most worrying conditions and diseases, such as HIV/AIDS, malaria, tuberculosis (TB), and other neglected tropical diseases. These programmes/initiatives aim to foster the development of new treatments, improve access to existing treatments and, in part, address disease-relevant issues surrounding resistance.<sup>20,21</sup>

As illustrated in Table 1, the level of market failure for R&D activities in the realm of infectious diseases varies significantly. Neglected tropical diseases are a typical example where the costs of the R&D cannot be offset by future product sales. Fostering R&D for neglected diseases is, therefore, addressed within the follow-up process of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG). Other diseases (hepatitis C and B, for example) harness market forces and attract investments by industry. In some cases, global public health market mechanisms create a commercial market that drives investments in R&D. As suggested in A69/24 Add.1, the WHO Secretariat will follow a stepwise approach starting with antibiotics, including treatment of TB.

Likewise, the speed with which antimicrobial resistance emerges and spreads varies considerably from one pathogen to another. This underscores the important need for investment in strategies and approaches for infectious disease prevention and control that are not heavily dependent upon the development of new medicines that will also become ineffective in the near future. Given that a specific function of the framework is to harmonize stewardship policies in the human, animal, and plant health and food sectors across the three organizations and Member States, the framework will mainly focus on health technologies that can be used for human and animal health, and plant protection.



**Table 1: Characterizing antimicrobial pathogens by sector involvement, level of market failure and R&D entities/initiatives (October, 2017)**

<b>Disease/Disease group</b>	<b>Targeted towards human health, animal health, and/or food production</b>	<b>Level of market failure <sup>c</sup></b>	<b>Dedicated global and regional R&amp;D entities/initiatives</b>
<b>Bacterial infections <sup>a</sup></b>	All three sectors	High	GARDP, CARB-X, IMI
<b>Fungal infections</b>	All three sectors	High	--
<b>HIV</b>	Humans	Low, but very high for paediatric applications	IAVI, IPM
<b>Influenza</b>	Humans and animals	Low	OFFLU
<b>Malaria</b>	Humans	High	MMV, MVI
<b>Neglected tropical diseases</b>	Mostly humans; for some, possible use in animals to decrease transmission to humans	Very high	TDR, DNDi, Sabin Institute, FIND, GHIT, WHO HAT/FAO PAAT
<b>Emerging diseases with pandemic potential <sup>b</sup></b>	Mostly humans; for some, possible use in animals to decrease transmission to humans	Very high	WHO R&D Blueprint CEPI, FIND
<b>Tuberculosis</b>	Humans animals <sup>d</sup>	High	Global Alliance for TB Drug Development, TB Vaccine Initiative, Global Research, GRABTB, the Union
<b>Viral hepatitis</b>	Humans	None	--

<sup>a</sup> Bacterial infections that are not classified as neglected tropical diseases. TB is listed separately.

<sup>b</sup> R&D Blueprint: Revised list of priority diseases. Arenaviral hemorrhagic fevers (including Lassa Fever); Crimean Congo Haemorrhagic Fever; Filoviral diseases (including Ebola and Marburg); Middle East Respiratory Syndrome Coronavirus; other highly pathogenic coronaviral diseases (such as Severe Acute Respiratory Syndrome; Nipah and related henipaviral diseases; Rift Valley Fever; Severe Fever with Thrombocytopenia Syndrome; Zika; Disease X.<sup>22</sup>

<sup>c</sup> Very high: no commercial market/no financing mechanisms; High: limited commercial markets; Low: significant commercial markets/financial incentives (adapted from the Special Programme for Research and Training in Tropical Diseases <sup>23</sup>).

<sup>d</sup> Streptomycin is used to treat fruit trees in certain countries.

## 2. RESEARCH AND DEVELOPMENT

One of the three objectives of the framework is to foster R&D of new antimicrobial medicines, diagnostic tools, vaccines and other interventions for detecting, preventing and controlling antimicrobial resistance. The activities that are required are identification of R&D priorities, incentives and investment in R&D as well as coordination.

### 2.1 GUIDING R&D INVESTMENT BY SETTING PRIORITIES

The FAO, OIE and WHO have started to identify R&D priorities in the human, animal and plant sectors and will seek for cross sectoral collaboration when appropriate.

#### 2.1.1 Human R&D priorities

The WHO is currently supporting R&D priority setting for new medicines, vaccines and diagnostics to combat antimicrobial resistance. In February 2017, the WHO published a list of priority pathogens to identify needs for R&D in the area of antibiotic resistance (Box 1).

#### **Box 1. Prioritization of human pathogens to guide R&D of new antibiotics**<sup>24</sup>

The WHO report on prioritization of pathogens for R&D identified 12 classes of priority pathogens (critical, high and medium priority), along with *Mycobacterium tuberculosis* that are increasingly resistant to existing antibiotics. R&D programmes should focus urgently on new antibiotics specifically active against TB (including multi- and extensively drug-resistant strains) and against multi- drug resistant Gram-negative bacteria that cause acute clinical infections in both hospital and community settings worldwide. Development strategies should also focus on new formulations for paediatric use and user-friendly (e.g. oral) formulations.

Subsequently, in September 2017, the WHO published an analysis of the current antibacterial clinical pipeline including biologicals and treatments for TB.<sup>25</sup> The current pipeline was found to be insufficient and lacking potential treatment options for most of the resistant bacteria, especially for multi-drug resistant Gram-negative pathogens.<sup>26</sup> This analysis, to be updated annually, focused both on the quantity and the potential added value of products in the pipeline and will inform future discussions of the WHO Expert Committee on Health Research and Development.

In parallel, the WHO is also undertaking an evidence-based prioritization exercise for human vaccines that may reduce the impact of antimicrobial resistance to guide future priority R&D investments. WHO is working closely with stakeholders to prioritise which vaccines (existing or under development) would have the greatest impact on either antibiotic use, or antibiotic resistance. This will take into account the relative contribution of the vaccine-preventable diseases to the overall antibiotic consumption, and the costs of administering the vaccines.

Lastly, WHO is supporting R&D initiatives for Rapid Point of Care (PoC) in vitro diagnostics (IVDs). PoC IVDs are needed to help address appropriate therapy and the occurrence of antimicrobial resistance by informing health professionals on the exact nature of the pathogen and the presence of drug-resistance. The most effective treatment can then be determined during the patient's visit. PoC IVDs improve antimicrobial stewardship by

reducing the use of broad spectrum antimicrobials. WHO will coordinate the mapping of existing IVDs for antimicrobial resistance, identify the gaps and lead the development of consensus target product profiles (TPPs) to inform IVD developers about the precise characteristics of the needed IVDs. In addition, WHO will develop a Model List of Essential In Vitro Diagnostics.

### 2.1.2 Animal R&D priorities

Priorities for R&D in the animal sector will include work to support the development of quality and affordable animal vaccines to decrease the use of antibiotics in food-producing and companion animals. OIE already published a report highlighting priority animal diseases for which the development of a vaccine would have potential to reduce the use of antimicrobials in poultry, swine and fish.<sup>27</sup> OIE will extend this work to other animal species, including cattle, sheep, and goats in the near future.

#### **Box 2. Priority list of animal diseases for vaccine development**

OIE, in 2015, developed a list of priority diseases in chicken, swine and farmed fish where the development of vaccines would have a high impact on reducing the use of antibiotics.<sup>27</sup> For chicken, two bacterial pathogens were identified (*Escherichia coli* and *Clostridium perfringens*). For swine, eight bacterial pathogens and three viral agents were identified where vaccines would significantly reduce the need for antibiotic use (*Streptococcus suis*, *Pasteurella multocida*, *Mycoplasma hyopneumoniae*, *Actinobacillus pleuropneumoniae*, *E. coli*, *C. perfringens*, *Lawsonia intracellularis*, *Brachyspira* spp, Porcine Reproductive and Respiratory Syndrome virus, Swine Influenza virus and rotaviruses). For farmed fish, six primary pathogens for which a vaccine would reduce the need for antibiotics were listed (*Aeromonas hydrophila*, *Pseudomonas* spp., *Vibrio* spp., *Photobacterium* spp., *Edwardsiella ictaluri* and *E. tarda*).

Another area that urgently requires more research is finding or developing alternatives to antibiotics and other antimicrobials as growth promoters for animal production including aquaculture.

#### **Box 3. Measures to reduce use of antimicrobials as growth promoters**

Various measures can be implemented to reduce the use of antimicrobials for growth promotion purposes while still maintaining comparable growth rates. Measures include application of good husbandry and housing practices, biosecurity, using rigorous disease control measures, including vaccination, and ensuring good nutrition and animal welfare. Additionally, the use of feed ingredients/additives other than antibiotics can enhance the efficiency of feed conversion to improve growth rates, for example enzymes, probiotics, prebiotics, acidifiers, plant extracts, or essential oils. More research is needed to fully characterize the effectiveness and costs associated with the various practices and alternatives in different production systems.

The ability to accurately diagnose disease in animals in a timely manner is often a challenge. Samples collected need to be transported from farms to laboratories and then tested. This leaves veterinarians to empirically treat animals in order to prevent disease progression. Guidance for empirical diagnosis based on knowledge of prevalent diseases in a given

country, can help prioritize the use of narrow spectrum over the use of broad spectrum antimicrobials. Ensuring that rapid and affordable PoC tests are available for critical animal diseases where antimicrobials are most commonly used will improve antimicrobial stewardship and animal health and welfare. The Global Strategic Alliances for Coordination of Research on Major Infectious Diseases of Animals and Zoonoses (STAR IDAZ) International Research Consortium on Animal Health (STAR IDAZ IRC) collects and conducts research gap analysis on priority animal diseases including identification of needs for diagnostics and vaccines.<sup>28</sup>

#### **Box 4. Diagnostics and AMR surveillance**

OIE Terrestrial and Aquatic Manuals include standards for diagnostic tests to be used for safe trade and establishment of official disease status of countries. As part of capacity building programmes, FAO conducts laboratory diagnostic training for priority zoonotic diseases, sample collection and transport, biosafety and biosecurity, and quality assurance. FAO has developed two assessment tools including the Laboratory Mapping Tool (LMT) which assesses general capacity for disease detection and the Assessment Tool for Laboratory and Surveillance Systems (ATLASS) which assesses laboratory capabilities for diagnostics for AMR as well as a country's overall surveillance system for AMR.

More investment is needed to develop rapid and affordable PoC diagnostics to guide treatment decisions in both the human and animal sector.

## **2.2 INCREASING INVESTMENT IN R&D**

Given the lack of market incentives to develop new antibiotics, public investment is needed to ensure that necessary medicines, vaccines, diagnostics tests, and other strategies are developed to tackle priority pathogens, including TB.

A number of studies have been published recently<sup>29-31</sup> suggesting different funding mechanisms for R&D and ways to implement the concept of delinkage. Several national and regional initiatives have been set up to fill the R&D pipeline, including Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), financed by the Biomedical Advanced Research and Development Authority (BARDA) in the United States of America and the Wellcome Trust; the European Commission's (EC) Innovative Medicines Initiative (IMI); the EC Joint Programming Initiative on Antimicrobial Resistance; and prize funds for diagnostics, such as the UK Longitude Prize on diagnostics for antimicrobial resistance.

Having assessed a number of possible R&D models, WHO, together with Drugs for Neglected Diseases *initiative* (DNDi), has set up a new product development partnership, the Global Antibiotic Research and Development Partnership (GARDP) as described in Box 5.

**Box 5: GARDP: an R&D initiative for global public health needs**

GARDP is a not-for-profit research and development organization that addresses human global public health needs by developing new antibiotic treatments while endeavouring to ensure sustainable access. GARDP is part of the implementation of the Global Action Plan on Antimicrobial Resistance that calls for new public-private partnerships for encouraging research and development of new antimicrobial agents and diagnostics. GARDP is a joint initiative of WHO and DNDi who is hosting it during the start-up phase. On 4 September 2017, a pledging event was held in Berlin, Germany under the leadership of the German Minister of Health. The governments of Germany, Luxembourg, the Netherlands, South Africa, Switzerland, the United Kingdom of Great Britain and Northern Ireland as well as the Wellcome Trust pledged more than EUR 56.5 Million.<sup>32</sup> All countries that would also like to invest in the developing of new antibiotics and their appropriate use are invited to join GARDP.

In its first partnership with a company in July 2017, GARDP announced its plans to co-develop zoliflodacin, one of the few drugs in the pipeline to treat drug-resistant gonorrhoea that is in a global Phase III clinical trial. On neonatal Sepsis, GARDP will initiate work to develop new treatment regimens for neonatal sepsis.

How to incentivize the development of antibiotics was also on the agenda of the Group of 20 (G20) that decided to set-up a Global Antimicrobial Resistance R&D Hub to increase and coordinate funding for research and development for combating antimicrobial resistance. WHO is ready to support the future Hub by providing R&D priorities as well as clinical pipeline data. Additional data and analyses produced by the Hub should be fed into the WHO Global Observatory on R&D that can function as a fit-for-purpose for R&D related data

With respect to animals and plants the G20 Agriculture Ministers' Declaration 2017 - *Towards food and water security: Fostering sustainability, advancing innovation* – recognized the need to strengthen analysis and sharing of international scientific evidence for the development, transmission and control of antimicrobial resistance in animals, plants, food, and the environment, including voluntary transfer of technology on mutually agreed terms in this area.<sup>33</sup>

While initiatives to develop new antibiotics for human use are under development, the investment into new tools, including vaccines to reduce the need of antimicrobials in animals, is less advanced and will need support. Collaboration between human and animal health sectors in research projects, such as vaccine development and new diagnostic technologies, needs to be encouraged for the benefit of both sectors in particular for diseases with zoonotic potential.

Another challenge for animal health and food production is the effective uptake of good husbandry practices which can have capacity, labour and economic impacts. While there are numerous long term benefits of improving practices, beyond antimicrobial resistance, for those having to implement change these can seem indirect and costly in the short term. Hence there is a need to assess the economic impact of implementing such improvements across various production scenarios (encompassing pastoral to commercial production in LMICs and HICs) to demonstrate to primary food production sectors the economic case for

implementing good husbandry practices Where necessary, mechanisms should be explored to assist the primary food production sector in transitioning to implementation of better practices.

Good agricultural practices reduce the need for antimicrobials, thereby reducing the risk for antimicrobial resistance. FAO has published several documents on good practices for various sectors and has conducted trainings and developed a toolkit on biosecurity for swine and poultry operations or family farms. FAO is currently undertaking a survey of existing guidance on good agricultural practices and guidance on prudent use of antimicrobials by sector, including aquaculture, poultry, dairy cattle, and swine production, to identify gaps and to develop recommendations based on OIE standards on responsible and prudent use of antimicrobial agents in terrestrial and aquatic animals. Beyond identifying and recommending good practices, implementation of those practices is key to mitigating the risk of antimicrobial resistance.

Based on the ongoing identification of R&D priorities in the human, animal and plant health sectors, the global framework needs to include mechanisms to address the lack of R&D investment where there is market failure. In this context, the future work will build upon existing studies, reports and initiatives in this area.

Taking into account the principle of delinkage and the experience gained in the follow up of the CEWG report both push (for example research grants) and pull (for example market entry rewards or prize funds) mechanisms will be considered.

In general the antibiotic market is dominated by generic products that account for approximately 80% of prescriptions in the human health sector. High prices thus are less of an issue than in other disease areas. However, antibiotics need to be affordable for those who need them which can be challenging with respect to new patented products. One example is the newly developed treatments for TB; bedaquiline and delamanid. While it is important to ensure that these new therapeutic options to treat TB are used appropriately, namely in the context of appropriate combinations and under directly observed treatment, they have to be accessible and affordable to patients and health systems. Different approaches exist and one can learn from the experience with expanding HIV and Hepatitis C treatments. Based on this experience, WHO has expanded its prequalification programme to include these new TB treatment options allowing quality assurance of possible generic versions.

Voluntary licenses and the use of World Trade Organization (WTO) TRIPS flexibilities are possible means to overcome intellectual property related barriers and allow for generic competition. In the framework of its work on fair pricing, WHO will provide more transparency around pricing and costs of manufacturing and can assist countries in negotiating with suppliers and procurement.<sup>44</sup>

### **3. STEWARDSHIP AND ACCESS**

The second main element of the global framework is the development of a global approach to stewardship and access. The framework will have to define the term stewardship and related rules and obligations. The following section advances an initial definition of stewardship and the potential scope of the global framework with respect to stewardship. It

also presents the recent revision of the WHO Model List of Essential Medicines (EML) chapter on antibiotics which will serve as a starting point to the categorization of antibiotics and related stewardship measures in the human health sector.

Definitions and rules for the animal sectors are defined by standards and guidelines developed by the OIE that apply for terrestrial and aquatic animal health, in particular the chapters on responsible and prudent use. Codex develop guidelines regarding food safety.

### **3.1 THE DEFINITION OF STEWARDSHIP**

In general the term 'stewardship' describes the careful and responsible management of something entrusted to one's care. For antibiotics and other antimicrobials, this means appropriate use to improve patient outcomes while minimizing the development and spread of resistance.

Antimicrobial stewardship, addressed through the concept of responsible and prudent use of animals, is an overarching term that includes practices to foster appropriate use:

- in human, animal and plant health;
- at different societal levels, from the individual to the multidisciplinary team or group at the hospital or community-level, under the umbrella of a national programme; and
- in terrestrial and aquatic animal health sectors, through OIE standards that define responsible and prudent use through allocation of responsibilities to all actors in the antimicrobial supply chain from regulators, manufacturers, distributors, veterinarians or other professionals with authority to prescribe, and animal owners
- at the global level to coordinate activities across countries across the value chain of antibiotics.<sup>34</sup>

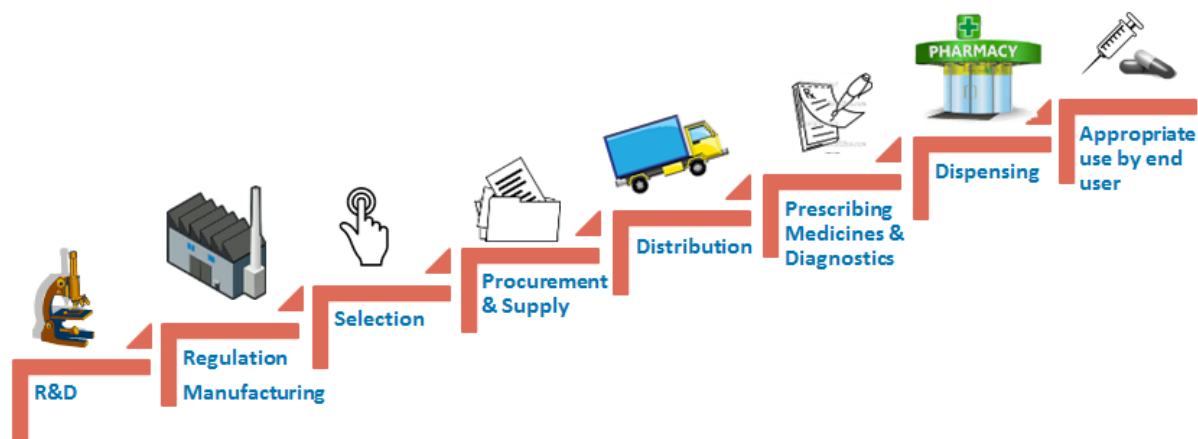
The content of antimicrobial stewardship programmes heavily depends on the context and the capacity of national regulatory authorities relevant for human and animal health and plant production. This could include for example at:

- global level: how new antibiotics are introduced to the market, labelled, priced and distributed;
- national level: legislation, regulation and national treatment guidelines;
- hospital level: optimizing the use of antibiotics for patients in hospitals; and at
- community level: fostering access and appropriate use in primary health care settings and in animal health through awareness raising and targeted interventions.<sup>34</sup>

Stewardship and access cannot be dealt with in isolation. Any stewardship framework must also ensure that access to antibiotics is not compromised and is expanded where needed. A wider recognition of antimicrobial medicines, in particular antibiotics, as a global public good is needed to undertake stewardship at the various levels.

### 3.2 SCOPE OF THE FRAMEWORK ON STEWARDSHIP

According to WHA68.7, the framework should support the development, control, distribution and appropriate use of different tools to tackle antimicrobial resistance. The framework thus will encompass the whole lifecycle of a product from its development, marketing authorization and regulatory requirements to end-users; for example, labelling requirements, the manufacturing process and its impact on the environment, the selection of the right antimicrobials, how they are marketed and promoted, distributed, prescribed, used and discarded as waste (expired and unused), as well as aspects of pharmacovigilance for ongoing assessment of product efficacy, quality and safety (Figure 2).



**Figure 2: Stewardship covers the whole spectrum of a product, from R&D to use**

Regarding human use, the question on how antibiotics are paid for or reimbursed as well as how they are dispensed in inpatient and outpatient settings and finally used by patients and users also needs to be addressed. This includes developing new reimbursement or pay-for-service models that further appropriate use and conservation of new antibiotics and provide incentives for companies to develop new treatments. Such models are also possible pull mechanisms that could contribute to creating a more viable market for both new and old antibiotics.

Disposal of unused or expired medicines also needs to be explored. Stewardship also entails that professional groups, including physicians, veterinarians, dentists, and pharmacists, are well-qualified and proficient in prescribing the right medicine at the most appropriate dose for optimal duration and correct indication.

The life cycle approach entails the definition of clear roles and obligations for the various stakeholders involved within the cycle: manufacturers, including generic manufacturers, food-animal producers, regulatory authorities, prescribers, dispensers, wholesale and retail distributors, physicians and veterinarians, farmers and citizens.

### 3.3 REGULATION OF ANTIMICROBIALS IN THE HUMAN AND ANIMAL SECTORS

Some of the key drivers of the misuse and overuse of antimicrobials are the lack of awareness, gaps in legislation, and absence of or poorly implemented enforcement of legislations.<sup>36</sup> Efforts at the national level to strengthen this area include the development and enforcement of national regulations to restrict over-the-counter (OTC) sales of



antibiotics without a prescription, and to restrict or prohibit the use of antimicrobials as growth promoters in order to promote rational use in the human and animal health sector. However at the same time, in particular in LMICs, it is important to ensure that access to life saving antimicrobials is not compromised to all who need them while restricting overuse. However implementing this in countries may vary depending on the systems and regulatory environment currently in place and will require a phased approach.

**Box 6. Promotional marketing of antibiotics**

A review of existing promotional marketing practices of antibiotics within the human health sector to support the global stewardship efforts is currently underway. The report will likely be available beginning of 2018 and will provide recommendations for marketing of antibiotics, for example to restrict marketing of antibiotics in the reserve group of the WHO EML AWaRe categorization. For the animal health sector, the OIE standards on responsible and prudent use of antimicrobial agents include articles on advertising directed to the veterinary pharmaceutical industry to respect principles of responsible and prudent use including not advertising Veterinary Medicinal Products containing antimicrobial agents directly to the food animal producer.

To curb the potential for overuse and misuse of antimicrobials in the animal sector, there should be appropriate policy objectives, supported by adequate legislation, regulatory control and enforcement mechanisms. Encompassing the broader food and agriculture perspective, the FAO has developed a policy review framework and guidelines to help countries assess existing antimicrobial resistance policy and to strengthen future policy response. FAO is conducting a legislative study to identify good regulatory practices to address the key drivers of overuse and misuse, in order to help minimize the risks of development and spread of antimicrobial resistance. These regulatory responses span multiple regulatory areas, including, among others: the production, distribution and use of veterinary medicines; food safety; feed; crop production and pesticide management; animal production, water quality, environment and waste. The good regulatory practices identified could help countries formulate the appropriate regulatory solutions to support and sustain the policy objectives to tackle antimicrobial resistance. To facilitate the identification of current legislation that could have an impact on the control and/or development of antimicrobial resistance across the different regulatory areas in the different jurisdictions, the FAO is also adding antimicrobial resistance as a search term for the FAOLEX legal database.<sup>37</sup>

There are numerous barriers to access to antimicrobials where many are rooted in deficiencies of national regulatory and health systems, but also in shortages (Section 3.4) and quality problems (Section 3.5).

### **3.4 SHORTAGES OF ANTIMICROBIALS**

One reason for the lack of access to antibiotics is shortages of antibiotics in the human and animal sector due to unavailability of certain antibiotics on the market. For certain inexpensive injectable antibiotics very few quality manufacturers remain on the market, which may be due to too-low profit margins in that market or for the animal sector, and low interest in development of treatment for minor species due to the small market size. WHO

is currently undertaking an assessment of the extent of shortages of antibiotics in the human sector and the underlying reasons. Preliminary results show that in the eight countries included in the review (Australia, Canada, Belgium, France, Germany, Italy, Spain and Switzerland) shortages of antibiotics are significant in each of the countries and represented more than 10 percent of the total records of shortages. Higher number of shortages was reported for injectable antibiotics. This assessment will be expanded to LMICs. The current work on gathering overall antibiotic consumption data will also provide a better assessment of access to antibiotics and prices paid by buyers and patients.

### **3.5 ENSURING QUALITY OF ANTIMICROBIALS**

The prevalence of substandard and falsified medical products for both human and veterinary use is recognised as an important factor contributing to antimicrobial resistance.<sup>38</sup> Substandard antibiotics are considered to contribute to the development of resistance due to inadequate dosing, since such products often contain an insufficient amount of active ingredient. In many cases, the quality of the medicine makes it ineffective. An example for human use are the substandard and falsified antimalarials containing sub-therapeutic amounts of artemisinin derivatives or only one of the two active ingredients in artemisinin combination therapy.<sup>39</sup>

WHO leads and coordinates a global programme for surveillance and monitoring of the quality of medicines, vaccines and IVDs. Core to this is the Global Surveillance and Monitoring System (GSMS), a global system for the reporting and analysis of information of substandard and falsified medical products. About 50 percent of the GSMS reported cases are antimicrobials, with antimalarials and antibiotics being the most frequently reported. Of the reported antibiotics in the WHO GSMS, approximately 90 percent are listed by WHO as either critically important or highly important antimicrobials for human medicine and includes those reflected in the Access, Watch, and Reserve groups on the WHO EML AWaRe categorization. Last line treatments for a number of infections including for multidrug-resistant tuberculosis (MDR TB) are also reported to the GSMS. In November 2017, WHO will publish two reports on a) the socioeconomic and public health impact of substandard and falsified medical products (including cost and prevalence estimates) and b) a report on the first four years of data from the Global Surveillance and Monitoring System on substandard and falsified medical products including antimalarials and antibiotics.

To address the issue of the quality of antimicrobials for veterinary use, FAO has initiated research on the regulatory aspects of substandard or falsified veterinary medicinal products. In addition, OIE is strongly involved in the work of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) and its Outreach Forum (VOF). The VOF provides a basis for wider international harmonisation of pre- and post-marketing authorization of veterinary medicines providing clarification on their quality and encouraging exchange of information. This process will facilitate the registration of and access to approved quality assured products including in LMICs. (<http://www.oie.int/en/our-scientific-expertise/veterinary-products/vich-outreach-forum/>).

The importance of the quality of veterinary products including antimicrobial agents has been included since 2009 in the training of OIE National Focal Points on Veterinary products,

conducted in a two years cycle on a regional basis.<sup>40</sup> For several years, the OIE has also initiated collaboration with the World Customs Organisation and included the issue on falsified veterinary drugs in the trainings of Focal Points.

The global programme for the sustainable improvement of Veterinary Service compliance with OIE standards on the quality of Veterinary Services, the evaluation of performance of veterinary services (OIE PVS pathway) intends to reinforce sections related to antimicrobial resistance. Within the OIE Pathway, the OIE has developed guidelines on all the essential elements to be covered in veterinary legislation and supports countries providing advice and assistance to modernise the national veterinary legislation.<sup>3</sup>

(<http://www.oie.int/en/support-to-oie-members/veterinary-legislation/status-of-missions/> )

### **3.6 ENSURING ACCESS AND APPROPRIATE USE OF ANTIMICROBIALS IN THE HUMAN HEALTH SECTOR**

While some antibiotics should be used in a more restrictive and responsible way, affordable access to quality essential medicines, vaccines, as well as diagnostics needs to be increased in both the human and animal sectors. Stewardship and access are closely linked and should not be dealt with separately. Any stewardship measure needs to be designed in a way that does not impede access. In general, stewardship models that are based on persuasive rather than restrictive measures are less likely to impede access to needed treatment as an unwarranted side effect. They are also likely to be more acceptable to human and animal health professionals, patients and farmers and generate more sustainable impact.

If the framework is to define certain stewardship measures and obligations, it needs to clearly define which antibiotics will be submitted to which stewardship regimes. To allow for this, WHO has undertaken a comprehensive review of the antibiotics' chapter in the WHO EML. The objective of the revision was to summarize the evidence supporting antibiotic use for the most common and relevant human infections, define a subset of antibiotics that should always be available in any health facility, and define the antibiotics that should be primarily used to treat infections and those that should be reserved for example through restricted prescribing.<sup>35</sup> The comprehensive review of 25 common syndromes generated a new classification for antibiotics for use in humans: the WHO AWaRe categorization (Box 7).

#### **Box 7. THE AWARE MODEL AS A STARTING POINT FOR STEWARDSHIP**

The 2017 WHO EML revision categorizes antibiotics into three groups (AWaRe: **A**ccess, **W**atch and **R**eserve) that can guide stewardship measures at the local, national and international level.

**Access group:** the group of antibiotics that are recommended as empiric first and second choice antibiotics for treatment of the most common infectious syndromes that should be widely available, at an affordable price, in appropriate formulations and of assured quality. Access to this group of antibiotics should be expanded.

**Watch group:** a subgroup of the Access group of antibiotics, but with higher resistance potential, whose use as first and second choice treatment should be limited to a small

<sup>3</sup> <http://www.oie.int/en/support-to-oie-members/veterinary-legislation/status-of-missions>

number of syndromes or patient groups. These antibiotics which should be prioritized in local and national stewardship and monitoring programmes. This list also includes the highest priority agents on the list of Critically Important Antimicrobials (CIA) for Human Medicine, should also be restricted for the use in animals and plants.

**Reserve group:** antibiotics to be used mainly as ‘last resort’ treatment options, or tailored to highly specific patients and settings, or when alternatives are inadequate or have failed. These antibiotics should be protected and prioritized as key targets of high intensity national and global stewardship programmes to preserve their effectiveness.

### 3.7 ENSURING ACCESS AND APPROPRIATE USE OF ANTIMICROBIALS IN THE ANIMAL AND PLANT SECTORS

In parallel, the global framework will address responsible and prudent use of antimicrobials in the animals and plant sectors, without depriving veterinarians and farmers the needed access to antimicrobial medicines of assured quality. The OIE standards on responsible and prudent use of antimicrobial agents published in the Terrestrial and Aquatic Animal Health Codes cover each step from production to use.<sup>10, 11</sup> The challenge of how to make sure that antibiotics for disease prevention are used under veterinary oversight, but also how to avoid the use for growth promotion through feed and water will require particularly close collaboration with FAO and OIE. As noted above, other relevant standards and instruments will need to be considered to avoid duplication of work. Importantly, as a prerequisite to a reduction in the use of antimicrobials in animal and plant health the following must be taken into consideration: improved biosecurity at sites of primary production, good husbandry and farming practices, veterinary oversight, adequate and safe animal feed, increased animal welfare, improved hygiene along the production and marketing chain, awareness, capacity development among farmers, veterinary paraprofessionals, agronomists, and feed producers.

Over past years, OIE, FAO and WHO have been working to foster appropriate use of antibiotics in the terrestrial and aquatic animal sector and in plant production. In 2003 and 2004, two expert workshops on Non-Human Antimicrobial Usage and Antimicrobial Resistance, jointly convened by FAO, OIE and WHO, recommended that:

- WHO should develop a list of antimicrobial agents critically important for humans with a view to enabling specific resistance-prevention actions for these antimicrobials within the context of non-human use;
- OIE should identify antimicrobials that are critically important in veterinary medicine to complement the identification of such antimicrobials used in human medicine.

OIE adopted, based on scientific criteria, a list of antimicrobial agents of veterinary importance that takes into account the animal health needs of the major food-producing animal species and addresses the needs to treat animal diseases with a global perspective.<sup>12</sup>

Among the OIE List, some classes of antibiotics are considered to be critically important both for human and animal health. This is the case for fluoroquinolones and for the third and fourth generation of cephalosporins. Therefore, these antibiotics should:

- not be used as preventive treatment applied by feed or water in the absence of clinical signs in the animal(s) to be treated; and
- not be used as a first line treatment unless justified and when used as a second line treatment, this should ideally be based on the results of bacteriological tests.

Extra-label/off label use should be limited and reserved for instances where no alternatives are available. Such use should be in agreement with the national legislation in force. The OIE List will be updated taking into account the recent revision of the WHO EML with the participation of FAO and WHO.

In November 2016, OIE published its Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials.<sup>19</sup> Aligned with the Global Action Plan, the strategy recognizes the importance of a “One Health” approach involving human and animal health, as well as agricultural and environmental needs.

Since 2005, WHO has reviewed the WHO List of Critically Important Antibiotics every two years. The objective of this list is to preserve the effectiveness of antimicrobials and to help formulate and prioritize risk assessment and risk management strategies for containing resistance coming from the food chain. The list ranks antimicrobial agents as:

- Critically important
- Highly important
- Important

The Fifth Revision was published in May 2017.<sup>7</sup> This list was also taken into account in the revision of the WHO EML with the critically important antimicrobial agents cross referenced with the WHO EML watch group of antibiotics where resistance is more likely to occur and stewardship measures should be put in place. Overall the intent and purpose of the EML includes different factors than the List of Critically Important Antibiotics, namely efficacy and access while the purpose of the List of Critically Important Antibiotics is to assess the impact of resistance as well as the risk of transmission through the food chain. Hence while there is considerable overlap between the two lists (e.g. between the critically important and the watch group), there will be some differences due to the varying purposes.

**Box 8: WHO List of Critically Important Antimicrobials for Human Medicine 5<sup>th</sup> revision**

Critically important antimicrobials of highest priority are identified based on either of the following: an antimicrobial that is the sole therapy (or one of a few therapies) for treatment of serious bacterial infections in humans, or an antimicrobial that treats infections caused by a bacteria that may be transmitted to humans from a non-human source or that may acquire resistance genes from non-human sources. The classes of drugs that have been identified as the highest priority critically important antimicrobials that align with the WATCH group of the WHO EML AWaRe categorization are quinolones, third- and fourth-generation cephalosporins, macrolides and ketolides, glycopeptides and polymyxins.

A revision of particular importance in the recent list is the inclusion of polymyxins in the highest priority *critically important antimicrobials*, because of the increasing usage of colistin to treat serious infections in humans, the discovery of *mcr1* and *mcr2* plasmid-

mediated resistance gene to colistin, and the identified spread of colistin resistant bacteria via the food chain.<sup>41</sup>

Taking into account the WHO List of Critically Important Antimicrobials for Human Medicine, WHO is developing guidelines to preserve the effectiveness of critically important antimicrobials for human medicine. The guidelines will provide guidance on how to use antimicrobials in food-producing animals. They are being developed following WHO guideline development rules and will be published by the end of 2017.

Following a request from the FAO/WHO Codex Alimentarius Commission (CAC), WHO and FAO in collaboration with OIE will consider providing additional scientific<sup>42</sup> advice as necessary to Codex to support the revision of the Code of Practice to Minimize and Contain Antimicrobial Resistance by the Codex Intergovernmental Task Force on Antimicrobial Resistance (TFAMR) and ensure that it is based on the most recent evidence and scientific analysis regarding foodborne antimicrobial resistance. Scientific advice related to the role of antimicrobials in plant production in foodborne antimicrobial resistance has been prioritized in this request.

Additionally, in response to the request from the CAC and to reflect the needs of relevant stakeholders and the need for a multisectoral approach to address antimicrobial resistance, FAO, OIE, and WHO are considering convening a tripartite expert consultation to develop recommendations relative to both the OIE and WHO Lists of Critically Important Antimicrobials after the next revision of the OIE List.

In addition to antimicrobial resistance specific standards and guidelines developed by the CAC<sup>42</sup> and the OIE<sup>43</sup>, other standards developed by the CAC such as those on good animal feeding and the maximum residue limits of veterinary drugs and pesticides in food are also relevant. Together, these standards and guidelines promote the responsible and prudent use of antimicrobials thereby contributing to reducing the risk of the emergence of resistance or spread of resistant bacteria, including through food, that result from the use of antimicrobial agents in food-producing animals and plants.

Overall, more work is needed to assess the feasibility and impact of measures to foster appropriate use and to identify the most cost-effective measures, including on behavioural change amongst physicians, veterinarians, and farmers, while ensuring continued safe and sufficient food supply, animal welfare and the livelihoods of farmers. Antimicrobial resistance can have a negative impact on the economy and development as a whole as it leads to longer hospital stay, higher risk of death and an overall increase in health-care costs, or unsafe food and loss of efficiency to treat animal diseases. The appropriate use of antimicrobials will not only lead to better health outcomes, but also economic benefits to countries.

The framework will have to define the obligations of different actors along the value chain (Figure 2) taking into account existing standards and guidelines adopted by the FAO, OIE and WHO Member States. Ultimately the question of the instrument of these obligations will have to be answered, see for the different options Figure 1.

### **3.8 DISPOSAL OF PHARMACEUTICAL WASTE**

The WHO is undertaking a systematic review of existing literature on the health impact of pharmaceutical waste, in particular antibiotics persisting in the environment, the health impacts and solutions to mitigate this and reduce the further emergence and spread of antimicrobial resistance. In 2018, WHO will initiate a revision of the Guidelines for Safe Disposal of Unwanted Pharmaceuticals in and after Emergencies in order to provide countries with guidelines on overall safe disposal unused and/or expired pharmaceuticals, in particular antibiotics.

FAO is also reviewing available data on the agricultural sources of antimicrobials and antimicrobial resistance organisms entering the environment and the impact of environmental sources of antimicrobials and antimicrobial resistance on food contamination

Additional elements of the global framework will build on the existing work streams in the three organizations (FAO, OIE and WHO). Appropriate tools and instruments will be developed in consultation with Member States with each organization, and taking into account the WHO AWaRE categorization in the EML, the WHO List of Critically Important Antimicrobials for Human Medicine and the OIE List of Antimicrobials of Veterinary Importance and other regional or national lists supporting the preservation of the efficacy of antimicrobial agents.

## **4. PROPOSED WAY FORWARD**

The development of a global development and stewardship framework is work in progress by FAO, OIE and WHO. All three organizations will proceed further with building elements of the framework and, in parallel, develop the overall concept. As outlined in this document, a number of elements are already in place to guide global development and stewardship:

### **R&D:**

- OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (2017)
- OIE Manual of Diagnostic Tests for Aquatic Animals (2017)
- OIE Report of the meeting of the OIE *ad hoc* Group on prioritisation of the diseases for which vaccines could reduce antimicrobial use in animals (2015)
- WHO Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections (2017)
- WHO Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis (2017)
- WHO/DNDi Global Antibiotic Research & Development Partnership: Business plan 2017-2023.

### **STEWARDSHIP AND ACCESS:**

- Global Action Plan on Antimicrobial Resistance (2015)
- FAO Good agricultural practices (2004)
- FAO Responsible use of antibiotics in aquaculture. Fisheries Technical Paper 469 (2005)

- FAO and IFIF Good practices for the feed Industry – Implementing the Codex Alimentarius code of practice on good animal feeding. FAO Animal Production and Health Manual no.9 (2010)
- FAO and IDF. Guide to good dairy farming practice. Animal Production and Health Guidelines No.8 (2011)
- FAO Action Plan on Antimicrobial Resistance 2016-2020
- CODEX General Principles of Food Hygiene (CXC 1-1969)
- CODEX Code of Practice to Contain and Minimise Antimicrobial Resistance (CXC 61-2005)
- CODEX Guidelines of Risk Analysis of Foodborne Antimicrobial Resistance (CXC 77-2011)
- CODEX Code of Practice on Good Animal Feeding (CXC 54-2004).
- OIE List of antimicrobial agents of veterinary importance (2015)
- OIE Principles for responsible and prudent use of antimicrobial agents in aquatic animals (2011)
- OIE responsible and prudent use of antimicrobial agents in veterinary medicine in terrestrial animals (2012)
- OIE Risk analysis for antimicrobial resistance arising from the use of antimicrobial agents in terrestrial animals (2015)
- OIE Risk analysis for antimicrobial resistance arising from the use of antimicrobial agents in aquatic animals (2015)
- WHO Global principles for containment of antimicrobial resistance in animals intended for food (2000)
- WHO List of critically important antimicrobial for human medicine 5<sup>th</sup> edition (2017)
- WHO Guidelines on use of medically important antimicrobials in food producing animals (2017)
- WHO Essential medicines list – AWaRe categorization of antibiotics (2017)

## **4.1 PROCESS**

### *4.1.1 Secretariat*

A dedicated team has been set up within the WHO Department of Essential Medicines and Health Products to work towards the development of the global framework. The group works closely with the WHO antimicrobial resistance secretariat, and other relevant internal and external entities, namely with FAO and OIE. The latter is an essential prerequisite for success. To ensure close collaboration, the framework will be a standing agenda item in the discussions of the tripartite group. A specific face-to-face tripartite meeting was held on 21 September 2017 and will continue to be arranged when necessary.

The tripartite collaboration will also regularly inform the Interagency Collaboration Group (IACG) and the WHO Strategic Advisory Group (STAG) on progress achieved and challenges encountered drawing on its expertise and guidance where necessary.

WHA68.7 requests the Director-General to submit biennial reports on progress achieved in implementing resolution WHA68.7. These need to be submitted to the Seventieth (2017),



Seventy-second (2019) and Seventy-fourth (2021) World Health Assemblies. The first progress report was provided at the Seventieth (2017) WHA.

The implementation of OIE Resolution No 26 (2015) on combating Antimicrobial resistance and promoting the prudent use of antimicrobial agents in animals and of the OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials, including stewardship, published in November 2016 will be monitored by the OIE World Assembly of Delegates and progress will be reported on a yearly basis.

The implementation of FAO Resolution (4/2015), which recognized the threat that antimicrobial resistance poses to public health and sustainable food production, and of the FAO Action Plan on antimicrobial resistance 2016-2020 will be monitored by the FAO Committee on Agriculture via regular reporting mechanisms.

The United Nations high-level meeting on antimicrobial resistance that took place during the Seventy-first UN General Assembly requested the UN Secretary-General to submit a report for Member State consideration by the Seventy-third session (September 2018 – September 2019) of the General Assembly on the implementation of the declaration which includes the mandate to WHO to finalize the global framework together with FAO and OIE.

#### *4.1.2 Member States*

Further consultations with relevant stakeholders will be considered, including with the animal, plant and environmental sectors, professional associations, civil society and industry in collaboration with FAO and OIE. Involvement of stakeholders will be key for the development of the framework.

Consultation with Member States and feedback to the governing bodies of FAO, OIE and WHO and adoption of any instruments will be organised according to the relevant rules of each organisations. An informal Consultation with Member States, relevant partners and non-state actors in official relationship with WHO will take place 9-10 November 2017 to inform the further work on the framework. Following the consultation, the WHO secretariat together with FAO and OIE will update the roadmap of the framework and prioritize the development and finalization of specific elements of the draft framework as advised by the Consultation.

The FAO, OIE and WHO will ensure appropriate consultation of their respective Member States throughout the process subject to further guidance from their governing bodies.

## **4.2 DEVELOPMENT OF THE OVERALL FRAMEWORK**

In the development of the overall framework, the following key elements are for discussion at the informal Consultation of Member States and relevant partners, 9-10 November 2017:

1. Further develop the concept for the “umbrella” framework based on the feedback received during the consultation. This will include work around the possible form and content of the overarching framework.
2. Develop an appropriate model to incentivize and guide the R&D of antibiotics, diagnostics, vaccines and alternatives for health needs to combat antimicrobial

resistance in the human and animal sector based on an assessment of possible push and pull mechanisms to further enhance R&D.

3. Develop an options paper for global stewardship of antimicrobial medicines for human use with a specific view to ensure access to essential antibiotics to be implemented through possible binding and non-binding instruments. The options will address the key components of the supply chain that include regulation, manufacturing, selection, procurement and distribution of quality antimicrobials that can be adapted to LMICs and facilitate access to essential antibiotics following the EML AWaRE categorization.
4. Develop appropriate instruments to tackle access issues specific to antibiotics and foster wider access to the ACCESS category of the EML AWaRE categorization while ensuring their appropriate use.

Based on the outcome of the informal Consultation, FAO, OIE and WHO will develop different instruments where needed (Figure 1) corresponding to the different key elements (1-4) of the framework in consultation with their Member States.

#### **4.3 TECHNICAL PLAN OF WORK OF THE SECRETARIAT**

Subject to the input that will be received during the informal Consultation of Member States and partners, FAO, OIE and WHO are considering undertaking the following activities:

##### **R&D:**

- In this context, further develop and support GARDP and increase the number of countries and foundations participating.
- Develop a WHO methodology for the development of TPPs to guide R&D and start developing TPPs for priority diseases.
- Continue monitoring the clinical development pipeline of antibiotics and expanding to other areas.
- Develop research collaboration between human and animal sectors on topics of common interest.
- Support investment in vaccine development for priority animal diseases.
- Further proceed with analysis on research needs related to alternatives to antibiotics.

##### **STEWARDSHIP AND ACCESS:**

- Analyse the underlying reason for shortages of antibiotics and propose practical solutions.
- Provide more transparency around pricing and costs of manufacturing antibiotics that can assist countries in negotiating with suppliers and procurement.
- Continue to provide technical assistance to countries to enhance access to affordable treatments, including through the use of TRIPS flexibilities.
- Provide technical assistance to countries in the prevention, detection and response to substandard and falsified medical products.
- Identify a list of simple stewardship measures with the potential to have high impact that are easily implementable in LMICs.
- Develop a tool to implement the new EML AWaRE categorization at the country level.

- Develop practical guidance for LMICS for the implementation of stewardship programmes.
- Provide antimicrobial consumption data to better assess the dimension of the problem of access and appropriate use.
- Provide support to LMICs for implementation of OIE and Codex standards and other relevant international standards.
- Develop good agricultural practices, good regulatory practices and treatment guidelines for animal health that can be adapted for use at country level.
- Provide support to LMICs on disease diagnostics and access to appropriate, good quality, antimicrobials.
- Support countries in the implementation of Responsible and Prudent Use Standards and Guidelines for the use of antimicrobials in animals (terrestrial and aquatics). Support countries to achieve appropriate coverage of well-trained veterinarians and veterinary paraprofessionals

In conclusion, the development of the framework will follow a stepwise approach. Thus, over the next years FAO, OIE, and WHO will develop different elements and their instruments of the tripartite framework, including the overarching framework. Some parts may require a formal endorsement by the governing bodies of the responsible organization(s).

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