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WORLD ORGANISATION  
FOR ANIMAL HEALTH



World Health  
Organization

# Global Framework for Development & Stewardship to Combat Antimicrobial Resistance

## Draft

In collaboration with







Global Framework for  
Development & Stewardship  
to Combat Antimicrobial Resistance

Draft

WHO/EMP/IAU/2018.05

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## Executive summary

Over the past few years, in line with the mandate provided by the Political Declaration of the High-Level Meeting of the United Nations (UN) General Assembly on Antimicrobial Resistance (AMR), the Tripartite organizations – the Food and Agricultural Organization of the United Nations, the World Organisation for Animal Health and the World Health Organization (WHO) – have begun developing a global development and stewardship framework to combat AMR. In the Draft Roadmap for a Global Framework for Development & Stewardship to Combat Antimicrobial Resistance,<sup>1</sup> the Tripartite proposed a modular approach for developing the framework, according to which it would form an “umbrella” uniting different instruments, including existing standards and guidelines. Following a consultation with Member States, relevant international organizations and non-state actors on 9 – 10 November 2017, the Tripartite in collaboration with UN Environment developed a concept for the overarching framework that would define objectives, principles, governance, and possible accountability and financing mechanisms. The aim of this document is to present the possible goals, form, structure and content of such a global framework. The document aims to stimulate a discussion among Member States and stakeholders to chart the way forward, and allow the Tripartite and UN Environment to further develop the concept and content of a global AMR framework.

## Goals of the framework

The goal of the framework is to promote and protect the health of humans, animals, plants and to protect the environment in recognition of their interconnection under the One Health approach. The framework aims to address current gaps in the global governance of AMR through setting overarching goals, norms and standards as well as targets, ensuring their implementation and accountability across countries, organizations and relevant stakeholders. In line with the concept of the umbrella approach, the framework would provide mechanisms for defining appropriate goals, standards and targets to drive change on the national and local level. The framework will:

- support the development of new and affordable diagnostics, treatments and alternatives to antibiotics, and vaccines in the human, animal and plant sectors, where the market does not provide sufficient incentives;
- stimulate the research needed to fill remaining knowledge gaps on AMR, including in the environmental sector;
- adopt and implement standards, regulations and targets for improving access to and responsible and prudent use of antimicrobials<sup>2</sup> and for emissions into the environment based on the national context and needs;
- increase access and reduce shortages of existing essential antibiotics;

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<sup>1</sup> Global framework for development and stewardship to combat antimicrobial resistance: draft roadmap. Geneva: World Health Organization; 2017 ([http://www.who.int/phi/implementation/research/Roadmap-Global-Framework-for-Development-Stewardship-to-combatAMR\\_2017\\_11\\_01.pdf?ua=1](http://www.who.int/phi/implementation/research/Roadmap-Global-Framework-for-Development-Stewardship-to-combatAMR_2017_11_01.pdf?ua=1), accessed 1 September 2018).

<sup>2</sup> See Chapter 1.2: The development and stewardship framework will follow a stepwise approach focusing on health technologies that can be used for human and animal health, and plant protection, starting with antibiotics, including treatment of TB.

- ensure appropriate financial flows to foster the necessary research and assist countries and stakeholders in improving access to needed health products, and in driving change in the responsible and prudent use of antimicrobials in the human, animal and plant sectors;
- establish sustainable global multisectoral governance to coordinate action to combat AMR as a development agenda with an accountability framework; and ensure that all relevant stakeholders – including intergovernmental organizations (IGOs), civil society and the private sector are included in the collective action to combat AMR.

The framework builds on the Global Action Plan on AMR developed by the WHO in collaboration with FAO and OIE and national action plans, focusing on the global level and the roles of the Tripartite organizations and UN Environment. However, a global framework will only provide added value if it drives change and has impact at the local level. Consequently, the fundamental challenge of AMR must be addressed at the level of hospitals, health facilities, and farms and aquaculture facilities, and tools provided directly to them. Setting targets and monitoring them will be one important element in the overall framework. Other elements that can help countries to commit themselves and take action, provide incentives and remove disincentives for appropriate and prudent use will be further developed building on existing national action plans and experience in other areas, including environmental protection and climate change. The framework structure thus would put Member States at the centre, but would involve all stakeholders, including civil society, academia, the private sector, professional associations, and other IGOs beyond the Tripartite and UN Environment as key partners.

The concept encompasses different legal forms and ways to adopt a global framework. As a general rule, the form and method of adoption should reflect the intended purpose and content of the framework. Further discussions both on content and form are needed, recognizing that the ultimate goal should be an ambitious international instrument to protect human health as well as to preserve development achievements such as poverty reduction and to prevent negative impacts of AMR on trade and economic growth.

### **Scope and content**

The development and stewardship framework will follow a stepwise approach focusing on health technologies that can be used for human and animal health, including treatment of TB, and plant protection, starting with antibiotics. The framework can later be expanded to include other antimicrobials. Access, stewardship, and research and development are the main pillars of the framework that will also address the environmental aspects of AMR. The concept also recognizes and includes aspects of infection prevention and control as an essential element for combatting AMR.

One key factor that determines the impact of international instruments is sustainable financing. The concept presents a number of financial mechanisms suggesting a mixed model to meet the financial requirements for the secretariat and governing bodies; driving change towards better stewardship; and financing R&D and access for both animal and human health. Another key condition in maximizing impact is the accountability of the different actors. Independent of

their legal form, international agreements without accountability mechanisms have limited impact. In the future process, appropriate accountability mechanisms that provide oversight and possible complaint procedures and that facilitate enforcement need to be considered.

The document is structured in five chapters describing the concept as such and the potential structure of the framework (Chapter 1), the possible legal form (Chapter 2), followed by three chapters covering the content (research and development (R&D) to foster access, access and stewardship policies, and the environmental aspects of AMR. Two annexes provide an overview of the current R&D landscape and possible financing mechanisms.

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## ABBREVIATIONS

AMR	antimicrobial resistance
BARDA	Biomedical Advanced Research and Development Authority
CARB-X	Combatting Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
ESBL	extended-spectrum beta-lactamase
FAO	Food and Agriculture Organization of the United Nations
FCTC	Framework Convention on Tobacco Control
GARDP	Global Antibiotic Research and Development Partnership
HIC	high-income country
IACG	Inter-Agency Coordination Group
IGO	intergovernmental organization
IHR	International Health Regulation
IPC	infection prevention and control
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
LMIC	low- and middle-income country
NGO	non-governmental organization
OIE	World Organisation for Animal Health
PIP	Pandemic Influenza Preparedness
R&D	research and development
SMEs	small and medium-sized enterprises
SPS	sanitary and phytosanitary
TB	tuberculosis
TISSA	Tripartite Integrated System for Surveillance on AMR and Antimicrobial Use
UN	United Nations
UNGA	United Nations General Assembly
UNICEF	United Nations Children's Fund
WASH	water, sanitation and hygiene
WHA	World Health Assembly
WHO	World Health Organization
WTO	World Trade Organization
WWT	waste water treatment

## Introduction

As recognized by the United Nations General Assembly (UNGA), antimicrobial resistance (AMR) is a threat to achieving the UN Sustainable Development Goals and making progress towards the goal of universal health coverage. AMR endangers current and future treatment options for HIV, tuberculosis (TB) and malaria, as well as other infectious diseases acquired in community and health-care settings. AMR also challenges animal and plant production, in particular the current prevention and treatment options for infectious diseases in veterinary medicine, as well as food safety, nutrition and global food security. Containing AMR is a global public good to ensure effective antimicrobial treatment options for humans, animals and plants.<sup>3</sup> Concerted global multisectoral action is required to combat AMR.

In September 2016, the UNGA issued its Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance, calling upon the World Health Organization (WHO), together with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE),<sup>2</sup> to finalize a global development and stewardship framework based on the initial mandate provided by resolution 68.7 of the World Health Assembly (WHA). Over the past few years, the three organizations (the Tripartite) have begun developing different components of the framework. On 9–10 November 2017 at WHO headquarters in Geneva, the Tripartite presented a Draft Roadmap for a Global Framework for Development and Stewardship to Combat Antimicrobial Resistance<sup>4</sup> at a consultation with Member States, relevant international organizations and non-state actors. The draft roadmap proposed a modular approach for developing the framework, according to which it would form an “umbrella” uniting different instruments, including existing guidelines.

Based on the feedback received, WHO, together with FAO and OIE, and in collaboration with UN Environment developed a concept for the overarching framework that defines objectives, principles, and possible accountability and financing mechanisms. The document provides an overview of the possible goals, form, structure and content of a global framework for development and stewardship to be presented at the second informal consultation of Member States and relevant partners on the global development and stewardship framework to combat AMR which will take place at WHO headquarters on 1–2 October 2018. The document aims to stimulate a discussion among Member States and stakeholders, to provide guidance on the way forward and to allow the Tripartite and UN Environment to further develop the global AMR framework.

The document is structured in five chapters:

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<sup>3</sup> Drug-resistant infections: a threat to our economic future. Washington, DC: World Bank Group; 2017.

<sup>4</sup> Global framework for development and stewardship to combat antimicrobial resistance: draft roadmap. Geneva: World Health Organization; 2017 ([http://www.who.int/phi/implementation/research/Roadmap-Global-Framework-for-Development-Stewardship-to-combatAMR\\_2017\\_11\\_01.pdf?ua=1](http://www.who.int/phi/implementation/research/Roadmap-Global-Framework-for-Development-Stewardship-to-combatAMR_2017_11_01.pdf?ua=1), accessed 1 September 2018).

## **Chapter 1. Why we need a framework**

This chapter describes the goals and scope of the AMR framework, the mandate, how the documentation was developed and proposes a way forward.

## **Chapter 2. What legal form could the framework take?**

This chapter presents different options for how the overarching framework could be legally conceived and ultimately adopted by the Tripartite and UN Environment, and discusses the advantages and disadvantages of possible legal avenues.

## **Chapter 3. Research and development to foster access**

This chapter describes the key challenges and objectives to fostering R&D and access, defines key principles that should apply to the further development of the part of the framework governing access and R&D-related aspects, and contains information on the possible roles of the Tripartite organizations and UN Environment under the framework.

## **Chapter 4. Access and stewardship policies**

This chapter describes the main challenges with respect to access and stewardship policies and detailed information on the possible roles of the Tripartite organizations and UN Environment.

## **Chapter 5. Environmental aspects of AMR**

This chapter was developed in collaboration with UN Environment; it describes the environmental aspects of AMR and contains information on the possible roles of UN Environment and the Tripartite organizations.

## **Annex 1. Selected financing mechanisms**

## **Annex 2. The current R&D landscape**

## **1. Why we need a framework**

This chapter describes the goals and scope of the AMR framework, the mandate, how the documentation was developed and proposes a way forward.

### **1.1 What do we want to achieve?**

The goal of the framework is to promote and protect the health of humans, animals, plants and the environment in recognition of their interconnection under the One Health approach. The framework will also serve as an example of enhanced multisectoral collaboration, which is needed to successfully combat cross-sectoral issues such as AMR and will be an important enabler in reaching the UN Sustainable Development Goals.

In line with the mandate provided by the UNGA and the WHA (see Chapter 1.2), the proposed development and stewardship framework addresses the need to:

- support the development of new and affordable diagnostics, treatments and alternatives to antibiotics, and vaccines in the human, animal and plant sectors, where the market does not provide sufficient incentives;
- stimulate the research needed to fill the remaining knowledge gaps on AMR, including in the environmental sector;
- adopt and implement standards, regulations and targets for improving access to and responsible and prudent use of antimicrobials and for emissions into the environment based on the national context and needs;
- increase access and reduce shortages of existing essential antibiotics;
- ensure appropriate financial flows to foster the necessary research and assist countries and stakeholders both in improving access to needed health products and in driving change regarding the responsible and prudent use of antimicrobials in the human, animal and plant sectors;
- establish sustainable global multisectoral governance to coordinate action to combat AMR as a development agenda with an accountability framework, and ensure that all relevant stakeholders – including intergovernmental organizations (IGOs), civil society and the private sector – are included in the collective action to combat AMR.

These needs have been translated into the 10 main goals of the AMR framework summarized in Box 1.

**Box 1. The main goals of the global framework to combat AMR**

- Countries set individual long-term/realistic targets with a stepwise implementation plan and timeline to reduce the need and, consequently, the use of antimicrobials in the human, animal and plant sectors.
- Increase access to and appropriate use of quality-assured first-line antibiotics for human health and limit the use of reserve/last-resort antibiotics by implementing antimicrobial stewardship programmes.
- Increase access to and reduce shortages of essential and effective antibiotics by ensuring their continued availability.
- Implement international codes and standards to promote worldwide responsible and prudent use of antimicrobials in animals (terrestrial and aquatic) and plants.
- Phase out the use of antibiotics for animal growth promotion and plant protection in the absence of risk analysis.
- Use of fluoroquinolones, third- and fourth-generation cephalosporins, and colistin should be guided by the following considerations:
  - Do not use as preventative treatment applied by feed or water.
  - Do not use as first-line treatment unless justified.
  - Use as second-line treatment should ideally be based on bacteriological tests.
  - Extra-label or off-label use should be reserved to instances where no alternatives are available.
- Increase investment and capacity building in clean water, sanitation and hygiene (WASH), infection prevention and control (IPC), vaccination programmes, and good animal (terrestrial and aquatic) husbandry practices and biosecurity measures where needed to limit the emergence and spread of AMR.
- Increase investment in developing new antibiotics, alternatives to antibiotics, diagnostics and vaccines for use in humans, animals and plants.
- Increase investment, research and surveillance of antimicrobials and resistant microorganisms in the environment to better understand the role of the environment in the dynamics of AMR and the relevance of the contributions from anthropogenic sources.
- Limit the release of active pharmaceutical ingredients into the environment, especially into water, and ensure environmentally sound management of obsolete stocks.

## **1.2 Scope of the global development and stewardship framework**

Resolution WHA68.7 takes a broad approach, encompassing new antimicrobials, diagnostic tools, vaccines and other interventions. The term “antimicrobials”, which subsumes antibiotics and other medicines, includes antiviral, antifungal, antibacterial and anti-parasitic agents. All such antimicrobials, when over- or misused, contribute to the emergence and spread of resistance, but there are large differences as well.

- For some of the most worrying conditions and diseases in humans, such as HIV/AIDS, malaria, TB and neglected tropical diseases, special initiatives have been established to foster the development of new treatments and access to existing ones.
- The commercial incentive to invest in developing new treatments, diagnostics and vaccines varies significantly between, for example, neglected tropical diseases or hepatitis C and B.
- Not all treatments are used in parallel in the human, animal and plant sectors.
- The speed with which resistance emerges and spreads varies considerably from one pathogen and drug to another.

As suggested in WHA report A69/24 Add.1 and the Draft Roadmap, and to avoid duplicating existing initiatives, the development and stewardship framework will follow a stepwise approach, focusing on health technologies that can be used for human and animal health, and plant protection, starting with antibiotics, including treatment of TB. The framework can later be expanded to include other antimicrobials.

The inclusion of the environmental aspects of AMR in this proposal expands on the original scope of the framework and follows the recent directive provided to UN Environment to work on specific areas of AMR. The UN Environment Assembly at its third session adopted resolution EA.3/Res.4<sup>5</sup> on Environment and Health, providing UN Environment for the first time with a clear mandate to contribute to ongoing work carried out on AMR at the global and national levels by UN agencies and relevant stakeholders, in particular through the development and subsequent implementation of national action plans on AMR. This proposal also recognizes and includes aspects of IPC and WASH as crucial for combatting AMR.

## **1.3 Relationship with the global action plan on AMR**

The Global Action Plan on AMR that was agreed by the WHA and formally endorsed by the FAO and OIE membership is an ambitious blueprint for tackling AMR in many areas at the international and national levels. Nonetheless, the WHA agreed to develop a global AMR framework to tackle remaining challenges and to further accelerate discussions on how countries can collectively and individually address the challenges of combatting AMR.

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<sup>5</sup> UNEP/EN.3/Res.4. Environment and health. New York: United Nations Environment Programme; 2017 (<https://papersmart.unon.org/resolution/uploads/k1800154.english.pdf>, accessed 1 September 2018).

The proposed concept for a global AMR framework addresses some of the gaps in the Global Action Plan on AMR. It also recommends additional steps that bring AMR governance to the next level by providing more clarity on common norms and standards, and ensuring accountability across countries, organizations and additional stakeholders, where needed. The proposed framework does not duplicate or replace the Global Action Plan. Rather, it builds on ongoing initiatives that stem from the Global Action Plan, including national action plans. In addition, by filling gaps, the political declaration of the high-level meeting of the UNGA aims in particular to strengthen R&D, access and stewardship, and environmental aspects across the human, animal, plant sectors to combat AMR through collective and sustainable action. The proposed framework thus keeps Member States at the centre, but aims to expand the stakeholders to include civil society, academia, the private sector, professional associations, NGOs and other IGOs as partners through an appropriate multisectoral engagement mechanism.

Monitoring and evaluation of the implementation and impact of the future AMR framework should be based on the framework for monitoring and evaluation of the Global Action Plan on AMR to avoid any duplication.

#### **1.4 How this document was developed**

Since the adoption of the Global Action Plan on AMR, the Tripartite has carried out technical work and built specific elements that could form part of the framework and that were described in the Draft Roadmap. This approach avoided any slowdown in progress on the necessary technical work of the three organizations and Member States on AMR resulting from the political discussions around a possible framework.

This document was jointly developed by the Tripartite, in close consultation with UN Environment and is based on a One Health approach, including the human, animal, plant and environmental health sectors. The discussion papers published by the Inter-Agency Coordination Group (IACG) on AMR were taken into account.

#### **1.5 The way forward**

If Member States agree to take the framework process forward, more discussion and input from countries and other stakeholders will be needed to further develop the overall concept, content, roles and responsibilities of Member States, other IGOs and stakeholders, including civil society and industry. The elements will have to be developed over time through a consultative process that WHO could lead together with FAO, OIE and UN Environment.

Next steps could include the Tripartite and UN Environment to:

- further develop the overall concept and legal form based on the feedback received during the 1–2 October 2018 consultation;
- hold additional informal consultations with Member States on specific aspects of the framework to allow for robust discussions on process and content;
- hold consultations with other relevant partners, including civil society, the private sector, NGOs, academia and professional organizations;



- have a continuous dialogue with Member States and civil society to help guide the discussions; and
- establish and agree on a timeline for completing a draft framework and subsequent negotiation process to reach agreement as efficiently as possible, and keep the focus on the overarching goal, which is a robust, useful instrument for collective action on AMR.

## **2. What legal form could the framework take?**

The mandate to develop the framework does not specify its legal nature. As outlined in the Draft Roadmap, the framework is envisaged to form an umbrella uniting different instruments that could take different legal forms. The legal nature of the overall framework should ultimately follow the content of the framework. This chapter presents different options on how the overarching framework could be conceived and eventually adopted, discussing the pros and cons of possible legal avenues.

### **2.1 Scope of the framework and competencies of relevant organizations and agencies**

As conceived, the framework is anticipated to spell out the principles and responsibilities of Member States, IGOs and public and private stakeholders. With regard to organizations, the framework's content spans the mandate of the Tripartite, as well as UN Environment, including:

- WHO as the lead agency for human health and related issues;
- OIE as the lead agency mandated to develop and disseminate animal health- and welfare-related standards;
- FAO as the lead agency for food and agriculture; and
- UN Environment as the lead agency responsible for the coherent implementation of the environmental dimension.

The framework elements fall within the mandate of all four organizations and will cover the responsibilities for all organizations as well as their respective Member States.

### **2.2 Existing Tripartite and UN Environment international framework agreements**

In considering the approach to developing this framework, a number of different approaches have been taken by the Tripartite and UN Environment. These are identified in Table 1. The normative instruments listed in rows 1 and 2 of Table 1 are not legally binding, whereas those listed in rows 3 and 4 are. However, non-legally-binding instruments can take on a legally important status if referred to or incorporated by a legal instrument. For example, the World Trade Organization's (WTO's) Agreement on the Application of Sanitary and Phytosanitary Measures (SPS) recognizes the Terrestrial and Aquatic Animal Health Codes and Manuals, which include the OIE Standards for Quality of Veterinary Services, as a legitimate basis for countries to enact sanitary measures. The SPS agreement also names the joint FAO/WHO Codex Alimentarius as the relevant standard-setting organization for food safety with specific reference to standards, guidelines and recommendations established by the Codex Alimentarius Commission.

**Table 1. International framework agreements adopted or endorsed by the governance structures of the Tripartite organizations or UN Environment**

Type of instrument	Examples
1. Frameworks, strategies, plans of action, voluntary guidelines, codes and standards	<p><i>Frameworks</i></p> <ul style="list-style-type: none"> <li>- WHO Pandemic Influenza Preparedness Framework for sharing influenza viruses and access to vaccines and other benefits</li> <li>- FAO/OIE Global Framework for the Progressive Control of Transboundary Animal Diseases (2004)</li> <li>- Strategic Approach to International Chemicals Management adopted in 2006 as a policy framework</li> </ul> <p><i>Strategies and action plans</i></p> <ul style="list-style-type: none"> <li>- WHO Global Action Plan for the 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> <li>- WHO Global Action Plan on Antimicrobial Resistance (2015) endorsed by OIE and FAO</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> <li>- WHO Global Code of Practice on the International Recruitment of Health Personnel</li> <li>- OIE Performance of Veterinary Services Pathway</li> <li>- FAO International Code of Conduct on Pesticide Management</li> <li>- Codex Alimentarius Code of Practice to Contain and Minimize Antimicrobial Resistance</li> </ul> <p><i>Standards</i></p> <ul style="list-style-type: none"> <li>- OIE Standards on the Quality of Veterinary Services</li> <li>- OIE Terrestrial and Aquatic Code chapters on responsible and prudent use of antimicrobial agents in animals. <ul style="list-style-type: none"> <li>* Codex Alimentarius: General Standard for Contaminants and Toxins in Food and Feed (1995/2017)</li> <li>* General Standard for the Labelling of Prepackaged Foods (1985/2010)</li> <li>* Maximum Residue Limits and Risk Management Recommendations for Residues of Veterinary Drugs in Foods (2017)</li> </ul> </li> </ul>
2. Regulations	- WHO International Health Regulations (2005)
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>- United Nations Framework Convention on Climate Change</li> <li>- FAO International Treaty on Plant Genetic Resources for Food and Agriculture</li> <li>- Vienna Convention for the Protection of the Ozone Layer</li> <li>- Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and Their Disposal</li> <li>- Stockholm Convention on Persistent Organic Pollutants</li> <li>- Convention on Biological Diversity</li> </ul>

All four organizations are mandated to adopt, endorse and promulgate non-binding technical guidance and norms, including codes of conduct. Additionally, FAO, WHO and UN Environment have the mandate to develop and approve legally binding instruments and submit them to their member states. FAO's constitution refers to these kinds of instruments in articles XIV. In WHO, these instruments fall under the rubric of normative mechanisms foreseen in articles 19–23 of its constitution. UN Environment derives its authority to negotiate and implement internationally legally binding instruments from the UN Charter. In all cases, whether an instrument is legally binding or not, the content of a given text must fall within the technical mandate of the organization(s) developing and adopting it.

### 2.3 Options for the global development and stewardship framework

Given the range of authorities/powers of the Tripartite organizations and UN Environment, the proposed global AMR framework might therefore be designed in various ways, including:

- as a non-legally-binding instrument constituted as, or approved by, a resolution of the governing bodies of the Tripartite, as with Global Action Plan on AMR, the International Code of Conduct on Pesticide Management or the standards, codes of practice, guidelines and other recommendations approved by the Codex Alimentarius Commission or the Pandemic Influenza Preparedness (PIP) Framework;
- as a set of legally binding regulations such as the WHO International Health Regulations (IHR) (2005); or
- as a legally binding convention or treaty such as the WHO Framework Convention on Tobacco Control (FCTC) or the FAO International Treaty on Plant Genetic Resources for Food and Agriculture.

Each of these options would be developed or negotiated, as relevant, through distinct procedural pathways.

- **Non-legally binding:** The resulting text would be endorsed as a non-binding global framework, for example as a Tripartite and UN Environment code of conduct, by the governing bodies of the organizations following the example of the Global Action Plan on AMR that was adopted by the WHA and subsequently by the FAO and OIE governing bodies through resolutions.
- **WHO Regulation:** Subject to its final content and design, such a global AMR framework could be developed under WHO's auspices pursuant to article 21 (a) as "procedures designed to prevent the international spread of disease". In this case, the governing bodies of FAO and OIE could endorse this instrument via mechanisms (e.g. resolutions, decisions, etc.) appropriate to their own governance procedures.
- **Convention:** Either WHO or FAO could develop the framework as a convention. The WHA would have the authority to adopt a global development and stewardship framework to combat AMR in the form of a convention or agreement under article 19 of the WHO Constitution. Alternatively, a convention could be negotiated by FAO under its constitutional article XIV, as an agreement "concerning questions relating to food and agriculture which are of particular interest to Member Nations" and submitted to FAO Member States "for consideration with a view to their acceptance by the appropriate

constitutional procedure”. Article XIV of the FAO Constitution requires that the new instrument create “financial or other obligations going beyond those already assumed” under the constitution itself and thus must include new obligations to be justified. In either scenario, the instrument could be submitted to the governing body of the other organizations for adoption, and OIE could present it to its governance structures for relevant endorsement.

## **2.4 Discussion of different legal options**

The question of non-binding instruments versus legally binding instruments is often presented as binary, with legally binding instruments being perceived as stronger and having more impact. However, the reality is not quite so black and white.

- Convention or treaty

If adopted as a WHO convention or FAO treaty, the framework would set internationally binding law by establishing rights and obligations for each party to the convention and among and between those parties. Depending on the terms negotiated, typically a convention or treaty needs a minimum number of countries to “opt in” or become party to – that is to ratify, accede to, approve or accept the convention – before it would “enter into force” and become an active, binding piece of international law. The processes of ratification, accession, approval or acceptance of a convention are largely undertaken through a decision by national government, including in many cases parliaments rather than, for example, the governing body of an international organization. This could ensure a whole-of-government approach to AMR at the country level.

While this threshold may seem high, in recent decades such binding agreements have often been designed to enter into force relatively quickly by containing “softer” obligations rather than a full suite of firm commitments. This approach builds on the early approach to multilateral environmental agreements which pioneered the innovation of framework conventions that provided countries with the opportunity to agree on an approach and principle, as well as a mix of hard and qualified obligations.

- WHO FCTC

One example of this approach is the FCTC, which entered into force in 2005 and contains formulations stipulating that parties shall implement a given provision “as appropriate” or “as determined by national law” or “in accordance with national law”. By contextualizing international commitments and giving parties the opportunity to tailor implementation to national circumstances, this approach to making international law has achieved broad membership, wide acceptance and sustained implementation in a variety of technical areas. At the same time, to achieve nearly universal membership, the obligations that are included in these kinds of treaties are often quite diluted.

- Paris Agreement

Recently, a new approach to setting international obligations through treaties has emerged with the Paris Agreement under the UN Framework Convention on Climate Change. Rather than include language in the treaty itself that contextualizes each obligation to country circumstances, this new generation of treaties stipulates areas of obligation, but then requires parties to set their own standards/targets in a particular area. Those self-described standards/targets then become legally binding under international law in that country. The multidimensional nature of AMR and the persistence of scientific uncertainties make it challenging to set static targets, but different countries have already demonstrated that this is possible on a national level. The model of the Paris Agreement thus could be used for AMR where countries would have to set their own targets adapted to their situation and needs in human and animal health, plant production and the environment in their national action plans on AMR and/or implementation plan. In this model, the challenge is to get countries to make sufficiently robust commitments.

Notably, while both the WHO FCTC and Paris agreements took new approaches to treaty making, this has not necessarily lessened the impact of the instruments, as qualifying the obligations made it easier for countries to become party to them, broadening the geographic scope of both instruments. In such a case, each country may fashion a unique implementation process, but that process will be guided by the principles and objectives of the convention to which the country is party, as would related national policy decisions, ensuring that the ultimate goals are all shared.

- WHO regulation

Another legally binding option is a regulation negotiated and adopted under Article 21 of the WHO Constitution that becomes automatically binding on all WHO Member States, unless a state affirmatively chooses to opt out, as with the IHR (2005). In practice, this means that once adopted by the WHA, such regulations enter into force according to a timeline rather than to a threshold membership number and apply to all Member States unless they actively articulate a wish for them not to. The IHR (2005) achieved near-total universality only two years after the negotiations concluded. Regulations like these have many of the same advantages and disadvantages as a convention and often have similar qualifiers in the text of the obligations. The main advantage is that under the WHO Constitution, such regulations are binding unless countries take action to opt out, which increases membership and accelerates the timeline for entry into force.

- Non-binding

Non-binding instruments have often been used to set-up common goals and guide countries on how national policies and legislation should be targeted in a specific area. Non-binding instruments do not include binding obligations. On the other hand, binding instruments are regularly considered to have higher rates of compliance and greater impact. However, in practice, much more depends on the actual content of the instrument, whether binding or not and the countries' political consensus to work towards its implementation.

Depending on their design, any kind of instrument may have incentives and/or financial mechanisms that make them appealing across most countries and increase the likelihood of implementation. An example of this is the non-binding WHO PIP Framework, which has set up a functioning system on virus sharing with annual contributions paid by the users of the system. The PIP Framework is widely considered a successful model that may have broad application in other areas. The Global Action Plan on AMR was a good example of an instrument that had an impact as the Tripartite organizations' memberships endorsed its principles. Other examples are the various codes of conduct adopted by WHO, FAO and OIE in different areas.

- *Discussion*

Quantitative evaluations of international treaties in different topical areas have produced mixed results in real-world settings, indicating that even binding treaties may have little or no effect. For example, despite having agreed, negotiated objectives and commitments, treaties may not materially contribute to achieving goals like reducing pollution or improving life expectancy or infant mortality.<sup>6</sup> This may be because the topics themselves do not have broad consensus or agreed solutions, the structure and content of the instrument itself may not create appropriate incentives or disincentives, or the evolving geopolitical or economic context may have shifted the bar or the possibilities.

At the same time, non-binding instruments do not necessarily guarantee a more impactful, cost-effective approach. It is worth repeating that content is as important in determining a given instrument's impact as its final legal form. Another key factor in determining the impact of international instruments is sustainable financing. Typically, international legal instruments – whether legally binding or not – will have limited impact in the absence of a sustainable financing mechanism to facilitate implementation of the various activities and obligations (see Annex 1 for proposed financing options). Finally, the accountability of the different actors is critical for maximum effect. Independent of their legal form, international agreements without accountability mechanisms have limited impact.

The advantages of non-binding instruments are a potentially simpler and faster process of negotiation, and conclusion. Additionally, although there is scope for flexibility in legally binding instruments, the greater flexibility of non-binding instruments might better suit the current dynamic nature of the science of AMR, given that new evidence could have a bearing on obligations. On the other hand, a binding instrument automatically would have a defined membership and its own distinct governing body, which would simplify the governance structure.

Regardless of the approach chosen, the framework will constitute the umbrella agreement under which areas in which scientific evidence is evolving will be regulated by other instruments such as evidence-based guidelines and standards that would be updated regularly.

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<sup>6</sup> S. J. Hoffman and J. A. Røttingen. Assessing the expected impact of global health treaties: evidence from 90 quantitative evaluations. *American Journal of Public Health*. 2015;105: 26–40.

## **2.5 Governance**

The legal form will also impact the governance of the AMR Framework. As is the case with the Tripartite organizations, Member States would exercise ultimate oversight over the implementation of the framework. This would be straightforward if the framework is adopted as an international instrument with a specific membership, for example as a treaty, as the parties to the instrument would then form its governing body. Its membership would be distinct from the membership of FAO, OIE, WHO and UN Environment depending on which countries would join, ratify or accept the new instrument. The situation would be more complex if the framework would be adopted by the Tripartite and UN Environment and would not have a distinct membership. In that case oversight would have to be exercised by the governing bodies of the organizations, which would blur responsibilities/commitments and would be more difficult to coordinate. To preserve effectiveness and ensure impact, it is essential that responsibilities are clearly attributed and that one governing body supervises the implementation of the framework.

## **2.6 Conclusion**

Both the WHA and the UN High-Level Declaration on AMR left the legal form of the future global AMR framework open. Different options, along with their individual strengths and weaknesses, need to be taken into account. As a general rule, the form and method of adoption should reflect the intended purpose and content of the framework. Further discussions both on content and form are needed. Such discussions must also recognize that the ultimate objective of action taken on AMR is to protect human health, including food security and to preserve achievements in development such as poverty reduction and to prevent negative impacts of AMR on trade and economic growth. Appropriate accountability mechanisms that provide oversight, possible complaint procedures and facilitate enforcement also need to be considered. Any future instrument should be negotiated under the auspices of the Tripartite endorsed by the WHA and the governing bodies of FAO, OIE and UN Environment, as it will touch on the mandates of all organizations. The guidance from the IACG on AMR should also be taken into account.





### 3. Research and development to foster access

This chapter describes the key challenges and objectives to fostering R&D and access, defines key principles that should apply to the further development of the part of the framework governing access and R&D-related aspects, and contains information on the responsibilities of the Tripartite and UN Environment under the framework. The role and responsibility of Member States and other stakeholders as well as additional norms and standards that might be needed will have to be developed and support provided for their implementation.

#### 3.1 Key challenges and objectives

It is widely acknowledged that the current antimicrobial development pipeline is insufficient to address increasing resistance of priority pathogens, especially for multidrug-resistant Gram-negative bacteria. Following the golden era of R&D of new antibiotics in the mid-20<sup>th</sup> century, scientific challenges and lack of investment resulted in very few new classes of antibiotics being developed. The fact that new antibiotics must compete with existing generic treatments and should be used prudently to slow the development of resistance limits their market potential. Consequently, private investment is insufficient to fill the current R&D gap, although the market potential varies widely between new, superior antibiotics and “me-too” antibiotics. The market-driven R&D model also does not direct investment to the most urgent public health needs, such as fighting multidrug-resistant pathogens, where the patient population is still relatively small. More affordable point-of-care diagnostics in both human and animal health are also urgently needed to support responsible and prudent use of antimicrobials.

In addition to product development, critical needs include applied and interventional research on preventing AMR development and transmission, promoting appropriate and prudent use, improving animal husbandry and preventing hospital-acquired infections. In many cases, improved IPC measures will represent better value for money and a quicker solution than developing new health technology solutions.

Available evidence on the human health and environmental impact of antimicrobial residues in the environment is limited, particularly in terms of understanding the role of environmental pollution in the development of AMR; the availability, tools for and use of environmental surveillance of anthropogenic-sourced antimicrobials; and understanding of the long-term effects of antimicrobials in the environment on the health of humans, animals, plants and ecosystems.

The lack of investment in R&D to address AMR has been discussed in many political fora, and a number of reports have analysed the problem and suggested solutions. Examples include the *Review on antimicrobial resistance* (the Jim O’Neill report<sup>7</sup>) and the Drive-AB Report *Revitalizing the antibiotic pipeline*.<sup>8</sup> It is broadly acknowledged that a combination of push

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<sup>7</sup> J. O’Neill. Review on antimicrobial resistance: tackling drug-resistant infections globally. London: Wellcome Trust; 2016 ([https://amr-review.org/sites/default/files/160525\\_Final%20paper\\_with%20cover.pdf](https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf), accessed 8 July 2018).

<sup>8</sup> C. Årdal, D. Findlay, M. Savic, Y. Carmeli, I. Gyssens, R. Laxminarayan, K. Outterson and J. H. Rex. Revitalizing the antibiotic pipeline: stimulating innovation while driving sustainable use and global access (DRIVE-AB Report). Brussels: DRIVE-AB; 2018 (<http://drive-ab.eu/news/drive-ab-report/>, accessed 13 August 2018).

strategies (e.g. direct funding, research grants, government laboratories or tax credits) that support research inputs and pull strategies (e.g. milestone prizes, new reimbursement models or market entry rewards) that reward research output would stimulate investment and the development of new products. While countries have not reached consensus on how to sustainably finance new pull and existing push mechanisms, in recent years a number of regional and global initiatives have been established (see Annex 2). Annex 1 presents a possible mix of models to expand investment into R&D.

### **3.2 Basic principles for needs-driven R&D that fosters access to new products**

- Invest in R&D for new antimicrobials, improvement and reformulation of existing antibiotics, alternatives to antimicrobials, diagnostic tools, vaccines for human, animal and plant health with the ultimate goal of promoting access to affordable health products in the human and animal health and plant protection sectors. This is a shared responsibility that requires coordinated effort.
- R&D should be needs-driven, evidence-based and guided from the outset by principles of affordability, effectiveness and efficiency, equity, and appropriate and prudent use of antimicrobials.
- FAO, OIE and WHO should define R&D priorities and roadmaps, analyse gaps in the pipeline and develop target product profiles to steer R&D investment towards public health priorities.
- Public investment in R&D needs to increase and market incentives should be preserved.
- New partnerships can spur innovation in AMR control across plant production, the environmental sciences, and human and animal health sectors.
- The cost of investing in R&D on AMR should be delinked from the price and volume of sales to facilitate equitable and affordable access and to avoid perverse incentives that lead to excessive use.
- All relevant stakeholders, including governments, industry, NGOs, academic institutions and the private sector must be involved.
- The value of new antimicrobials and how they are paid for must be redefined to align market forces with public health priorities.
- Uptake of vaccines that have the potential to reduce the use of antimicrobials should be explored.
- Regulatory requirements must be revisited to facilitate the approval of new antimicrobials without compromising their safety and efficacy profile and to develop appropriate regulatory pathways for alternative products.

### **3.3 Framework targets for R&D**

Targets are an essential tool in setting objectives, driving change and measuring progress. Targets for overall R&D could be global in nature and could be formulated in different ways, for example:

- increasing the number of innovative treatments in the clinical pipeline that target priority pathogens to/by [absolute number or percentage of increase] by [year];

- increasing public/private investment in the development of new treatments, diagnostics and vaccines to combat AMR in the human, animal and plant sectors, following FAO, OIE and WHO priorities where available to/by [absolute number or percentage of increase] by [year]; and
- increasing public investment in new and alternative terrestrial and aquatic animal and plant treatments as well as in waste management solutions.

Targets for R&D must be in line with the global indicators for monitoring and evaluation of the Global Action Plan on AMR and could be monitored by the Global AMR R&D Hub.

### 3.4 Responsibilities of the Tripartite and UN Environment

Table 2 summarizes the responsibilities of the Tripartite and UN Environment. The biggest burden of implementation, however, will have to be borne by Member States and other stakeholders, including increased funding for R&D and implementation. Next steps will thus focus on identifying responsibilities of Member States in particular and other IGOs and relevant stakeholders.

**Table 2. R&D-related responsibilities of the Tripartite and UN Environment**

Goal	Objectives (outputs)	Responsibilities
<b>3.4.1 R&amp;D coordination</b>	Effective global coordination of R&D activities and financing	<b>Tripartite:</b> Provide support to global coordination of R&D activities (e.g. Global AMR R&D Hub; STAR-IDAZ International Consortium on Animal Health)
<b>3.4.2 R&amp;D prioritization</b>	Alignment of R&D efforts to combat AMR	<p><b>WHO:</b> Update the priority pathogens list on a regular/timely basis to guide R&amp;D efforts.</p> <p>Undertake a landscape analysis of in vitro diagnostics (IVDs) for AMR and develop an R&amp;D priority list for AMR IVDs.</p> <p><b>FAO:</b> Improve knowledge of antimicrobial use and AMR in plant production.</p> <p>Develop a list of antimicrobials used for plant protection.</p> <p><b>FAO/OIE:</b> Prioritize rapid diagnostics for high-impact diseases for which antimicrobials are currently overused/misused and research into alternatives to antimicrobials, including non-specific stimulation of immune systems in animal health.</p> <p><b>OIE:</b> Develop a list of prioritized diseases for which vaccines could reduce antimicrobial use in animals.</p>
<b>3.4.3 Gap analysis for R&amp;D</b>	Review of R&D landscape and identification of gaps	<p><b>WHO:</b> Update the antibacterial pipeline analysis on a regular/timely basis and provide an overview of the pre-clinical pipeline.</p> <p><b>FAO:</b> Review the current situation and identify gaps in the R&amp;D landscape for plant protection practices.</p>

<b>3.4.4 Target definition</b>	Targeted R&D efforts to develop new prevention tools and treatments to combat AMR	<b>Tripartite:</b> Develop target product profiles (TPPs) for priority pathogens to guide R&D efforts.
<b>3.4.5 Regulatory aspects</b>	Strengthening of regulatory framework, including streamlined regulatory pathways for clinical trials	<p><b>Tripartite:</b> Support the implementation of Codex Alimentarius texts relating to AMR.</p> <p><b>WHO:</b> Provide support to improving clinical trial design/regulatory review and oversight.</p> <p><b>OIE:</b> Provide support for the development and implementation of Veterinary International Conference on Harmonization (VICH) guidelines, standards and norms related to AMR.</p>
<b>3.4.6 R&amp;D mechanisms</b>	Enhanced partnerships and financing mechanisms to support R&D	<p><b>WHO:</b> Continue to support Global Antibiotic Research and Development Partnership (GARDP) and similar initiatives in developing new treatment options with an access and stewardship strategy.</p> <p><b>FAO:</b> Support resource mobilization for R&amp;D focused on animal health/production needs.</p>

## 4. Access and stewardship policies

This chapter describes the main challenges with respect to access and stewardship policies and actions and detailed information on the possible roles of the Tripartite organizations and UN Environment. The role and responsibility of Member States and other relevant stakeholders as well as additional norms and standards that will be needed will have to be further developed and their implementation supported.

### 4.1 Key challenges and objectives

Access to affordable, quality assured antimicrobials remains a major problem, particularly in low- and middle-income countries (LMICs), with barriers to access rooted inter alia in health systems, procurement and supply chain management, affordability, deficiencies of national regulatory systems, reported national and global shortages of certain antimicrobials, and the circulation of substandard and falsified antimicrobials. On the flip side, the misuse and overuse of antimicrobials also remains a challenge, and efforts are needed to ensure more restrictive and responsible use of antimicrobials across the human, animal and plant sectors.

Stewardship describes the careful and responsible management of something entrusted to one's care, which for antibiotics and other antimicrobials means appropriate use to improve human, animal or plant health outcomes while minimizing the development and spread of AMR and ensuring food safety/security. In this context, antimicrobial stewardship is an overarching term that includes practices to foster appropriate/prudent use in human and animal health and plant protection. The goal of stewardship is to improve the quality and cost-effectiveness of care and patient/animal outcomes, and decrease the further emergence and spread of AMR.<sup>9</sup>

The content of antimicrobial stewardship programmes depends heavily 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
- community level: fostering access and appropriate use in primary health care settings and in animal health through awareness raising, training and targeted interventions.

The AMR framework supports the whole lifecycle of a product from development, authorization/registration, regulation, manufacturing, promotion, selection, procurement and supply, distribution and appropriate/prudent use, and disposal to address AMR in the human and animal health and plant protection sectors as described in the Draft Roadmap.

Stewardship policies need to be designed in a way that ensures that access to antimicrobials is not compromised and is expanded where needed. In addition, effective IPC, WASH measures,

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<sup>9</sup> C. Van Dijck, E. Vlieghe and J. A. Cox. Antibiotic stewardship interventions in hospitals in low- and middle-income countries : a systematic review. *Bull World Health Org.* 2018;96:266–80.

waste water treatment and good animal husbandry and agriculture practices also need to be in place to prevent infections and the emergence and spread of AMR in the first place.

Affordable access to existing and new antimicrobials, vaccines and diagnostics should be a global priority and should take into account the needs of all countries. For human health, the *WHO global strategy and plan of action on public health, innovation and intellectual property* and its internationally agreed follow-up processes need to be taken into account.

#### **4.2 Key principles and goals**

- Universal health care provides the best enabling framework for addressing AMR in the human health sector.
- Increase access to and reduce shortages of essential and effective antibiotics by ensuring their continued availability.
- Promote access to and appropriate use of quality assured first-line antibiotics for human health and limit the use of reserve/last-resort antibiotics through the implementation of stringent regulatory frameworks and stewardship programmes.
- Implement international codes and standards to promote responsible and prudent use of antimicrobials in animals (terrestrial and aquatic) and plants worldwide.
- Phase out the use of antibiotics for animal growth promotion and plant protection in the absence of risk analysis.
- Use of fluoroquinolones, third- and fourth-generation cephalosporins, and colistin should be guided by the following considerations:
  - Do not use as preventative treatment applied by feed or water.
  - Do not use as first-line treatment unless justified.
  - Use as second-line treatment should ideally be based on bacteriological tests.
  - Extra-label or off-label use should be reserved to instances where no alternatives are available.
- Implementation of the International Health Regulation (IHR) and OIE Performance of Veterinary Services pathway can accelerate AMR action.
- Build laboratory capacities for AMR detection and surveillance and create synergistic national/regional laboratory networks.
- Build capacity for collecting and disseminating national and local antimicrobial consumption and use data in the human and animal health sectors to inform and monitor stewardship and responsible and prudent use activities.
- Increase investment and capacity building into WASH, IPC and good animal (terrestrial and aquatic) husbandry practices and biosecurity measures in countries to limit the spread of AMR.
- All countries should implement responsible and prudent use standards in human and animal health and in plant production.
- Strengthen country surveillance and monitoring systems for tracking the consumption and use of antimicrobials and the spread of AMR in humans, animals and plants as well as in other environmental matrixes.

#### 4.1.1 Surveillance

The Tripartite is working side by side on reviewing areas for improvement, and challenges and recently made proposals on the development of a Tripartite global platform as a precursor to the development of TISSA.<sup>10</sup> This system would involve agreed monitoring using standardized methodology for data sharing and provide information needed to inform strategies against AMR locally, regionally and globally. The Tripartite also agreed on the future establishment of a Tripartite Advisory Group on Intersectoral Support on AMR that will provide technical guidance and input to the Tripartite activities at the human-animal-plant-environment interface, aimed at containing AMR.

#### 4.1.2 Stewardship and access

While global guidance such as the WHO Essential Medicines List AWaRe Categorization and standards regarding which antibiotics to use for animals and plants can support access, appropriate use and stewardship, implementation on the ground in farms and hospitals remains a key challenge. The regulatory frameworks need to be strengthened to support their implementation, including restricting over-the-counter sales of antimicrobials where access is not an issue and phasing out the use of antimicrobials as growth promoters in the absence of risk assessment.

To make a difference on the national and facility level, the global AMR framework will have to include action at the regional or community level, building on national action plans for AMR. In addition innovative stewardship initiatives should be considered as part of the framework. These could include voluntary certification schemes for antimicrobial stewardship programmes in hospitals following international, regional or national standards and guidelines as well as responsible and prudent use commitments in the animal and plant sectors. Innovative initiatives, such as the Baby-friendly Hospital Initiative certification<sup>11</sup> promoted by the UN Children's Fund (UNICEF)/WHO and the C40 Cities Climate Leadership Group,<sup>12</sup> could serve as models for engagement at the regional or local level to drive enhanced access and stewardship.

### 4.3 Framework targets for access and stewardship

Targets will be key to driving change on access and stewardship. Unlike for R&D, access and stewardship targets are more appropriately set at the country level, based on individual country situations and needs and aligned with the national action plans on AMR. Following the example of the Paris Agreement on climate change and certain national action plans, the AMR framework could suggest that countries set their own targets to reduce the need and, consequently, the use of antimicrobials in the human, animal and plant sectors through a stepwise implementation plan and a timeline aligned with the implementation of national action plans. Examples of national targets include the following:

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<sup>10</sup> Including antimicrobial consumption monitoring in the human health sector.

<sup>11</sup> [http://www.who.int/nutrition/publications/infantfeeding/bfhi\\_trainingcourse/en/](http://www.who.int/nutrition/publications/infantfeeding/bfhi_trainingcourse/en/), accessed 2 September 2018.

<sup>12</sup> <https://www.c40.org/>, accessed 2 September 2018.



- National IPC programmes in place and functioning at national and health facility levels according to WHO IPC core component guidelines or other relevant international, regional or national standards;
- Nationwide implementation of good animal health practices plan in line with the OIE terrestrial and aquatic codes or other internationally agreed standards;
- Overall percentage of availability of essential antibiotics in health facilities;
- Overall reduction of global shortages of essential antibiotics;
- Overall percentage of reduction/increase in national sales/optimized use of antimicrobials in line with clinical guidelines in the human health sector;
- Overall percentage of reduction in the national sales/use of antimicrobials in the animal health sector; and
- Overall percentage of reduction in the national sales/use of antimicrobials in the plant sector.

The framework would monitor achieving those commitments through a global stock-take/inventory every one to two years to assess collective progress. Note that rates of antimicrobial consumption in LMICs might rise over time in part due to the higher burden of disease than in high-income countries (HICs) and current lack of access.<sup>13</sup> This would have to be reflected in the national target-setting process.

#### 4.4 Responsibilities of the Tripartite and UN Environment

The following table summarizes the responsibilities of the Tripartite and UN Environment. The biggest burden of implementation however will have to be borne by Member States and other stakeholders, including implementing instruments to achieve reduction of use where appropriate and strengthening of health systems to increase access using national targets. This should include clear responsibilities of Member States under the framework and a set of innovative instruments to foster stewardship and access on regional and local level to achieve measurable impact on the ground. The further process thus will focus on identifying responsibilities of Member States in particular (on national, sub-national or regional and where appropriate facility level) and other IGOs and relevant stakeholders.

**Table 3. Access- and stewardship-related responsibilities of the Tripartite and UN Environment**

Goal	Objectives (outputs)	Responsibilities
<b>4.4.1 Prevent the need for antimicrobials</b>	Effective IPC, WASH standards, biosecurity and good agriculture practices implemented	<b>WHO:</b> Support countries in implementing effective IPC and WASH standards in the hospital and community settings. <b>FAO:</b> Support countries in implementing good practices in

<sup>13</sup> E. Y. Klein, T. P. Van Boeckel, E. M. Martinez, S. Pant, S. Gandra, S. A. Levin, H. Goossens and R. Laxminarayan. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci U S A*. 2018;115:E3463–70. <https://doi.org/10.1073/pnas.1717295115>

		<p>animal husbandry, hygiene and biosecurity in animal (terrestrial and aquatic) production.</p> <p>Support countries in implementing good agricultural practices and use of alternatives in plant production (biological controls, application of bio-rational products, integrated pest management).</p> <p><b>OIE:</b> Support countries in implementing the OIE Terrestrial and Aquatic Animal Health Code and vaccination campaigns.</p> <p>Support Performance of Veterinary Services pathway to strengthen veterinary services in countries.</p>
<b>4.4.2 Rational selection of antimicrobials</b>	Effectiveness of antimicrobials preserved	<p><b>Tripartite:</b> Articulate a roadmap for developing Tripartite guidance for maintaining the efficacy of critically important antimicrobials for humans and animals based on WHO and OIE lists.</p> <p>Support the implementation of standard codes of practice and guidelines for appropriate and prudent antimicrobial use, and pesticide management.</p> <p><b>WHO:</b> Roll out the global strategy on the WHO Essential Medicines List AWaRe categorization of antibiotics and support its implementation in countries.</p> <p><b>FAO:</b> Fill the knowledge gap on the use of alternative agents to antimicrobials in animal husbandry practices.</p>
<b>4.4.3 Surveillance</b>	AMR surveillance and antimicrobial consumption/use monitoring strengthened to inform action on AMR	<p><b>Tripartite:</b> Support capacity building for AMR diagnostics and surveillance at the country level to ensure harmonized and quality data to support interventions and policy.</p> <p>Support the development of integrated surveillance systems.</p>
<b>4.4.4 Procurement and Supply (Gaps)</b>	Global overview of antibiotic shortages	<p><b>WHO:</b> Undertake an assessment on the extent of shortages of antibiotics in the human sectors and identify solutions.</p> <p><b>UN Environment:</b> Identify environmental gaps in existing international guidelines on sustainable procurement and update as appropriate.</p>
<b>4.4.5 Procurement and supply (efficiency)</b>	Increased availability of antibiotics in short supply	<p><b>WHO:</b> Explore the establishment of regional/subregional/joint pooled procurement hubs/schemes to support joint bid solicitation of antibiotics vulnerable to shortages.</p>
<b>4.4.6 Quality of antimicrobials</b>	Global effort to combat substandard and falsified medical products	<p><b>WHO:</b> Conduct risk-based quality surveys of antimicrobials in countries to measure the quality of antimicrobials, prevalence of substandard antimicrobials and potential impact on resistance levels.</p> <p><b>FAO:</b> Research the regulatory aspects of substandard or</p>

		<p>falsified veterinary medicinal products; support the revision of national regulatory frameworks to aid global efforts.</p> <p><b>OIE:</b> Support registration and implementation of VICH guidelines and support countries in the traceability of the use of antimicrobials in animals.</p>
<b>4.4.7 Sales and distribution</b>	Promotion of transparency in monitoring national sales/use of antimicrobials	<b>WHO/OIE:</b> Support countries in monitoring antimicrobial consumption and use in the human and animal health sectors.
<b>4.4.8 Prescribing</b>	Promotion of responsible and prudent use of antimicrobials	<p><b>Tripartite:</b> Support awareness raising and education of human and animal health workers on the responsible and prudent use of antimicrobials through annual world antibiotic awareness week campaigns and other initiatives.</p> <p>Optimize the use of antimicrobials by improving access to antimicrobial susceptibility testing and diagnostic tests to inform prescribing of antimicrobials.</p> <p>Review and develop/update guidance to restrict the inappropriate promotional and marketing antibiotic practices in countries.</p> <p><b>WHO:</b> Develop and support implementation in countries of guidance on antimicrobial stewardship programmes in hospital and community settings and on optimal antibiotic use.</p> <p><b>FAO:</b> Provide training to animal health workers and raise awareness in producers on the prudent use of antimicrobials.</p> <p><b>OIE:</b> Support focal point training of veterinarians and related professionals in the prudent use of antimicrobials.</p> <p><b>OIE:</b> Support training of focal points in government veterinary authorities. Develop competency standards and model curricula for training of veterinarians and veterinary paraprofessionals, and support implementation through twinning between Veterinary Education Establishments. Develop a repository of clinical guidelines for treating infectious diseases developed by national veterinary associations.</p>
<b>4.4.9 Dispensing and regulation</b>	Strengthening of regulatory aspects for AMR	<p><b>Tripartite:</b> Develop guidance for countries to analyse and update their national legislation at all stages of the antimicrobial life cycle (manufacture, labelling requirements, marketing, registration/selection, procurement, distribution, import and export, use, prescription, dispensing, waste management).</p> <p><b>WHO:</b> Develop guidance on phasing out over-the-counter</p>

		<p>sales of antibiotics without prescription while ensuring continued access.</p> <p><b>WHO/FAO:</b> Conduct a global survey on pesticide registration and management in countries, and pesticide application in agriculture.</p>
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## 5. Environmental aspects of AMR

Developed in collaboration with UN Environment, this chapter describes the environmental aspects of AMR and contains information on the possible roles of UN Environment and the Tripartite organizations. Next steps will thus focus on identifying the responsibilities of Member States in particular, and other IGOs and relevant stakeholders.

### 5.1 Key challenges and objectives

There is a growing concern that the presence of resistant microorganisms, resistance genes and antimicrobial residues in the environment, especially in the aquatic environment, may contribute to the emergence, persistence and spread of AMR. There are three potential routes for their origin and spread to and from the environment: human use of antimicrobials; agriculture use, including animal (terrestrial and aquatic animals) and plant use of antimicrobials; and the pharmaceutical industry. In its *Discussion paper on the future governance of antimicrobial resistance*, the IACG identified key needs with respect to the environmental aspects of AMR, including the need for global standards and more research where knowledge gaps remain and engagement of relevant regulators and industries.

Available evidence on the human health and ecological impact of antimicrobial residues in the environment is limited. The release into the environment of sub-lethal levels of various antimicrobial compounds in effluents from households and hospitals and in animal and manufacturing plant run-off, combined with the direct contact between bacterial communities, may drive bacterial evolution and the emergence of more resistant strains.<sup>14</sup>

Moreover, the minimum threshold concentrations that will induce or support propagation of resistance in environmental microorganisms are still undefined for most antimicrobials and environmental conditions. What is clear is that many antimicrobials are not removed through conventional waste water treatment (WWT). Hence, levels of antimicrobials and resistant microorganisms are higher in the aquatic environment (including coastal areas) downstream of urban centres. Water is a particular risk vector as it mobilizes and spreads antimicrobials and resistant microorganisms, e.g. from hospitals, waste water treatment facilities, manufacturing plants, manure application on land and from aquaculture ponds, multiplying the risks even at high dilution and low concentrations. There is evidence of increased human exposure to resistant microorganisms in recreational waters.<sup>15</sup>

In addition, the impact of the excretion of antimicrobial residues and resistance genes into the environment, and the potential for the environment to act as an (additional) exposure pathway for humans, animals and plants, are not considered in the current legislative framework for

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<sup>14</sup> Antimicrobial resistance: an emerging water, sanitation and hygiene issue. WHO/FWC/WSH14.07. Geneva: World Health Organization; 2014 ([http://www.who.int/water\\_sanitation\\_health/emerging/AMR\\_briefing\\_note.pdf](http://www.who.int/water_sanitation_health/emerging/AMR_briefing_note.pdf), accessed 2 September 2018); Frontiers 2017: emerging issues of environmental concern. Nairobi: United Nations Environment Programme; 2017 (<https://www.unenvironment.org/resources/frontiers-2017-emerging-issues-environmental-concern>, accessed 13 August 2018).

<sup>15</sup> A. F. C. Leonard, L. Zhang, A. J. Balfour, R. Garside, W. H. Gaze. Human recreational exposure to antibiotic resistant bacteria in coastal bathing waters. *Environ Int.* 2015;82:92–100 (<https://www.sciencedirect.com/science/article/pii/S0160412015000409>, accessed 2 September 2018).

most countries. Some of the strategies to minimize environmental contamination by antimicrobials and resistance microorganisms include responsible use of the antimicrobials, risk assessment, risk management, and environmental monitoring and surveillance of resistant microorganisms and antimicrobial residues. Activities need to take into consideration the entire life cycle of antimicrobials in relation to the environment (e.g. manufacturing, use, disposal, waste management, emission to environment and transfer between environmental compartments). For instance, more appropriate use of antimicrobials and their proper disposal may reduce the release of antimicrobials to the environment. On the other hand, introducing environmental criteria for the selection and procurement of antimicrobials may increase their price. Therefore, it is imperative to protect access to antimicrobials for humans, animals and plants while considering potential environmental impacts.

## **5.2 Key principles and goals**

- Adopt standards, regulations and targets for improving access to and responsible and prudent use of antimicrobials and for emissions into the environment based on national context and needs;
- Apply the precautionary approach set forth in principle 15 of the Rio Declaration on Environment and Development, as well as support and facilitate the regular exchange of evidence and science-based knowledge;<sup>16</sup>
- Increase investment, research and surveillance of antimicrobials and resistant microorganisms in the environment to better understand the role of the environment in the dynamics of AMR and the relevance of contributions from anthropogenic sources; and
- Limit the release of active pharmaceutical ingredients into the environment, including water, and ensure environmentally sound management of obsolete stocks.

## **5.3 Framework targets for AMR and the environment**

Targets are an essential tool in setting objectives, driving change and measuring progress. Thus, appropriate targets for the emission of resistant microorganisms and active pharmaceutical ingredients into the environment should be formulated during development of the framework.

## **5.4 Responsibilities of the Tripartite and UN Environment**

Tables 4–6 summarize the responsibilities of the Tripartite and UN Environment regarding the environmental aspects of AMR.

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<sup>16</sup> UNEP/EA.3/Res.4.

**Table 4. R&D responsibilities of the Tripartite and UN Environment relating to the environmental aspects of AMR**

<b>Goal</b>	<b>Objectives (outputs)</b>	<b>Responsibilities</b>
<b>5.4.1 Health impact (risk assessment)</b>	Expanded evidence base of approaches to the human health impact of antimicrobials in the environment	<b>WHO:</b> Support an in-depth review of the impact of pharmaceutical waste on human health and the environment.
<b>5.4.2 Setting targets/limits</b>	WWT targets for antimicrobial residues developed	<b>Tripartite and UN Environment:</b> Develop target WWT values for antimicrobial residues (based on a pragmatic approach of using the best available treatment technologies), including for hospital and veterinary waste waters, public sewage and industry waste waters.
<b>5.4.3 Development of new WWT technologies</b>	WWT technologies to prevent the diffusion of antimicrobial residues and resistant microorganisms into the environment	<p><b>UN Environment:</b> Work in collaboration with the private sector on best practices and innovative solutions to WWT technologies.</p> <p><b>WHO:</b> Support the development of new treatment technologies for refractory antimicrobial compounds (i.e. those not broken down in conventional treatment) and for destroying AMR microorganisms.</p> <p>Identify habitat niches that generate AMR microorganisms within sewerage and WWT and disposal systems.</p> <p>Monitor AMR bacterial pathways through WWT plants.</p>
<b>5.4.4 Strengthen surveillance</b>	Enhanced understanding of the environment as a potential source of AMR	<b>WHO:</b> Support the ESBL (extended-spectrum beta-lactamases Tricycle AMR Surveillance project in countries.
<b>5.4.5 Risk vectors</b>	Comparison of aquaculture practices and containment methods to mitigate AMR	<b>FAO/OIE:</b> Explore different risk vectors for AMR from aquaculture ponds on land (contained), aquaculture in lakes and inland wetlands, and coastal aquaculture.
<b>5.4.6 Gap analysis for R&amp;D</b>	Identification of gaps and provision of tools to mitigate AMR	<p><b>Tripartite and UN Environment:</b> Conduct a needs and gaps analysis and provide guidance to minimize the spread of AMR in the environment.</p> <p><b>FAO:</b> Support research to fill the knowledge gaps in best practices for treating and managing both manure and waste milk containing residues of antibiotics.</p> <p>Develop a procedure on the use of nuclear technology to determine the source and transport of antibiotics through the soil and water.</p>
<b>5.4.7 R&amp;D mechanisms</b>	Enhanced partnerships and financing mechanisms to support R&D	<b>Tripartite and UN Environment:</b> Support initiatives where environmental factors play a role as well as actions to avoid development and spread of AMR in the environment.

**Table 5. Regulation and waste management responsibilities of the Tripartite and UN Environment relating to the environmental aspects of AMR**

Goal	Objectives (outputs)	Responsibilities
<b>5.4.8 Waste water treatment (WWT)</b>	Improved conditions for the safe disposal of waste water	<p><b>Tripartite and UN Environment:</b> Provide recommendations on risk management technologies for WWT.</p> <p><b>WHO:</b> Provide recommendations on risk management technologies and possible revision of related standards, including good manufacturing practices.</p> <p><b>FAO:</b> Promote good production practices as well as clear obligations/responsibilities for the safe disposal of waste from antimicrobials (for livestock and crop production) and products containing antimicrobial residues.</p> <p><b>UN Environment:</b> Support pilot projects in LMICs on safe disposal of antimicrobials, including through innovative solutions.</p>
<b>5.4.9 Regulatory systems strengthening</b>	Strengthen regulation on WWT targets and monitoring	<p><b>Tripartite:</b> Develop guidance for countries on antimicrobials (and antimicrobial waste) disposal regulation.</p> <p><b>WHO:</b> Provide recommendations on target values for WWT, monitoring of WWT.</p> <p><b>FAO:</b> Develop guidance on regulatory mechanisms to control waste resulting from activities that produce, manufacture or use antimicrobials, and its release into the environment, and other sources of environmental pollution with antimicrobial residues and the spread of AMR into the environment.</p> <p>Develop guidance to introduce appropriate regulatory frameworks to regulate the use, disposal and waste management of antimicrobials used in plant production.</p> <p><b>UN Environment:</b> Support global discussions on approaches to national regulatory frameworks and promote discussions on the Beyond 2020 process to sound management of chemicals and waste.</p>



**Table 6. Responsibilities of the Tripartite and UN Environment relating to risks from human, animal and plant use of antimicrobials**

Goal	Objectives (outputs)	Responsibilities
<b>5.4.10 Awareness</b>	Promote awareness of need to monitor the environment and take control measures at source points	<p><b>UN Environment:</b> Raise awareness of policymakers on the environmental causes for the development and spread of AMR.</p> <p>Mainstream environmental aspects into national action plans on AMR and encourage monitoring programmes.</p> <p>Develop a recommendation kit on environmental practices to combat AMR, and provide regular information on knowledge available.</p>
<b>5.4.11 Safe disposal</b>	Safe disposal of unused and expired antibiotics	<p><b>Tripartite and UN Environment:</b> Develop guidance on the safe disposal of unused, expired, and/or substandard and falsified antibiotics in human, animal and plant health settings (e.g. health-care facilities, pharmacies, veterinary small animal clinics, farms).</p> <p><b>UN Environment:</b> Compile a compendium of best practices for disposing of pharmaceutical waste in an environmentally sound manner.</p>
<b>5.4.12 Collection and safe disposal of antibiotics from homes and farms</b>	Raised awareness of the correct disposal of unused and expired antibiotics in homes and farms	<p><b>Tripartite and UN Environment:</b> Develop awareness and advocacy materials for the safe disposal of unused/expired antibiotics by patients and farmers (e.g. patients and farmers to bring antibiotics to pharmacies) and on take-back schemes.</p>

## Annex 1. Selected financing mechanisms

### Summary

A key factor in determining the impact of international instruments is sustainable financing. This annex presents a number of financial mechanisms. In light of the multifaceted needs of the Global Framework, a mixed model is proposed. Such a model could meet the financial requirements for the secretariat and governing bodies; driving change towards better stewardship, appropriate use of and access to antimicrobial treatments in human and animal health and plant protection; and financing R&D and access for both animal and human health.

### Financing required to implement the framework

One key factor in determining the impact of international instruments is sustainable financing. Typically, international legal instruments – whether legally binding or not – have a limited impact if there is no sustainable financing mechanism to facilitate implementation of the various activities and obligations.

The cost of containing AMR is considerable: in March 2017, the World Bank<sup>17</sup> presented an overview of the global total cost of key measures for AMR containment amounting to US\$ 9 billion annually. About half is for building core veterinary and human public-health capacities in LMICs. The Jim O’Neill report<sup>18</sup> estimated that taking global action on AMR would cost up to US\$ 40 billion over a 10-year period, of which about US\$ 16 billion would go into R&D, using new market incentives such as market entry rewards. However, this investment is small when compared against the impact on gross domestic product of not investing in combatting AMR, which the World Bank estimates would be worse than the global financial crisis of 2008.

While the overall financing required to implement the Global Framework can only be assessed when its content has been defined and agreed in detail, these estimates show that considerable financial resources are needed to achieve real change for containing AMR. This annex reviews various options and proposes a mixed financing model for generating the financial resources needed to implement the Global Framework.

### 1. Guiding principles for selecting financing mechanisms

The selection of suitable financing mechanisms follows four guiding principles:

- **Sustainability:** Providing a sustainable and predictable flow of new funds.
- **Flexibility:** Ensuring that the resources provided are not earmarked for specific projects.

<sup>17</sup> World Bank Group, Drug-resistant infections.

<sup>18</sup> O’Neill, Review on antimicrobial resistance.

- **Delinkage:** Delinking R&D financing from the price of resulting products and sales volumes to ensure affordability and facilitate stewardship.
- **Burden sharing:** Accepting and encouraging contributions from a broad donor base, as combating AMR is a shared responsibility.

## 2. Diversifying the funding options for the global AMR framework

Financial resources will be needed to fund implementation in the key areas of the Global Framework.

### 2.1 Financing R&D and access for both animal and human health

A substantial part of implementing the Global Framework will be to finance relevant R&D. As shown in Annex 2, Table 1, considerable financial resources are already available through various regional and global mechanisms. To scale these mechanisms, more resources are needed. These could be generated through one or several new mechanisms devoted to financing existing initiatives and possible new initiatives.

This section presents a possible mix of models to expand investment to finance existing and possible new mechanisms. Most of the antibiotic R&D investment still comes from the private sector. Public investment should be complementary and should seek to attract additional private investment by risk sharing and increasing the net present value of innovative antibiotics addressing key public health needs.

### 2.2 Driving change towards better stewardship, appropriate/responsible and prudent use and access to antimicrobial treatments in humans, animal health and plant protection

The Global Framework aims to increase access to antibiotics where needed and to foster their appropriate use across all sector. This will include providing assistance in the selection of appropriate antibiotics, management of supply chain and procurement, appropriate/prudent use and monitoring of consumption. To ensure that such changes are firmly embedded in country-level implementation will require financial and technical resources to build capacity and foster change through health systems strengthening and working towards universal health coverage.

In the animal and plant sectors, technical and financial assistance is needed to drive the reduction of use of antibiotics, particularly those critically important for human medicine, in animal husbandry practices and plant management. A considerable amount of funding is already available on the regional and national level for this work, though it should be increased to implement the Global Framework. While funding should continue on a national and regional level, some of the funds should be pooled to support the implementation of the framework.

### 2.3 Secretariat and governance structure

Some resources will be needed to finance a secretariat to manage the administration and implementation of the Global Framework including meetings of the different bodies under the future governance structure.

### 2.4 Possible financing instruments

The most common mechanism for financing the administration and implementation of an international legal instrument is assessed and voluntary contributions by the parties to the agreement. If assessed contributions, which are based on gross domestic product, do not cover the whole budget, they need to be complemented by voluntary contributions.

It is unlikely that countries and other funders would voluntarily commit to contribute the substantial resources required to finance R&D, fostering access and driving change in stewardship and appropriate use without a specific mechanism. Further, the financial needs for access and stewardship, where funds will typically be lost, are different from those for investing in R&D, which often follows a co-funding model with private investors, with additional required resources occasionally coming in the form of loans. Table 1 reviews the suitability of a number of different instruments that have been used to finance responses to global challenges in light of the principles described above.<sup>19</sup>

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<sup>19</sup> This analysis draws on previous work undertaken for R&D in neglected diseases: *Options for sustainable funding of a voluntary pooled fund to support health research and development: background document to EB140/21: "Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination."* Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/handle/10665/254831/WHO-EMP-PHI-2016.08-eng.pdf;jsessionid=14806D99CBBB6F1FCC6B49AC8F562D03?sequence=1>, accessed 8 May 2018).

**Table 1. Selected possible financing mechanisms**

	<b>Description</b>	<b>Examples</b>	<b>Funding source</b>	<b>Advantages</b>	<b>Disadvantages</b>	<b>Suitability</b>
<b>Bond programmes</b>	Private investors buy shares of the bond and are paid back gradually with public money, allowing pre-financing against legally binding commitment of public funders	Gavi International Finance Facility for Immunisation	Private pre-finance	Augments and accelerates availability and predictability of funds; sustainable if broad donor base	Requires legally binding public funding promises; interest rates depend on a country's credit rating; relatively high set-up and operating costs	Advances availability of funds, but still requires public funding commitments
<b>Social impact bonds (SIBs)</b>	Pay-for-performance model: private investor finances and implements and gets paid back if certain social objectives are achieved	Several, for example prisoner integration in the labour market	Private pre-financing; governments pay back with profit if agreed social objectives are achieved	De-risks the investment for the public funder; efficiency gains if service provider is more efficient than the government	Requires social investors who are ready to take the risk for limited gain; sustainable if substantial pledges from broad donor base	More suitable for access, stewardship, appropriate use interventions; R&D too long term and uncertain
<b>Priority review vouchers (PRVs)</b>	PRVs granted for innovative antibiotics targeting priority pathogens	PRVs for neglected diseases and pathogens with pandemic potential	Company can realize revenues through earlier market entry of another treatment	Financed through company revenues on other products	Value of PRVs diminishes with number of PRVs granted	PRVs can contribute to an increased net present value of antibiotics
<b>Tax incentives</b>	Tax credits, allowances or deferrals that are tied to R&D investment	US Orphan Drug Act	Reduces tax liability	Reduces public income instead of disbursing funds	Risk to finance inefficient R&D projects; tax break needs to be focused on public health priorities; not actively supporting de-linkage	Suitable for R&D, but not for early stage SME projects that need real money

<b>National (sin) taxes dedicated to financing AMR</b>	Tax that is levied on a national level on sales of unhealthy or environmentally unfriendly products or services to discourage their consumption	Unitaid airline tax; tobacco tax; sugar tax; pharmaceutical promotion tax in Italy; pay-or-play tax on pharmaceutical companies suggested by the O'Neill report	New funding source	Sustainable and highly predictive sources of funding; discourages unhealthy or environmentally unfriendly behaviour	Governments usually reluctant to introduce new taxes; unlikely to find agreement on a global tax; administrative costs for specific taxes are relatively high	Suitable for all AMR investments
<b>Matching contributions</b>	Funder promises to match contributions from other funders	WHO demonstration projects	Governmental or private investment depending on who matches	Additional incentive to provide funds; enhances predictability	If donors who are matched do not commit, matching funds will be lost as well	Suitable for all AMR investments
<b>Replenishment fund</b>	Donors fix their contributions in the form of pledges that are public, legally non-binding statements on planned contributions	Global Fund to Fight AIDS, Tuberculosis and Malaria; Gavi	Governmental or private pre-finance	Voluntary, but provides for some planning security as pledges span a certain time period	Still voluntary mechanism with low predictability	Suitable for all AMR investments
<b>Insurance bonds</b>	Insurance-based mechanism where countries pay premiums in exchange for insurance coverage that provides funds to enable rapid response for a public health problem	Pandemic Emergency Financing Facility	Insurance premiums	Works if occurrence of public health problem is uncertain, such as outbreaks of infectious diseases	Not suitable for AMR, which is an increasing problem over time	Not suitable
<b>Reimbursement models/pay for service</b>	Reimbursement models based on fee for service (availability of the antibiotic) instead of on volume	Pilot in Norway	Public money from health insurance	Make investment in developing and producing reserve antibiotics	Increases health-care costs; does not delink R&D from cost, but only from volume	Would increase net present value of reserve antibiotics

				more attractive		
<b>Transferable market exclusivity extension period</b>	Entities that are bringing a new antibiotic to the market would receive a voucher that can be used to prolong the market exclusivity of another medicine	Was included in the draft Re-Valuing Anti-Microbial Products Act of 2018 (REVAMP Act) submitted to the Congress of the United States of America <a href="https://www.congress.gov/bill/115th-congress/house-bill/6294/text">https://www.congress.gov/bill/115th-congress/house-bill/6294/text</a>	Financial incentive comes from prolonging market exclusivity of blockbuster drugs, thus ultimately from health insurance/patients	Indirect funding	Delays generic entry and thus incurs high costs for health systems; links R&D investment with high prices in other disease areas	Could contribute to making R&D investment more attractive
<b>Multilateral Implementation Fund</b>	Governing bodies fix the size of fund and replenishments; parties to the framework pay based on UN scale of assessment	Multilateral Fund for the Implementation of the Montreal Protocol	Public money	Sustainable and flexible funding	More predictable than voluntary contributions	Suitable for all AMR investments

### **3. A mixed model for financing the global AMR framework**

Considering the above financing models, none is sufficient alone to underwrite the requirements of implementing the Global Framework. As such, a possible mixed model combining different instruments might look as follows.

#### **3.1 Financing the secretariat and governing bodies**

In the case of the framework being adopted as a legally binding instrument, assessed contributions from parties to the agreement should be used to finance the secretariat and the overall governance structure.

#### **3.2 Driving change towards better stewardship, appropriate/responsible and prudent use of and access to antimicrobial treatments in human and animal health and plant protection**

Financial resources for technical and financial assistance could be managed by and distributed through the secretariat of the framework, as well as other relevant organizations. While there is a need for some centralized funding, funds are already made available directly on a national or regional level and could be increased to implement the framework. A possible mix could thus include an increase in domestic and regional resources, as well as a new set of multilateral resources, pooled at the international level and distributed according to critical need.

##### *3.2.1 Domestic resource mobilization dedicated to AMR*

Domestic resources mobilization (DRM) represents the most stable, long-term source of financing available. DRM is defined as a mix of financial resources available to a government to fund its operations, including direct and indirect taxes, other revenue and borrowing from capital markets. Countries could either finance AMR-related activities from these revenues or – subject to a cost-benefit analysis – consider specific financing tools such as national taxes or fees dedicated to financing AMR to ensure fresh funding resources.

Social impact bonds could be used for certain interventions that can be carried out by third parties, including the hospital or animal husbandry setting. According to this model, the public sector would only pay out a certain sum of money if success milestones (e.g. overall reduction of the use of antibiotics) are reached. Such social impact bonds could be used under the framework to finance specific interventions.

##### *3.2.2 Multilateral resource mobilization*

Multilateral resource mobilization plays an essential role in complementing DRM, especially in countries with limited domestic resources. FAO, OIE, WHO and other relevant organizations will have to mobilize resources for access and stewardship initiatives. To finance technical assistance, countries are expected to make voluntary contributions. This could be enhanced by a multilateral fund modelled after the Multilateral Fund for the Implementation of the



Montreal Protocol,<sup>20</sup> where countries' contributions are assessed according to the UN scale of assessment. Where countries introduce specific taxes or fees dedicated to financing AMR-related activities, the monies collected should be used as contributions, transmitted through the secretariat to a centralized fund.

### **3.3 Financing R&D and access for animal, human, plant and environment health**

Given that most R&D investment still stems from private investors, public investment should be focused on human, animal and plant priorities and the needs of specific high-risk populations that private investors are not addressing or are addressing insufficiently due to limited return on investment. A main objective is to mobilize additional private investment through targeted public investment.

#### *3.3.1 Increase and coordinate R&D funding*

First, countries that already engage in financing R&D should continue doing so. Under the Global Framework, parties should sign up to support one or several of the existing mechanisms listed in Annex 2, Table 1. Among the different initiatives, GARDP, which WHO co-founded, covers the whole value chain, promotes open-research models, is needs-driven and is underpinned by the principles of affordability, effectiveness and equity. GARDP could become a global R&D partnership to which all countries contribute at different scales.

Other initiatives could be scaled, including CARB-X, which has already broadened its donor base, or JPIAMR, which has developed into an effective global R&D mechanism along with the newly established Global AMR R&D Hub. Countries may also want to revisit their reimbursement and pricing systems to adjust them in a way that decouples payments from volumes to make the investment in needed (reserve) antibiotics more attractive and to keep existing antibiotics in the market.

#### *3.3.2 Industry contribution matching public investment*

Given that most of the investment in R&D flows to the R&D-based industry, there is a case to make for investment by the pharmaceutical industry. This could happen through in-house engagement or contributions to existing mechanisms or instruments, such as the REPAIR Impact Fund. Established by Novo Nordisk Foundation, the REPAIR Impact Fund is an example of how industry could contribute to replenishing the pipeline of anti-infectives.

To set an additional incentive, industry could also commit to matching overall public investment. The matching funds could be pooled in one entity that already receives public financing and used to finance innovative preclinical research projects. Bigger portfolios of early R&D projects would strengthen the overall pipeline and decrease the risk of R&D investment in antimicrobials. Industry has an interest in strengthening the early pipeline and innovative approaches, as late-stage drug development pipelines are typically filled by acquiring

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<sup>20</sup> For more information, see <http://www.multilateralfund.org/default.aspx> (accessed 11 July 2018).

compounds from small companies. This approach would allow for risks to be pooled, lower (salary) costs and economies of scale.

### *3.3.3 Social investor bond model*

The World Bank has indicated that development banks could play a role in creating fresh incentives for pharmaceutical companies to engage in antimicrobial research, following the delinking approach.<sup>21</sup> In this vein, to mobilize additional capital, one or several development banks could launch and administer a social investor bond to finance R&D.

A social bond is a vehicle that brings together private investors, government and non-profit entities to address a particular social problem. The financial institution administering the bond initially puts up some of its own capital and then seeks out investors such as governments, foundations, and financial companies or industries to buy long-term social bonds. The bond would invest in R&D in the animal and human sector in line with global R&D priorities and target product profiles developed under the Global Framework. Product development partnership, small and medium-sized enterprises (SMEs) and other R&D initiatives for the human and animal sectors will be the recipients of the funds collected through this scheme. They would also be responsible for bringing resulting products to market and ensure their accessibility and responsible use.

Bondholders would receive a periodic investment return, which would be paid by the international financial institution administering the bond. This payment would be funded by partial reimbursements by the product developers, which in turn would be matched by contributions from donor governments.

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<sup>21</sup> World Bank Group, Drug-resistant infections.

## Annex 2. The current R&D landscape

Over the past years, a number of regional and global initiatives have been established, which are presented in Table 1.

The **Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)** was launched in July 2016 to accelerate a diverse portfolio of priority antibacterial products towards clinical development. It is financed by the Biomedical Advanced Research and Development Authority (BARDA) (US\$ 250 million), the Wellcome Trust (US\$ 155.5 million), the UK Government (Department of Health and Social Care, Global AMR Innovation Fund (US\$ 27 million) and the Bill & Melinda Gates Foundation (US\$ 25 million). CARB-X has so far financed 35 projects disbursing US\$ 87.4 million as of 1 June 2018.

The **Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)** was established in 2011 and today has 27 member states that coordinate their direct national funding towards basic and exploratory research on new antibiotics, stewardship and control of the spread of antibiotic resistance between humans, animals and the environment from a One Health perspective.

The **Global Antibiotic Research and Development Partnership (GARDP)**, a joint initiative of the Drugs for Neglected Diseases Initiative and WHO, aims to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists. It has received overall funding of €66 million out of an envisaged budget of €236 million.

The European Union has been supporting research to combat AMR since 1999. Under **Horizon 2020**, AMR-related projects with a cumulative budget of €350 million will receive an additional €200 million in the last three years of the Horizon 2020 work programme. The projects cover human and animal health and environmental aspects addressing bacteria, viruses, parasites and fungi. Special attention is given to developing novel antimicrobial therapies; understanding how AMR develops; early detection methods; new rapid, cost-effective diagnostic tests; and new strategies for prudent/rational use of antibiotics in human medicine, food-producing animals and aquaculture. Last year's EU Horizon prize for better use of antibiotics of €1 million was awarded for a finger-prick test that diagnoses whether a patient can be treated safely without antibiotics in less than 10 minutes. This finger-prick test is expected to be available for patients by 2018. As part of the Innovative Medicines Initiative, a partnership between the EU and the European Federation of Pharmaceutical Industries and Associations, the ND4BB programme focuses on the discovery and development of novel antibiotics for humans.

**InnovFin Infectious Diseases** is a finance facility established jointly by the European Investment Bank and the European Commission in 2015. It provides loans for the development of innovative vaccines, drugs, medical and diagnostic devices or novel research infrastructures to companies, universities and non-profit organizations, among others, in the area of infectious diseases for projects that have completed the preclinical stage. Eight loans totalling €149

million were granted to six SMEs and two medium-sized biopharmaceutical companies, with five of the loans supporting innovation specifically in the area of AMR.

The **REPAIR Impact Fund** was set up by the Novo Nordisk Foundation in 2018 to invest US\$ 20–40 million per year over three to five years in about 20 projects involved in discovery and the early-stage development of new antimicrobial therapies.

**Table 1. Existing global, regional and industry initiatives to foster product development**

Initiative	Budget	Role	Products	Stages of development	Geographical scope	Appropriate use and access	Targets specific high-priority medical needs
<b>Multi-lateral</b>							
CARB-X	US\$ 502 m (2016–21)	Funding and expert support	Therapeutics, diagnostics, preventatives, devices	Hit-to-lead through end of Phase 1	Global	✓	WHO and CDC
GARDP	€236m (2017–23)	Developer	Therapeutics	Any stage of development	Global	✓	WHO
JPIAMR	€234m (2012–24)	Public funder	Health products and research on resistance	Discovery research and early stage	Global	X	WHO and national priorities
<b>EU</b>							
IMI: ND4BB	€700m (2014–18) €200–300m (2018–20)	Financial, in-kind and expertise	Therapeutics, diagnostics	Whole value chain	Global	✓	Priority pathogens, including WHO priority list
InnovFin Infectious Diseases	€180m (2015–20) €80m (2018–20)	Loan to be paid back in event of success	Vaccines, drugs, medical and diagnostic devices	Clinical development	EU Member States and Horizon 2020-associated countries	X	Priority pathogens, including WHO priority list
<b>Industry</b>							
REPAIR Impact Fund	US\$ 165 m (2018–23)	Convertible loans and royalty-based	Novel therapeutics, companion diagnostics	Lead optimization through end of Phase 1	Europe and US	In progress, to be established	WHO and CDC

Abbreviations: CARB-X, Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator; CDC, Centers for Disease Control and Prevention; GARDP, Global Antibiotic Research and Development Partnership; IMI, Innovative Medicines Initiative; JPIAMR, Joint Programming Initiative on Antimicrobial Resistance; ND4BB, New Drugs for Bad Bugs; REPAIR, Replenishing and Enabling the Pipeline for Anti-Infective Resistance.

Some countries have invested through bilateral mechanisms, occasionally partnering with other countries. For example, the UK has done this through its £50 million Global AMR Innovation Fund, part of which has been used to establish bilateral partnerships with Argentina and China to fight AMR.

Germany has committed up to €500 million in investment over 10 years in AMR-related R&D, including to fund the Global AMR R&D Hub. The Hub was launched in May 2018 to further improve coordination of different AMR R&D efforts and initiatives and to further increase investment in R&D for AMR.

Since 2010, BARDA within the Office of the Assistant Secretary for Preparedness and Response in the US Department of Health and Human Services has invested US\$ 1.03 billion worldwide to support the development of new antibiotics. This includes US\$ 140 million to CARB-X for early-stage preclinical R&D and US\$ 889 million that was disbursed to 12 companies for advanced clinical-stage development of 15 antibacterial products, two of which have been approved. This investment does not include additional funding by other US government entities.