



# **Antimicrobial resistance: Invest in innovation and research, and boost R&D and access**

[IACG discussion paper](#)

**June 2018**

## IACG disclaimer

This document reflects the discussions of the IACG subgroup responsible for innovation, research, and development, and improved access area so far and will be subject to change as the discussions continue. It does not necessarily reflect the views of the IACG as a whole.

The document provides only preliminary elements on plant health and environmental health.

### Key messages

- Antimicrobial resistance (AMR) is a global, multisectoral issue that affects all countries and requires coherent, comprehensive action in human, animal, plant and environmental health in the framework of a One Health approach.
- A successful response to AMR will address not only antimicrobials but also diagnostics, vaccines and alternatives to antibiotics for human and animal health.
- There are multiple challenges in research and development (R&D) and to access to AMR- related health technologies, and there are gaps to be addressed in the current response.
  - Funding of R&D for priorities that are underfunded should be increased and optimized, and R&D should be coordinated to ensure appropriate priority setting, funding allocation and unproductive duplication of activities.
  - There are no global access initiatives on AMR beyond those related to HIV, TB and malaria, in which a more concerted effort and coordination among initiatives is required, and there is little consideration of gaps in access in animal, plant and environmental health.
  - Further guidance should be given to funders on investing in AMR in order to maximize the impact of their investments in meeting the challenges of R&D and access.
  - More work is required to operationalize the One Health approach in AMR R&D and access.

## Introduction and scope

The threat of antimicrobial resistance (AMR) would be reduced if everywhere in the world human and animal diseases could be correctly diagnosed, existing treatments were accessible and correctly used and the pipeline of new treatments addressed priority diseases at risk of resistance. Yet, the inadequacy of the clinical pipeline of new vaccines, medicines and diagnostics to combat AMR<sup>1</sup> and of alternatives to antibiotics (hereafter referred to collectively as “AMR-related health technologies”) is consistently highlighted. In addition, today, access to the available products remains insufficient: more than one million children die each year from pneumonia and sepsis;<sup>2</sup> many of these infections could be treated or prevented if access to existing technologies were improved.

The Inter-Agency Coordination Group (IACG) on AMR, established to provide practical guidance for approaches to ensure sustained, effective global action to address AMR, recognized the critical importance of research and development (R&D) and access in the global fight against AMR by establishing a subgroup to look specifically at these issues.<sup>3</sup>

This discussion paper identifies the challenges and gaps facing R&D and access to AMR-related health technologies and invites discussion of how to address these in the framework of a global response. It will serve as a basis for **consultation** to inform the IACG’s deliberations in making robust, practical recommendations to address challenges to AMR R&D and access.

It acknowledges **AMR as a global and multi-sectoral issue** that affects all countries and requires coherent, comprehensive action in human, animal, plant and environmental health in the framework of a **One Health approach**, recognizing that the health of people is strongly connected to that of animals and the environment.

<sup>1</sup> Antibacterial agents in clinical development - an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017 (<http://apps.who.int/iris/bitstream/handle/10665/258965/WHO-EMP-IAU-2017.11-eng.pdf;jsessionid=6B4F38B27BBFD7CA5217AF0027CA507?sequence=1>)

<sup>2</sup> Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen JA, Klugman K, et al. Access to effective antimicrobials: a worldwide challenge. *Lancet*. 2016; 387:168-75.

<sup>3</sup> Subgroup 4 of the IACG is formed of experts from FAO, OECD, OIE, South Centre, The Global Fund, UNEP, Unitaaid, WHO and WIPO, WTO and the Chief Medical Officer, United Kingdom.

It further acknowledges that the response to AMR does not concern only antimicrobials but must include **diagnostics**, which form a core element of the response in helping to select appropriate antimicrobials to treat a disease; **vaccines**, which play an important role in preventing diseases, thus limiting the need for antimicrobials; and **alternatives to antibiotics**, which could reduce the use of antibiotics, for example as animal growth promoters. Further, the group recognizes the need for research into best or “fit-for purpose” policies to support and facilitate R&D in AMR and access to new and existing AMR-related health technologies.

It builds on recent **reviews and research**<sup>4</sup> on AMR and on interviews with various stakeholders conducted as part of the IACG’s ongoing work. It aims to ensure coherence with existing policy frameworks, including the draft global development and stewardship framework developed by WHO, FAO and OIE<sup>5</sup>. It is guided by the United Nations political declaration on AMR<sup>6</sup> and the consideration that all R&D efforts should be “needs-driven, evidence-based and guided by the principles of affordability, effectiveness and efficiency and equity, and should be considered as a shared responsibility”.

The paper is divided into three sections: R&D, access and cross-cutting issues. Each section provides an overview of challenges identified, the existing response and gaps in the response and open questions for discussion. R&D and access are presented separately from one another; however, it is acknowledged that access considerations need to be built into the R&D process end-to-end, as part of a value chain that extends from basic research to use of a new or improved product in human, animal or plant health. This may be done, for example, by defining target product profiles that could provide signals to industry and other R&D stakeholders over what key parameters define a public health priority for antimicrobial R&D and to support access.

Finally, this paper reflects the state of discussions within the IACG at a certain point in time<sup>7</sup>. The work of the IACG on innovation, R&D and access is ongoing and its scope is expanding to include areas not captured in the present

version of the discussion paper. These areas notably include R&D capacity in low- and lower-middle income countries and access issues in high income countries, including shortages.

---

<sup>4</sup> Including O’Neill J, Chair. Antimicrobial resistance: tackling a crisis for the health and wealth of nations (the AMR review). London: Her Majesty’s Government, Wellcome Trust;.2016; and OECD, WHO, FAO, OIE. Tackling antimicrobial resistance. Ensuring sustainable R&D. Paris: OECD; 2017.

<sup>5</sup> WHO, OIE, FAO Global framework for development and stewardship to combat antimicrobial resistance - draft roadmap. 2017 (<http://apps.who.int/medicinedocs/en/d/Js23198en/>)

<sup>6</sup> United Nations General Assembly resolution 71/3 Political declaration of the high-level meeting of the General Assembly on antimicrobial resistance (A/RES/71/3). New York City (NY): United Nations; 2016 (<http://www.who.int/antimicrobial-resistance/interagency-coordination-group/UNGA-AMR-RES-71-3-N1631065.pdf?ua=1>).

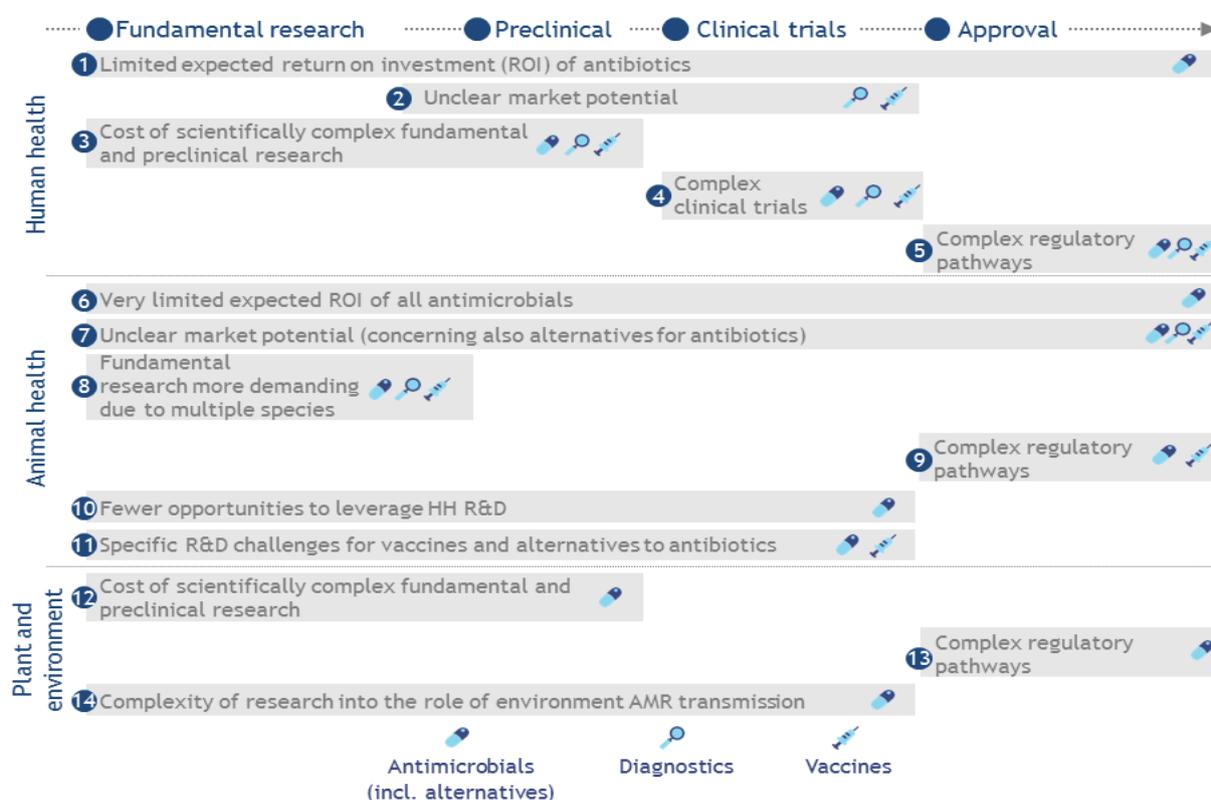
<sup>7</sup> End April 2018

## 1. Research and development

### 1.1. Multiple challenges in R&D for AMR

The current R&D pipeline of new AMR-related health technologies must be strengthened to address priority diseases at risk of resistance. The challenges in R&D on AMR-related health technologies are illustrated in Fig. 1, which shows challenges identified by the IACG along the R&D value chain, which covers fundamental research, preclinical research, clinical trials, through to regulatory approval.

Fig. 1. Several challenges identified in R&D



### Human health

The number of approved novel antibiotics fell from 19 between 1980 and 1984 to 6 between 2010 and 2014.<sup>8</sup> Moreover, most of the new approved antibiotics were additions to existing drug classes or for the same indication.<sup>9</sup> The 2017 WHO Antibacterial Clinical Pipeline Report confirms that there are few innovative antibiotics<sup>10</sup> in development;

only 9 of the 33 antibiotics developed for priority pathogens belong to five distinct new antibiotic classes.<sup>1</sup>

In human health, five main challenges were observed along the R&D value chain.

1. **There is uncertainty in the expected return on investment of antibiotics.** This is explained by:<sup>11</sup>
  - the high costs of development;
  - the low success rates: only 1.5% of antibiotic compounds identified in preclinical research reach the market;<sup>12</sup> and
  - the limited expected revenues in terms of price and volume of sales, because of:
    - low prices, due to the availability of generic alternatives;

<sup>8</sup> Ventola CL. The antibiotic resistance crisis. *PT*. 2015;40(4):277-83.

<sup>9</sup> Deak D, Outtersson K, Powers JH, Kesselheim AS. Progress in the fight against multidrug-resistant bacteria? A review of U.S. Food and Drug Administration-approved antibiotics, 2010-2015. *Ann Intern Med*. 2016;165(5):363-72.

<sup>10</sup> WHO classifies antibiotics as innovative if they meet one of the following criteria:

- no cross-resistance to existing antibiotics,
- new chemical class
- new target or
- new mechanism of action.

Antibacterial agents in clinical development, an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017

<sup>11</sup> WHO, WIPO, WTO. Antimicrobial resistance - a global epidemic. Background paper for the Joint Technical Symposium on Antimicrobial Resistance. Geneva: WIPO; 2016 ([http://www.wipo.int/edocs/mdocs/mdocs/en/wipo\\_who\\_wto\\_ip\\_ge\\_16/wipo\\_who\\_wto\\_ip\\_ge\\_16\\_inf\\_2.pdf](http://www.wipo.int/edocs/mdocs/mdocs/en/wipo_who_wto_ip_ge_16/wipo_who_wto_ip_ge_16_inf_2.pdf)).

<sup>12</sup> OECD, WHO, FAO, OIE. Tackling antimicrobial resistance. Ensuring sustainable R&D. Paris: OECD; 2017 (<http://www.oecd.org/g20/summits/hamburg/Tackling-Antimicrobial-Resistance-Ensuring-Sustainable-RD.pdf>)

- limited volumes, due to increasing stewardship requirements for some new antibiotics;
- the risk of resistance developing and resulting in their decreased effectiveness; and
- the short duration of antibiotic treatment in comparison with treatment for chronic illnesses.

Antibiotics are generally less profitable than drugs used to treat chronic diseases; for example, the net present value of drugs used in oncology is three times higher than that of antibiotics.<sup>13</sup>

2 **Unclear market potential**,<sup>14</sup> including for diagnostics and vaccines, discourages private innovation in these products at preclinical and clinical stages. With limited competition from generic products and no stewardship requirements on volume, diagnostics and vaccines could have attractive markets; however, public health care systems and patients are not always willing to purchase and use these products. Diagnostics are often perceived as an additional expense to the cost of treatment, even though their use may be associated with significant cost savings and efficiency downstream. This is especially true in some low- and lower middle-income countries (LMICs), where there is limited reimbursement for these products.

3 **Scientifically complex fundamental research and costly preclinical research** in antimicrobials, diagnostics and vaccines discourage R&D. Fundamental research by academia and by small and medium-sized enterprises is not sufficiently funded by the public, philanthropic or private sector or adequately resourced. In addition, AMR has been described as a fairly unattractive field of research,<sup>15</sup> characterized by high attrition and, hence, knowledge loss for the industry. The preclinical phase of development of antibiotics is in general also driven by small and medium-sized enterprises, which have to assume the combination of high risks and considerable cost, which may amount to approximately US\$ 10 million per compound.<sup>12</sup>

4 **Clinical trials** for health technologies against resistant strains are particularly complex. Identifying a sufficient number of eligible patients who are infected with resistant strains and are available to participate in clinical trials can be difficult and result in long and/or costly trials.

5 **Regulatory pathways** to secure registration and ensure commercialization of antimicrobials, diagnostics and vaccines can be complex and burdensome. Moreover, divergences in approval requirements and processes in the many countries in

which these products are needed pose additional hurdles for manufacturers.

### **Animal health**

Most challenges in animal health are similar to those identified in human health, differing essentially in the scope of health products.

6 There is also a **very limited expected return on investment for antimicrobials in animal health**.

7 The **unclear market potential** of diagnostics, vaccines and alternatives to antibiotics discourages innovation in these products. It is still unclear whether farmers are willing to pay for vaccines and diagnostics, particularly in LMICs, if they do not receive higher coverage from reimbursement policies. This is also the case for alternatives to antibiotics, and more evidence is required on the efficacy and cost-effectiveness of these products and/or more coverage from public resources, as in human health.

8 **Fundamental research in animal health is more demanding than in human health because of the large variety of animal species** and the diversity of pathogen species involved.

9 **Regulatory pathways** for antimicrobials and vaccines in animal health have also been described as complex and burdensome<sup>15</sup>. While this applies to all species, the scale of the challenge is larger for “minor species”, for which the market potential is lower. As in human health, divergences in the approval requirements and processes in different countries pose additional hurdles for manufacturers, as for all AMR-related health technologies, suggesting scope for research into the policy pathway.

10 Because of restrictions on the use of new antibiotics in animals, there are now **fewer opportunities to leverage human health R&D in antibiotics**. With the threat of AMR, new classes of antibiotics that are active against priority pathogens will probably be restricted for use in humans in order to preserve their effectiveness in human health.

11 **There are also specific challenges for R&D on vaccines and alternatives to antibiotics**. Developing vaccines that can differentiate infected from vaccinated animals (DIVA vaccines) is particularly complex. So too is the development of vaccines for mass delivery, for example for fish in aquaculture. No commercial vaccine exists for crustaceans because they lack an adaptive immune system; the role of alternatives, including nanotechnologies, should be explored. The costs of discovery and development of therapeutic alternatives to antibiotics are, however, high, with an estimated development expense of US\$ 50-300 million<sup>15</sup> in animal health, depending on the product characteristics. The mechanism of action of growth promoters is often unclear, and more work is needed to develop suitable alternatives.

<sup>13</sup> Mossialos E, Morel CM, Edwards S, Berenson J, Gemmill-Toyama M, Brogan D. Policies and incentives for promoting innovation in antibiotic research. Geneva: World Health Organization for the European Observatory on Health Systems and Policies; 2010.

<sup>14</sup> Rickwood S. Prescription medicines trends: an overview and perspective on two therapy areas. PowerPoint presentation. Durham (NC): IQVIA; 2017 (<http://www.who.int/phi/2-SarahRickwood.pdf>).

<sup>15</sup> Key stakeholder interview conducted by the IACG.

R&D to characterize pathogen and host genomics could facilitate early diagnosis of resistance or tolerance and indicate preventive or control measures.

#### *Plant and environmental health*

Several challenges were identified in plant and environmental health, some of which are similar to those identified in human and animal health.

12 **Scientifically complex fundamental research and costly preclinical research into plant protection products** such as pesticides discourages R&D. It takes approximately 10 years and an estimated cost of US\$ 260 million to develop new crop protection products.<sup>16</sup> and the market potential is sometimes unclear.

13 **Regulatory pathways** for plant protection products may also be complex, in the context of rising concern about the effects of chemicals on the environment and their safety to humans, the environment and other mammals and organisms.<sup>17</sup>

14 A specific challenge is the **complexity of research into the role of the environment in the transmission of AMR to humans and animals**. A limited amount of research is under way to further identify and quantify human exposure by different pathways.<sup>15</sup>

The occurrence or detection of AMR genes or pathogens in the environment and their direct threat to human and animal health is not fully understood. Mapping of one transmission cycle (human-environment-human) has been considered to be separate from the animal-environment-animal cycle, with little overlap; however, other studies link cycles of animal-environment-human as a major threat. In reality, there is no standard or agreed method for studying the interaction or the risk posed. Cost-effective environmental surveillance for AMR genes merits further study, rather than surveillance for heavy metals or polychlorinated biphenyls and their impact on health. Combination of surveillance is another possibility.

---

<sup>16</sup> Leadbetter A. Recent developments and challenges in chemical disease control. *Plant Prot Sci.* 2015;51(4):163-9.

<sup>17</sup> R&D solutions for chemicals. White paper. Increasing pressures in agricultural chemical R&D demand new workflow solutions. New York City (NY): Elsevier; 2017 ([https://www.elsevier.com/\\_\\_\\_data/assets/pdf\\_file/0006/278124/CHEM-RD-WP-Agricultural-Workflow-WEB.pdf](https://www.elsevier.com/___data/assets/pdf_file/0006/278124/CHEM-RD-WP-Agricultural-Workflow-WEB.pdf)).

## 1.2. Existing response to R&D challenges, remaining gaps and open questions to bridge those gaps

This section addresses R&D funding and coordination and specifically the current response to the identified challenges and remaining gaps. We invite contributions and insights from stakeholders on how best to overcome the gaps.

Fig. 2. Main gaps in R&D identified in existing response



### Public and philanthropic funding for R&D

Potential to optimize funding to target priorities, in particular the following underfunded areas:

- In human health, in fundamental research and clinical development of new antibiotics and specific diagnostics and vaccines where there is market failure
- In animal, plant and environmental health, for all health products and in all R&D activities

Potential to use de-linkage mechanisms to stimulate R&D



### Coordination in R&D

Potential to strengthen coordination

- Expand R&D priority setting
- Ensure alignment of funding with global priorities
- Avoid duplication
- Monitor coordination in a "One Health Approach"

### Public and philanthropic funding for R&D

Existing response: several R&D initiatives address antibacterial treatments for human health and very few for animal health

In human health, several international initiatives have been launched to stimulate R&D for antibiotics, including:<sup>18</sup>

- **the Joint Programming Initiative on Antimicrobial Resistance (JPI AMR)**, which finances basic and preclinical research (US\$ 80 million invested in research projects to date<sup>19</sup>), partly addressing human health R&D challenge ③;
- **Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)**, launched in 2016 (US\$ 455 million over 5 years<sup>20</sup>), with projects at preclinical and clinical phase I, responding in part to human health R&D challenges ③ and ④ and focusing on critical and high priorities on the WHO priority pathogens list;

- **New Drugs for Bad Bugs (ND4BB)**, one of the European Union initiatives<sup>21</sup> to address AMR, is a public-private partnership (US\$ 860 million<sup>22</sup>) covering the full R&D value chain, contributing to a response to challenges ③, ④ and ⑤;
- **the Global Antibiotic Research & Development Partnership (GARDP)**, a product development partnership established in 2016 by WHO and the Drugs for Neglected Diseases initiative to promote and stimulate R&D on new or improved antibiotic treatments (US\$ 69 million raised by September 2017<sup>23</sup>). It covers the full R&D value chain, answering R&D challenges ③, ④ and ⑤; and
- **the Novo REPAIR Impact Fund**, established in February 2018 by Novo Holdings and commissioned by the Novo Nordisk Foundation to invest in the discovery and early-stage development of therapy against priority pathogens as defined by WHO and the Centers for Disease Control and Prevention in the USA (US\$ 165 million over 3-5 years), responding in part to human health R&D challenges ③ and ④.

<sup>18</sup> A comprehensive overview is available in Jenner A, Bhagwandin N, Kowalski S. Antimicrobial resistance (AMR) and multidrug resistance (MDR): overview of current approaches, consortia and intellectual property issues. In: Global Challenges Report. Geneva: WIPO; 2017 ([www.wipo.int/policy/en/global\\_health/documents.html](http://www.wipo.int/policy/en/global_health/documents.html)).

<sup>19</sup> € 65 million per website.

<sup>20</sup> Funded by the Biomedical Advanced Research and Development Authority (USA) and Wellcome Trust

<sup>21</sup> The European Union has a number of additional projects along the value chain for new antibiotics as well as diagnostics, including for example the European and Developing Countries Clinical Trials Partnership and InnovFin, a joint initiative between the European Commission and the European Investment Bank Group to support research and innovation including tools to fight AMR.

<sup>22</sup> € 700 million per website

<sup>23</sup> € 56 million per website

A number of product development partnerships address challenges in antibiotics and other antimicrobials, including the TB Alliance, the Drugs for Neglected Diseases initiative, the Foundation for Innovative Diagnostics and the Medicines for Malaria Venture.

There are few global R&D initiatives in animal health, and none focuses specifically on AMR:

- **GALVmed**, a product development partnership for the development of therapeutics, diagnostics and vaccines for small-scale producers in LMICs (portfolio of US\$ 150 million); and
- the **Livestock Vaccine Innovation Fund**,<sup>24</sup> which supports the development of new and improved vaccines against neglected livestock diseases in LMICs (budget of US\$ 45 million<sup>25</sup> for 2015-2020).

These initiatives operate with limited budgets and contribute to the response to R&D challenges ⑧ and ⑨.

Additional initiatives in animal health have an international outlook but are funded through individual government investments or bilateral partnerships. This is the case of the **International Vaccine Veterinary Network**,<sup>26</sup> funded by the British Government, which addresses early problems in R&D on vaccines against major livestock and zoonotic diseases in LMICs (budget of US\$ 3 million for 2017-2021<sup>27</sup>).

*Gaps: potential to optimize funding for priorities*

**Funding for priorities could be optimized, in particular in the following underfunded areas:**

- in human health, basic research and clinical development of new antibiotics, specific diagnostics, vaccines and alternatives where there is market failure,<sup>15</sup> and,
- in animal, environmental and plant health, all R&D and for antimicrobials, diagnostics and vaccines.

One way of optimizing and increasing the impact of funding for R&D could be by **use of “delinkage” mechanisms**. As stated above, there is little expectation that price- and volume-based sales will drive R&D in solutions to tackle priority pathogens. By disconnecting the cost of investment in R&D from the expected price and volume of sales of the products, delinkage incentivizes R&D while ensuring that priorities are targeted. If designed correctly, these mechanisms could also ensure equitable, affordable access to new and improved products that represent effective

solutions to AMR.<sup>6</sup> The concept of delinkage has been supported by the United Nations General Assembly<sup>6</sup> and the G20.<sup>28</sup> Delinkage can be facilitated by well-designed “push and pull” incentive mechanisms.

**Push mechanisms** are incentives such as grant funding and tax credits to support early-stage research (basic to preclinical).<sup>29</sup> Therefore, they directly address challenges ③ and ⑧ related to the complexity of basic research and the cost of preclinical research. These mechanisms are commonly used in R&D: for example, through CARB-X, GARDP and JPI AMR; however, funding for these mechanisms is too limited to fully address challenges ③ and ⑧. Three recent reports - the AMR Review by Jim O’Neill<sup>4</sup>, the BCG / German Federal Ministry of Health report<sup>30</sup> and the DRIVE AB report<sup>31</sup> - suggest that additional investment is needed for push mechanisms in basic research of up to US\$ 400 million per year<sup>4</sup>, including US\$ 200 million<sup>30</sup> to 250 million<sup>31</sup> per year for antibiotics alone.

**Pull mechanisms** are rewards for R&D of new products.<sup>29</sup> They directly address challenges ①, ②, ④, ⑤, ⑥, ⑦ and ⑨. Further data are required on the optimal design and application of such mechanisms; however, several are being discussed and already being used, as described below.

Some of these mechanisms are monetary in nature:

- **market entry rewards** are paid to the developers of novel products. These prizes are either paid gradually, in stages or at certain milestones, or at early stages, including pre-clinical research; and
- **advance market commitments**, which allow developers of new products to sell a defined volume of their products to funders at a pre-specified price.

<sup>24</sup> A partnership between the Bill & Melinda Gates Foundation, Global Affairs Canada and the International Development Research Centre.

<sup>25</sup> CA\$ 57 million for 2015-2020 per website

<sup>26</sup> One of five vaccine R&D networks launched in August 2017 by the United Kingdom Medical Research Council, the Biotechnology and Biosciences Research Council and the Global Challenges Research Fund. It is the only network that addresses only animal health.

<sup>27</sup> £ 2.1 million for an initial 4-year period per website.

<sup>28</sup> Berlin Declaration of the G20 Health Ministers. Berlin: Ministry of Health; 2017 ([https://www.bundesgesundheitsministerium.de/fileadmin/Daten/3\\_Downloads/G/G20-Gesundheitsministertreffen/G20\\_Health\\_Ministers\\_Declaration\\_engl.pdf](https://www.bundesgesundheitsministerium.de/fileadmin/Daten/3_Downloads/G/G20-Gesundheitsministertreffen/G20_Health_Ministers_Declaration_engl.pdf)).

<sup>29</sup> WTO, WIPO, WHO. Promoting access to medical technologies and innovation. Geneva: World Trade organization; 2012 ([https://www.wto.org/english/res\\_e/booksp\\_e/pamtiwhowipowtweb13\\_e.pdf](https://www.wto.org/english/res_e/booksp_e/pamtiwhowipowtweb13_e.pdf)).

<sup>30</sup> The Boston Consulting Group, German Federal Ministry of Health. Breaking through the wall: a call for concerted action on antibiotics research and development. Berlin: Ministry of Health; 2017 ([https://www.bundesgesundheitsministerium.de/fileadmin/Daten/5\\_Publikationen/Gesundheit/Berichte/GUARD\\_Follow\\_Up\\_Report\\_Full\\_Report\\_final.pdf](https://www.bundesgesundheitsministerium.de/fileadmin/Daten/5_Publikationen/Gesundheit/Berichte/GUARD_Follow_Up_Report_Full_Report_final.pdf)).

<sup>31</sup> Drive-AB. Revitalizing the antibiotic pipeline - DRIVE-AB final report. Brussels: Innovative medicines Initiative and the European Federation of Pharmaceutical Industries and Associations; 2018 (<http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf>).

There is limited experience in use of these mechanisms, and the debate with respect to AMR is on use of market entry rewards. Only very small rewards have been offered in recent years.<sup>32</sup> It has been suggested that the value of an innovation for society should be reflected in its price. Others have estimated that a prize of US\$ 1 billion<sup>33</sup> for each new antibiotic that is commercialized could be an adequate incentive for investment by the industry in the antibiotics pipeline. Others are exploring how antibiotics should be valued and regional and national options rather than a single global mechanism.

Other pull mechanisms are not monetary. These include:

- **streamlined clinical trials**, such as a requirement for smaller test populations;
- **fast-track reviews** to reduce the time for registering a product and obtaining market approval;
- **transferable priority review vouchers**, similar to fast-track reviews, in which the developer is given the possibility of either transferring the voucher to other products in its portfolio or selling it to another company; and,
- once marketing approval has been received, **market exclusivity** of up to 10 years in some jurisdictions for medicines with a particular therapeutic indication, in order to incentivize the development and marketing of “orphan” medicinal products, without prejudice to intellectual property rights and usually granted by a health regulatory authority.<sup>34</sup>

Experience in use of these mechanisms is also limited. Market exclusivity and fast-track reviews are available, for example, under legislation in the European Union, Japan and the USA. Additionally, law in the USA includes the following incentives: the Generating Antibiotic Incentives Now Act, under which an additional exclusivity period can be awarded to foster investment into new antibiotics; the Food and Drug Administration Revitalization Act, which established transferable priority review vouchers for all drugs to treat neglected tropical diseases or rare paediatric diseases; and streamlined clinical trials, also for high-priority antibiotics in terms of resistance, through the Limited Population Antibacterial Drug Act.

### *R&D coordination*

R&D on animal, human, plant and environmental health should be coordinated to ensure that:

<sup>32</sup> Including the Longitude Prize to develop a point-of-care diagnostic test for bacterial infections (US\$ 14 million) in 2014 and the Brucellosis Vaccine Prize (US\$ 30 million) to develop viable vaccines against *Brucella melitensis* for use in LMICs (<https://longitudeprize.org/>; <https://brucellosis.org/>).

<sup>33</sup> Approximate figures suggested by BCG, German Federal Ministry of Health report, DRIVE-AB final report and the AMR review.

<sup>34</sup> In the European Union, market exclusivity is awarded by the European Commission: Article 8 of Regulation (EC) No. 141/2000 on Orphan Medicinal Products, OJ L 18/1 of 22 January 2000.

- global priorities are set and monitored and gaps identified;
- sufficient funds are allocated to tackling global priorities;
- the impact of research is maximized through joint approaches; and
- unproductive duplication of activities is avoided.

### *Existing response: current coordination*

WHO, OIE and FAO provide global guidance, set priorities and identify gaps in the development of new antimicrobials, diagnostics and vaccines.

WHO has issued a list of priority pathogens for R&D, emphasizing the critical need for new antibacterial treatments and a report on the antibacterial clinical pipeline, which matches the current pipeline against priorities and highlight gaps in R&D. It will develop a method for designing target product profiles, which define the optimal performance and operational characteristics of new health products and are a necessary condition for any future pull mechanism.

OIE has convened ad-hoc groups to provide guidance on the prioritization of diseases for which available and new vaccines could reduce antimicrobial use in pigs, poultry and fish (2015) and cattle, sheep and goats (planned for 2018). Through the Global Strategic Alliances for the Coordination of Research on the Major Infectious Diseases of Animals and Zoonoses (STAR-IDAZ) of the International Research Consortium, the OIE supports expert working groups on priority diseases in animal health that were established to analyse gaps in R&D and draft research plans. When required, these groups also prepare target product profiles according to a harmonized procedure.

FAO has numerous manuals for the recognition, prevention and management of outbreaks of priority diseases in terrestrial animals and is finalizing a book on 10 bacterial disease groups in aquaculture in order to guide the response. FAO contributes to STAR-IDAZ and hosts the secretariat of the multistakeholder Global agenda for sustainable livestock.<sup>35</sup>

JPI-AMR coordinates national research programmes on AMR to avoid duplication in basic and preclinical research in the human, animal and environmental sectors through a strategic research agenda that maps its members' initiatives. Established in 2011 by 15 European countries, JPI AMR has grown into a global institution, with a diverse membership of 26 high- and middle-income countries.<sup>36</sup>

<sup>35</sup> A partnership of livestock sector stakeholders committed to sustainable development of the sector ([www.livestockdialogue.org](http://www.livestockdialogue.org))

<sup>36</sup> Argentina, Belgium, Canada, Czechia, Denmark, Egypt, Estonia, Finland, France, Germany, Greece, Ireland, Israel, Italy, India,

**STAR-IDAZ IRC**, a global network of research funders and managers, was established in 2016 as a continuation of a European project (2011-2015). It ensures that funds are allocated to global priorities in animal health, in collaboration with OIE. Although STAR-IDAZ IRC does not focus on AMR, it will establish an expert working group to investigate new tools and integrated pathogen control for AMR in 2018. Its activities in diagnostics and vaccines research are indirectly related to AMR.

The **Global AMR R&D Collaboration Hub** was created after G20 discussions in July 2017 and will be launched on 22 May 2018 during the World Health Assembly. The Hub is expected to address the full scope of AMR R&D, including antimicrobials, diagnostics and vaccines and all sectors (human, animal, plant and environmental health), although it will initially focus on bacteria and human health.

Domestic coordination is also important to ensure that information on AMR-related activities is shared among national stakeholders. For example, the AMR Funders Forum in the United Kingdom brings together all R&D funders in the country three times a year and enables offline discussions throughout the year on what each funder is doing, what they plan to do, their priorities and opportunities for collaboration. This ensures a strategic overview of the national research base and understanding of its output, skills, resources and impact, creating a common vision of the future of AMR research.<sup>37</sup>

*Gaps: opportunities to extend priorities for R&D, ensure alignment of funding with global priorities, avoid duplication and monitor coordination in a One Health approach*

Global priorities and gaps beyond HIV, malaria, tuberculosis and other bacterial infections in humans should be identified, such as antiviral, antifungal and antiparasitic agents for use in humans and terrestrial and aquatic animals.

Funding decisions should be better aligned with global priorities.<sup>38</sup> As there is limited transparency about the areas of research that are receiving funding,<sup>15</sup> there may be ineffective duplication in R&D, especially in preclinical research.<sup>12</sup>

Finally, coordination among initiatives on human, animal, plant and environmental health should be improved<sup>15</sup> and cross-sectoral lessons learned could be better leveraged. For example, successful R&D models in human health such as PDPs could be replicated in animal, plant and environmental health and made sustainable with increased funding.

### *Open questions*

How could R&D funding be better channeled?

What will it take to increase and sustain donor and private funding of R&D in AMR?

Which incentives and de-linkage mechanisms could best address each of the challenges and barriers identified?

How should the design of incentive mechanisms be coordinated at global, regional and national levels?

How could current efforts in R&D coordination be strengthened?

---

Japan, Netherlands, Norway, Poland, Romania, South Africa, Spain, Sweden, Switzerland, Turkey, United Kingdom.

<sup>37</sup> <https://mrc.ukri.org/research/initiatives/antimicrobial-resistance/antimicrobial-resistance-funders-forum/>.

<sup>38</sup> G20 Presidency proposal: global R&D collaboration hub on AMR. Cologne: German Aerospace Agency; 2017 ([https://www.jpiaamr.eu/wp-content/uploads/2017/10/Junker-B\\_Akkoyun-A\\_G20\\_DLR.pdf](https://www.jpiaamr.eu/wp-content/uploads/2017/10/Junker-B_Akkoyun-A_G20_DLR.pdf)); OECD, WHO, FAO, OIE. Tackling antimicrobial resistance. Ensuring sustainable R&D. Paris: OECD; 2017; key stakeholder interview conducted by the IACG.

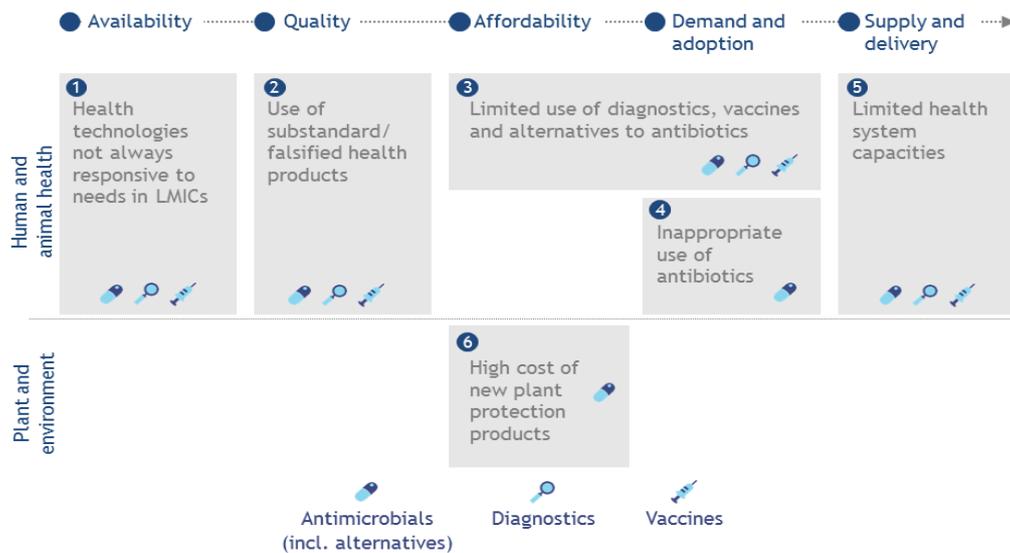
## 2. Access

### 2.1. Multiple challenges

The IACG defined “access” broadly as all the activities necessary to ensure the right product in the right place at the right time. This definition covers the several dimensions of access: availability, quality, affordability, demand and adoption and supply and delivery (Fig. 3). These dimensions are referred to collectively as the “access value chain”.

Stewardship and appropriate use, although closely linked to R&D and access considerations, are tackled in a separate IACG discussion paper on reducing the need for and unintentional exposure to antimicrobials and optimizing use<sup>39</sup>. As stated in the United Nations political declaration on AMR, <sup>Error! Bookmark not defined.</sup> lack of access to essential antimicrobials contributes to more deaths in LMICs than AMR. The IACG therefore analysed the difficulties of LMICs in accessing antimicrobials, as they have the greatest difficulty in accessing good-quality, safe, efficacious, affordable AMR-related technologies. The IACG will broaden its scope in its next phase of work to ensure that “access” in its broadest sense is addressed. In particular, the IACG will extend its lens to include shortages in LMICs and HICs.

Fig. 3, Challenges in access to AMR-related technologies in LMICs



<sup>39</sup> Discussion paper to be posted online in the next wave of consultation

### Human health and animal health

There are five main challenges in accessing AMR-related health technologies in LMICs, which are common to human and animal health.

#### 1 All health technologies do not meet the needs of LMICs.

Examples of successful product adaptations include:

- HIV and tuberculosis treatments that are dosed and adapted to children, encouraging appropriate use and adherence;
- affordable, non-electric rapid diagnostic tests at points of care to overcome unreliable or unavailable electricity supplies and lack of laboratory facilities;
- controlled temperature chain vaccines that can be stored outside the traditional cold chain for a limited period, without affecting antigen stability; and
- packaging adapted to LMICs, such as smaller herds or species in animal health.

More is needed to develop and adapt health technologies to LMIC needs. Ensuring R&D efforts are needs-driven and evidence-based and are guided by the principles of affordability, effectiveness, efficiency and equity<sup>5</sup> would ensure that technologies developed in the future meet the requirements of low resource settings.

#### 2 Substandard or falsified health products contribute critically to the development of resistance. For example, resistance to the most important antimalarial medicines, artemisinins, appeared in Africa and South-East Asia, where 38-90% of commercialized medicines were found to be either substandard or falsified.<sup>40</sup>

Additionally, in a study published in 2015, 41% of drug samples failed to meet quality standards.<sup>41</sup> Quality is a disproportionate challenge for antibiotic and antimalarial agents, which represent about 40% of substandard or falsified drug samples.<sup>42</sup>

In animal health, it has been estimated conservatively that at least 3% of the total value of veterinary medicines consists of substandard, unregistered or falsified products, and other studies reported as many as 15% in some countries.<sup>43</sup>

<sup>40</sup> Global surveillance and monitoring system for substandard and falsified medical products. Geneva: World Health Organization; 2017 ([http://www.who.int/medicines/regulation/ssffc/publications/GSMS\\_Report.pdf?ua=1](http://www.who.int/medicines/regulation/ssffc/publications/GSMS_Report.pdf?ua=1)).

<sup>41</sup> =Global pandemic of fake medicines poses urgent risk, scientists say (based on a global study of about 17,000 drug samples published in 2015). Bethesda (MD): National Institutes of Health; 2015 (<https://www.nih.gov/news-events/news-releases/global-pandemic-fake-medicines-poses-urgent-risk-scientists-say>).

<sup>42</sup> Based on 100 publicly available studies published over the past 10 years involving over 48 000 drug samples in 88 countries based on WHO global surveillance and monitoring system for substandard and falsified medical products. Geneva: World Health Organization; 2017.

<sup>43</sup> Illegal veterinary medicines, impact and effective control. London: Health for Animals; 2017.

#### 3 There is limited use of diagnostics and vaccines in LMICs, for several reasons.

- They are perceived as an additional out-of-pocket expense, as they are often not reimbursed and may cost more than the treatment itself or indicate treatment that is not available.
- Health care practitioners, veterinarians and veterinary paraprofessionals have limited training for administering tests and analysing the results.
- There are often delays in obtaining reliable results.

The barriers to increased, equitable vaccination coverage include:

- their cost: as for diagnostics, out-of-pocket payments are often required. There is little awareness of the benefits of vaccination in terms of direct health gains, saving of health-care costs and reduced time and costs of care;
- misinformation about the side-effects of vaccines, e.g. that vaccinated fish are dangerous for human consumption;
- supply shortages;
- insufficient numbers of trained health care practitioners, veterinarians and veterinary paraprofessionals;
- difficulty in maintaining an adequate cold chain, when required; and
- complex vaccine delivery, including multiple doses and follow-up visits.

#### 4 Inappropriate use of antibiotics is a global problem and contributes significantly to AMR. While misuse has been reported in all regions of the world, More antibiotics are sold without prescription over the counter in LMICs (66%) than in high-income countries.<sup>44</sup> This is due to:

- less restrictive institutional and governmental policies on antibiotic use;
- weak supply chains;
- limited use of diagnostics or lack of access to indicated treatment; and
- inadequate education of health professionals and the public.

Antibiotics are used not only for the prevention and treatment of human diseases but also used in animal health as growth promoters, which contributes to AMR.

#### 5 Limited health system capacity remains a key problem.

- The limited human and financial resources and domestic financing for AMR in human and animal health slow progress towards universal health coverage. Costs can strain government health budgets<sup>45</sup> and reinforce reliance on out-of-pocket payments, which affects

<sup>44</sup> Bebell, LM, Muiru, AN. Antibiotic use and emerging resistance - how can resource-limited countries turn the tide? *Global Health*. 2014;9(3):347-58.

<sup>45</sup> Mendelson M, Röttingen JA, Gopinathan U, Hamer DH, Wertheim H, Basnyat B et al. Maximising access to achieve appropriate human antimicrobial use in low-income and middle-income countries. *Lancet*. 2016; 387:188-98.

- affordability, especially for new antibiotics, diagnostics and vaccines.
- Few financial resources are dedicated to animal health and disease prevention, detection and control.
- National regulations on implementation and enforcement of health policies (for example, against substandard and falsified health products) are weak.

- There is limited ability to address frequent shortages of essential medicines and antibiotics, thus accelerating development of resistance.
- Not all data systems are effective.

- 6 **Plant and environmental health**  
**Use of new plant protection products is limited by their high cost.** Consequently, farmers may prefer older products, which may result in higher levels of resistance

## 2.2. Existing response to challenges of access, gaps identified and open questions to bridge the gaps

This section first describes the existing response to the identified challenges, identifies the main gaps and poses open questions to advance thinking on how and by whom the gaps in access could be bridged (Fig. 4).

Fig. 4. Main gaps in access identified from existing response



### No existing initiative with specific AMR focus

- AMR access challenges such as the limited capacity of healthcare systems, out-of-pocket payments or the use of substandard / falsified health products not entirely addressed



### Opportunity to coordinate and complement fragmented response

- In human health, limited attention to AMR-related diseases beyond HIV, TB, and malaria
- In animal health, few diseases and animals covered
- Plant and environmental health not adequately reflected in the AMR agenda

*Existing response: some global access initiatives in human health but they do not specifically include AMR in their mandate, and there are only few access initiatives in animal health.*

In human health, only a few noncommercial global funds for the broad field of access to health technologies have direct or indirect experience in addressing AMR in LMICs, although these are not specifically mandated to address AMR. These include:

- Gavi, the Vaccine Alliance, which accelerates access to vaccines against 15 diseases in humans,<sup>46</sup> thus preventing infection and addressing challenges to access 3, 4 and 5;
- The **Global Fund** and **Unitaid** address, respectively, scaling-up and catalysing access to prevention, diagnostics and treatment for HIV, tuberculosis and malaria and support rational drug use; both

organizations cover AMR as it relates to the three diseases, and notably around drug resistant TB, and together contribute to addressing challenges 1, 2, 3, 4 and 5; and

- **UNICEF**, which supports both access to medicines and diagnostics for the integrated management of childhood illnesses and rational drug use.<sup>47</sup> UNICEF therefore partly addresses challenges 3, 4 and 5 in human health.

WHO provides guidance on the use of antibiotics in human health through its Essential Medicines List, which was recently updated with advice on which antibiotics to use and which to preserve for the most serious syndromes by categorizing them into three groups: access, watch and reserve.

In animal health, OIE sets standards and provides guidance on the use of antimicrobials through its List of Antimicrobial Agents of Veterinary Importance.

<sup>46</sup> Papillomavirus, polio, Japanese encephalitis, measles, meningitis A, cholera, diphtheria, tetanus, pertussis, hepatitis B, haemophilus influenzae B, rubella, bacterial pneumonia, rotavirus, yellow fever.

<sup>47</sup> IACG activity mapping exercise. Geneva: 2017 ([http://www.who.int/antimicrobial-resistance/interagency-coordination-group/ActivityMapping\\_Nov2017.pdf](http://www.who.int/antimicrobial-resistance/interagency-coordination-group/ActivityMapping_Nov2017.pdf)).

Few initiatives address access in animal health, none focuses on AMR, and they cover a limited number of species and diseases. For example, the Zoonose Anticipation and Preparedness Initiative (ZAPI) addresses zoonoses only, and the FishMedPlus Coalition fish only.

*Gaps: current initiatives lack a specific focus on AMR. The fragmented response should be coordinated and strengthened and better leverage lessons learned and best practices in expanding access to essential medicines*

As these access initiatives do not focus on AMR, many of the access challenges identified remain unaddressed. The rapid mapping above suggests there is limited attention to AMR beyond drug resistance in HIV, tuberculosis and malaria in human health; that few diseases and species are covered in animal health; and that plant and environmental health are not adequately reflected in the AMR agenda.

In access, the response should focus on tackling the following gaps:

- Addressing the limited capacity of health care systems, out-of-pocket payments and quality issues.
- Coordinating fragmented initiatives, and establishing AMR as one element of universal health coverage.
- Complementing the existing response, in animal, plant and environmental health for all diseases and in human health for all AMR-related diseases other than HIV, tuberculosis and malaria.

Extending the mandates of existing funds to include AMR would ensure that the capacity of these organizations could be leveraged immediately for the global AMR response, and their credibility and reputations could be used to raise additional funding to combat AMR and meet the One Health objectives.

Creating a new access initiative could accelerate the operationalization of the One Health approach, as existing funds do not focus sufficiently on plant or environmental health. International donors might not be attracted to such an initiative, however, which could lead to further

fragmentation. Furthermore, launching a new initiative would take time, in particular for establishing a new secretariat, infrastructure, policies and processes, while a response is required urgently.

Beyond the creation of a new initiative, or extending the mandate of existing initiatives to ensure a coherent and comprehensive approach to tackling AMR-related access challenges, there are lessons learned and best practices in expanding access to essential medicines that could be leveraged in AMR across human, animal, plant and environmental health. These include the pooled procurement of medicines to support uninterrupted access to high-quality medicines and technologies, with potential to drive down prices, thus addressing challenges ② and partially addressing challenges ③ and ⑤.

In addition, voluntary licensing, including patent pooling, have been proven to facilitate innovation while increasing access to treatment. For example, the Medicines Patent Pool supports access to affordable and appropriate medicines in LMICs, through bringing down prices and fostering the development of better-adapted formulations for resource-limited settings. Patent pooling for medicines, diagnostics and vaccines could tackle challenge ① and potentially challenge ②.

Finally, implementation research could play a role in facilitating uptake of new products entering the market and, in the case of antibiotics, could also help in building the evidence base for appropriate use and stewardship, and inform innovation in practice, thus contributing to the response to challenges ④ and ⑤.

#### Open questions

Are there other mechanisms that should be considered to expand access to AMR-related health technologies and address the challenges identified?

Should the mandates of one or several existing funds be extended to include AMR? Or should a new access initiative be created?

### 3. Cross-cutting topics in R&D and access

Two areas have been identified by the IACG as transversal between R&D and access: the need for additional guidance for funders of R&D and access and operationalization of the One Health approach. Both areas are linked to attainment of the SDGs, increasing investments in AMR R&D and access and fostering further synergies among human, animal, environmental and plant health.

*Additional guidance is needed to increase investments in R&D and access*

*Existing response: technical guidance identifies gaps in the AMR response, but there is no guidance on mobilizing further investment to fill the gaps.*

Technical agencies, including FAO, OIE and WHO, set priorities and support identification of critical gaps in AMR R&D and access, but they do not fund R&D. As described in further detail in section 1.2, FAO's AMR action plan for 2016-2020 that includes animal, plant and environmental health, OIE's prioritization of research and gap analyses and WHO's list of priority pathogens and its antibacterial clinical pipeline report are essential for guiding the global response to AMR.

*Gaps: absence of mechanism to encourage and guide resource allocation by the main stakeholders and donors*

Strong technical guidance and clear priorities are crucial for a coordinated response to AMR. They do not, however, necessarily increase investments in the priorities. **Guiding principles** could help funders to target investments where they are needed most to ensure an effect against the challenges of AMR R&D and access and facilitate appropriate adaptation for regions and countries. Moreover, the guiding principles are in line with the request of the United Nations General Assembly to WHO to develop, with OIE and FAO, a global development and stewardship framework to foster R&D and enhance access to existing and new health technologies and their appropriate use. They could become one element of that framework.

Any guiding principle should build on, be aligned with, and also facilitate the implementation of the United Nations

### *An operational One Health approach in the context of R&D, innovation and access*

*Existing response: reflection on operationalization of the One Health approach is currently led by the Tripartite collaboration*

The political declaration on AMR<sup>6</sup> recognizes that the overarching principle in addressing AMR is the promotion and protection of human health within a One Health approach. It emphasizes that coherent, comprehensive, integrated, multisectoral action is required, recognizing that human, animal, plant and environmental health are interconnected.

Initiatives to operationalize the One Health approach already exist, such as the Tripartite collaboration of FAO, OIE and WHO to minimize the emergence and spread of AMR by fostering collaborations across sectors at national, regional and global levels.<sup>48</sup> The collaboration provides support for

political declaration on AMR, which states that efforts must be “needs-driven, evidence-based and guided by the principles of affordability, effectiveness and efficiency and equity”. Error! Bookmark not defined.

The guiding principles could include the following.

- **Global public benefit:** Ensure that investments address AMR priorities, taking into account disease burden and transmission in human, animal, plant and environmental health, and are prioritized according to their impact on the SDGs other than health (e.g. hunger, food security and sustainable development).
- **Equity:** Ensure that investments address the needs of both LMICs and high-income countries and of the most vulnerable populations (such as women and children).
- **Gaps in response:** Ensure that investments target priority pathogens and scientific, technological and/or funding gaps in the pipeline.
- **Value for money:** Ensure that investments are allocated to projects that are expected to have the greatest benefit for global health (e.g. number of lives saved) at the lowest cost and at a certain level of risk and that high-risk investments that could generate high rewards are not neglected.

### *Open questions*

**How should the guiding principles be operationalized? Are there additional relevant guiding principles to be considered?**

the development and implementation of national action plans in a One Health approach through manuals, checklists and international workshops. There are also many national and regional initiatives to operationalize the One Health approach, though consortia, academic institutions and regional networks.

*Gaps: further leveraging of synergies among human, animal, plant and environmental health*

**More could be done to operationalize the One Health approach** and better leverage synergies among the different sectors, both in R&D and in access. **More could also be done to include the plant and environmental sectors**, where there are more knowledge gaps and where needs tend to be under-represented in the One Health approach.

<sup>48</sup> WHO/FAO/OIE factsheet on antimicrobial resistance. WHO, FAO and OIE unite in the fight against AMR. Paris: World Organisation for Animal Health; undated

([http://www.oie.int/fileadmin/Home/eng/Media\\_Center/docs/pdf/FAO\\_OIE\\_WHO\\_AMRfactsheet.pdf](http://www.oie.int/fileadmin/Home/eng/Media_Center/docs/pdf/FAO_OIE_WHO_AMRfactsheet.pdf)).

There might be ways to address similar challenges to access in human and animal health simultaneously, by common training for doctors and veterinarians or using technical innovations in human health products to animal health, such as electricity-free diagnostics or controlled temperature chain vaccines.

*Open questions*

Which practical One Health activities would have the greatest impact on R&D and access and would be most feasible?

How and which organization(s) could take the lead to ensure that the next generation of scientists is trained in the One Health approach and that sufficient resources are allocated to attract researchers?