Response by MSF Access Campaign to the consultation on IACG discussion paper, 'Antimicrobial resistance: Invest in innovation and research, and boost R&D and access'

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

1. How could R&D funding be better channelled?

1.1. The framework for R&D funding has been set by the United Nations Declaration on AMR (2016). This states clearly that all R&D funding 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.' It further acknowledges, 'the importance of delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales so as to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines and other results to be gained through research and development…'

1.2. In establishing a 'Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics' (global PPL), WHO has provided the basis for measuring whether R&D funding is 'needs-driven' in the area of new antibiotic drugs including TB. All funding for new antibiotics should therefore follow this guide to ensure it is aligned with the UN Declaration.

1.3. However, it is important to note that investments in R&D should not focus exclusively on bringing new antibiotic drugs to market, but also on other areas of innovation that are needed to most effectively combat AMR. As acknowledged in the discussion paper, a successful response to AMR will also need to address vaccines and diagnostics, as well as developing novel approaches and clinical algorithms that are adapted to specific local contexts. In these areas, further work is needed by WHO to set global priorities in order that R&D funding can be aligned with unmet needs.

1.4. The principle of affordability can be ensured by attaching conditions for access to R&D funding. Funding for upstream R&D can and should be coupled with access and stewardship requirements downstream as these products enter the market. AMR products and technologies that have benefited from significant public support should be considered public goods, and a public return on investment, through affordability and accessibility for all, should therefore be ensured. To this extent, public funders should ensure the traceability of taxpayer money invested in R&D. This is a necessary prerequisite for providing transparency and building public accountability for R&D as a shared responsibility.

1.5. The principle of efficiency can be ensured by fostering collaboration in order to accelerate delivery time of new treatments from 'bench to bedside' through the sharing of research results, including clinical trial data, providing access to well characterized sample banks and compound libraries, as well as the pooling of intellectual property rights as needed to further optimise development. These conditions will speed up development, reduce costs, and increase efficiency. The IACG should recommend incentives that foster these approaches.

1.6. In order to ensure the principle of equity is addressed in R&D, funding must be specifically made available for adapting drugs to the needs of specific patient populations that are often overlooked. This includes providing funding for the development of heat-stable, paediatric and oral formulations of existing and new antibiotics.

1.7. There is also a need to look at recommendations for how to address the following areas of innovation: repurposing of older or withdrawn antibiotics; exploring the as-yet-untapped potential of combination products (rational fix dose combinations (FDCs)); sustainable implementation of new technologies within health programmes; and piloting, evaluating and scaling-up improved practices for infection control and antimicrobial use.

1.8. Finally, all R&D funding should operationalize the principle of delinking investment in R&D from the expectation of high prices and volume of sales, as set out in the funding framework provided by the UN Declaration on AMR.

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

2.1. Increasing and sustaining donor funding of R&D on AMR requires political will. One way to build political will is to increase public support for the issue. In this regard the traceability of public funding is critical as it allows the public to see whether they are getting a return on their investment in the form of the development of new technologies to meet their needs at prices they and their governments can afford.

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

3.1. The 5 challenges identified in the human health R&D value chain set out clearly the barriers to product development for new antibiotics, diagnostics and vaccines. The paper then identifies where existing initiatives contribute in part to addressing each of these challenges. This is useful, but it omits two important elements of analysis that are needed to get a full picture of the global response: an indication of the scale of the challenge versus the scale of the response; and the extent to which existing initiatives are aligned with the key principles outlined in the UN Political Declaration on AMR.

3.2. The question of scale is important because a particular initiative may contribute to ameliorating a particular challenge, but perhaps only with a fraction of the necessary budget to do this sufficiently. It is important to present the estimated scale of the *required* response against the scale of the *existing* response in order to see the size of the gap to be filled.

3.3. Analysing the extent to which existing and future initiatives address a specific challenge (such as challenge 1: the uncertainty in the expected return on investment of antibiotics) in isolation does not provide a necessary qualitative assessment of whether these initiatives operationalize the principles set out in the UN Political declaration on AMR. For instance, it may be possible to address the uncertainty in the expected return on investment in antibiotics by providing large financial rewards for any new antibiotic successfully completing phase 2 studies and entering the market without attaching any conditions to ensure affordability or stewardship. This type of incentive is clearly not fit for purpose and could lead to a perpetuation of the cycle of profit focus, expensive drugs, and limited patient access, at the expense of public finance.

3.4. Rather than looking to add incentive after incentive to address discrete challenges in isolation, as the framing of this question encourages, the IACG should look to support an investment framework from bench to bedside to ensure that clinical benefit, access and stewardship are guaranteed throughout the entire product development process. This would begin with defining target product profiles (TPPs) for priority unmet needs (based on the global PPL in the area of new antibiotics, for example); ensuring that access and affordability are set out as key target characteristics within these TPPs, including target price points to guide investment choices; and then seeing products through to the bedside by supporting the sustainable implementation of new AMR technologies within health systems.

3.5. Moreover, approaches that foster collaboration through the sharing of research results should be supported, as they will speed up development, reduce costs, and increase efficiency. This includes sharing clinical trial data, providing access to well characterized sample banks and compound libraries, as well as the pooling of intellectual property rights, as needed, to further optimise development. In this light, the Medicines Patent Pool should be looked at as a suitable mechanism for promoting collaborative research through the pooling of intellectual property rights during the development phase, while ensuring populations in need globally can benefit. This can be particularly useful in facilitating the development of rational FDCs, and improved combination regimens for drug resistant TB, for example.

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

4.1. As stated above in 1.1, coordination starts with adhering to the framework set by the UN Declaration on AMR. If incentives are built on these principles[1] and follow the needs-driven prioritization set by the global PPL, coordination should follow and research and development efforts will be more successful. The Global Development and Stewardship Framework (GDSF) under development by the WHO, FAO and OIE should also provide a more tangible coordination framework, once agreed. The GDSF seeks to follow the entire value chain of product development from bench to bedside and, as such, should provide clear guidance to coordinate incentive mechanisms at the national, regional and global level.

4.2. Mechanisms that promote transparency and traceability of funding will allow donors and implementers to see where the gaps are in the response and provide the first building blocks for coordination. Without transparency on the R&D portfolios and funding flows the risk of overlap and duplication remain.

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

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

5.1. The mechanisms described in the paper are limited to the following:

- Specific 'global' funds for certain diseases and certain LMICs (such as Gavi, the Vaccine Alliance, the GFATM and UNITAID)
- The WHO's Essential Medicines List
- Voluntary licensing, including patent pooling
- Implementation research

As the paper notes, the global funds identified lack a specific focus on AMR. Moreover, the scope of countries covered by these initiatives is limited and differs from one to the other. In recent years these funds have insisted on 'transitioning' or 'graduating' middle-income countries out of eligibility for support. As such the usefulness of these funds to address the access issues of a wider range of countries is further diminished. The IACG should recommend that any mechanism to expand access to AMR-related health technologies be global in scope. This could start with revisiting and reversing the current trend towards restricting support for LMICs through 'graduation' and 'transition'.

[1] '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 importance of delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales so as to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines and other results to be gained through research and development…'

5.2 In the area of vaccines this is particularly pertinent. Increasing affordable access to vaccines should be a high priority within the global AMR response as there is overwhelming evidence supporting vaccination as an effective, safe, low-cost measure to reduce the burden of both infectious diseases and AMR at every level[2]. For example, it has been estimated that introduction of Haemophilus influenzae type b (Hib) conjugate vaccine and pneumococcal conjugate vaccine (PCV) to 75 developing world countries could reduce antibiotic use for these diseases by 47% and avert 11.4 million days of antibiotic use in children younger than 5 years old each year [3]. Other vaccines for diarrhoeal and respiratory infections, in particular, have similar potential. Yet, currently, vaccination coverage is unacceptably low in many countries where MSF works. PCV, to take one example, remains unaffordable for a number of LMICs. By May 2018, globally 53 countries (27%) had not introduced a PCV vaccine in their national immunisation programme[4]. Of these 53 countries only 7 are Gavi-eligible countries[5], which illustrates a trend seen for years whereby low-income countries are introducing new vaccines at a faster pace than middle-income countries (MICs) due to availability of international donor financial support. The lowest price of ~USD 10 per child is available to those countries that are subsidised by Gavi, the Vaccine Alliance and, since 2017, to humanitarian organizations through the Humanitarian Mechanism, a mechanism for accessing affordable and timely supply of vaccines for use in humanitarian emergencies[6]. Even some Gavi-supported countries are not scaling up PCV coverage in their immunisation programmes for fear that they won't be able to sustain an affordable supply once they transition out of Gavi funding and have to pay much higher prices. The IACG should recommend measures to address this situation as a priority.

5.3 Governments must be supported to address situations of monopolies and high prices where these are barriers to access for needed AMR technologies. This involves avoiding the granting of poor quality patents as well as making use of compulsory licensing to overcome unaffordable prices of monopoly products.

5.4 Pooled procurement, as specifically modelled by the Global Drug Facility (GDF), should be explored as a key mechanism for ensuring both lower prices for antibiotics and improved stewardship. The GDF represents a large portion of the market for TB drugs and diagnostics, and uses this to negotiate prices with companies based on larger volumes. GDF's international tenders allow both generic and innovator companies to compete in supplying quality-assured TB health products. It rejects tiered pricing; encourages suppliers to enter

[2] Kathrin U Jansen & Annaliesa S Anderson (2018): The role of vaccines in fighting antimicrobial resistance (AMR), Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2018.1476814

[3] *Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen JA, Klugman K, Davies S. 2016. Access to effective antimicrobials: a worldwide challenge. Lancet 387:168 175.doi:10.1016/S0140-6736(15)00474-2*

[4] WHO Data, statistics and graphics , http://www.who.int/immunization/monitoring_surveillance/data/en/
Access 5th July 2018

[5] IVAC's digital platforms contain downloadable vaccine introduction maps : http://view-hub.org/viz/
Access 5th July 2018

[6] Accessing Affordable and Timely Supply of Vaccines for use in Humanitarian Emergencies: the Humanitarian Mechanism
http://www.who.int/immunization/programmes_systems/sustainability/The_Humanitarian_Mechanism_ToRs.pdf?ua=1

into markets; provides forecasting to suppliers as well as providing governments with forecasting assistance and orders (which is important given different shelf lives). It anticipates and addresses global supply issues and provides advice to countries on switching to optimal from sub-optimal formulations. In the area of diagnostic tools, GDF has been able to negotiate improved service and maintenance terms from companies.

Cross-cutting topics in R&D and access

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

6.1 The guiding principles are set out clearly in the UN political declaration on AMR, as referenced in the paper on page 15 and noted in this submission under point 1.1. It is unclear why one of those principles, 'Equity' has been expanded upon in the consultation paper, and three new 'guiding principles' (Global public benefit, Gaps in the response and value for money) have been added. The IACG takes its mandate from the UN Declaration on AMR and, as such, should focus on these globally agreed principles to guide its work.

6.2 Please see answers 1.1 to 1.8 for MSF's response on how to operationalize the principles of the UN Declaration on AMR.