MSF Access Campaign
FEBRUARY 2019

MSF Access Campaign response to the public discussion on the draft recommendations of the Ad hoc Interagency Coordination Group on Antimicrobial Resistance (IACG)

Overview

Médecins Sans Frontières (MSF) welcomes the opportunity to provide comments on the draft recommendations of the IACG ahead of the report's submission to the UN Secretary-General by April 2019.

As a medical humanitarian organisation with operations in over 70 countries, MSF is deeply concerned by the rapidly growing global burden of antimicrobial resistance (AMR) – a highly complex health challenge that defies borders and spares no one. Among those disproportionately affected are the poor, rural, neglected, conflict- and disaster-affected populations that are our primary concern. Our efforts to draw attention to the problem of AMR in the settings where we work have helped us understand that drug-resistant infections are present and spreading everywhere. We see this evidence directly when we identify resistant bacteria in the blood of newborn babies in West Africa or the bones of war-wounded patients in the Middle East – and we see it indirectly when our best available anti-infective treatments fail or we witness the widespread misuse of antimicrobials, particularly through their unregulated sale.

From Iraq to India, Yemen to Sudan, and from Syria to the Central African Republic, wherever we have looked for evidence of AMR, we have found it. We therefore acknowledge with respect and appreciation the efforts of the IACG to date, but feel compelled to point out some key areas within this critically important work where the needs of our patients and healthcare professionals remain inadequately addressed.

Overall, it is encouraging to see that this draft is anchored in the 2016 UN Political Declaration on Antimicrobial Resistance, and that many of the principles set out in the Declaration are taken into account. This is evidenced in the considerations for recommendation B1, where the IACG reiterates that *"…all research and development efforts to address antimicrobial resistance should be needs-driven, evidence-based and guided by the principles of affordability, effectiveness, efficiency and equity"*. However, we note with concern that this current draft does not reflect the UN Political Declaration's prioritisation of "…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…". High medicines prices due to unchecked monopoly powers and the consequent access challenges have become a globally recognised issue – from pneumococcal vaccines to newer drugs for the treatment of hepatitis C virus and cancer. Given the massive injection of public and philanthropic funding into R&D for drugs, diagnostics and vaccines to address AMR, it is critical to establish novel approaches on pricing based on the full transparency of underlying costs and recognising the collective effort of different contributors to the R&D process, from basic research to implementation and patient access.

Moreover, as discussed below in relation to the recommendations outlined under Section B, "Innovate to Secure the Future", we urge the IACG not merely to reference the principles of the UN Political Declaration, but to provide concrete guidance as to how such principles can be adhered to. Given the unfortunate disconnect between the noting of the Declaration's principles and the considerations on incentives that are subsequently elaborated, the draft recommendations do not adequately reflect the guiding principles of the Declaration.

The manner in which this report's recommendations and considerations will be taken forward remains an unanswered question. Much of the guidance to governments is listed as a "consideration for this recommendation", but is written in the form of a recommendation that "governments should establish…". Further clarity is needed to ensure that some of the important "considerations" are not treated merely as footnotes, but are taken up as recommendations.

Below we provide comments on several of the specific recommendations and considerations outlined in the report.

Section A: Accelerate progress in countries

Recommendation A1: "The IACG calls on all Member States to ensure equitable and affordable access to existing and new quality-assured antimicrobials and their prudent use by competent, licensed professionals across human, animal and plant health."

- The headline objective focuses exclusively on antimicrobials, whereas under *"considerations for the recommendations"* this is expanded to cover drugs, diagnostics and vaccines. We support the wider focus, as it is right to focus on all three technologies. 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. For example, it has been estimated that introduction of the Haemophilus influenzae type b (Hib) conjugate vaccine and pneumococcal conjugate vaccine (PCV) to 75 developing countries could reduce antibiotic use for these diseases by 47% and avert 11.4 million days of antibiotic use each year in children younger than 5 years of age. MSF has been campaigning for several years for more affordable versions of PCV to be made available to developing countries and humanitarian organisations. This is something the IACG should concretely support.
- We strongly support the recommendation on *"Establishing antimicrobial production facilities",* that *"governments or regional entities may consider establishing production facilities or contracting manufacturers to help mitigate shortages and ensure a resilient supply of antimicrobials, particularly antibiotics and vaccines for human and animal health, paying due consideration to manufacturing standards and quality assurance for health commodities."* It is clear that market forces are not serving the interests of patients and healthcare professionals in the case of AMR. In many countries where we work, MSF sees that certain essential ACCESS antibiotics are not adequately available, while other WATCH and RESERVE antibiotics are freely available without sufficient controls. Market exits, inflexible production cycles, and sole-sourcing negatively affect access to basic antibiotics internationally. Several manufacturing sites, including those of international pharmaceutical companies, are ceasing production of basic essential antibiotics deemed 'not viable'. Meanwhile, global demand for drugs such as penicillins is not adequately secured. The above recommendation calling on governments and regional entities to consider solutions beyond the market, such as establishing production facilities or contracting manufacturers to ensure a resilient supply of antimicrobials, is a welcome practical solution.
- The challenges identified in this section for global shortages of existing antibiotics will also be faced for new antibiotics in development that are indicated for WATCH and RESERVE use. We know from the situation described above that relying on market forces will not deliver what is needed by patients and healthcare professionals when it comes to treating infections appropriately. This must be acknowledged, and whether in terms of contract manufacturing, direct establishment of production facilities or other initiatives, we must start designing measures to prevent shortages and stockouts, ensure a sustainable supply of critically needed antimicrobials and vaccines, and facilitate the rationale manufacture and supply of antibiotics that have not yet been developed or attained marketing authorisation. These measures must start with those public health goals in mind and, as such, look for solutions beyond the market.
- We support the recommendation on *"Pooled procurement mechanisms: Leveraging existing pooled procurement mechanisms in human health and potentially establishing them for animal health could help to secure both the supply of quality-assured medicines and ensure predictability of demand for manufacturers."* Pooled procurement mechanisms such as the Global Drug Facility (GDF) model should be explored as a mechanism for ensuring both lower prices for antibiotics and improved stewardship in the immediate term. 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 originator companies to compete in supplying quality-assured TB medicines. GDF rejects tiered pricing, encourages suppliers to enter into markets, provides forecasting to suppliers, and provides 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 from sub-optimal to optimal formulations. In the area of diagnostic tools, GDF has been able to negotiate improved service and maintenance terms from companies.
- We highlight with concern the final consideration outlined with regard to ensuring equitable and affordable access to and stewardship of existing and new quality-assured drugs, diagnostics and vaccines: the assertion that, *"complementary efforts to improve antimicrobial resistance surveillance and supply chain mechanisms - including the implementation of low-cost technologies and track-and-trace systems - could*

help to address [the problem of substandard and falsified medical products] *in low- and middle-income countries."* Tackling this complex problem requires extensive work on regulatory systems strengthening. There are no silver bullets when it comes to building strong, resilient regulatory systems. Implementing track-and-trace systems in the absence of such regulatory work is doomed to failure.

Section B: Innovate to secure the future

Recommendation B1: "The IACG calls upon public, private and philanthropic donors and other funders to increase investment and innovation in new antimicrobials - particularly antibiotics, diagnostics, vaccines, waste management tools, and safe and effective alternatives to antimicrobials - for human, terrestrial and aquatic animal and plant health..."

- MSF welcomes the call for an increased investment in innovation in new antimicrobials, antibiotics, diagnostics and vaccines, as well as waste management tools and safe and effective alternatives. However, as stated in our response to the previous IACG consultation, investments in R&D should not focus exclusively on bringing new antibiotics, diagnostics and vaccines to market, but also on other areas of innovation that are needed to effectively combat AMR. This includes (1) the repurposing of older or withdrawn antibiotics, (2) exploring the as-yet-untapped potential of both combination products (rational FDCs) and non-traditional therapeutics (such as antibody and phage therapies), (3) sustainably implementing new technologies within health programmes, and (4) developing novel approaches and clinical algorithms that are adapted to the local context. It also requires adapting existing drugs to the needs of specific patient populations that are often overlooked, such as the development of heat-stable, paediatric and oral formulations of existing and new antibiotics. For example, there is a lack of narrow-spectrum oral drugs to treat defined diseases that are commonly caused by antibiotic resistant bacteria, such as UTIs or typhoid. The IACG must recognise the need for financial support for the above areas of work and not focus too narrowly on 'new tools'.
- We would further suggest including a recommendation to the WHO to establish global priorities in the above areas of unmet medical need, in order that R&D funding can be aligned accordingly.
- While we welcome the statement under recommendation B1 that incentives be *"…based on the principles of affordability, effectiveness, efficiency and equity, as outlined in the 2016 UN Political Declaration on Antimicrobial Resistance",* we note with concern that no guidance is provided as to how these principles can be met. We believe that the IACG should provide such guidance.
    - For the principle of affordability, for example, the IACG should advocate for the attachment of conditions for access to public and philanthropic 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. Medicines that have benefited from significant public support should be considered public goods, and this collective investment should be secured through affordability and accessibility for all. To enable affordability, the IACG should recommend that public funders 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.
    - The principle of efficiency can be ensured by fostering collaboration in order to accelerate delivery time of new treatments from 'bench to bedside' through (1) sharing research results, including clinical trial data, (2) providing access to well-characterised sample banks and compound libraries, and (3) pooling intellectual property rights as needed to further optimise development. These conditions will expedite development, reduce costs, and increase efficiency. DND*i* have piloted many of these approaches to collaboration, so can be looked to to provide concrete examples of best practice in this area. The IACG should recommend incentives that foster these approaches.
    - The principle of equity can be addressed by ensuring that funding is made available for adapting drugs to the needs of specific patient populations that are often overlooked – such as children and pregnant women – as we have outlined above.
- The first consideration outlined under this recommendation focuses too narrowly on 'market pull' incentives as a means to address the lack of innovation in the area of antibiotic, diagnostic and vaccine development. Such pull incentives are often narrowly focused on the attainment of market authorisation. Given the current meagre state of the antibiotic pipeline, with only very few innovative compounds in all stages of development, MSF would argue that this focus is misplaced. We emphasise that it is important to

ensure that the prioritisation of funding allocations is targeted towards overcoming scientific barriers and bottlenecks and ensuring demonstrable therapeutic advance. As such, it is worth considering increasing the amount of funding available in grants to those involved in upstream, early-stage drug discovery and development.

- The process of prioritisation in antibiotic R&D has to be needs-driven, use the WHO Priority Pathogen List as a starting point, and assess the therapeutic benefit of potential leads for patients based on the definition of innovativeness provided in the WHO analysis of the antibacterial clinical development pipeline, including *Mycobacterium tuberculosis*. This is critical, as a majority of the agents currently in the pipeline are 'me-too' modifications of molecules that are currently marketed; a majority of others are modified agents of known antibiotic classes. If widely used, modified agents of old drug classes can drive rapid development of cross-resistance and co-selecting resistance.
- The "considerations" further note that, *"the IACG recognizes the need to develop and provide* financial and non-financial market incentives *for research and development to address antimicrobial resistance…"*. As stated above, there is a need to look beyond the market when it comes to finding the appropriate means of stimulating the necessary R&D to address AMR. A focus on market-fixing can lead to expensive solutions that hone in narrowly on one particular challenge in the product life cycle, while failing to address equally important aspects further along. For example, a focus on pull incentives that aim to fast track the registration of novel antibiotics can be very costly (especially if the pull attempts to provide an incentive that competes with otherwise commercially attractive areas of investment[1], such as oncology), but since the incentive is only focused on the achievement of registration in one or two markets, it neglects a very large part of the development challenge – that is to ensure that products are not only registered in all countries in need, but are manufactured in sufficient quantities and not commercially marketed (but instead are appropriately stewarded). Few late-stage antibiotics currently have any form of access or stewardship plans: three have access plans; two have stewardship plans; two have both access and stewardship plans. This of course says nothing about the quality of such plans, which must also be examined.

Recommendation B2: "The IACG recommends that existing and future global access initiatives should promote and support equitable and affordable access to existing and new antimicrobials, diagnostics, vaccines, waste management tools and safe and effective alternatives to antibiotics for human, terrestrial and aquatic animal and plant health."

- MSF is concerned that this recommendation focuses on *"leveraging existing global access and scale-up initiatives in human health"*, without proposing how the significant gaps that currently exist in these initiatives will be filled. That is to say, the report identifies CEPI, Gavi, Global Fund to Fight AIDS, Tuberculosis and Malaria, Medicines Patent Pool, and Unitaid as the examples, yet does not highlight that these initiatives currently lack a specific focus on AMR. While some of these initiatives cover certain aspects of the AMR challenge – such as HIV, TB and malaria – they do not as yet cover the full scope of 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'.
- Without significant additional investment, it is difficult to see how these organisations will be able to meet their existing mandates – let alone expand to cover the full breadth of the AMR response.

Recommendation B3: "The IACG calls upon the public, private and philanthropic research funders and other stakeholders to build upon current research and development efforts and strengthen research collaboration in a One Health context…"

- MSF supports the call within this recommendation for research funders to undertake a number of activities, such as a coordinated global mapping of research and development activities and funding to address AMR,

[1] In the Final Report and Recommendations of the Review on Antimicrobial Resistance, chaired by Jim O'Neill and published in May 2016, it is noted on page 6 that the global market for patented antibiotics is currently about $US4.7 billion in sales per year. This compares unfavourably with the global oncology market, where just one top-selling cancer drug will command that level of sales. https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

and promoting openness and transparency in data from all research and monitoring and surveillance sources. We agree with the considerations outlined under this recommendation, which highlight (1) the lack of information, collaboration and transparency across different research and development activities, funding agencies and partners, and (2) the significant barriers this lack of transparency poses to advancing research and development.

- Clear actions should be proposed to address the lack of transparency in such initiatives, particularly those led by the public and philanthropic sectors.

Section C: Collaborate for more effective action

Recommendation C2: "The IACG calls for the systematic and meaningful engagement of and enhanced action by the private sector... in order to ensure [among other things] affordable access, prudent use and stewardship of antimicrobials; ethical production, distribution and marketing practices…"

- The recommendation notes, under considerations, that *"…the urgency and threat posed by antimicrobial resistance demand significantly more action by and enhanced engagement of the private sector…"*.
- Yet both the recommendation and considerations stop short of recommending that governments adopt legally binding measures to regulate these actors, which must at a minimum be considered. Operational research conducted by MSF in resource-limited settings such as Afghanistan, Central African Republic, Democratic Republic of the Congo and Sudan has demonstrated that both prescribers and patients are often poorly informed about the role and risks of antibiotics. Furthermore, soon-to-be published MSF studies from West Bengal, India show that pharmaceutical company representatives are key providers of information to prescribers and that this information is typically biased and often misleading. This raises serious concerns about conflicts of interest, compromised patient care and unethical commercial practice. Legislation is needed not only to guide the introduction, labelling, pricing and distribution of antibiotics, but also their manufacture and promotion. Leaving this to voluntary measures is not working: over a year after the launch of the Industry AMR Alliance, only 4 of the 100 companies who have joined have stopped rewarding sales agents with bonuses based on the volume of sales of antibiotics.

Section E: Strengthen global accountability and governance

Recommendation E1: "The IACG recommends the urgent establishment of a One Health Global Leadership Group on Antimicrobial Resistance (GLG), supported by a Secretariat…"

The recommendation notes, under considerations, the proposed composition of the GLG as "…a small group of current and former Heads of State, Ministers of Agriculture, Health and Environment, Heads of the Tripartite agencies, other UN and international agencies, Heads of Regional Banks and other prominent global leaders and eminent persons representing human, animal and plant health, as well as food production and the environment."

- MSF notes that this proposal does not indicate whether private sector directors would be permitted under the umbrella of *"other prominent global leaders and eminent persons"*. MSF urges the IACG to clarify that the inclusion of private sector directors in future global governance arrangements would be unacceptable due to conflicts of interest.
- If the decision is taken to establish a GLG, it will be essential to ensure the group's mandate is firmly anchored in the 2016 Political Declaration of the High-level Meeting on Antimicrobial Resistance (Resolution A/RES/71/3). There is a risk of mission drift if the GLG is not given this mandate for action.
- For MSF, it is essential that the needs of developing countries, and particularly neglected people, are not left behind in future global governance. This must be assured through a transparent, accountable governance structure – led by and inclusive of all Member States – that provides for civil society engagement, oversight and consultation.
- MSF agrees that processes for engaging all relevant actors must be created, but believes it is essential to draw red lines between the roles and responsibilities of different actors. We have addressed this above, under Section C.

Recommendation E2: "The IACG requests the Secretary-General, in close collaboration with the Tripartite agencies (FAO, OIE and WHO), UNEP and other international organizations, to convene an Independent Panel on Evidence for Action against Antimicrobial Resistance in a One Health context to monitor and provide Member States with regular reports on the science and evidence related to antimicrobial resistance, its impacts and future risks, and recommend options for adaptation and mitigation."

- If such an Independent Panel is established, it will be essential to play close attention to potential conflicts of interest, and to have a clear and robust policy for dealing with any such conflicts should they arise.
- For the Panel to achieve its stated goal, it will need to be a trusted source of data and evidence, free of vested interests. It is also important the that the evidence generated by the Panel is comprehensive so that it can reliably inform prioritisation of interventions, including those targeting resource-limited settings.

Recommendation E4: "The IACG recognizes the ongoing process led by Member States to develop the Global Development and Stewardship Framework to Combat Antimicrobial Resistance and urges the Tripartite agencies… and UNEP to expedite its development in line with the scope described in the 2015 World Health Assembly resolution on antimicrobial resistance (WHA68.7)..."

- To ensure accountability and emphasise the need for policy coherence, there should be a clearer call for the IACG recommendations to be considered in the Global Development and Stewardship Framework (GDSF). The GDSF is needed to guide countries in the design of access and stewardship measures that are practical and meaningful at a country level. As such, it is critical that the GDSF fully takes into account and is designed to meet the access and stewardship needs of low- and middle-income countries.
- We support the final consideration put forward by the IACG that, *"…ongoing discussions and finalization of the process to develop the [GDSF] can be used as an initial platform by Member States to advance a stepwise approach towards potential new, binding or non-binding international instruments. Such instruments may need to include a stronger focus on supporting the distribution and appropriate use of existing and new antimicrobial medicines, diagnostics, vaccines and other interventions, while also preserving existing antimicrobial agents, including using the WHO ACCESS, WATCH and RESERVE categorization of antibiotics."* Lasting and binding commitments at the level of Heads of State are necessary to effectively respond to the challenge of AMR, and it is essential that the eventual legal framework to emerge from the GDSF negotiations overcomes the real challenge of potential non-adherence.