Consultation of Member States and relevant partners on options for establishing a global development and stewardship framework to combat antimicrobial resistance

Geneva, 29 February 2016

Background Paper

This document is a background paper for the consultation of Member States and relevant partners on options for establishing a global development and stewardship framework to combat antimicrobial resistance (henceforth ‘framework’).

I. MANDATE

Resolution WHA68.7 (henceforth ‘the Resolution’) endorsed the global action plan on antimicrobial resistance (GAP-AMR), in particular through requesting that the Director-General develop:

‘...options for establishing a global development and stewardship framework to support the development, control, distribution and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines, and other interventions, while preserving existing antimicrobial medicines, and promoting affordable access to existing and new antimicrobial medicines and diagnostic tools, taking into account the needs of all countries, and in line with the global action plan on antimicrobial resistance, and to report to the Sixty-ninth World Health Assembly.’

II. OBJECTIVE AND SCOPE

According to the Resolution, the objectives of a possible global framework can be summarized as follows:

- Preservation of existing antimicrobial medicines through a stewardship framework covering control, distribution and appropriate use
- Development of new health technologies for addressing antimicrobial resistance
- Promotion of affordable access to existing and new antimicrobial medicines and diagnostic tools.

The overall aims of the framework are to develop new antibiotics; ensure that both existing and new products are used appropriately or that their usage is avoided; and ensure their affordability and accessibility to all those in need. Complementary technologies such as vaccines, diagnostics and medical instrument surfaces resistant to bacterial colonization can also help reduce the use of antibiotics. The Resolution points out that while any framework must be in line with the GAP-AMR, if it is to bring added value it may need to exceed the scope and ambition of the GAP-AMR.
III. **Preserving Antimicrobial Medicines Through a Global Stewardship Framework**

Resolution WHA68.7 uses the term ‘stewardship,’ which describes the careful and responsible management of something entrusted to one’s care. Antimicrobial stewardship can be defined as the promotion of appropriate use of antimicrobials while reducing their inappropriate use; improving patient outcomes; reducing microbial resistance; and decreasing the spread of infections caused by multidrug-resistant organisms. The ultimate aim of such stewardship is to conserve the effectiveness of antimicrobial medicines by delaying the formation of resistance as long as possible through appropriate use.

There is currently no blueprint for a global stewardship framework that balances the objectives mentioned above, and the development of such a blueprint poses particular challenges. While a more lenient framework will fail to yield the desired conservation goals, provisions that are too strict might impede access to medicines. Furthermore, the framework will have to adhere to the one-health approach and include agricultural use and use in animal husbandry, requiring close collaboration with the Food and Agricultural Organization (FAO) and the World Organisation for Animal Health (OIE).

1. **Which Medical Products Should Be Subject to a Possible Global Stewardship Framework?**

Any global stewardship framework will have to define its product scope—that is to say, define the products to be subjected to the framework and the rules applying to those products.

The Resolution uses the broad term ‘antimicrobial medicines.’ Thus its scope encompasses all agents active against microbes, including antibiotics and other treatments against bacteria; antivirals; antifungal drugs; and treatments against parasites. Formation of resistance is an issue for all these medicines, and their inclusion in the framework should be guided and regularly reviewed according to rational principles (for example, analysis of the risk of resistance through greater use and the value of particular medicines in treating disease in humans and animals).

A global stewardship framework would also have to clarify which antibiotics should be subject to a conservation scheme, a process that requires prioritization. There is work underway in this area at time of writing in February 2016: WHO intends to revise its list of critically important antimicrobials for human medicine, and is reviewing which antibiotics should be included in the WHO Lists of Essential Medicines (WHO EML). The OIE has also developed a list of antimicrobial agents of veterinary importance to complement the WHO list for human medicine. A global framework, however, would likely require a more consolidated approach.

2. **Control and Distribution**

Following the definition of those treatments that should be subject to the global stewardship framework, it will be necessary to define rules for their use, along with the corresponding responsibilities of different actors in the human health, agricultural and animal health sectors. In this context, the Resolution addresses control and distribution of antimicrobial medicines.

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2. Based on the definition of the United States Association for Professionals in Infection Control and Epidemiology: [http://www.apic.org/Professional-Practice/Practice-Resources/Antimicrobial-Stewardship](http://www.apic.org/Professional-Practice/Practice-Resources/Antimicrobial-Stewardship)
The distribution of medical treatments can be controlled in a number of ways. The UN Drug Control Conventions provide one example in relation to narcotic drugs and psychotropic substances. The obligation under these Conventions to prevent misuse and non-medical use as well as diversion and trafficking of controlled substances has, however, received far more attention than the obligation to ensure their adequate availability for medical and scientific purposes. This has resulted in many countries adopting laws and regulations that consistently and severely impede legitimate access to controlled medicines.\(^5\)

Another example is provided by the controlled distribution of treatments for multi-drug resistant tuberculosis (MDR-TB). WHO and the Stop TB Partnership support countries in managing MDR-TB through the Green Light Committee (GLC) Initiative, which has operated a reformed and access-oriented approach to distribution since 2011.\(^6\) Access to treatment is facilitated by the Global Drug Facility, an international procurement mechanism that also provides technical assistance.\(^7\)

A third example is provided by the Codex Alimentarius Commission’s maximum residue limits (MRLs) of veterinary drug residues in food.\(^8\) While the Codex MRLs, Code of Practice and Guidelines are not legally binding, they do have certain legal status under WTO Agreements that makes them effective in promoting appropriate use of antimicrobials in animal production.

Any future stewardship framework for AMR should build on the lessons so far identified by these and other mechanisms.

### 3. LEVEL OF CONTROL

A global framework may have to define different levels of control for antimicrobial medicines of differing levels of importance. Options include:

- Mandatory provider prescription limiting inappropriate consumer access
- Limiting dispensing to certain providers and settings (see 4)
- Reserving certain antibiotics for human use and others for animal use.

Treatment guidelines, along with regulatory approval mechanisms in both the human and animal health sectors, can play an important role in a stewardship framework; but any global framework would have to take into account the absorptive capacity of different health systems as well as differences between cities and rural areas. It would also have to ensure that access to antibiotics is not impeded in situations of need.

### 4. HOW TO CONTROL?

Ensuring appropriate use through better control is a responsibility shared between multiple actors and throughout all stages of a process that runs from manufacturing, through distribution and promotion of drugs, to their use in hospital and non-clinical environments. As shown in Figure 1, a

\(^5\) Based on document EB138/11 paragraph 16-19.


\(^7\) GDF is today the largest supplier of quality assured patient treatments (first line drugs, second line drugs and paediatric forms) worldwide in the public sector: [http://www.stoptb.org/gdf/](http://www.stoptb.org/gdf/).

global stewardship framework must address and define the responsibilities of all relevant actors in the distribution chain. This includes manufacturers of treatments for both human and animal use; distributors such as wholesalers and pharmacies; and hospitals.

One control option is to build on market authorizations that could include specific regulatory pathways at regional and national levels. Existing approaches include a number of measures to impose distribution controls and stricter levels of market surveillance on certain medicines posing elevated risk to patients (e.g. chemotherapeutics). These measures include:

- Limiting prescription or dispensing to certified institutions, trained providers, or specific healthcare settings
- Requiring demonstration of need through clinical algorithm or diagnostic test findings
- Monitoring through a clinical registry of treated patients.

Other options could also be considered, including centralized procurement mechanisms. As most existing antimicrobial medicines are, or will soon be, off-patent, they are open to generic manufacturing. Reliance on intellectual property rights is therefore not a realistic option for controlling distribution—at least of existing medicines—as it would only affect a small fraction of antimicrobial medicines or antibiotics on the market.

5. **Appropriate use**

Stewardship should promote appropriate use and diminish inappropriate use; it is therefore necessary that a global stewardship framework define what kind of uses in human health, agriculture and animal husbandry are considered appropriate. Options for defining what is appropriate include reserving certain antibiotics for human or animal use; imposing restrictions on their use as growth promoters and prophylactics; and providing guidelines both for use in humans and for prevention and treatment in animal husbandry. Different instruments could be considered that promote appropriate or penalize inappropriate use, including the imposition of user fees for certain drugs and for use in the agricultural and animal sector, in order to make the low-value usage of antibiotics less economically attractive. Such instruments would have to take into account the varied potential impacts of applying such approaches across differently resourced settings.

Another important aspect to consider is the manner in which companies, wholesalers and distributors market and sell their antimicrobial medicines. In this context, marketing to healthcare providers as well as consumers must be addressed. Certain distribution routes can encourage inappropriate use—for example through the internet, or through models that provide a financial incentive (e.g. to veterinarians) to sell antibiotics. The size of packs and how they are sold by pharmacies also influence treatment adherence, and thus formation of resistance.
IV. DEVELOPMENT OF NEW ANTIMICROBIAL MEDICINES, DIAGNOSTIC TOOLS, VACCINES AND OTHER INTERVENTIONS

The need for increased investment in research and development (R&D) around AMR and, in particular, for the development of new antibiotics has been widely recognized—including by the GAP-AMR. A global framework for R&D therefore requires the thorough identification of R&D needs. This process must include quantitative and qualitative analysis of the R&D pipeline in order to list all products in preclinical and clinical development and identify priority products to be developed, including through the definition of target product profiles in different product categories. For vaccines and antibiotics—as well as for alternatives to antibiotics—WHO will undertake an assessment of the R&D pipeline and R&D needs within the implementation framework of the GAP-AMR. The outcome of this assessment will feed into the WHO Global Health R&D Observatory.

The financing of necessary R&D would have to be at the heart of any global framework meant to deliver new health products. Different options have been proposed to fill research gaps where the

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Resolution WHA68.7 does not specify whether development should include treatments for animals. The important role of vaccines in reducing antibiotic use in animal husbandry and fish farming shows that veterinary vaccines can make an important contribution. The OIE has recently set up an ad hoc Group to investigate the possible role of vaccines in reducing antibiotic consumption in animal husbandry and fish farming.
market alone does not provide sufficient incentives, and a number of initiatives have already been implemented in the field of AMR. These include the United States’ Biomedical Advanced Research and Development Authority (BARDA); the European Innovative Medicines Initiative (IMI); and various prize funds for diagnostics, such as the Longitude Prize.

With particular respect to antibiotics, in 2015 the G7 Health Ministers agreed to ‘investigate various instruments, such as a global antibiotic research fund and a market entry reward mechanism for truly new antibiotics targeting the most important pathogens and [those] most needed for global public health,’ and to ‘explore the feasibility and need of setting up a global antibiotic product development partnership for new and urgently needed antibiotics, vaccine development, alternative therapies and rapid point of care diagnostics, and seek collaboration with others such as WHO and the Drugs for Neglected Disease Initiative (DNDi)’.

The GAP-AMR emphasizes the principle of de-linking the cost of investment in R&D from price and sales volume. If implemented, this principle removes pressure on companies to maximize prices and/or volume, thereby facilitating the implementation of access and conservation policies.

Any new products developed under a global development framework should be submitted to the global stewardship framework. This principle touches, however, upon questions of ownership. Different models for resolving ownership questions have been discussed; for example, the UK Independent Jim O’Neill Review on Antimicrobial Resistance suggests market entry rewards to incentivise the development of new antibiotics, including the use of public health-oriented licensing agreements following the model of the Medicines Patent Pool. Not-for-profit product development partnerships such as the Global Antibiotic Research and Development Facility, a joint project of WHO and DNDi, could provide cost-effective platforms for the development of needs-based new treatments according to identified priorities. These can then be submitted to a global stewardship programme without ownership conflicts.

V. PROMOTING AFFORDABLE ACCESS

Resolution WHA68.7 requires the framework to promote access to new and existing antimicrobial medicines and diagnostic tools. The principle of de-linkage described above could contribute in this regard by allowing for affordable prices; but the question of ex-factory prices is just one element of ensuring access. Other measures that could also contribute include streamlining of guidance for treatment; identifying essential antimicrobial treatments as currently done for the WHO EML; and streamlining procurement and regulatory mechanisms.

Another important aspect of the access question is the quality of antibiotics sold. Antibiotics are a product for which cases of substandard quality and falsification are frequently reported, and these can further the build-up of resistance. One option to counter this would be to expand the WHO Prequalification Programme to antimicrobial medicines in general as well as to related diagnostics, and to strengthen further the Global Surveillance and Monitoring System for SSFFC.


See for further details: http://www.who.int/phi/implementation/consultation_imnadrp/en/
(substandard/spurious/falsely-labelled/falsified/counterfeit) medical products\textsuperscript{12}. Depending on the eventual nature of the stewardship programme, there may also be a need for different systems. For high priority antibiotics that should be used conservatively, one option could be to learn from the example of MDR-TB drugs, for which countries receive support in procurement, but must first submit national plans on how to provide treatment.

Overall, access to quality essential medicines is intrinsically linked to the strength of health systems. In the long run, building strong health systems is the best way of ensuring access to essential medicines, including antimicrobial medicines, vaccines, diagnostics and other interventions.

VI. OVERARCHING CONSIDERATIONS

A number of overarching aspects should be considered when discussing options for a global framework.

1. IMPLEMENTATION

Setting global norms and standards is a first step, but without being implemented these standards will remain ineffectual. Effective compliance and enforcement mechanisms must therefore be addressed. As an alternative to bans and restrictions, instruments should be considered that can drive and change the behaviour of patients, farmers, medical and veterinary personnel and those in industry. Such instruments could consist of financial incentives or disincentives, or voluntary commitments in addition to binding rules.

2. MONITORING AND REPORTING

To implement and monitor the appropriate use of antimicrobial medicines, reliable data must be available. Ideally, this should cover both manufacturing and consumption data for antimicrobial medicines for human, agricultural, animal and other uses. The OIE has committed to establishing a global database on sales of antibiotics for animal use.

An option to be considered in developing the framework is that of establishing mechanisms to capture total sales of active pharmaceutical ingredients disaggregated according to animal, human and other intended uses. For this, the collaboration of both researching and generic manufacturers will be essential.

3. FORM SHOULD FOLLOW CONTENT

As shown in Figure 2, a framework could be adopted in many different ways—for example, through a resolution of the World Health Assembly, as with the Pandemic Influenza Preparedness (PIP) Framework; through WHO Regulation such as the International Health Regulations (2005); or through a treaty such as the Framework Convention on Tobacco Control. As a general rule, form should follow content to make the framework as effective as possible.

\textsuperscript{12} \url{http://www.who.int/medicines/regulation/ssffc/surveillance/en/}
4. CONCLUSIONS

This background paper outlines options for essential elements of a global framework for development and stewardship of, and access to, antimicrobial medicines. Any such framework would have to define its scope; the rules for conservation of the products identified; and the various obligations of relevant actors. It would have to identify R&D gaps and priorities and provide a mechanism for financing the development of new products addressing public health needs. Finally, the whole framework would have to be designed to foster access to existing and new antimicrobial treatments.

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Figure 2: Possible legal forms of the framework on antimicrobial stewardship

Figure 3: Different functions and elements of a global framework
Overall, any global framework would have to:

• Define obligations and objectives of different actors
• Coordinate different actors
• Provide leadership and governance
• Foresee implementable and realistic measures adapted to local needs
• Include a sustainable financing mechanism to ensure appropriate funding
• Include an enforcement and compliance mechanism to promote implementation.

The Secretariat would welcome the views of Member States on the options for possible elements of a global framework to combat antimicrobial resistance described in this paper, and on any other aspects of importance that may be missing and sincerely thanks all those who have provided input to this paper.