Global development and stewardship framework to combat antimicrobial resistance: state-of-play
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"Antimicrobial resistance is a global health emergency that will seriously jeopardize progress in modern medicine."

"There is an urgent need for more investment in research and development for antibiotic-resistant infections including TB, otherwise we will be forced back to a time when people feared common infections and risked their lives from minor surgery."
Scope

Three elements: R&D, access & stewardship

Stepwise approach: starting with existing & new antibiotics, including TB, diagnostics and vaccines

One health: multi-sectoral perspective working closely with FAO and OIE

Legal form follows content: hybrid solution possible, some elements could

• use different instruments
• non-binding, others binding
• For consideration by WHO’s governing bodies and where relevant by FAO and OIE respective governing bodies
Starting point: Research & Development

Identification of priorities in the human & animal sector

Antibacterial Clinical Pipeline Analysis
Prioritization of human vaccines
List of essential in vitro diagnostic

New Expert Committee on Health R&D
Validate priorities

WHO/DNDi Global Antibiotic R&D Partnership (GARDP) can tackle R&D priorities

Global R&D/funding mechanism?
Priority pathogens for R&D

Critical needs:

- drug-resistant TB
- Gram-negative bacteria:
  - Carbapenem-resistant *A. baumannii*
  - Carbapenem-resistant *P. aeruginosa*
  - Carbapenem-resistant and 3rd generation cephalosporin resistant *Enterobacteriaceae*

Source: http://www.who.int/entity/medicines/areas/rational_use/PPLreport_2017_09_19.pdf?ua=1
R&D: Antibacterial agents in clinical development

- 51 new antibiotics in the clinical pipeline
- 33 against priority pathogens
- Only 9 are innovative

Insufficient to treat priority pathogens & TB
- Of 10 phase I tackling gram-negative bacteria only 1-2 will make it to market in 7 years

Source: http://apps.who.int/iris/bitstream/10665/258965/1/WHO-EMP-IAU-2017.11-eng.pdf?ua=1
R&D: Vaccines

WHO:
• Study on *Evidence-based prioritization of vaccines to reduce impact of AMR* that will determine future actions (forthcoming 2017/18)
• Modelling of impact of vaccines on antibiotic use and AMR (ongoing)
• WHO policy on typhoid vaccine includes antibiotic resistance as prioritization parameter (SAGE, Oct 2017)

OIE:
• Prioritization of diseases for which vaccines could reduce antimicrobial use focusing on cows, pigs, chicken and aquaculture
R&D: Diagnostics

WHO develops

• A list of the essential in vitro diagnostics, including diagnostics for AMR
• A WHO R&D priority list of missing IVDs for AMR & related target product profiles to facilitate development of new diagnostics

Animal and Agricultural side: need for

• Rapid & affordable point-of-care/use diagnostics to guide treatment decisions
Global Antibiotic R&D Partnership (GARDP)
Joint initiative of WHO and Drugs for Neglected Diseases initiative (DNDi)

Focus:
Drug-resistant bacterial infections for which adequate treatment is not available

Global scope:
Low-, middle- and high-income countries

2023 Objectives

- Develop 4 new treatments
- Build a robust pipeline of pre-clinical and clinical candidates
- Foster appropriate use of and access to new antibiotic treatments
Global Antibiotic R&D Partnership (GARDP)

- **Neonatal Sepsis**: develop treatments for highly drug-resistant infections
- **Sexually-Transmitted Infections**: develop a new treatment for drug-resistant gonorrhea and other STIs
- **Paediatric Antibiotics**: optimize current and develop new antibiotics for children
- **Memory Recovery & Exploratory**: revive old knowledge and abandoned projects

**Financing:**
More than 60 million Euro raised
(Member States & foundation)
Access & Stewardship: starting point

Classification of essential antibiotics into three categories: access, watch and reserve
EML revision May 2017

How will we use these three categories?
Measures to facilitate access & conservation

Global stewardship principles/measures
To be identified for human/animal use across whole value chain with OIE/FAO
## Access & Stewardship: Essential Medicines List

1<sup>st</sup> and 2<sup>nd</sup> choice empiric antibiotics defined for:

### Syndromes

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<tbody>
<tr>
<td>2. Pharyngitis</td>
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<td>3. Sinusitis</td>
<td>15. Shigellosis</td>
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<td>4. Otitis media</td>
<td>16. Cholera</td>
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<td>5. Hospital acquired pneumonia (HAP)</td>
<td>Children - WHO GL updates</td>
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<td>6. Ventilator associated pneumonia</td>
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<td>7. Urinary tract infections (UTI)</td>
<td>17. Chlamydia - WHO GL</td>
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<tr>
<td>8. Meningitis</td>
<td>18. Gonorrhoea - WHO GL</td>
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<td>10. Exacerbations of chronic obstructive pulmonary diseases (COPD)</td>
<td>20. Bone and joint infections</td>
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<tr>
<td>11. Skin &amp; soft tissue infections</td>
<td>21. Febrile neutropenia</td>
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<td>12. Cellulitis</td>
<td>22. Severe acute malnutrition</td>
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<tr>
<td>13. Surgical site infections</td>
<td>23. Sepsis</td>
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<td>Children - WHO GL updates</td>
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</table>
**AWaRe**

Can guide stewardship measures at the local, national and international level

**Access group:**
- Empiric 1\(^{st}\) & 2\(^{nd}\) choice antibiotics for treatment of the most common infectious syndromes
- Should be widely available, at affordable prices, in appropriate formulations & of assured quality
- **Access should be expanded**

**Watch group:**
- Subgroup of the Access group, but with higher resistance potential
- Use as 1\(^{st}\) & 2\(^{nd}\) choice treatment should be limited (small number of syndromes/patient groups)
- **Access should be expanded, but also prioritized for stewardship programmes**

**Reserve group:**
- Mainly ‘last resort’ treatment options
- **Key targets of stewardship programmes**
Access and shortages

• Core objective of the framework to promote affordable access

• Antibiotic market is dominated by generic products, but patents/high prices can be a challenge for new treatments, e.g. new TB treatments

Possible solutions:

• Health systems strengthening
• Mitigate shortages
• Quality assurance
• Patents: Voluntary licenses, including through Medicines Patent Pool and WTO TRIPS flexibilities
• Procurement and prices: WHO to provide transparency around pricing and costs of manufacturing and can assist countries in negotiations
Shortages of antibiotics: preliminary results

Survey of 8 national shortage reporting systems (August 2017)

Shortages of antibiotics are still a serious problem:

- 9% of all records are for systemic antibiotics
- 67 active ingredients affected in 80 pharmaceutical forms
- Penicillins represent 36% of all records
- All EML classes impacted

Issuance of national guidelines to manage prolonged shortages

<table>
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<tr>
<th>Active Ingredient</th>
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<th>Canada</th>
<th>Belgium</th>
<th>France</th>
<th>Italy</th>
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Grand Total: 43 2 38 28 6 11 7 138

Further work:
- Identification of antibiotics at risk of supply chain interruptions
- Best practices for active monitoring of market and supply chain
- Identify opportunities and mechanisms to address market risks
Regulatory aspects

- Accelerating development and marketing of new antimicrobials, diagnostics and vaccines
  - FDA, EMA and PMDA working on harmonizing regulatory requirements for new interventions
- Applying international standards for evaluating the safety, efficacy/performance and quality of products – including generics
- Ensuring appropriate product labelling, conditions of use and promotion and contributing to the appropriate use of medicines
  - Particularly relevant in context of AWaRe categorization
- Establishing effective inspection, vigilance and post market surveillance systems – including measures to ensure supply chain integrity and prevent, detect and respond to substandard and falsified products
Regulatory aspects: What WHO can do?

- Raise awareness of the role of regulatory authorities
- Develop appropriate norms and standards
- Strengthen regulatory authorities, including through WHO benchmarking tool
- Ensure appropriate, flexible and enforceable regulatory frameworks and approaches that also promote innovation and access through flexible regulatory pathways, work-sharing and reliance
- Work on regulation of promotional marketing
- Support regulators and Member States to prevent, detect and respond to substandard and falsified products
- Expand Prequalification programme to include antibiotics
Quality of antimicrobials: Substandard & Falsified

- Over 40% of GSMS reported cases are antimicrobials
- Antibiotics from Access, Watch & Reserve Group
- 90% of reported antibiotics are listed by WHO as critically or highly important antimicrobials

*GSMS is a case reporting system in which trained national focal points send reports to WHO and receive support when requested
The term **framework** refers to a basic structure that can be skeletal/conceptual providing a system or a concept.

**Working definition:**
A specific overarching structure to fulfil some key objectives of the Global Action Plan (GAP) that will be developed over time.
Covers the whole value chain

There is a veterinary side to all these steps and an agricultural side to many, some linked to the human side (e.g. selection)
## Potential Structure of the Framework

### Legal form of the overall Framework

<table>
<thead>
<tr>
<th>Scope</th>
<th>Objective</th>
<th>R&amp;D</th>
<th>Stewardship &amp; Access</th>
<th>Monitoring</th>
<th>Accountability</th>
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**Priority setting:**
- Priority pathogens, TPPs
- List of essential diagnostics

**Development:**
- GARDP
- Other push & pull mechanisms

**Stewardship & Access:**
- Increase access to ACCESS group
- Restrictions for RESERVE group
- Use in animals
- Environment
- Promotion
- ...

**Monitoring:**
- Antimicrobial consumption
- Impact
- Access
- R&D progress
- .....  

**Accountability:**
- e.g.,
  - Aarhus Convention
  - WTO dispute settlement
  - ...

Different interventions will take different legal forms, e.g. regulation, code of conduct, resolution, guidelines; voluntary participation; voluntary agreements/commitments of stakeholders.

**Global funding mechanism needed for R&D, stewardship and access**
Possible legal forms

- WHO Pandemic Influenza Preparedness Framework
- FAO Global Plan of Action for Animal Genetic Resources
- OIE Performance of Veterinary Services Pathways
- Codex Alimentarius Code of Practice to Contain and Minimize AMR

- WHO Framework Convention on Tobacco Control
- FAO International Plant Protection Convention

- WHO International Health Regulations (2005)
## Normative frameworks

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Options</th>
<th>Example</th>
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<tr>
<td>Commitments</td>
<td>Treaties and convention</td>
<td>Stockholm Convention on Persistent Organic Pollutants</td>
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<tr>
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<td>Framework Convention on Tobacco Control</td>
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<td>Montreal Protocol for Ozone Depleting Substances</td>
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<td>Framework</td>
<td>WHO Pandemic Influenza Preparedness Framework</td>
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<td>UNGA Resolution</td>
<td>SC resolution 2177/2014 on the Ebola outbreak</td>
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<td>Regulations</td>
<td>International Health Regulations 2005</td>
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<tr>
<td>Prioritization mechanisms</td>
<td>Declaration</td>
<td>Universal Declaration of Human Rights</td>
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<td>Intergovernmental Conferences / Summit</td>
<td>Stockholm Conference on the Human Environment</td>
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<tr>
<td>Standards</td>
<td>Code, guidelines (global, regional, national)</td>
<td>International Code of Marketing for Breast-Milk Substitutes, Codex Alimentarius, WHO Guidelines</td>
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<tr>
<td>Market</td>
<td>Trade agreements</td>
<td>Trade Related Aspects of Intellectual Property Rights</td>
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<tr>
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<td>Import / Export Regulations</td>
<td>EU ban on the use of antibiotics as growth promoters in animal feed</td>
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<tr>
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<td>Pooled procurement</td>
<td>PAHO Revolving Fund, GAVI</td>
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Development of the overall framework

1. Further develop the concept for the “umbrella” framework (form and content)

2. Develop an appropriate model to incentivize and guide R&D of:
   - antibiotics, diagnostics, vaccines and alternatives for health needs

3. Develop an options paper for global stewardship of antimicrobial medicines for human use
   - implemented through possible binding and non-binding instruments

4. Develop appropriate instruments:
   - to tackle access issues specific to antibiotics and foster wider access and the appropriate use of the ACCESS group of the EML AWaRE categorization
Misuse of **ANTIBIOTICS** puts us all at risk.

Taking antibiotics when you don’t need them speeds up antibiotic resistance. Antibiotic resistant infections are more complex and harder to treat. They can affect anyone, of any age, in any country.

Always seek the advice of a healthcare professional before taking antibiotics.

Link to the updated draft roadmap:
http://www.who.int/phi/implementation/research/Roadmap-Global-Framework-for-Development-Stewardship-to-combatAMR_2017_11_01.pdf?ua=1