Global development and stewardship framework to combat antimicrobial resistance: state-of-play

9-10 November 2017, Geneva, Switzerland

Peter Beyer
Senior Advisor, Innovation, Access and Use
Department of Essential Medicines and Health Products
"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 cephelosporin 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

<table>
<thead>
<tr>
<th>Name (synonym)</th>
<th>Phase</th>
<th>Antibiotic class</th>
<th>Route of Administration (Developer)</th>
<th>Expected activity against priority pathogens</th>
<th>Innovativeness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delafloxacin&lt;sup&gt;®&lt;/sup&gt;</td>
<td>NDA</td>
<td>Fluoroquinolone</td>
<td>IV &amp; oral (Mekina)</td>
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<tr>
<td>Vaborbactam + meropenem&lt;sup&gt;®&lt;/sup&gt; (Carbavance)</td>
<td>NDA</td>
<td>Bactericidal</td>
<td>IV (The Medicines Co)</td>
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<td>Cedhalonicol</td>
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<td>Siderophore- cephalosporin</td>
<td>IV (Phionag)</td>
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<tr>
<td>Eubacterin + mipemycin/ clindamycin</td>
<td>3</td>
<td>Carbapenem/ degradation inhibitor</td>
<td>IV (Merek &amp; Co)</td>
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</table>
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

1st and 2nd choice empiric antibiotics defined for:

**Syndromes**

1. Community acquired pneumonia
   - Children - WHO GL updates
2. Pharyngitis
3. Sinusitis
4. Otitis media
5. Hospital acquired pneumonia (HAP)
6. Ventilator associated pneumonia
7. Urinary tract infections (UTI)
8. Meningitis
9. Complicated intra-abdominal infections
10. Exacerbations of chronic obstructive pulmonary diseases (COPD)
11. Skin & soft tissue infections
12. Cellulitis
13. Surgical site infections
14. Acute infectious diarrhoea
   - Children - WHO GL updates
15. Shigellosis
   - Children - WHO GL updates
16. Cholera
   - Children - WHO GL updates
17. Chlamydia - WHO GL
18. Gonorrhoea - WHO GL
19. Syphilis - WHO GL
20. Bone and joint infections
21. Febrile neutropenia
22. Severe acute malnutrition
   - Children - WHO GL updates
23. Sepsis
   - Children - WHO GL updates
**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

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.

**Tools and Instruments**
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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</thead>
<tbody>
<tr>
<td><strong>Commitments</strong></td>
<td>Treaties and convention</td>
<td>Stockholm Convention on Persistent Organic Pollutants</td>
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<td>Framework</td>
<td>WHO Pandemic Influenza Preparedness Framework</td>
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<td></td>
<td>UNGA Resolution</td>
<td>SC resolution 2177/2014 on the Ebola outbreak</td>
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<tr>
<td></td>
<td>Regulations</td>
<td>International Health Regulations 2005</td>
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<tr>
<td><strong>Prioritization mechanisms</strong></td>
<td>Declaration</td>
<td>Universal Declaration of Human Rights</td>
</tr>
<tr>
<td></td>
<td>Intergovernmental Conferences / Summit</td>
<td>Stockholm Conference on the Human Environment</td>
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<tr>
<td><strong>Standards</strong></td>
<td>Code, guidelines (global, regional, national)</td>
<td>International Code of Marketing for Breast-Milk Substitutes, Codex Alimentarius, WHO Guidelines</td>
</tr>
<tr>
<td><strong>Market</strong></td>
<td>Trade agreements</td>
<td>Trade Related Aspects of Intellectual Property Rights</td>
</tr>
<tr>
<td></td>
<td>Import / Export Regulations</td>
<td>EU ban on the use of antibiotics as growth promoters in animal feed</td>
</tr>
<tr>
<td></td>
<td>Pooled procurement</td>
<td>PAHO Revolving Fund, GAVI</td>
</tr>
</tbody>
</table>
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
Lessons to be learned from HIV, TB and Malaria

Informal Consultation of Member States and relevant partners on the global development and stewardship framework to combat antimicrobial resistance
Stewardship of TB treatment to contain drug resistance

Dr Karin Weyer
Coordinator: Laboratories, Diagnostics & Drug Resistance
WHO Global TB Programme
Different mycobacterial populations require drugs in combination and prolonged drug exposure.
Long stewardship history in TB

- Vibrant & dynamic WHO policy landscape
- Widely acknowledged WHO standards of care
- Longstanding drug resistance surveillance programme
- Regulation and control of TB medicine use
- Global Drug Facility for procurement
- Global partnerships to ensure use of quality medicines
- Strong technical support networks (rGLCs)
- Strong WHO monitoring & evaluation system
30 High MDR-TB burden countries

**TB**
- Cambodia
- Sierra Leone
- Brazil
- Central African Republic
- Congo
- Lesotho
- Liberia
- Namibia
- UR Tanzania
- Zambia

**MDR-TB**
- Bangladesh
- DPR Korea
- Pakistan
- Philippines
- Russian Federation
- Viet Nam
- Azerbaijan
- Belarus
- Kazakhstan
- Kyrgyzstan
- Peru
- Republic of Moldova
- Somalia
- Tajikistan
- Ukraine
- Uzbekistan

**TB/HIV**
- Angola
- China
- DR Congo
- Ethiopia
- India
- Indonesia
- Kenya
- Mozambique
- Myanmar
- Nigeria
- Papua New Guinea
- South Africa
- Thailand
- Zimbabwe
- Botswana
- Cameroon
- Chad
- Ghana
- Guinea-Bissau
- Malawi
- Swaziland
- Uganda
WHO MDR-TB policy landscape
Anti-TB drugs

First-Line
- (H) Isoniazid
- (R) Rifampicin
- (Z) Pyrazinamide
- (E) Ethambutol
- (S) Streptomycin
- Standardised regimen 2HRZE/4HR, FDC-based

Second-Line
- Parenteral: kanamycin, amikacin, capreomycin
- Fluoroquinolones: ofloxacin, levofloxacin, moxifloxacin
- Oral, bacteriostatic: ethionamide, prothionamide, cycloserine, terizidone, p-aminosalicylic acid (PAS)
- Agents with unclear efficacy: clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, imipenem/cilastatin
- New agents: Bedaquiline, delamanid
<table>
<thead>
<tr>
<th>GROUP A</th>
<th>Fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Levofloxacin</td>
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<tr>
<td></td>
<td>Moxifloxacin</td>
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<tr>
<td></td>
<td>Gatifloxacin</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP B</th>
<th>Second-line injectable agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amikacin</td>
</tr>
<tr>
<td></td>
<td>Capreomycin</td>
</tr>
<tr>
<td></td>
<td>Kanamycin (Streptomycin)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP C</th>
<th>Other Second-line Agents</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Ethionamide / Prothionamide</td>
</tr>
<tr>
<td></td>
<td>Cycloserine / Terizidone</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
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</table>

<table>
<thead>
<tr>
<th>GROUP D</th>
<th>Add-on agents to the longer MDR-TB regimen</th>
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<tbody>
<tr>
<td>D1</td>
<td>Pyrazinamide</td>
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<tr>
<td></td>
<td>Ethambutol</td>
</tr>
<tr>
<td></td>
<td>High-dose isoniazid</td>
</tr>
<tr>
<td>D2</td>
<td>Bedaquiline</td>
</tr>
<tr>
<td></td>
<td>Delamanid</td>
</tr>
<tr>
<td>D3</td>
<td>p-aminosalicylic acid</td>
</tr>
<tr>
<td></td>
<td>Imipenem-Cilastatin</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin-Clavulanate (Thioacetazone)</td>
</tr>
</tbody>
</table>
New additions to the WHO Essential Medicines List related to TB treatment

The 20th WHO Expert Committee meeting on the selection and use of essential medicines has recommended the inclusion of five medicines (bedaquiline, delamanid, linezolid, rifapentine and terizidone) in the anti-tuberculosis (TB) medicines section of the WHO Model List of Essential Medicines (EML). Rifapentine is indicated for the treatment of latent TB infection (LTBI). The other four medicines are used as part of treatment regimens for multidrug and extensively drug-resistant TB (MDR-TB and XDR-TB respectively), two conditions with high lethality and poor treatment outcomes. Bedaquiline and delamanid are two new drugs which have recently been granted conditional approval by stringent regulatory authorities for use in the treatment of MDR-TB. Linezolid and terizidone are old drugs and their off-label use for severe forms of drug-resistant TB has now also been approved by the EML.
rGLCs for technical assistance

- Technical expertise
  - Regional coordination mechanism
  - Expertise on the management of MDR-TB
  - Technical assistance through networks of partners
- Technical assistance
  - Peer support and knowledge sharing
  - Independent external monitoring and evaluation
- Monitoring and evaluation
  - High-quality drugs to treat MDR-TB at considerably lower than market prices
- Access to drugs at low cost
Global partnerships

- GLI & GDI secretariats hosted by WHO/GTB
- Broad stakeholder membership
- Donor alignment on use and procurement of TB diagnostics and TB medicines
- Dedicated Task Forces to address specific technical issues and monitor progress in MDR-TB response (e.g., policy uptake, access to diagnostics and medicines)
## The global TB situation

<table>
<thead>
<tr>
<th>Category</th>
<th>Estimated incidence, 2016</th>
<th>Estimated number of deaths, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>All forms of TB</td>
<td>10.4 million (8.8–12.2 million)</td>
<td>1.3 million* (1.2–1.4 million)</td>
</tr>
<tr>
<td>HIV-associated TB</td>
<td>1.0 million (0.9–1.2 million)</td>
<td>374,000 (325,000–427,000)</td>
</tr>
<tr>
<td>Multidrug-/rifampicin-resistant TB (MDR/RR-TB)</td>
<td>600,000 (540,000–660,000)</td>
<td>240,000 (140,000–340,000)</td>
</tr>
</tbody>
</table>

* Excluding deaths attributed to HIV/TB

**Source:** WHO Global Tuberculosis Report 2017
MDR/RR-TB and financing (4)

*Estimated cost per patient treated for MDR-TB, 2016*

*Limited to 80 countries with at least 20 patients on MDR-TB treatment in 2016*
Stewardship framework: Lessons learned from malaria

Dr Pascal Ringwald
Drug Efficacy and Response Unit

Global Malaria Programme

World Health Organization
Key WHO recommendations on ACTs

- The WHO Guidelines for the Treatment of Malaria (MTGs),
  - provide comprehensible, global and evidence-based guidelines for the formulation of policies and protocols for the treatment of malaria.

Treating uncomplicated *P. falciparum* malaria

**Treatment of uncomplicated *P. falciparum* malaria**

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following recommended artemisinin-based combination therapies (ACT):

- artemether + lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- dihydroartemisinin + piperaquine
- artesunate + sulfadoxine–pyrimethamine (SP)

*Strong recommendation, high-quality evidence*

**Duration of ACT treatment**

ACT regimens should provide 3 days' treatment with an artemisinin derivative.

*Strong recommendation, high-quality evidence*
New medicines/indications in WHO MTG

Scope of prequalification
- Limited to priority medicines as published in Invitations for Expression of Interest (EOIs) on PQT-m website
- Medicines eligible for prequalification as determined by WHO disease-oriented programmes (“perceived medical need”)
- From products in WHO Model List of Essential medicines and/or WHO treatment guidelines
- Mostly generics
Recommendations on malaria diagnostics

Quality assured RDT and microscopy are the primary diagnostic tools for the confirmation and management of suspected clinical malaria in all epidemiological situations, including areas of low transmission, due to their high diagnostic performance in detecting clinical malaria, their wide availability and relatively low cost. Similarly, RDT and microscopy are appropriate tools for routine malaria surveillance (of clinical cases) in the majority of malaria-endemic settings.
Managing threats

Global Malaria Programme

Ban of artemisinin-based monotherapies

"It is critical that artemisinins be used correctly," said Dr LEE Jong-wook, WHO's Director-General. "We request pharmaceutical companies to immediately stop marketing single-drug artemisinin tablets and instead market artemisinin combination therapies. Only by moving towards guidelines we are making today can we empower countries with clear and evidence-based direction on the best treatment options for malaria."

According to the new WHO malaria treatment guidelines, uncomplicated falciparum malaria must be treated with ACTs and not by artemisinin alone or any other monotherapy.

Decision of Cambodia in March 2009

- Widespread dissemination of new regulation (posters + leaflets);
- Empowerment of drug inspections (confiscation, fines, prosecution);
- Letters of appreciation + logos for approved outlets.
Antimalarial medicine pipeline: MMV-supported projects

### Antimalarial medicine pipeline:

<table>
<thead>
<tr>
<th>Research</th>
<th>Translational</th>
<th>Product development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead optimization</td>
<td>Candidate profiling</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Injectable Prodrug</td>
<td>OZ609 Nebraska/Monash/STPHI</td>
<td>M5717 Merck KGaA</td>
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<tr>
<td>Miniportfolio 3 series GSK</td>
<td>MMV253 Zydus Cadila</td>
<td>SJ733 Kentucky/Eisai</td>
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<tr>
<td>DHODH Backups UTSW/UW/Monash</td>
<td>AN13762</td>
<td>UCT943 H3D Cape Town</td>
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<td>Pantothenates TropIQ/RUMC</td>
<td>SAR121 Sanofi</td>
<td>M5717 Merck KGaA</td>
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<td>Phenotypic Lead Daiichi-Sankyo</td>
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<td>Open Source Series University of Sydney</td>
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<td>Phe tRNA lygase Broad Institute/Eisai</td>
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<td>Purines Celgene</td>
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<td>DHODH Broad/Eisai</td>
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<tr>
<td>Molecular Target DDU Dundee</td>
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#### Data source:
https://www.mmv.org/research-development/mmv-supported-projects

MMV support to projects may include financial, in-kind, and advisory activities.

Footnotes:
- 🌟 Included in MMV portfolio after product approval and/or development. DNDi and partners completed development and registration of ASMQ and ASAQ. WHO TDR completed PhaseIII trials of rectal artesunate. 🌟 Global Fund Expert Review Panel (ERP) reviewed product – permitted for time-limited procurement, while regulatory/WHO prequalification review is ongoing. 🌟 WHO Prequalified OR approved/positive opinion by regulatory bodies who are ICH members/observers. 🌟 Pediatric formulation. 🌟 For children 13 – 60 months; ** For infants 3 – 12 months.


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Global Malaria Programme
Global malaria vaccine pipeline

**TRANSLATIONAL PROJECTS**

<table>
<thead>
<tr>
<th>Phase 1a</th>
<th>Phase 2a</th>
<th>Phase 1b</th>
<th>Phase 2b</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td>ChAd63/MVA ME-TRAP + Matrix M™</td>
<td>RTS,S-AS01 ChAd63/MVA ME-TRAP</td>
<td>ChAd63/MVA MSP 1</td>
<td>Pfs25-EPA</td>
<td>ChAd63/MVA ME-TRAP</td>
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<td>PfCelTOS FMP012 fractional dose</td>
<td>RTS,S-AS01 ChAd63/MVA AMA1</td>
<td>ChAd63.AMA1/MVA.AMA1</td>
<td>AMA1-DiCo</td>
<td>PfSPZ</td>
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<td>PfPEBS</td>
<td>FMP2.1/AS01B</td>
<td>P27A</td>
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</tr>
<tr>
<td>ChAd63/MVA PvDBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfs25-VLP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**VACCINE CANDIDATES**

- **P. falciparum vaccines:**
  - Pre-erythrocytic
  - Blood-stage
  - Transmission-blocking

- **P. vivax vaccines:**
  - Pre-erythrocytic
  - Blood-stage

Completed, Reporting overdue:

- Ad35.CS/Ad26.CS
- Polypeptide DNA EP 1300 Phase 1a
- ChAd63/MVA (CS, TRAP, AMA)
- GMZ2 Phase 2b
- EBA 175.R2 Phase 1b
- MSP3 [181-276] Phase 2b

HIV Stewardship and response to HIVDR

Meg Doherty, MD, MPH, PhD
Coordinator Treatment and Care, HIV/Hep Department, WHO HQ

10 November 2017
Current WHO ARV Treatment Recommendations

Table 4.3. Summary of first-line ART regimens for adolescents

<table>
<thead>
<tr>
<th>Preferred regimens*</th>
<th>TDF + 3TC (or FTC) + EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative regimens</td>
<td>TDF (or ABC) + 3TC (or FTC) + DTG</td>
</tr>
<tr>
<td></td>
<td>TDF (or ABC) + 3TC (or FTC) + EFV &lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>ABC + 3TC + EFV</td>
</tr>
<tr>
<td></td>
<td>ABC + 3TC + NVP</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + EFV</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + NVP</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC (or FTC) + NVP</td>
</tr>
<tr>
<td>Special circumstances&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>Regimens containing boosted PIs</td>
</tr>
</tbody>
</table>

<sup>a</sup> To date, there is limited experience with the use of low-dose EFV and DTG in adolescents. While no age or weight restrictions apply to the use of EFV 400 mg/day, which can be used starting from a weight of 20 kg (Annex 11c), the use of DTG is approved only for adolescents who are older than 12 years and weigh more than 40 kg (311). In addition, safety and pharmacokinetic data on TB coinfection and pregnancy are still pending.

<sup>b</sup> Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug-drug interactions, drug procurement and supply management issues or for other reasons.

<sup>c</sup> Using d4T as an option in first-line treatment should be discontinued.

3TC lamivudine, ABC abacavir, AZT zidovudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, NVP nevirapine, PI protease inhibitor, TDF tenofovir.

Table 4.19. Summary of sequencing options for first-, second- and third-line ART regimens in adults, adolescents, pregnant women and children

<table>
<thead>
<tr>
<th>Population</th>
<th>First-line regimens</th>
<th>Second-line regimens</th>
<th>Third-line regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents</td>
<td>2 NRTIs + EFV</td>
<td>2 NRTIs + ATV/r or LPV/r&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DRV/r&lt;sup&gt;b&lt;/sup&gt; ± DTG&lt;sup&gt;c&lt;/sup&gt; (or RAL) ± 1–2 NRTIs</td>
</tr>
<tr>
<td>(&gt;10 years)</td>
<td></td>
<td>2 NRTI + DRV/r&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 NRTIs + DTG</td>
<td>2 NRTIs + ATV/r or LPV/r</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTI + DRV/r&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Pregnant or breastfeeding</td>
<td>2 NRTIs + EFV</td>
<td>If less than 3 years:</td>
<td></td>
</tr>
<tr>
<td>women</td>
<td></td>
<td>2 NRTIs + RAL&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>If older than 3 years:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTIs + EFV or RAL</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>2 NRTI + LPV/r</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0–10 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 NRTI + EFV</td>
<td>2 NRTIs + ATV/r&lt;sup&gt;a&lt;/sup&gt; or LPV/r</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTIs + DRV/r&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>ARV Drug Optimization: Key Principles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Reduce toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Improve palatability/pill burden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Increase resistance barrier</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Reduce drug interactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Safe use across different age groups and populations Harmonization”)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Reduce cost</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gallant, 2002
National pretreatment HIVDR surveys, 2014-2016 and beyond
The Emerging Threat of HIV Drug Resistance

WHO’s Report on HIV drug resistance 2017

NNRTI (EFV/NVP) pretreatment drug resistance
(national surveys, 2014-2016)

Prevalence of NNRTI pre-treatment resistance
by calendar year (systematic review)
Pretreatment HIVDR in first-line ART initiators by drug (national surveys), 2014-2016
Acquired HIVDR surveys 2014-2016 and beyond

- Guatemala (12 and 48+)
- Cameroon (12 and 48+)
- Zambia (12)
- Viet Nam (36+)
Acquired HIVDR by drug and country (national surveys), 2014-2016
WHO recommended response to pretreatment HIV drug resistance: SUMMARY

Are nationally representative PDR data available?

- YES
  - Implement viral load monitoring; prevent HIVDR emergence and transmission
  - ≥10% PDR to EFV/NVP
    - Is it feasible to introduce non-NNRTI first-line ART for ALL starters?
      - YES
        - Urgently consider using non-NNRTI first-line ART for ALL starters
      - NO
        - Consider introducing pre-treatment HIVDR testing
  - <10% PDR to EFV/NVP
    - Prioritize use of non-NNRTI containing first-line ART in people with prior exposure to ARV drugs
- NO
  - Implement nationally representative PDR survey

ART: Antiretroviral therapy
ARV: Antiretroviral
EFV/NVP: Efavirenz or nevirapine
HIVDR: HIV drug resistance
PDR: Pre-treatment drug resistance
<table>
<thead>
<tr>
<th></th>
<th>Global Action Plan (GAP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Prevention &amp; Response</strong></td>
</tr>
<tr>
<td>2</td>
<td><strong>Monitoring &amp; Surveillance</strong></td>
</tr>
<tr>
<td>3</td>
<td><strong>Research &amp; Innovation</strong></td>
</tr>
<tr>
<td>4</td>
<td><strong>Laboratory Capacity</strong></td>
</tr>
<tr>
<td>5</td>
<td><strong>Governance &amp; Enabling Mechanisms</strong></td>
</tr>
</tbody>
</table>
Conclusions: GAP is a Framework for collective action

Each strategic objective has actionable items specific for each stakeholder

1. Prevention & Response

2. Monitoring & Surveillance

3. Research & Innovation

4. Laboratory Capacity

5. Governance & Enabling Mechanisms
How WHO support countries in transitioning to new ARV drugs?

- evaluating efficacy and safety data in **clinical studies** with new drugs
- providing **guidance and tools** for monitoring drug toxicity and HIVDR
- providing advice on **how to phase in** new drugs
- sharing **country experiences**

# Summary of optimization profiles of new ARVs recommended in 2016 WHO ARV guidelines - comparative analysis

<table>
<thead>
<tr>
<th>Optimization criteria</th>
<th>DTG</th>
<th>EFV400</th>
<th>DRV/r</th>
<th>RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy and safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High virologic potency</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Low toxicity</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>High genetic barrier to resistance</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Simplification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Available as generic FDC</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Low pill burden</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Harmonization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in pregnant women</td>
<td>?</td>
<td>⬤</td>
<td>⬤</td>
<td>?</td>
</tr>
<tr>
<td>Use in children</td>
<td>?</td>
<td>⬤</td>
<td>⬤</td>
<td>?</td>
</tr>
<tr>
<td>Use in HIV-associated TB</td>
<td>?</td>
<td>⬤</td>
<td>⬤</td>
<td>?</td>
</tr>
<tr>
<td>Few drug interactions</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low price</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

- ✓: Strongly recommended
- ✓: Recommended
- ⬤: Weakly recommended
- ?: Not recommended
- Red: Not recommended for use in pregnant women
- Blue: Weakly recommended for use in children and HIV-associated TB
# Estimated timelines for completion of new clinical trials of DTG and EFV 400

<table>
<thead>
<tr>
<th>ARV</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q3-Q4</td>
<td>Q1-Q2</td>
<td>Q3-Q4</td>
<td>Q1-Q2</td>
</tr>
<tr>
<td>DTG</td>
<td>RADIO DAWNING ADVANZ-4</td>
<td>IMPAACT 1093</td>
<td>DOLPHIN 1 NAMSAL</td>
<td>DOLPHIN 2 D2EFT</td>
</tr>
<tr>
<td>EFV400</td>
<td>SSAT 062 SSAT 063</td>
<td>NAMSAL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Pregnant women**
- **Children**
- **TB**
- **Adults**

Adapted from Vitoria et al, Current Opinion HIV/AIDS, 12: 369-76 2017
Some programmatic factors that can influence the transition to DTG in 1\textsuperscript{st} Line ART

- DTG introducing policy (eligibility criteria/priority populations)
- Regulatory issues: availability of low cost generic formulations (FDCs)
- Supply chain management (procurement preparedness, current stocks of EFV containing regimens)
- Pre-treatment levels of HIVDR to NNRTIs
- Programme monitoring for toxicity and pregnancy safety (pharmacovigilance)
- “Bandwidth” capacity to develop multiple implementation polices (training, logistic management, monitoring capacity, quality)
Licensing and pricing of DTG in LMICs

<table>
<thead>
<tr>
<th>Country</th>
<th>DTG U$ price (pppy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMICs (generic)</td>
<td>48 - 60</td>
</tr>
<tr>
<td>LMICs (originator)</td>
<td>396 - 1740</td>
</tr>
<tr>
<td>Botswana</td>
<td>272</td>
</tr>
<tr>
<td>Brazil</td>
<td>547</td>
</tr>
<tr>
<td>Mexico</td>
<td>2200</td>
</tr>
<tr>
<td>Belarus</td>
<td>2300</td>
</tr>
<tr>
<td>Ukraine</td>
<td>72</td>
</tr>
</tbody>
</table>

Sources: MSF, GFTAM, CHAI, MoH Brazil, Botswana, Mexico & Ukraine

Tentative SRA Approval Timeline for DTG, TDF/3TC/DTG, and TDF/3TC/EFV400 formulations*

(2016-2019)

<table>
<thead>
<tr>
<th>ARV</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H2</td>
<td>H1</td>
<td>H2</td>
<td>H1</td>
</tr>
<tr>
<td>DTG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF/3TC/DTG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF/3TC/EFV400</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Assumes SRA approval received 12 months after filing date.

TDF/3TC/DTG in 92 LMICs = 75 U$ pppy (Sep/2017)
WHO support to DTG routine toxicity monitoring in 2017

- Malawi - full time consultant
- Technical support to Zimbabwe, Tanzania, South Africa, RDC in partnership with University of Cape Town (Collaborating Center)
- Evaluation and technical assistance missions in Brazil, Botswana, Kenya, Mozambique
- Dissemination workshops – Harare May 2017, Senegal February 2018 for francophone AFRO countries

WHO priorities for 2018:
- Phase 1: 10 early adopter fast track countries
- Phase 2: any adopter country with patient and toxicity monitoring
Conclusions: GAP is a Framework for collective action

Each strategic objective has actionable items specific for each stakeholder

1. Prevention & Response
2. Monitoring & Surveillance
3. Research & Innovation
4. Laboratory Capacity
5. Governance & Enabling Mechanisms
Informal Consultation of Member States and relevant partners on the global development and stewardship framework to combat antimicrobial resistance
<table>
<thead>
<tr>
<th>R&amp;D and Access: What we are planning to do</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO methodology to develop target product profiles</td>
</tr>
<tr>
<td>WHO R&amp;D priority list of IVDs for AMR + related target product profiles</td>
</tr>
<tr>
<td>WHO continue to monitor the clinical development pipeline and expand to pre-clinical pipeline</td>
</tr>
<tr>
<td>Further develop and support GARDP</td>
</tr>
<tr>
<td>Develop research collaboration between human and animal sectors (topics of common interest)</td>
</tr>
<tr>
<td>FAO Analysis on research needs related to alternatives to antibiotics</td>
</tr>
<tr>
<td>OIE R&amp;D support investment - vaccine development for priority animal diseases</td>
</tr>
<tr>
<td>R&amp;D and Access: key discussion points</td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Harmonization of clinical trials and other regulatory aspects</td>
</tr>
<tr>
<td>Need for public health driven clinical trials</td>
</tr>
<tr>
<td>TPPs and priority setting</td>
</tr>
<tr>
<td>Diagnostics and vaccines in animal health</td>
</tr>
<tr>
<td>Link R&amp;D with access</td>
</tr>
<tr>
<td>Financing of R&amp;D and technical assistance and capacity building</td>
</tr>
<tr>
<td>Looking beyond antibiotics to alternative products</td>
</tr>
<tr>
<td>Delinking of product development and pricing</td>
</tr>
<tr>
<td>Linking framework to the UNGA HL political Declaration</td>
</tr>
<tr>
<td>Coherence between IACG, tripartite and G20 Collaboration Hub needed</td>
</tr>
</tbody>
</table>
New technologies (including vaccines)

<table>
<thead>
<tr>
<th>OBJECTIVE</th>
<th>OBJECTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>New developments for diagnosis, vaccines and alternatives to antimicrobials</td>
<td>Identify what areas to invest in</td>
</tr>
</tbody>
</table>

**HOW**

- Identification of research gaps by STAR-IDAZ International Research Consortium (IRC) priority diseases and areas (vaccinology, alternatives to antibiotics)
- Prioritisation on vaccine development to reduce the use of antimicrobials
- Participation in the WHO R&D Blueprint
- Collect information on funded research projects from STAR-IDAZ IRC partners (i.e. research funders)
- Draft research roadmaps on shared priority diseases
- Common research platforms (vaccinology, new diagnostic technologies, antimicrobial developments)
- Common modelling consortium
- Actions against substandard and falsified drugs
Access and Stewardship

Informal Consultation of Member States and relevant partners on the global development and stewardship framework to combat antimicrobial resistance
Access & stewardship: What we are planning to do

- WHO Analyse the underlying reason for shortages of antibiotics
- WHO Provide transparency around pricing/costs of manufacturing antibiotics
- WHO Support prevention, detection and response to SF medical products
- WHO Support implementation of AWaRE categorization
- WHO Guidance for the implementation of antimicrobial stewardship programmes
- WHO and OIE Monitor antimicrobial consumption
- WHO Enhance access to affordable treatments
## Access & stewardship: What we are planning to do

<table>
<thead>
<tr>
<th>Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAO, OIE, WHO Support implementation of OIE and Codex standards in LMICs</td>
<td></td>
</tr>
<tr>
<td>FAO and OIE Develop good agricultural practices, good regulatory practices and treatment guidelines for animal health</td>
<td></td>
</tr>
<tr>
<td>OIE and WHO Provide support on disease diagnostics and access to appropriate, good quality, antimicrobials</td>
<td></td>
</tr>
<tr>
<td>OIE Support implementation of Responsible and Prudent Use Standards and Guidelines for use of antimicrobials in animals (terrestrial and aquatic)</td>
<td></td>
</tr>
<tr>
<td>OIE Support achieving appropriate coverage of well-trained veterinarians and veterinary paraprofessionals</td>
<td></td>
</tr>
</tbody>
</table>
Access and Stewardship: key discussion points

- Scope of framework vs the GAP on stewardship
- More focus on behaviour change
- Tripartite alignment and guidance on national stewardship
- Focus on LMICs and HICs
- Role of pharmacists in stewardship
- Stewardship and access need to be closely linked
- More focus needed on solution of shortages
- Expansion of environmental waste management
- Mapping the manufacturing of pharmaceuticals
- Emphasize health systems strengthening
- Need for quantitative targets
Process and moving forward

Informal Consultation of Member States and relevant partners on the global development and stewardship framework to combat antimicrobial resistance
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

<table>
<thead>
<tr>
<th>Scope</th>
<th>Objective</th>
<th>R&amp;D &amp; Access</th>
<th>Stewardship &amp; Access</th>
<th>Monitoring</th>
<th>Accountability</th>
</tr>
</thead>
</table>
| √√√   | √√√       | Priority setting:  
  - Priority pathogens, TPPs  
  - List of essential diagnostics  
  Development:  
  - GARDP  
  - Other push & pull mechanisms | • Increase access to ACCESS group  
  • Restrictions for RESERVE group  
  • Use in animals  
  • Environment  
  • Promotion  
  • … | • Antimicrobial consumption  
  • Impact  
  • Access  
  • R&D progress  
  • ….. | 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

### 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)
For discussion:
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
For discussion: Crazy ideas

1. Framework convention on antimicrobial R&D?

2. Regulation under WHO constitution on manufacturing standards?

3. New PDP to reinforce manufacturing of old antibiotics in short supply?

4. Pooled procurement and/or advance market commitment for old antibiotics?
Future process: for discussion

- Prioritization and stepwise approach
- How best to involve Member States?
- How best to involve other Stakeholders?
- How to report back to Governing Bodies?
Global Action Plan on Antimicrobial Resistance
State of Play

Dr Marc Sprenger
Director, AMR Secretariat
8 November 2017
AMR is the Greatest Threat to Modern Medicine

Profound health consequences
  – Individuals, health systems, food systems, and practice of medicine

Economic and other intersectoral implications
  – Development, agriculture, food, business, etc.

Long-term threat with no end in sight unless fundamental changes are made
Recent Timeline on AMR (UN and WHO)

World Health Assembly 2015

UNGA (September 2016)

Global Action Plan on AMR

National Action Plans

Global Monitoring Questionnaire

Guidelines on Antimicrobial Use

And more…
Global Action Plan's 5 Strategic Objectives

1. Improve awareness and understanding
2. Strengthen knowledge through surveillance & research
3. Reduce the incidence of infection
4. Optimize the use of antimicrobial medicines
5. Ensure sustainable investment in R&D
Objective 1: “Improve awareness and understanding of AMR through effective communication, education and training.”

A) World Antibiotic Awareness Week

B) Behaviour Change Group

C) Health Workforce Education
Behaviour Change Expert Group

Will provide guidance to WHO on best practices within behavior change.
World Antibiotic Awareness Week (13 – 19 November 2017)

Antibiotic resistance is a global health crisis that should be addressed with the utmost urgency.

- Dr. Tedros Adhanom Ghebreyesus, Director General, World Health Organization

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.
Health Workforce Education & AMR

Consultation on health workforce education in March 2017

Defined tools/resources needed to ensure health workers are educated and trained on AMR
Strengthening Educational Materials on AMR

New Materials Include
- Courses and educational materials in ALL regions
- In-service and pre-service training
- Focus on physicians and pharmacists

WHO is Leading
- Competency framework
- Curricula development
- Survey of health workers’ knowledge and attitudes
Country Progress - National Action Plans

Country progress on development of national action plans on antimicrobial resistance (as of 08 November 2017)

Data Source: Country self-assessment questionnaire (2016) and other updated information received by WHO, some of which is not validated.
Country Progress - National Action Plans

92 NAPs are in place
61 NAPs in development
(*as of 8 Nov 2017)

Data source: Country self-assessment questionnaire (2016) and other updated information received by WHO - some of which are not validated.
Status of countries enrolled in GLASS
As of 21 July 2017*

Enrolment completed (n=47)
Enrolment in progress (n=9)

* Call for country enrolment issued on 21 March 2016
Surveillance of Human Pathogens

Global Antimicrobial Surveillance System (GLASS) - 43 countries

- IT platform: aggregated & individual data
- WHONET adapted for GLASS

Implementation package developed (with focus on LMICs)

Rapid alert portal being developed
Monitoring Antimicrobial Consumption

Training
- Trained 12 AFRO + 2 EMRO African countries in monitoring consumption

Results
- 7 countries provided data on antibiotic consumption
- Most provided data for TB, Malaria, HIV
- Most provided data from public and private sectors
"One Health" Approach

AMR affects humans, animals and the environment

Partnering with FAO and OIE on a comprehensive approach

WHO is collaborating with UNEP to develop evidence base on AMR’s impact on the environment
Guidelines on use of antimicrobials in animals

Include formal WHO recommendations and best practice statements on the use of medically important antimicrobials in food-producing animals.

Aim is to preserve the effectiveness of critically important antimicrobials for human and veterinary medicine.

Evidence-based recommendations are backed up by findings from recent systematic reviews.

Reflect decades of work on Critically Important Antimicrobials (CIA) for Human Medicine.
### AT A GLANCE: Recommendations in the WHO guidelines on use of medically important antimicrobials in food-producing animals

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<tbody>
<tr>
<td>Highest Priority</td>
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<td>High Priority</td>
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<tr>
<td>Highly Important</td>
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<tr>
<td>Important</td>
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</tbody>
</table>

#### Recommendations

1. Overall use
2. Growth promotion use
3. Prevention use (without disease)
4a. Control use (with disease)
4b. Treatment use (with disease)

#### Best practice statements

1. Concern new class of antibiotics
2. Concern antibiotics currently NOT being used in food production

- Complete restriction.
- Responsible and prudent use.

† The use may be permitted if a veterinary professional familiar with the disease history in the herd judges that a high risk of contraction of a particular infectious disease exists. The antimicrobials used should start with those of least importance for human medicine.

* The use may be permitted if no other drug from lower categories is available to treat infected animals or to prevent dissemination of diagnosed disease within groups of animals.
GAP Implementation

Objective 3: Reduce incidence of infection through effective sanitation, hygiene and infection prevention measures
Facets of AMR

- Health Security
- Joint External Evaluation
- One Health
- Medicines
- Maternal and Child Health
- Water, Sanitation, and Hygiene
- Infection Prevention and Control
- Communicable Diseases
- Health System Strengthening
WHO Guidelines and Resources

**WHO Model List of Essential Medicines**

- Updated in 2017
- Added 30 medicines for adult and 25 for children
- Antibiotics are now grouped to 3 categories:
  - **ACCESS** Antibiotics that should be available at all times
  - **WATCH** Antibiotics recommended as first- or second-choice treatments for a small number of infections
  - **RESERVE** Antibiotics that are last-resort options

WHO undertook analysis of the antibiotic pipeline
- Released in September 2017
WHO highlights on IPC during WAAW


- Online publication of a **Lancet Global Health Commentary** on 10 November on national and global priorities for IPC, authored by WHO, US CDC, and informed by the WHO’s Global Infection Prevention and Control Network (GIPCN)

- **Launch of the new WHO Guidelines** for Carbapenem-resistant *Enterobacteriaceae* (CRE), Carbapenemase-producing (CP) *Pseudomonas aeruginosa* and *Acinetobacter baumannii* during WAAW

- **Presentation** on these new guidelines by Professor Lindsay Grayson (Austin Health and University of Melbourne, Australia) on **13 November 2017** through Webber Training
WHO Priority Pathogens List for R&D

**Priority 1: CRITICAL**
- *Acinetobacter baumannii* carbapenem-resistant
- *Pseudomonas aeruginosa* carbapenem-resistant
- *Enterobacteriaceae* carbapenem-resistant, ESBL-producing

**Priority 2: HIGH**
- *Enterococcus faecium* vancomycin-resistant
- *Staphylococcus aureus* methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori* clarithromycin-resistant
- *Campylobacter spp.* fluoroquinolone-resistant
- *Salmonellae* fluoroquinolone-resistant
- *Neisseria gonorrhoeae* cephalosporin-resistant, fluoroquinolone-resistant

**Priority 3: MEDIUM**
- *Streptococcus pneumoniae* penicillin-non-susceptible
- *Haemophilus influenzae* ampicillin-resistant
- *Shigella spp.* fluoroquinolone-resistant

Source: WHO
www.who.int
AMR Inter-Agency Coordination Group

Chaired by UN Deputy Secretary-General and WHO DG
- Secretariat housed at WHO

Experts/representatives of agencies and key stakeholders to provide guidance for approaches to sustain global action

Recent meeting on 16-17 October in Paris / Stakeholder side event during PMAC in late January/early February 2018
How Can Member States Combat AMR?

- Maintain high level political engagement to implement NAPs
- Collaborate across national ministries to coordinate AMR response
- Ensure all relevant stakeholders are included - professional organisations, the private sector, civil society and development partners to encourage action and accountability
- Utilize WHO resources and tools to create and strengthen existing programmes that address AMR (access to medicines, lab strengthening, IPC and etc.)
Antibiotics are a precious resource

Our time with ANTIBIOTICS is running out.

Antibiotics are in danger of losing their effectiveness due to misuse and overuse, and in many cases they aren’t even needed.

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

World Health Organization
Activities of the Tripartite on Antimicrobial Resistance (FAO-OIE-WHO)

On behalf of the Tripartite Technical Focal Points
One Health collaboration

Global leader for food and agriculture

Global leader for animal health and welfare standards

Global leader for human health

Tripartite agreement
Collaborations
Joint priorities including Antimicrobial resistance (AMR)
What is the Tripartite?

- A strong collaboration between WHO, FAO and OIE
- Sharing responsibilities and coordinating global activities to address health risks at the animal-human-ecosystems interfaces
- Antimicrobial resistance is a ‘flagship’ topic identified by the Tripartite since 2010
FAO, OIE and WHO reaffirmed their commitment to provide multi-sectoral, collaborative leadership in addressing health challenges. The scope of their collaboration will be enlarged to more broadly embrace the “One Health” approach recognizing that the human health, animal health and the environment are interconnected.

Tripartite Coordination

1. Annual high level meeting at executive level
2. Technical Focal Points on AMR
3. Identified areas for cooperation
4. Developed common messages
5. Participation in relevant ad hoc Groups, meetings, trainings and projects
6. Common regional / sub-regional / country approaches and projects
The Tripartite: FAO-OIE-WHO Collaboration

- Global leader for food and agriculture
- Global leader for animal health and welfare standards
- Global leader for human health

Joint priorities including on AMR

- Global Action Plan on Antimicrobial Resistance
- National Action Plan (NAP) development support tools
  - Manual for developing NAP
  - Checklist to be used to assist with the development of NAP
- Communication tools
  - Joint media statements
  - Antibiotic Awareness Week
  - Common trainings and presentations
Global Action Plan for AMR

- Scientific & technical consensus blueprint on what to do
- FAO, OIE, WHO Member States consensus
- Highlights important principles
  - Multisectoral collaborations (“one health,” “whole of government,” “whole of society”)
  - Stepwise implementation because national conditions differ
AMR Global Action Plan Endorsed by Three Resolutions

- May 2015 OIE Resolution No 26 “Combating Antimicrobial Resistance and Promoting the Prudent Use of Antimicrobial Agents in Animals”
- June 2015 FAO Resolution 4/2015 “Antimicrobial Resistance in food, agriculture and the environment”
The Tripartite: FAO-OIE-WHO Collaboration

- Monitoring and Evaluation (ongoing)

- National Action Plans: Tripartite questionnaire to monitor implementation
WHO, FAO and OIE welcome governments and interested partners to take this opportunity to access the database to see all country responses which are visualized through interactive maps and can be sorted by WHO, FAO and OIE regions and by World Bank income groups.

The database can be accessed at: [http://www.who.int/antimicrobial-resistance/en/](http://www.who.int/antimicrobial-resistance/en/)

Materials for Tripartite communication on AMR
Thank you for your attention
WHO activities on containment of AMR from the Food Chain

9 November 2017

Awa Aidara-Kane

Coordinator Foodborne and Zoonotic Diseases Unit
Department of Food Safety and Zoonoses, WHO
Optimal use in food producing animals to protect consumers

- Ranking of medically important antimicrobials for risk management and containment of antimicrobial resistance mainly due to non-human antimicrobial use
- Developed by WHO since 2005, as recommended in a series of FAO-OIE-WHO expert meetings
**WHO list of Critically Important Antimicrobials for Human Medicine (WHO CIA list)**

Since 2005, WHO has produced a regularly updated list of all antimicrobials currently used for human medicine (mostly also used in veterinary medicine), grouped into 3 categories based on their importance to human medicine. The list is intended to assist in managing antimicrobial resistance, ensuring that all antimicrobials, especially critically important antimicrobials, are used prudently both in human and veterinary medicine.

### Classification

- **Critically important**
- **Highly important**
- **Important**
- **Highest Priority**
- **High Priority**

### Prioritize by Prioritization Criterion 1, 2, 3

### Antimicrobials

- **Drug resistant bacteria develop in animals**
- **Drug resistant bacteria can spread to the environment**
- **Drug resistant bacteria can be transferred to people by eating food**
- **Antimicrobial Resistance (AMR) along the food chain**

WHO supports optimization of the use of antimicrobial medicines in human and animal to preserve their effectiveness by taking a One Health approach.
Use of the List

Policy makers and regulators:
- Development and prioritization of risk management strategies for those antimicrobials characterized as critically important in order to preserve their effectiveness in human medicine
  - E.g. registration, cascade rules, limitations on off-label use, prescription-only
- AMR surveillance, risk assessment
- Risk communication

Veterinarians, industry:
- Antimicrobial stewardship, treatment guidelines
- Food industry policy
  - E.g. McDonalds requires suppliers to prohibit the growth promotion use of antimicrobials in food-producing animals of any antimicrobial on the WHO CIA List
WHO Guideline on Use of Medically Important Antimicrobials in Food-Producing Animals

Aims:

- To preserve the effectiveness of medically important antimicrobials, particularly those antimicrobials judged to be critically important to human medicine
- Provide formal recommendations for limitations of specific uses of medically important antimicrobials in food-producing animals, particularly antimicrobials judged to be critically important for humans

Supports the Global Action Plan on Antimicrobial Resistance

Published on 7 Nov
Builds on Previous Recommendations

- WHO convened Expert meetings
  - WHO Consultation on Medical Impact of the Use of Antimicrobials in Food-producing Animals (1997)
  - Joint FAO, OIE, and WHO Expert meetings on AMU in food producing animals, including aquaculture
    - Risk assessment: Geneva 2003 "There is clear evidence of the link between AMU if food producing animals and AMR in human"
    - Adverse health consequences in human
    - Concept of "Critically Important Antimicrobial Agents"
    - Request WHO to develop a CIA list

- Risk management – Oslo 2017
  - Recommendations to reduce AMU
  - Special consideration for WHO-CIA
  - Request to OIE to develop a list of antimicrobial agents of veterinary importance
  - Recommendation to establish a Codex Task Force on AMR

- WHO/FAO Codex Alimentarius
## WHO Critically Important Antimicrobials for Human Medicine 5th revision

Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)
October 2016

<table>
<thead>
<tr>
<th>Antimicrobial Class</th>
<th>CRITICALLY IMPORTANT ANTIMICROBIALS</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>P1</th>
<th>P2</th>
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<td>GNLSSes</td>
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<td>Macrolides and tetracyclines</td>
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<td>Cephalosporins (1st, 2nd and 3rd generation)</td>
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<td>Glycopeptides</td>
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<td>Monobactams</td>
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<td>Oxazolidinones</td>
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<td>Penicillins (natural, semi-synthetic, and antipseudomonal)</td>
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<td>Phosphonic acid derivatives</td>
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<td>Drugs used solely to treat tuberculosis or other mycobacterial infections</td>
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### C1: Priority criterion 1

- The antimicrobial class is the sole, or one of limited available therapies, to treat serious hospital-acquired infections in people.

### C2: Priority criterion 2

- The antimicrobial class is used to treat infections in people caused by either: (1) bacteria that may be transmitted to humans from non-human sources, or (2) bacteria that may acquire resistance genes from non-human sources.

### P1: Priority criterion 3

- High frequency of use of the antimicrobial class for any indication in human medicine, or other high proportion of use in patients with serious infections in health care settings, once use may favor selection of resistance in both settings.

### P2: Priority criterion 4

- The antimicrobial class is used to treat infections in people for which there is evidence of transmission of resistant bacteria or resistance genes from non-human sources.

### Medically Important Antimicrobials

- 

### Highly Important Antimicrobials

- 

### Important Antimicrobials

- 

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**World Health Organization**

[World Health Organization](http://www.who.int/reproductive-health/publications/antimicrobials-fifth/en/)

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**WHO CIA list 5th rev.**


**AT A GLANCE:** Recommendations in the WHO guidelines on use of medically important antimicrobials in food-producing animals

<table>
<thead>
<tr>
<th>Recommendation 1</th>
<th>Reduce overall use</th>
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<tbody>
<tr>
<td><strong>Recommendation 2</strong></td>
<td><strong>Recommendation 3</strong></td>
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<tr>
<td>Growth Promotion use</td>
<td>Prevention use† (In absence of disease)</td>
</tr>
<tr>
<td><strong>Medically Important Antimicrobials</strong></td>
<td><strong>Highest Priority</strong></td>
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<tr>
<td>Critically Important</td>
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<tr>
<td>High Priority</td>
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<td>Highly Important</td>
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<tr>
<td>Important</td>
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*Complete restriction.*

**Responsible and prudent use.**

**T:** The use may be permitted if a veterinary professional familiar with the disease history in the herd judges that a high risk of contraction of a particular infectious disease exists. The antimicrobials used should start with those of least importance for human medicine.

***: The use may be permitted if no other drug from lower categories is available to treat infected or to prevent dissemination of diagnosed disease within groups of animals.
WHO Department of Food Safety and Zoonoses Prevention

(absence of disease in the animal population)

- WHO Recommendation 3
- We recommend complete restriction of use of all classes of medically important antimicrobials in food-producing animals for prevention of infectious diseases that have not yet been clinically diagnosed.

Remarks: The use may be permitted if a veterinary professional familiar with the disease history in the herd judges that a high risk of contraction of a particular infectious disease exists. The antimicrobials used should start with those of least importance for human medicine.
Prevention when disease is already present is referred to as "Control"

- **WHO Recommendation 4a**

- WHO recommend that antibiotics classified as critically important for human medicine not be used for control of the dissemination of clinically diagnosed infectious disease identified within groups of food animals.

  - **Remarks:** Based upon the advice of a veterinary professional, these uses may be permitted if no other drug is available to treat infected animals or to prevent dissemination of diagnosed disease within groups of animals.
WHO Recommendation 4b

WHO recommend that antibiotics of highest priority for Human Medicine in the list not be used for treatment of sick animals when alternatives exist in the lower categories.

Remarks: Based upon the advice of a veterinary professional, these uses may be permitted after antimicrobial susceptibility testing, if no other drug is available to treat infected animals or to prevent dissemination of diagnosed disease within groups of animals.
WHO Department of Food Safety and Zoonoses

Executive summary and policy brief in all 6 UN languages
Infographics: Antimicrobial resistance in the food chain

November 2017

Taking antibiotics when you don’t need them speeds up antimicrobial resistance. This also happens when animals are given antibiotics.

USE OF ANTIBIOTICS* FOR GROWTH PROMOTION IN FOOD-PRODUCING ANIMALS SHOULD BE COMPLETELY RESTRICTED TO PRESERVE THEIR EFFECTIVENESS.

BACTERIA, INCLUDING THOSE RESISTANT TO ANTIBIOTICS, CAN BE TRANSMITTED FROM FOOD-PRODUCING ANIMALS TO HUMANS VIA FOOD.

*Medically important antimicrobials

WHO Department of Food Safety and Zoonoses
WHO Guideline on Use of Medically Important Antimicrobials in Food-Producing Animals

- Science Based: Systematics reviews, literature reviews, GRADE, Expert advice by a multidisciplinary group of experts, External Review
- FAO and WHO participated as "Observers"
- Will help preserve the effectiveness of medically important antimicrobials, particularly those antimicrobials judged to be critically important to human medicine
- Human Health focus, but due consideration given to other factors such as food security, animal health and welfare

Published on 7 Nov
Integrated Surveillance of AMR in Foodborne Bacteria - Information for Action

- guidance from WHO-AGISAR- in collaboration with FAO and OIE

Application of a One Health Approach
- AMR surveillance in humans, animals, food
- AMU surveillance in humans and animals
- Combined analysis and reporting

http://apps.who.int/iris/bitstream/10665/255747/1/9789241512411-eng.pdf?ua=1
Global protocol for ESBL E.coli surveillance ("Tricycle Surveillance")

- A global protocol to implement a simplified, integrated trans-sectoral surveillance system

- A single indicator: frequency of ESBL producing E.coli

- One Health approach involving multiple sectors (human, food chain and environment)
Thank you
FAO Activities on AMR

April Johnson
Animal Health Officer, FAO
9-10 November 2017
Antimicrobial usage in humans, animals and agriculture, and resulting dispersion of antimicrobial residues into aquatic and terrestrial environments (Berkner et al., 2014)
FAO Action Plan on AMR

• Improve awareness on AMR and related threats

• Develop capacity for surveillance and monitoring of AMR and AMU (antimicrobial use) in food and agriculture

• Strengthen governance related to AMU and AMR in food and agriculture

• Promote good practices in food and agricultural systems and the prudent use of antimicrobials
FAO focus areas of work as they relate to the five objectives of the Global Action Plan on AMR

<table>
<thead>
<tr>
<th>FAO Action Plan Focus Areas</th>
<th>Global Action Plan Objectives</th>
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<tbody>
<tr>
<td>Awareness</td>
<td>1. Information, education and training</td>
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<tr>
<td>Evidence</td>
<td>2. Surveillance, monitoring, record-keeping</td>
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<tr>
<td>Practices</td>
<td>3. Reduction of infection</td>
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<tr>
<td>Practices</td>
<td>4. Legislation, optimization of use</td>
</tr>
<tr>
<td>Practices</td>
<td>5. Sustainable investment for alternatives and reduced use</td>
</tr>
</tbody>
</table>
Awareness raising

- Basic information for stakeholders
- Videos and infographics
- Stakeholder events at national level
- World Antibiotics Awareness Week
Evidence, surveillance (AMR, AMU, residues)

- **Capacity development for surveillance and monitoring of AMR, AMU**

- **New/ongoing work**
  - Guidelines for harmonized sampling and laboratory diagnostics for AMR
  - Guidance on collection of AMU from food producing species at farm level
  - Aquaculture – workshops on bacterial pathogens in cultured fish and fishery products, AM usage for those diseases and AMR in fish - focus on Asia
  - Plant production – survey on identification of antimicrobials being used, extent of use
  - 3 recent expert consultations on horticulture, impact of biocides on AMR and AMR in the environment
  - ATLASS
Assessment Tool for Laboratory and AMR Surveillance System (ATLASS)

- Maps AMR activities: surveillance, lab testing, networks, data collation analysis and information dissemination

- Assesses capacities in AMR testing and epidemiological capacities, including:
  - pathogen isolation & identification
  - antimicrobial resistance testing

Qualitative questionnaire

Scored questionnaire
Governance

Legislation to be considered in relation to AMU and AMR:
- Veterinary medicines
- Feed
- Maximum residue limits of antimicrobials in food
- Antimicrobials and fungicides used for plant production
- Water quality
- Waste
- Environmental Legislation
Antimicrobial usage in humans, animals and agriculture, and resulting dispersion of antimicrobial residues into aquatic and terrestrial environments (Berkner et al., 2014)
Legislation
working at country level on animal, plant health and food safety legislation

www.fao.org/legal

Identification of legal elements and areas relevant for AMR and AMU
Recommendations to mainstream AMU-related obligations and responsibilities in the relevant legislation
Support to participatory processes for legal reform

LEGAL INFORMATION – FAOLEX (faolextfao.org/faolex)
New/ongoing work on Governance

- Policy review framework and guidelines to help countries assess existing AMR policy and strengthen future policy response

- Conducting a legislative study to identify good regulatory practices (in veterinary medicines, food safety, feed, crop production and pesticide management, animal production, water quality, environment and waste) to address the key drivers of overuse and misuse

- Adding AMR as a search term to the FAOLEX legal database to facilitate searches of current legislation that could impact on control/development of AMR
CODEX ALIMENTARIUS on AMR

- **Main documents:**

- **Other Codex texts relevant to AMR includes:**
  - *General Principles of Food Hygiene*
  - *Code of Practice on Good Animal Feeding*
  - Several Codes of hygienic practices for different commodities (e.g. milk and milk products)
Good Practices and Prudent Use Guidance

- Already available
  - Good enough or need revision
- Gaps
  - Impediments to implementation
- New guidance

Implementation
**Good Practices and Prudent use of antimicrobials in agriculture production systems**

**In terrestrial animal production systems and health and animal feed**
- Good husbandry and Good hygiene practices
- Improved biosecurity
- Animal welfare
- Animal feed – good nutrition, ‘alternatives’ to antimicrobials

**In aquatic animal production systems and health**
- Good practices
- Responsible management of Bacterial Diseases
- Biosecurity

**In crop production and health**
- Good Agriculture Practice
- International Code of Conduct - Regulation of pesticides (incl. antimicrobial pesticides) used for crop production
- Integrated Pest Management (IPM) for reducing use of pesticides
- Management and use of pesticides
- Registration of pesticides - toolkit
New/Ongoing work on Good Practices

- Surveys of existing guidance by sector to identify gaps and make recommendations on:
  - Good agricultural practices
  - Prudent use of antimicrobials

- Developing guidance on good practices. Examples:
  - Responsible Management of Bacterial Diseasess in Aquaculture
  - Animal nutrition options to reduce the use of antibiotics in animal production and AMR
  - Risk based meat and fish inspection
  - Management of dead stock and waste water from fish processing plants
Thank you

Website: www.fao.org/antimicrobial-resistance
E-mail: Antimicrobial-Resistance@fao.org
OIE activities on AMR related the Global Stewardship Framework
History

1924
Creation: Office International des Epizooties (OIE)

1945
Creation of the United Nations

2003
New Name: World Organisation for Animal Health (OIE)
Who we are today…

Protecting animals, Preserving our future

Dr Monique Eloit
Director General
2016 - 2020
OIE 6th Strategic Plan (2016-2020) - Strategic Objective 1
Securing animal health & welfare by appropriate risk management

- Holistic & interdisciplinary approach
- Climate change / eco-systems / impacts on disease control
- New technologies including for diagnostics and vaccines
- Support to the eradication of selected animal diseases (FMD, PPR, Rabies)
- Involvement in scientific platforms

‘effective & judicious management of the use of antimicrobial substances’
OIE strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials

Context

- 2015 Global Action Plan (GAP) on AMR and the Tripartite Partnership (WHO-FAO-OIE)
- OIE Resolutions on AMR in 2015 & 2016

Strategy

Consolidated work programme under 4 key objectives aligned with the GAP

- Improve awareness and understanding
- Strengthen knowledge through surveillance and research
- Support governance and capacity building
- Encourage implementation of international standards
In line with the AMR Global Action Plan (GAP)

| OIE Intergovernmental standards | Terrestrial & aquatic animals
Regularly updated |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Global OIE database on the use of antimicrobials in farmed animals</td>
<td>Information collected through the national Veterinary Services <em>(Third round started)</em></td>
</tr>
<tr>
<td>OIE List of antimicrobial agents of veterinary importance</td>
<td>To be updated in 2018</td>
</tr>
<tr>
<td>Capacity building programmes</td>
<td>Regional Seminars for OIE national focal points for veterinary products</td>
</tr>
</tbody>
</table>

Resolution adopted at the OIE’s 83rd General Session (May 2015)

http://www.oie.int/fileadmin/Home/eng/Media_Center/docs/pdf/PortailAMR/EN-book-AMR.PDF
OIE Intergovernmental Standards on AMR regularly updated

Preserving the efficacy of antimicrobials

- Distribution, restriction of free access
- Prescription and administration under veterinary supervision
- Monitoring of quantities used in animals, antibiotic resistance surveillance
- Oversight by Veterinary Statutory Bodies

OIE intergovernmental standards
- Use and surveillance of antimicrobials
- Veterinary legislation
- Quality of Veterinary Services

OIE List of antimicrobial agents of veterinary importance
OIE International Standards on AMR

Aquatic Animal Health Code

- Ch.6.2. Principles for responsible and prudent use of antimicrobial agents in aquatic animals

- Ch.6.3. Monitoring of the quantities and usage patterns of antimicrobial agents used in aquatic animals

- Ch.6.4. Development and harmonisation of national AMR surveillance and monitoring programmes for aquatic animals

- Ch.6.5. Risk analysis for AMR arising from the use of antimicrobial agents in aquatic animals
OIE International Standards on AMR

**Terrestrial Animal Health Code**

- Ch.6.7. Harmonisation of national AMR surveillance and monitoring programmes
- Ch.6.8. Monitoring of the quantities and usage patterns of antimicrobial agents used in food-producing animals
- Ch.6.9. Responsible and prudent use of antimicrobial agents in veterinary medicine
- Ch.6.10. Risk analysis for AMR arising from the use of antimicrobial agents in animals
Chapter 6.9. Responsible and prudent use of antimicrobial agents in veterinary medicine

Determined by the quality of the antimicrobial and by the distribution, prescription and administration of veterinary medicinal products containing antimicrobial agents

Recommendations for each of the parties involved:

- regulatory authority
- veterinary pharmaceutical industry
- wholesale and retail distributors
- veterinarians
- food-animal producers
- animal feed manufacturers
Ensure the Responsible & prudent use

- OIE List of Antimicrobial Agents of Veterinary Importance:
  - Will be updated in 2018
  WHO and FAO participate in this task as observers

Some are also of critical importance for human health:

- Not to be used as preventive treatment in feed or water or in absence of clinical signs
- Not to be used as first line, unless justified and bacteriological test
- Extra label/off label limited and reserved for instances no alternatives are available.

Monitoring the use of antimicrobials in animals based on OIE standards

OIE global database

1. A system where all can contribute
2. That safeguards information
3. That is pragmatic regarding the data collected
4. That will help to get comparable data and to measure trends

World Organisation for Animal Health · Protecting animals, Preserving our future | 58
OIE Global Database on Antimicrobial Use in Animals

1st results

% of OIE Member Countries submitting questionnaires by OIE region

<table>
<thead>
<tr>
<th>Region</th>
<th>Countries Submitting</th>
<th>% of OIE Member Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>44/54</td>
<td>81.5%</td>
</tr>
<tr>
<td>America</td>
<td>19/29</td>
<td>65.5%</td>
</tr>
<tr>
<td>Asia</td>
<td>26/32</td>
<td>81.3%</td>
</tr>
<tr>
<td>Europe</td>
<td>36/53</td>
<td>67.9%</td>
</tr>
<tr>
<td>Middle East</td>
<td>5/12</td>
<td>41.7%</td>
</tr>
</tbody>
</table>

130 (72%) Member Countries responded in the first phase (Mid-Dec.2015 - May 2016)

Including 54/74 (73%) LMIC
Antimicrobial growth promoters (AGPs) authorised for use in animals in 25 Member Countries, 2010-2015

Antimicrobial agents used as growth promoters

- Tylosin
- Bacitracin
- Olaquindox
- Virginiamycin
- Enramycin
- Colistin
- Lincomycin
- Tiamulin
- Oxytetracycline
- Chloramphenicol
- Saramycin
- Carbadox
- Sulfamethazine
- Neomycin
- Halquinol
- Lactulose
- Erythromycin
- Enrofloxacin
- Olaquindox
- Tetracycline
- Sulfaadiazine
- Penicillin G Procaine
- Nistamopicline
- Kitaamycin
- Bicazamycin
- Tilmicosin
- Norfloxacine
- Gentamicin
- Florenicol
- Eratoxymycin
- Dihydroriamycin
- Avoparcin
- Aminopenicillin

Number of Member Countries who submitted the OIE template, declared the authorisation of antimicrobial agents as growth promoters and provided a list of growth promoters in their countries.
Quantities of antimicrobial classes reported (first phase)

**Global:**

<table>
<thead>
<tr>
<th>Antimicrobial Class</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggregated class data</td>
<td>7%</td>
</tr>
<tr>
<td>Others</td>
<td>1%</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>48%</td>
</tr>
<tr>
<td>Sulfonamides (including trimethoprim)</td>
<td>7%</td>
</tr>
<tr>
<td>Streptogramins</td>
<td>0%</td>
</tr>
<tr>
<td>Quinoxalines</td>
<td>0%</td>
</tr>
<tr>
<td>Polypeptides</td>
<td>5%</td>
</tr>
<tr>
<td>Pleuromutilins</td>
<td>1%</td>
</tr>
<tr>
<td>Penicillins</td>
<td>7%</td>
</tr>
<tr>
<td>Other quinolones</td>
<td>0%</td>
</tr>
<tr>
<td>Orthosomycins</td>
<td>0%</td>
</tr>
<tr>
<td>Nitrofurans</td>
<td>0%</td>
</tr>
<tr>
<td>Macrolides</td>
<td>15%</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>1%</td>
</tr>
<tr>
<td>Glycophospholipids</td>
<td>0%</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>0%</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>4%</td>
</tr>
<tr>
<td>3-4 gen cephalosporins</td>
<td>0%</td>
</tr>
<tr>
<td>1-2 gen. cephalosporins</td>
<td>0%</td>
</tr>
<tr>
<td>Cephalosporins (all generations)</td>
<td>1%</td>
</tr>
<tr>
<td>Arsenicals</td>
<td>0%</td>
</tr>
<tr>
<td>Amphenicols</td>
<td>1%</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>2%</td>
</tr>
</tbody>
</table>

N = 89

% of reported quantities of antimicrobial agents used in animals by 89 Member Countries
OIE’s Ongoing AMR Work Programme

1. **Monitoring programmes** for implementation of GAP and OIE Strategy

2. Global **data collection and analysis** of antimicrobial agents intended for use in animals
   - more information on type of use, animal groups and route of administration
   - develop denominator for more valid comparison

3. Ongoing development and maintenance of OIE Standards
   - Key definitions: **therapeutic use, preventive use** and **growth promotion**
   - Update the OIE List of Antimicrobial Agents of Veterinary Importance taking into account recent WHO updates

4. **Alternatives to Antibiotics**
Prioritisation of Diseases for which Vaccines Could Reduce Antimicrobial Use in Animals

- “Provide guidance on prioritisation of disease for which the use of already available and new vaccines could reduce antimicrobial use in animals, focusing the first step on pigs, poultry and fish “

- Identify actions to improve utilisation of such vaccines

- To support the Global Action Plan on AMR which makes provision for such approach
Any questions?
Thank you for your attention
ANTIBIOTIC RESISTANCE
WHAT THE AGRICULTURE SECTOR CAN DO

Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.

1. Ensure that antibiotics given to animals—including food-producing and companion animals—are only used to control or treat infectious diseases and under veterinary supervision.

2. Vaccinate animals to reduce the need for antibiotics and develop alternatives to the use of antibiotics in plants.

3. Promote and apply good practices at all steps of production and processing of foods from animal and plant sources.

4. Adopt sustainable systems with improved hygiene, biosecurity and stress-free handling of animals.

5. Implement international standards for the responsible use of antibiotics and guidelines, set out by OIE, FAO and WHO.

www.who.int/drugresistance
www.oie.int/antimicrobial-resistance
www.fao.org/antimicrobial-resistance

#AntibioticResistance

THANK YOU