Value Attribution Framework For Vaccines Against Antimicrobial Resistance

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The Problem of AMR and the role of vaccines

- Global estimates suggest that drug-resistant infections result in 700,000 deaths per year
- Could rise to 10 million annual deaths by 2050
- Economical expenditure of US$10 trillion by 2050
- Mobilisation of efforts by WHO, UN, international organizations, member states, public health stakeholders to produce a list of recommendations to combat AMR

- **Vaccines** highlighted as having an important role in the process:
  - Vaccines prevent the infection and reduce carriage and transmission of AMR pathogen
  - Vaccines reduce the presence of clinical symptoms, reducing the pathogen associated antibiotic use
The role of WHO in vaccines and AMR

- Call from the AMR community to work on vaccines and AMR
- The aim of WHO is to highlight the role of vaccines and their impact against AMR
- To highlight priority activities around vaccines and AMR

Through:

- Creation of a roadmap that summarises priority actions around vaccines and AMR
- Developing a value attribution framework to articulate the value of vaccine against AMR
- Creation of a Working Group to oversee both processes, provide technical expertise and endorsement.
Aim

To create a semi-quantitative framework to assess the value of vaccine investments for their impact on AMR.

This framework will:

- Support the prioritisation of decisions and investments about vaccine development and use.
- Complement and inform the generation of a WHO technical roadmap expressing priority actions aimed to strengthen the role of vaccines against AMR.
- Support the narrative of pathogen specific priority activities
Methodology Outline

- Generate list of pathogens
- Define the strategic investment goal
- Assess feasibility of investment considered
- Highlight complementary approaches to contain AMR

Analysis of pathogens against the criteria (MCDA)

Results output and dissemination

Identification of key criteria

Criteria Weighing

Identification of data sources
## Generate list of pathogens

<table>
<thead>
<tr>
<th>Bacteria:</th>
<th>Viruses:</th>
<th>Fungi/Parasites:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter baumannii</td>
<td>HIV</td>
<td>Malaria</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Influenza virus</td>
<td></td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Measles virus</td>
<td></td>
</tr>
<tr>
<td>Cholera</td>
<td>Norovirus</td>
<td></td>
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<tr>
<td>Clostridium difficile</td>
<td>Rotavirus</td>
<td></td>
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<tr>
<td>Enterococcus faecium</td>
<td>RSV</td>
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<tr>
<td>E. coli</td>
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<tr>
<td>GAS</td>
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<tr>
<td>GBS</td>
<td></td>
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<tr>
<td>Haemophilus influenzae nt, b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td></td>
<td></td>
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<tr>
<td>Meningococcus</td>
<td></td>
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<tr>
<td>Mycobacterium tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella typhi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella paratyphi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella, non-typhoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shigella spp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
<td></td>
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<tr>
<td>Streptococcus pneumoniae</td>
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</tbody>
</table>
Define the strategic investment goal

For each pathogen area, we will specify the strategic investment goal

- **Existing vaccines**: known effectiveness profile, use case being considered
  - Reaching expressed public health goals in terms of coverage rates
  - Consider a new target population (expanded use case)
  - Consult WHO IVB, GAVI, UNICEF, vaccine implementation experts

- **Future vaccines, or pathogens with no vaccines in development**:  
  - Putative target population, effectiveness profile
  - WHO product characteristic preferences (tuberculosis, GBS, RSV, GAS, others) or other publicly available target product profile documents
  - Consult WHO IVR, PDVAC, vaccine R&D experts

- **Example, Mycobacterium tuberculosis**:  
  
  TB vaccine with 50% vaccine efficacy for prevention of adult pulmonary TB, implemented through routine adolescent immunization and adult vaccination campaigns.
Feasibility of reaching strategic goal

- **Working with PDVAC/PATH, considering:**
  - Biological Feasibility
  - Product Development Feasibility
  - Access and Implementation Feasibility

<table>
<thead>
<tr>
<th>Themes Considered</th>
<th>Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological Feasibility</td>
<td>Existence of immunity from natural exposure</td>
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<tr>
<td></td>
<td>The most advanced vaccine candidate</td>
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<tr>
<td></td>
<td>Understanding mechanisms of immunity</td>
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<tr>
<td></td>
<td>Multiplicity of pathogenic strains</td>
</tr>
<tr>
<td>Product Development Feasibility</td>
<td>Existence of animal models to facilitate vaccine development</td>
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<tr>
<td></td>
<td>Existence of in vitro assays to facilitate vaccine development</td>
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<td></td>
<td>Ease of clinical development</td>
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<td></td>
<td>Availability of clinical tools to facilitate vaccine development</td>
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<td>Access and Implementation Feasibility</td>
<td>Possibility of implementation within existing delivery systems</td>
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<td></td>
<td>Commercial attractiveness</td>
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<td></td>
<td>Barriers to uptake</td>
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<td></td>
<td>Clarity of licensure and policy decision pathway</td>
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</table>
Identification of Key Criteria

- A set of defined criteria will be used to assign overall value on investment goals being considered.
- Both qualitative and quantitative metrics will be used.
- The evidence will be graded.
- Ideally, the criteria should be complete, non-redundant, non-overlapping and independent, as is the case in multi-criteria decision analysis (MCDA) methodologies.
# Identification of Key Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
<th>Data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine-averted AMR fraction of the disease</td>
<td>The ability of a vaccine to reduce AMR caused mortality and morbidity</td>
<td>CDDEP, IHME, Cassini et al., Experts opinions</td>
</tr>
<tr>
<td>Reduction of antibiotic use</td>
<td>The ability of a vaccine to reduce antimicrobial consumption</td>
<td>SPA, PPS</td>
</tr>
<tr>
<td>Economic and Societal Burden</td>
<td>Cost of illness due to an AMR pathogen (direct, indirect, societal costs)</td>
<td>Systematic review</td>
</tr>
<tr>
<td>Sense of Urgency</td>
<td>The urgency of a pathogen to cause a threat due to AMR</td>
<td>Resistance Map</td>
</tr>
<tr>
<td>Ethical and Equity considerations</td>
<td>Vector of stigma, exclusion, poverty, inequity and discrimination</td>
<td>Systematic Review</td>
</tr>
</tbody>
</table>
Data collection, analysis and standardisation

- Weights will be assigned for each of the criteria depending on importance
- For each pathogen or vaccine, the data needs to be identified and extracted to support the criteria
- Evidence-based with a focus on high-quality studies, supported by experts opinion
- Strength of evidence documented throughout
- Collection of qualitative and quantitative data, translation of qualitative evidence to quantitative
Results Dissemination

Online tool that allows for adjustable, modular, flexible, user-centred view

Similar to IHME visualisations

Supported by narrative sections and case studies

Publication

Excel spreadsheet
Thank You

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Purpose of project:

To produce an overarching guidance document (‘Roadmap’) highlighting priority actions that will aim to highlight gaps and opportunities in a diverse set of topics.
Consultation Process

VAC-AMR working group

Further development and re-drafting of initial list of Action Priorities

Consensus building

Present Draft

Development of initial list of Action Priorities

2-Day Key Stakeholder Meeting (London)
Consultation Process: Next Steps

PDVAC discussion and review

Additional stakeholder consultations

Collaboration with WHO AMR secretariat

Present Draft

Open public review
Four Over-Arching Categories Identified

1. Policy and Communication
2. Research and Development
3. Evidence Generation
4. Animal Vaccines

10 Priority Actions were constructed from these.
1. Policy and Communication

1. Include vaccine recommendations when formulating global AMR strategy and prioritizing interventions.
   - Within the context of other interventions e.g. wastewater infrastructure and hygiene.

2. Make policy and financing decisions to ensure equitable and affordable access to vaccines that reduce AMR.
   - An example of this is the recent inclusion of AMR threat in Gavi’s Vaccine Investment Strategy.

3. Raise public awareness about the role of vaccines against AMR.
4. **Increase direct support for research and development of vaccines against priority AMR pathogens.**

5. **Develop regulatory and policy mechanisms that hasten approval of vaccines that will impact AMR.**

   - Consider options in regulatory and policy space to ease the path to licensure for vaccines with high AMR potential without undermining safety.

6. **Strengthen incentives and risk-sharing strategies to encourage the large investments needed to license and affordably deploy vaccines that will impact AMR.**

   - Long delays between initial licensure and wide-scale introduction are often observed in low- and middle-income countries.
3. Evidence Generation

7. Use available datasets and expand pathogen surveillance programs, epidemiological studies and randomized clinical trials to assess vaccine impact on AMR

8. Develop a model-based framework to assess the full public health, societal and economic value of vaccines in the prevention and control of AMR

- Herd immunity, transmission patterns, pathogen carriage rates, bacterial population dynamics, vaccine-driven reductions in antibiotic use and various molecular drivers of resistance must be evaluated.
4. Animal Vaccines

9. Expand use of existing animal vaccines to reduce antibiotic use in farming.

10. Increase research and development support for animal vaccines that would reduce antibiotic use in food production.
Supporting Evidence: Case Studies

Case study examples are included in support of the Action Priorities:

Gavi Adds AMR Impact to its Vaccine Investment Strategy
Gavi formally redevelops its guiding Vaccine Investment Strategy (VIS) document every five years. In 2018, Gavi decided to include impact of vaccination on AMR as a main indicator of a vaccine’s value.

CARB-X funds innovation in antimicrobial development
CARB-X is a non-profit organisation expressly founded to support R&D to tackle AMR. Its mission is to support “early development of antibiotics, diagnostics, vaccines and other products to combat the most serious drug-resistant bacteria.”

Setting Priorities Among Vaccines to Tackle AMR
A recent report from the Wellcome Trust and The Boston Consulting Group investigated which vaccines, among those for pathogens on the WHO AMR-priority pathogen list, would be both useful in the fight against AMR and be likely to be successfully brought to market.
Supporting Evidence: Current Vaccines and AMR-Related Vaccine R&D

Two additional tables outlining the role of Current Vaccines and Current AMR-related Vaccine R&D are included in the introduction. These highlight considerations about the role of current key vaccines and potential impact on AMR, and about priority vaccine candidates with the potential to have a high impact on AMR, that are in development.

### Current Vaccines

<table>
<thead>
<tr>
<th>Target Pathogen</th>
<th>WHO Recommended Use</th>
<th>Global Coverage</th>
<th>Coverage target</th>
<th>Vaccine impact on AMR</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Pneumoniae (Pneumoccus)</td>
<td>All children under 5 years of age</td>
<td>44%</td>
<td>90% nationally, 80% at district level</td>
<td>Proportionally reduces resistant and nonresistant pneumococcal disease; pooled estimates from &gt;50 publications indicate PCV use reduces antibiotic use in children.</td>
<td>(1)(2)(3)</td>
</tr>
</tbody>
</table>

### AMR-Related Vaccine Research and Development

Some Priority Candidates in AMR-Related Vaccine R&D

Many vaccines now in development have the potential to substantially impact AMR; efforts to prioritize these candidates for further funding are ongoing. We describe here the status of some of these candidates.

**Tuberculosis.** Tuberculosis (TB) causes more deaths annually than any other single infectious agent. A third of the world’s population is latently infected with *Mycobacterium tuberculosis*. In 2017, 10 million people developed active TB, and 1.6 million died of the disease……