A Roadmap for Research and Product Development against Middle East Respiratory Syndrome-Coronavirus (MERS-CoV)

Background on Technology Roadmaps

Technology roadmaps have been successfully used in several sectors where large-scale, collaborative efforts are required to deliver outcomes related to innovation including product development. In all such processes, it is critical to understand and articulate the goals and markets for innovative products. High-level priority objectives are identified, followed by agreement on specific activities to reach the objectives. It is critical to map baseline knowledge gaps and then develop a strategic plan to address those deficiencies. This also requires an assessment of capacity needs that can support these activities. Project management and implementation structures are subsequently established to pursue agreed activities to reach the goals. An example of this process can be found in the WHO Malaria Vaccine Technology Roadmap.

Introduction

The Scientific Advisory Group convened by WHO to advise the Blueprint included MERS CoV as one of the disease priorities, and this document was prepared for MERS as a prototype. It represents the results of a consultation process facilitated by WHO, working with international stakeholders, to develop a MERS-CoV Research and Product Development Technology Roadmap.

Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) is an emerging pathogen of growing importance. As of May 2016, MERS-CoV has been confirmed as cause of severe acute respiratory disease in 1728 people, resulting in 624 deaths. The high case fatality rate, growing geographic distribution, and poorly defined epidemiology have created an urgent need for applied research and product development in order to better characterise epidemiology, diagnose, treat and prevent transmission and disease related to MERS-CoV.

Since the identification of MERS-CoV in the Kingdom of Saudi Arabia in 2012, human cases have been confirmed in 27 countries, including a large outbreak in the Republic of Korea. It is generally believed that dromedary camels are the intermediate animal reservoir; a high prevalence of MERS binding or inhibitory antibodies has been reported in camels across the Middle East, North Africa, and in sub-Saharan Africa. Outbreak investigation reports are strongly suggestive of a link between contact with camels and human cases of MERS-CoV. However many gaps remain in understanding of epidemiology and transmission of MERS-CoV.

Strategic Goals

- A strengthened network of laboratories able to act as an early warning system for emerging highly pathogenic viruses with the potential to cause public health emergencies
- Stimulate basic research for better understanding of the MERS-CoV pathogen, pathogenesis, immunity, epidemiology, transmission including the intermediate animal reservoir as well as person to person transmission
- Development, testing, manufacturing, licensure and use for improved diagnostics, therapeutics and preventives, including preventives for dromedary camels.

- ***Enabling environment strategic goal***: Establish line of sight for manufacturers from pre-clinical proof-of-concept to procurement of MERS products once licensed, by establishing public health-oriented financing model for MERS products, and other products for emerging pathogens prioritized by WHO blueprint process

Priority Areas

Research

- **Acquire** understanding of naturally acquired immunity, and immunity acquired through vaccination
- **Explore** social and cultural questions related to camel vaccination in most affected countries
- **Develop** an immune correlate of protection during pre-clinical and clinical efficacy trials
- **Urgently define** and address epidemiological, biological, behavioural and environmental knowledge gaps related to the definitive host, the intermediate animal reservoir, transmission to humans, person to person transmission, and characterisation of target groups for deployment of preventives
- **Characterise** pathogen diversity of MERS-CoV isolates in different outbreaks as basis for diagnostics, therapeutics and preventives development
- **Model** possible progression of outbreaks of MERS-CoV in various countries, and model impact of alternate approaches to vaccination in camels and humans
- **Research** improved infection control strategies, including appropriate models for triage in healthcare facilities

Cross-Cutting Product Development Related Priority Areas

- **Improved** animal models more representative of human disease for evaluation of different classes of products, including an animal model for enhanced disease. It is expected that animal model data evaluating enhanced disease will be available before licensure of MERS products
- **Develop and endorse** an international standard panel of calibration reagents to allow for comparability between different operators, labs, and assays, for nucleic acid, binding antibody and inhibitory assays
- **Prioritization** for potential products through use of **Target Product Profiles**, head-to-head testing and use of comparable assays with reference reagents

Diagnostic

- **Develop** quality assured, point of care diagnostics for MERS-CoV.
- ***Preferred diagnostic goal***: Multivalent MERS-CoV point of care diagnostic as part of a panel, including RSV, influenza, and other respiratory infections.

Treatment

- **Develop** quality assured therapeutics with acceptable safety and proven efficacy against MERS-CoV in those at high risk of mortality without treatment
- **Pursue evaluations of GMP grade therapeutics in parallel** on an urgent basis with at least 2 products to be tested during 2016

    - **Phase 1 selection based on pre-clinical proof of concept data, time of GMP availability and regulatory/ethics approvals**
    - **Timings for Phase 1 start, and go/no go to Phase 2-3 is critical factor in decision-making**
    - **Proceed** into phase 2-3 evaluations in MERS affected countries and patients, once supportive phase 1 data is available.
- **Assess** the most effective approaches for supportive care, including for low technology settings.

Preventive

- Human vaccine 1: **Develop and license** single dose MERS-CoV vaccine suitable for reactive use in outbreak settings with rapid onset of immunity
- Human vaccine 2: **Develop and license** two dose vaccine with durable protection for administration to those at high ongoing risk of MERS-CoV such as healthcare workers, and those working with potentially infected animals
    - At least 2 different MERS vaccine approaches to be tested in Phase 1 during 2016, with contingency planning to proceed to Phase 2-3 if Phase 1 data supportive
- Dromedary camel vaccine: **Develop and license** a vaccine suitable for administration to camels to prevent transmission of MERS-CoV from animal reservoir to humans
    - Note that recombinant viral vectors and DNA vaccines are already licensed and in use as veterinary vaccines
    - Evaluation in camels of promising approaches to be conducted during 2016

Key capacities

- **Support** regulatory and ethics capacity strengthening in MERS-CoV most affected countries for oversight of clinical trials
- **Build** GCP Clinical Trial Capacity for product evaluation
- **Establish and coordinate** GCLP Laboratory Testing Capacity for product evaluation

Policy and commercialization

- **Define** scale-up needs and **develop** GMP Manufacturing capacity to meet these needs
- **Develop and encourage** responsible stewardship and support for MERS-CoV research and product development and implementation through appropriate project management and investment strategies (supported by Target Product Profiles vetted by key stakeholders).
- **Establish regulatory pathways** for MERS-CoV products
- **Secure** financing for procurement and deployment of MERS-CoV products once available
- **Ensure** post-approval pharmacovigilance and effectiveness evaluations occur to support product deployment and monitoring

The Stakeholders Group for the WHO Blueprint

Starting in 2015, WHO convened a group of key stakeholders in R&D preparedness for emergencies. These include the following funding agencies: BARDA, NIAID, IVI, Wellcome Trust, European Commission Directorate-General Research & Innovation, the GLOPID-R network of funders coordinated via the European Commission and the Bill and Melinda Gates Foundation. It is envisaged

that this group will meet by teleconference on a regular basis with WHO to review gaps in key activities at the global level, minimize unhelpful overlaps, and stimulate priority activities to maintain momentum. The roadmap can also be updated at the annual meetings if necessary. Other stakeholders include public health agencies particularly in affected countries, academia, the biotech sector, industry, regulators and ethics committees amongst others. A mechanism will be developed to implement the MERS R&D Roadmap by agreeing which activities should be carried out by the different stakeholders.