Ebola/Marburg Research and Development (R&D) Roadmap

Roadmap purpose: To provide a framework for identifying the vision, underpinning strategic goals, and prioritizing research areas and activities (from basic research to advanced development, licensure, manufacture, and deployment) for accelerating the collaborative development of medical countermeasures (MCMs)—diagnostics, therapeutics, and vaccines—against Ebola virus disease (EVD) and Marburg virus disease (MVD).

INTRODUCTION

Ebola virus disease (EVD) and Marburg virus disease (MVD), caused by several different filoviruses in the Filoviridae family, are severe hemorrhagic illnesses with similar clinical manifestations and high case-fatality rates. Sporadic outbreaks of EVD and MVD can occur following human contact with infected wild animal reservoirs. Subsequent human-to-human transmission may occur through contact with body fluids of infected persons. Filovirus diseases have significant epidemic potential in regions of Africa where there are reservoirs of the viruses in wild animal populations, including where human outbreaks have previously occurred, as well as in areas of Africa considered non-endemic but potentially at risk. Three highly virulent species of ebolavirus (Zaire, Bundibugyo, and Sudan) have been associated with large EVD outbreaks in sub-Saharan Africa, most recently the explosive 2014–2016 West African Ebola outbreak caused by the Zaire ebolavirus species. Two species of Marburg virus (Marburg and Ravn) have been associated with MVD outbreaks in sub-Saharan Africa, notably a recent outbreak in eastern Uganda.

The Ebola/Marburg R&D roadmap is a key component of the World Health Organization (WHO) R&D Blueprint for accelerating research and product development of MCMs to enable effective and timely emergency response to infectious disease epidemics. Ebola and Marburg viruses are identified in the Blueprint's initial list of priority pathogens (defined as pathogens that are likely to cause severe outbreaks in the near future and for which few or no MCMs exist). The WHO Blueprint calls for the development of R&D roadmaps for the priority pathogens to align and stimulate R&D of new or improved countermeasures, such as rapid diagnostic assays, novel therapeutics, and vaccines. The scope of R&D addressed in the roadmap ranges from basic research to late-stage development, licensure, manufacture, and early use of MCMs to prevent and control EVD/MVD outbreaks. The roadmap is organized into four main sections: cross-cutting topics and issues (for areas that apply to more than one MCM category), diagnostics, therapeutics, and vaccines.

In addition to the development of MCMs, other aspects of public health preparedness and response are critical for successful Ebola/Marburg disease prevention and control. Examples include well-equipped treatment units, improved personal-protective equipment, effective community engagement, and workforce development in at-risk regions. Many of these issues are beyond the scope of the R&D roadmap, but need to be addressed as part of a broader public-health control strategy.

VISION

Robust MCMs to detect, control, and prevent outbreaks of EVD and MVD that are available, affordable, and readily deployable when needed: (1) rapid, accurate, point-of-care diagnostics for Ebola/Marburg virus infection to inform treatment, outbreak detection, and clinical trials; (2) safe and effective treatment and post-exposure prophylaxis (PEP) to reduce morbidity and mortality from EVD/MVD; and (3) safe and effective vaccines to prevent EVD/MVD and stop filovirus transmission in human populations.

CROSS-CUTTING TOPICS AND ISSUES

Current Primary Challenges, Key Needs, and Knowledge Gaps

Primary challenges

- Commercial markets for Ebola/Marburg diagnostics, therapeutics, and vaccines are weak or nonexistent, given that EVD/MVD outbreaks occur episodically and unpredictably in low-income countries.
- Many of the critical resources for MCM development are scarce or limited, such as funding for research, stored biological samples, and high-biosafety level (BSL-4) containment facilities. Requirements for high-level biocontainment laboratory conditions, for example, pose a significant impediment and complicate Ebola/Marburg assay development and validation studies, as many assay reagents and assay validation materials must be generated in BSL-4 laboratories.
- Preparedness for conducting clinical trials quickly during future outbreaks poses a number of significant challenges, particularly since the location or timing of the next outbreak is unknown.
- Preclinical data are essential for licensing new therapeutics and vaccines via nontraditional regulatory pathways (e.g., the US Food and Drug Administration's [FDA's] Animal Rule) and for down-selecting promising therapeutic and vaccine candidates for human clinical studies. Nonhuman primates (NHPs) are regarded as the most relevant preclinical models for the development of filovirus therapeutics and vaccines, although high costs, insufficient standardization, ethical issues, and the need for BSL-4 facilities constrain their use.
- Insufficient data management capabilities in under-resourced areas may impede the sharing and reporting of clinical observations and study data regarding Ebola/Marburg diagnostic, therapeutic, and preventive interventions.
- Pharmacovigilance systems in affected regions may be inadequate to monitor and evaluate the safety, clinical benefit, delivery, and acceptability of licensed MCMs, as well as unlicensed therapeutic agents and vaccines deployed outside of clinical trials, e.g., via the WHO Emergency Use Assessment and Listing (EUAL) procedure or FDA Emergency Use Authorization (EUA).

Key needs

- Funding sources (such as public-private partnerships) and industry incentives and competitions for non-dilutive funding to encourage innovation and secure private-sector commitments to develop, manufacture, and stockpile critical filovirus MCMs.

- Strengthened scientific and regulatory capacity within the at-risk regions to enable greater input throughout the clinical development process for Ebola/Marburg MCMs.
- A collaborative and transparent process for prioritization of future preclinical and clinical studies, including sharing of biological samples, to optimize the use of limited resources and expedite the development of filovirus MCMs.
- An efficient, interoperable system for collecting data across study sites, reporting to WHO, analyzing results, and sharing information and outcome data to facilitate evaluation of filovirus MCMs during outbreak situations. (The Infectious Diseases Data Observatory's Ebola Data Sharing Platform provides a model for a novel platform for collecting, standardizing, and sharing clinical data under the authority of local leadership.)
- Standardized and validated assays, reagents, antibodies, nucleic acids, and stocks of challenge strains for research and development of Ebola/Marburg MCMs.
- Detailed planning and preparation for clinical trials before the next EVD/MVD outbreak to accelerate the evaluation of MCMs, including: (1) development of key components such as trial designs, protocols, and consent procedures; (2) obtaining ethical and regulatory approvals as far as possible in advance; and (3) prioritization of candidate MCMs for further study.
- Adequate supplies of experimental therapeutics and vaccines for future clinical trials and for expanded use, if clinical trials demonstrate efficacy.
- Adequate supplies of licensed filovirus therapeutics and vaccines for rapid deployment during outbreak situations.
- Development of material transfer agreements (MTAs) prior to outbreaks to expedite shipping and transfer of clinical samples during outbreak situations.
- Operational planning, coordinated by the WHO, to facilitate product-delivery contracts and establish, maintain, and deploy global stockpiles of licensed and experimental Ebola/Marburg MCMs.

Knowledge gaps

- Data to refine, standardize, and validate animal models for Ebola/Marburg infection and disease and to ensure that relevant animal models adequately recapitulate the clinical hallmarks of human infection and illness caused by filoviruses.
- Additional information on the immunology and pathogenesis of Ebola/Marburg viruses to develop a comprehensive understanding of the immune response to infection, which will facilitate development of filovirus MCMs. This includes evaluating immune responses in patients with natural immunity to these viruses, determining mechanisms of viral persistence in "sanctuary" sites in the body, identifying factors influencing the development of post-EVD syndrome, fully characterizing cell-mediated and humoral immune responses to filovirus infection, and identifying immune correlates of survival following infection.
- Additional research for development of MCMs specifically for Marburg virus; most research to date has focused on Ebola viruses.
- Integrated social science research on sociocultural and behavioral factors pertaining to the development and deployment of socially acceptable Ebola/Marburg MCMs.

Strategic Goals

1. Identify sources of funding (such as through public-private partnerships) and develop appropriate private-sector incentives and competitions to promote R&D of filovirus MCMs.
2. Conduct additional basic and preclinical research on Ebola/Marburg viruses to facilitate development of filovirus MCMs.
3. Develop standardized and validated animal models to enable licensure of Ebola/Marburg MCMs via nontraditional regulatory pathways.
4. Develop comprehensive plans and protocols for rapid implementation of clinical trials and field studies of promising MCMs during future filovirus outbreaks.

Milestones

[TBD once the strategic goals have been determined.]

Priority Areas/Activities

Research

- **Conduct** additional basic research on the immunology and pathogenesis of Ebola/Marburg viruses to inform the development and appropriate use of filovirus MCMs.
- **Generate** research tools to promote R&D of filovirus MCMs (i.e., standardized and validated assays, reagents, antibodies, nucleic acids, and stocks of Ebola/Marburg virus challenge strains).
- **Continue to research** promising filovirus MCM candidates.
- **Prioritize** preclinical/clinical studies and use of biological samples by research teams to ensure efficient use of limited resources.
- **Ensure** adequate preparation for clinical trials and field studies of promising MCMs in advance of EVD/MVD outbreaks to include the following:
    - **Agree** on preliminary trial designs, particularly regarding randomization and treatment arms, to be finalized at the time of an outbreak for specific products and outbreak settings.
    - **Identify** strategies for prioritizing MCMs for evaluation during future outbreaks, recognizing the challenge of achieving sufficient coordination of studies without stifling creativity.
    - **Develop** locally appropriate protocols, consent procedures, and ethics agreements.
    - **Promote** broad-based collaboration in planning and organizing clinical trials, e.g., by enhancing the involvement of healthcare providers, public health and community leaders, industry representatives, ethics committees, national regulatory officials in affected countries, and external regulatory agencies.
    - **Ensure** the eligibility of children and pregnant women in clinical trials (unless excluded for physiologic or metabolic reasons) to evaluate the safety, dosage, and toxicity of experimental filovirus MCMs.
    - **Develop** public communications in outbreak areas to enhance knowledge, acceptance, and support for clinical trials.

- **Engage** with local partners to build trust, particularly regarding sensitive sociocultural issues, such as drawing blood from trial participants and exporting samples for analysis.

Product development

- **Standardize and validate** relevant animal models that adequately recapitulate the clinical hallmarks of human infection and illness from Ebola/Marburg viruses to enable licensure of Ebola/Marburg MCMs via nontraditional regulatory pathways.
- **Obtain** in advance of future outbreaks, to the degree possible, MTAs and regulatory approvals.
- **Develop** plans for rapid development of MCMs specifically for Marburg virus.

Key capacities

- **Enhance** training for local clinical trial personnel.
- **Ensure** availability of institutional review boards in at-risk countries to facilitate approval of research studies during emergency situations.
- **Establish** an interoperable system to enhance capabilities for collecting, reporting, analyzing, and sharing data from clinical trials and field studies across different sites and outbreaks in resource-limited settings.
- **Ensure** that pharmacovigilance systems in affected areas are adequate for ongoing monitoring of licensed filovirus MCMs and unlicensed products administered via emergency-use procedures.

Policy and commercialization

- **Secure** funding (potentially through public-private partnerships) and promote use of incentives for private-sector R&D of filovirus MCMs.
- **Ensure** access to regulatory guidance, oversight, review, and authorization from appropriate regulatory agencies for filovirus MCMs, to include ongoing dialog with regulators during product development.
- **Promote** plans for adequate manufacturing and supply chains for the deployment of filovirus MCMs in at-risk areas.

Schedule of Resources, Coordination, and Implementation

[TBD; will obtain input later in the process.]

Critical Path Analysis

[TBD once the primary activities have been vetted by subject matter experts.]

DIAGNOSTICS

Current Primary Challenges, Key Needs, and Knowledge Gaps

Primary challenges

- Ebola/Marburg diagnostic testing is critical for patient management (e.g., initial detection, disease confirmation, determination of infectivity, and post-treatment follow-up) as well as epidemic control (contact tracing and outbreak detection and surveillance for epidemiologic

analysis). Different diagnostic methodologies are appropriate for different use cases: (1) rapid, point-of-care (POC) testing, e.g., nucleic acid detection via automated real-time reverse transcriptase polymerase chain reaction (rRT-PCR) assays for initial identification of EVD/MVD cases; (2) laboratory-based molecular, serologic, antigenic, and virologic assays for case confirmation and clinical management; and (3) genomic analysis of Ebola/Marburg viruses, e.g., using portable, handheld real-time sequencing devices such as the MinION, for surveillance and epidemiologic analysis.

- The use of venipuncture blood samples from symptomatic individuals for Ebola/Marburg diagnostic testing poses safety and logistical challenges for collection and transport of specimens in under-resourced areas, requiring BSL-4 capabilities in regional or international reference laboratories, which may not be readily accessible.
- Laboratory-based confirmatory testing for Ebola/Marburg often requires long turnaround times, resulting in diagnostic delays that may lead to: (1) greater likelihood of exposure for the suspect case, if the suspect case is being held in a treatment unit with other suspected or confirmed cases; (2) greater likelihood of exposure for close contacts and healthcare providers, if the suspect case is being treated with routine (non-isolated) care; (3) delayed outbreak detection and response; and (4) delayed initiation of antiviral therapy (this may be more important as effective therapies are identified).
- Laboratory infrastructure, diagnostic capability, and adequately trained personnel in at-risk areas are often inadequate in Ebola/Marburg-affected countries. Building infrastructure and capacity requires dedicated commitment, prioritization in relation to other pressing public health issues, and sustained resources from international partners and in-country national health ministries.
- Differentiating EVD and MVD from other diseases that present with similar symptoms (e.g., malaria, Lassa fever, yellow fever, dengue, cholera, and typhoid) complicates clinical care and management in areas where the occurrence of such diseases overlaps.

Key needs

- Rapid and deployable POC and laboratory-based diagnostic testing for different use cases, such as: (1) detection of EVD/MVD outbreaks; (2) case identification for treatment, isolation, and infection control, including safe burials; and (3) epidemiologic control via genomic analysis of cases, contacts, and transmission chains.
- Regulatory clearance of standardized and validated EVD/MVD diagnostic assays, e.g., via the US FDA's premarket notification 510(k) process or European CE-Marking.
- Shared data on the performance characteristics of each assay and algorithms for test usage.
- An updated diagnostic Target Product Profile (TPP) that includes all relevant Ebola and Marburg virus species, primary methodologies, and diagnostic use cases (e.g., initial case identification, confirmation, ongoing clinical management, contact tracing, surveillance, and epidemiologic analysis). Key characteristics of the field-deployable EVD/MVD diagnostics include the following:
    - *Rapid turnaround times* for diagnostic results, contact tracing, and epidemiologic analysis during outbreak situations.

- *Minimal requirements* for laboratory infrastructure, sensitive sample handling (including cold-chain maintenance) prior to analysis, molecular biology expertise, electrical power, temperature-sensitive reagents, and specialized equipment, to enable deployment in remote locations.
- *Automated technologies and low-risk alternatives to obtaining specimens*, such as oral swabs, capillary blood sampling, or alternative methods for performing venipunctures, including for post-mortem diagnosis (which is particularly important for safe burial practices).
- *Infectivity testing*, e.g., for risk evaluation of potential exposures, assessment of patients being discharged from treatment centers, and measurement of viral persistence among survivors, including testing of alternative specimen types (such as seminal fluid).
- *Appropriate sensitivity and specificity of diagnostic testing*, corresponding to the use case (e.g., high test sensitivity to inform clinical management and high test specificity to improve outbreak detection).
- *High negative-predictive value* of testing to enable rapid exclusion of uninfected individuals from treatment units where they may be at increased risk of exposure.
- *Diagnostic algorithms* for high prevalence (outbreak) and low prevalence (surveillance) settings, particularly needed as more testing options and clinical validation data become available.
- *Detection of infection earlier in the clinical course*, prior to the onset of symptoms, to enhance control efforts and allow for earlier therapy (once antiviral treatments become available).
- *Potential development of combinations of diagnostic testing* (e.g., in multiplex assays or testing panels) that can detect EVD/MVD infection while simultaneously screening for the presence of other high-consequence or common pathogens (e.g., Lassa virus in West Africa) to facilitate wider usage of the diagnostic methodologies.

- Standardization and validation of diagnostic methodologies to enable comparability of data from different studies and diagnostic assays.
- Repositories of well-characterized clinical and preclinical specimens for diagnostic test development.
- Proficiency testing to monitor and evaluate performance of diagnostic assays in the field.
- Improvements in laboratory capacity in at-risk areas, including the availability of supplies and reagents, pre- and post-analytical processing, culture-independent confirmatory testing, training of local laboratory technicians in molecular diagnostic methodologies, and enhanced biosafety practices and quality control methods. Overall, an integrated and sustained laboratory infrastructure in at-risk areas should include the presence of strategically-placed supporting field laboratories that can perform rRT-PCR or other rapid diagnostic testing, access to regional laboratories for further confirmatory testing as necessary, and access to international reference laboratories.

- Ongoing clinical training to enhance early identification of EVD/MVD using rapid diagnostic technologies.

Knowledge gaps

- Identification and validation of host biomarkers correlated with patient prognosis and disease progression, such as viral load and transcriptomic signatures.
- Comparative data on commercially available rRT-PCR assays for Ebola infection to assess the performance of testing options in different situations and patient populations, such as patients with low viral loads (i.e., those who are very early in the clinical course or close to the point of recovery).

Strategic Goals

1. Expedite the development and evaluation of rapid, inexpensive, and highly sensitive and specific diagnostic testing methodologies with minimal requirements for biosafety precautions and staff training for POC or decentralized healthcare facility use in Ebola/Marburg affected areas.
2. Strengthen laboratory infrastructure and capacity in affected areas to ensure rapid identification of suspect cases in outbreak and non-outbreak settings.
3. Stimulate research into novel diagnostic approaches, including infectivity testing, prognostic biomarker analysis, and the development of alternatives to single Ebola/Marburg assays, such as broad testing panels, platforms, or multiplex assays for ongoing use between outbreaks.

Milestones

[TBD once the strategic goals have been determined.]

Priority Areas/Activities

Research

- **Further determine** the analytical characteristics (including sensitivity, specificity, and limits of detection) of novel diagnostic platforms and commercially available rRT-PCR assays for Ebola infection.
- **Research and validate** methods to identify host factors (biomarkers) associated with a high predictive value for survival or fatal outcomes to enhance clinical management of patients with EVD/MVD.
- **Explore** new diagnostic approaches that may enhance EVD/MVD diagnostic testing (e.g., by measuring infectivity, allowing earlier detection of infection, shortening turnaround time to results, and/or predicting outcome [survival or fatality]).

Product development

- **Continue to develop and evaluate** safe and accurate rapid POC diagnostic tests for use during EVD and MVD outbreaks.
- **Define** use cases for Ebola/Marburg diagnostics and determine optimal test characteristics that correspond to those use cases.

- **Develop** multiplex diagnostic assays to distinguish among fever-related illnesses and allow differentiation of EVD/MVD from other diseases that present with similar symptoms (e.g., Lassa fever for use in West Africa).

Key capacities

- **Create** international partnerships to fund, support, and promote enhanced laboratory capacity and infrastructure in at-risk areas for early disease detection and outbreak response.
- **Establish** a network of filovirus surveillance laboratories that can provide early warning for EVD/MVD outbreaks and enhance understanding of the epidemiology of filovirus diseases.
- **Develop** a database on the performance characteristics of available diagnostic assays and algorithms for test usage.

Policy and commercialization

- **Develop** additional guidance on the testing of alternative specimen types (such as seminal fluid) for viral persistence in EVD survivors.
- **Generate and update** new EVD diagnostic screening algorithms for high prevalence (outbreak) and low prevalence (surveillance) settings as additional diagnostic tests become available.

Schedule of Resources, Coordination, and Implementation

[TBD; will obtain input later in the process.]

Critical Path Analysis

[TBD once the primary activities have been vetted by subject matter experts.]

THERAPEUTICS

Current Primary Challenges, Key Needs, and Knowledge Gaps

Primary challenges

- Efficacy data for therapeutic agents against EVD/MVD are lacking, particularly among special populations (e.g., children, pregnant women, immunocompromised patients), patients with late-stage disease, and EVD survivors with viral persistence.
- Ethical issues in therapeutic clinical trials need to be addressed, particularly regarding the assignment of patients to control (nontreatment) groups if preclinical data suggest potential efficacy of the experimental agent; alternative study designs for determining efficacy may be needed to address these concerns.

Key needs

- Development of a TPP that identifies optimal and desirable characteristics of EVD/MVD treatment interventions to guide the development of safe, effective, and appropriate treatment approaches.
- Safe and effective therapies to improve survival and decrease morbidity among patients with EVD/MVD.

- Safe, effective, and non-invasive (e.g., oral or intranasal) methods for PEP, including immune-stimulation via antibody therapy, to prevent EVD/MVD following exposure to filoviruses to protect healthcare workers, family caregivers, and burial teams, and to reduce transmission during outbreaks.
- Consistent standards for high-quality supportive care among Ebola/Marburg treatment centers.

Knowledge gaps

- Clinical data on the safety, tolerability, and efficacy of investigational treatments, including those evaluated during the Ebola epidemic in West Africa (e.g., ZMapp, TKM-130803, and favipiravir), including in special populations, such as pregnant women, immunocompromised persons, and children.
- Clinical data on the safety and effectiveness of administering combinations of treatment agents.
- Additional clinical data to inform the role of PEP in EVD/MVD outbreak control, including the development of a standard definition of PEP and guidance on the type of exposures that warrant such intervention and the most appropriate agents to administer.
- Research on the observed differences in outcome between NHP challenge studies and human trials of treatment candidates. This includes the evaluation of underlying factors such as biological differences between NHPs and humans, virus exposure routes, and infectious doses.
- Therapeutic options for eliminating persistent virus in the semen of EVD survivors, based on clinical evaluations of novel agents (such as the PREVAIL IV trial involving intravenous GS-5734).
- Research to characterize and validate biomarkers (e.g., transcriptomic signatures and multiplatform omics analysis) that can reliably predict the severity and outcome of illness in infected patients independent of viral load. The use of such biomarkers may enhance the design of therapeutic clinical trials and improve clinical care (e.g., through risk stratification).
- Additional research on the potential role of broadly protective filovirus immunotherapies. Priority agents include monoclonal antibodies (mAbs) that can recognize and neutralize viral targets (such as conserved elements of the virus's glycoprotein) and confer post-exposure protection. Key topics include analyzing cross-reactive and cross-neutralizing antibodies from Ebola survivors to address the challenge of achieving pan-Ebolavirus or pan-filovirus neutralization with mAbs targeting glycoprotein epitopes. Another key topic is evaluating the safety and efficacy of the "Trojan horse" strategy based on bi-specific antibodies (to neutralize ebolaviruses by co-opting viral particles themselves for endosomal delivery), potentially acting as broad antifilovirus immunotherapeutics.
- Additional research to optimize supportive care independent of specific EVD/MVD therapeutic agents. Key research areas include obtaining data on the safety and efficacy of various components of supportive care for EVD/MVD, such as optimal fluid resuscitation strategies, diagnosis of organ dysfunction, and the use of empiric antibiotics, antidiarrheal agents, NSAIDs, and vitamin K, to inform supportive care and best-practice guidelines. Clinical evaluation of various aspects of supportive care should focus on patients in at-risk regions to avoid extrapolating from conclusions based on patient outcomes in high-resource settings.

Strategic Goals

1. Develop a robust preclinical drug-development pipeline of potential therapeutic candidates with broad-spectrum activity against filovirus infection, relapse, post-Ebola syndrome, and viral persistence to expedite bridging studies in relevant animal models and clinical evaluation.
2. Complete preclinical and early-stage clinical studies of treatment and PEP approaches during inter-epidemic periods to facilitate the licensing/registration of safe and efficacious new agents and the prompt implementation of efficacy trials and post-marketing evaluation during future Ebola/Marburg outbreaks.
3. Determine optimal strategies for supportive care of patients with EVD/MVD disease.

Milestones

[TBD once the strategic goals have been determined.]

Priority Areas/Activities

Research

- **Continue to research** the safety, tolerability, and efficacy of investigational therapies for EVD/MVD, including those evaluated during the Ebola epidemic in West Africa. In the absence of outbreaks, this work can include animal studies, pharmacokinetics and pharmacodynamics evaluation, definition of optimal dosage, and phase 1/2 clinical trials to assess safety and tolerability.
- **Determine** the safety and efficacy of promising new therapeutic and PEP approaches (such as pan-filovirus mAbs) with demonstrated efficacy in NHP models for treatment of MVD.
- **Identify and validate** host biomarkers in patients with early stage EVD/MVD to improve clinical management and predict the likelihood of survival.
- **Research** optimal supportive care for infected patients in outbreak settings and determine best-practice guidelines.
- **Conduct** research on the mechanisms of viral persistence in immune-privileged sites to help identify further treatment options.

Product development

- **Generate** a TPP for Ebola/Marburg therapeutics.
- **Continue** to develop safe and effective therapeutic agents for treatment of EVD/MVD.
- **Identify** immunotherapeutic approaches for PEP that are broadly active against multiple species of filoviruses and can be administered via non-invasive methods.
- **Research** discrepancies in efficacy outcomes between NHP challenge studies and human trials of treatment candidates.

Key capacities

- **Develop** a database of preclinical studies regarding EVD/MVD therapeutic agents.

Policy and commercialization

- **Develop** clinical guidance as research demonstrates the safety and efficacy of new therapies.

Schedule of Resources, Coordination, and Implementation

[TBD; will obtain input later in the process.]

Critical Path Analysis

[TBD once the primary activities have been vetted by subject matter experts.]

VACCINES

Current Primary Challenges, Key Needs, and Knowledge Gaps

Primary challenges

- Filovirus vaccines are needed for multiple indications, including vaccines for rapid onset of immunity against a specific outbreak strain and vaccines to confer long-lasting immunity against one or more filoviruses.
- The availability of one or more licensed Ebola vaccines complicates the evaluation of other Ebola vaccine candidates, owing to ethical issues and challenges with efficacy trial design.
- Cold-chain requirements for some of the current Ebola vaccine candidates create challenges for vaccine deployment in clinical trials in affected regions.
- Side-effect profiles (e.g., vaccine-induced fever) of some of the current Ebola vaccine candidates, which mimic the symptoms of early EVD, complicate the evaluation of the vaccines and create diagnostic challenges among exposed persons.
- Time of onset of effective immunity following vaccination is unclear, which complicates the determination of appropriate vaccination strategies in outbreak situations.
- Vaccine skepticism, suspicion of outsiders, and suspicion of research during outbreaks are potential obstacles to community support for EVD/MVD vaccine clinical trials.
- Limited manufacturing capacity creates a risk of inadequate supplies of vaccines.
- The lack of field efficacy data and the uncertainties regarding the evidence from NHP data that would underpin the use of nontraditional approval pathways could create difficulties in licensing vaccines.

Key needs

- Broad-spectrum filovirus vaccines or multiple monovalent vaccines capable of inducing cross-reactive antibodies that can neutralize one or more Ebola/Marburg species.
- Additional guidance on vaccination strategies for preventive and reactive use. The WHO's Strategic Advisory Group of Experts (SAGE) on Immunization concluded in April 2017 that current evidence is insufficient to recommend population-based vaccination or prophylactic Ebola vaccination of healthcare workers in the absence of an outbreak. The SAGE has recommended a ring vaccination approach using the unlicensed rVSVΔG-ZEBOV-GP (Merck) vaccine candidate under expanded-access protocols in case of another Ebola outbreak; additional guidance is needed regarding vaccination of contacts and the role of PEP among contacts exposed to Ebola virus. Additional vaccination strategies for the Merck vaccine and other products need to be defined, following regulatory review and in coordination with SAGE

policy recommendations and the Global Ebola Vaccine Implementation Team (GEVIT) operational guidance for use of licensed vaccines, in case outbreaks occur in densely populated regions or megacities where ring vaccination would not be feasible.

- Bridging of vaccine outcome data between preclinical and clinical studies. Standardized assays are needed to compare vaccine-induced humoral immunogenicity, such as qualitative and quantitative differences between antigen-specific binding antibody responses.
- Guidance regarding the use and deployment in outbreak settings of two monovalent, prime-boost Ebola vaccines that have been approved in their countries of origin: the GamEvac-Combi rVSV/Ad5-vectored vaccine licensed in Russia in 2016 and the Ad5-vectored vaccine licensed in China in 2017.

Knowledge gaps

- Additional research to identify specific vaccine-induced immune responses (including binding antibody, neutralizing antibody, and/or cell-mediated immune responses) that can serve as biomarkers for clinical protection against EVD/MVD and predict the level of vaccine efficacy.
- Enhanced understanding of humoral and cell-mediated immune responses to Ebola/Marburg vaccines. Key topics include evaluating the protective roles of vaccine-induced neutralizing antibodies, glycoprotein-specific T-cells, and cytokine-producing peripheral blood mononuclear cells (PBMCs); and comparing naturally acquired immunity (such as among EVD survivors and individuals with asymptomatic Ebola virus infection) with vaccine-induced immune responses.
- Specific correlates of protection to facilitate clinical research on promising filovirus vaccine candidates and expedite licensing through nontraditional regulatory pathways, such as the FDA's Animal Rule and accelerated approval.
- Evaluation of vaccine safety in target populations to better understand the risk of adverse events in outbreak settings.
- Direct evaluation of Marburg vaccines, without relying on data extrapolated from Ebola preclinical or clinical studies. Further research is needed to determine the utility of potential platform technologies for the development of rapid, low-cost vaccines to protect against novel or multiple emerging Ebola/Marburg viruses. Suitable platform technologies require: (1) guidance on immune bridging from NHP data for each filovirus; (2) pre-established safety, reactogenicity, immunogenicity profiles in various at-risk age groups and special populations; and (3) plans for manufacturing, stockpiling, and deployment in field efficacy trials when outbreaks occur.
- Data on the duration of protective immunity for each type of vaccine and vaccination strategy (including single shot and prime-boost strategies) in different population groups.
- Data on the stability of different vaccine types and formulations under field conditions in at-risk regions.

Strategic Goals

1. Complete the evaluation of candidate Ebola and multivalent vaccines for safety, immunogenicity, correlates of protection, and duration of immunity to achieve licensure/registration of the vaccines

for different indications (e.g., monovalent, pathogen-specific vaccines for rapid onset of immunity against specific outbreak strains and multivalent filovirus vaccines for long-lasting immunity against multiple Ebola and Marburg virus strains).

2. Accelerate the development of safe and effective filovirus vaccines by integrating advanced R&D activities into the public-health response to future outbreaks, as guided by the WHO R&D Blueprint process, for planning and conducting phase 3 trials (or other evaluation strategies) of investigational products and other vaccines potentially approved through nontraditional regulatory pathways.
3. Develop comprehensive plans for emergency use of Ebola/Marburg vaccines in future outbreaks. Key priorities include clarifying public health and regulatory requirements to authorize and deploy unlicensed vaccines (particularly in countries that do not have EUA procedures), developing scenario-based reactive vaccination strategies specific to the needs and resources of the affected countries, protecting healthcare/frontline workers and other vulnerable groups, scaling up manufacturing, managing stockpiles, and addressing issues regarding vaccine delivery such as shelf-life and cold-chain requirements.

Milestones

[TBD once the strategic goals have been determined.]

Priority Areas/Activities

Research

- **Determine** the mechanisms of humoral and cell-mediated immune responses to Ebola/Marburg vaccines.
- **Identify** correlates of protection, which are specifically needed for ongoing vaccine research.
- **Determine** the duration of protective immunity for each type of vaccine and vaccination strategy.
- **Conduct** research aimed at the development and evaluation of Marburg vaccines.
- **Conduct** further research to assess safety profiles of filovirus candidate vaccines in target populations to better understand the risk of adverse events in outbreak settings.
- **Continue to conduct** social science research to address issues related to vaccine skepticism and concerns related to participation in research involving filovirus vaccines.

Product development

- **Develop**, clinically evaluate, and license filovirus vaccines, including multiple monovalent, multivalent, or pan-filovirus vaccines that provide protection against Ebola and Marburg virus species.
- **Develop** thermostable formulations of filovirus vaccines.
- **Determine** the utility of potential platform technologies for enhancing the rapid development of safe and effective low-cost vaccines.

Key capacities

- **Promote** the development of adequate manufacturing capacity to ensure adequate supplies of vaccines.

- **Establish and maintain** global stockpiles of filovirus vaccines (licensed and unlicensed) for rapid outbreak response.

Policy and commercialization

- **Develop** comprehensive plans for emergency use of Ebola/Marburg vaccines in future outbreaks.
- **Provide** additional guidance on vaccination strategies for potential reactive and prophylactic scenarios.
- **Develop** guidance on the evaluation and use of currently licensed Ebola vaccines, including the GamEvac-Combi rVSV/Ad5-vectored vaccine licensed in Russia in 2016 and the Ad5-vectored vaccine licensed in China in 2017.

Schedule of Resources, Coordination, and Implementation

[TBD; will obtain input later in the process.]

Critical Path Analysis

[TBD once the primary activities have been vetted by subject matter experts.]

BACKGROUND INFORMATION

World Health Organization R&D Roadmap Documents and Guidance

WHO. Ebola/Marburg: Baseline situation analysis (Jan 2018)

WHO. Target product profile for Zaïre ebolavirus rapid, simple test to be used in the control of the Ebola outbreak in West Africa, Oct 2014 [Full text]

WHO. Ebola virus disease (EVD) vaccine target product profile. Jan 2016 [Full text]

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