World Health Organization

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

January 2019 – Advanced draft

R&DBlueprint

Powering research
to prevent epidemics

Contents

ABBREVIATIONS & ACRONYMS 2
ACKNOWLEDGEMENTS and DISCLAIMERS 3
INTRODUCTION 3
VISION 4
CROSS-CUTTING ISSUES 4
Primary challenges, key needs and knowledge gaps 4
Strategic Goals and aligned milestones 6
Priority areas/activities 7
DIAGNOSTICS 9
Primary challenges, key needs and knowledge gaps 9
Strategic Goals and aligned milestones 11
Priority areas/activities 13
THERAPEUTICS 14
Primary challenges, key needs and knowledge gaps 14
Strategic Goals and aligned milestones 15
Priority areas/activities 17
VACCINES 18
Primary challenges, key needs and knowledge gaps 18
Strategic Goals and aligned milestones 19
Priority areas/activities 21
BACKGROUND INFORMATION 22

ABBREVIATIONS & ACRONYMS

BSL-4	biosafety level 4
CE	European conformity
CMC	chemistry, manufacturing, and control
Ct	cycle threshold
EUA	Emergency Use Authorization (FDA)
EUAL	Emergency Use Assessment and Listing (WHO)
EVD	Ebola virus disease
FDA	Food and Drug Administration (USA)
mAb	monoclonal antibody
MCM	medical countermeasure
MTA	material transfer agreement
MVD	Marburg virus disease
NHP	nonhuman primates
NRA	national regulatory authority
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamic
PEP	post-exposure prophylaxis
PK	pharmacokinetic
POC	point-of-care
PPE	personal protective equipment
R&D	research and development
rRT	real-time reverse transcriptase
TPP	target product profile
WHO	World Health Organization

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[to be added]

Roadmap purpose: to provide a 10-year 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

EVD and MVD, caused by several different filoviruses in the Filoviridae family, are severe illnesses with similar clinical manifestations and high case-fatality rates. Sporadic outbreaks of EVD and MVD are assumed to originate from human contact with infected wild animal host 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 filovirus reservoirs exist in wild animal populations, including areas 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 outbreak in West Africa and the 2018 outbreaks in Equateur, North Kivu and Ituri provinces, Democratic Republic of the Congo, 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 2017 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 issues (for areas that apply to more than one MCM category), diagnostics, therapeutics and vaccines. (Note: these topics are not presented in order of public-health priority). The strategic goals and milestones identified in the roadmap focus on key achievements for the next 10 years; the roadmap milestones will be tracked over time, with periodic assessment of progress and updating, as needed.

In addition to the development of diagnostics, therapeutics and vaccines, 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 (PPE); improved education about, and adherence to, infection control practices among caregivers; effective

community engagement; improved follow-up of exposed contacts; enhanced communications (for example, regarding practices to reduce the risk of disease transmission); adequate infrastructure (such as cold-chain maintenance) to deploy MCMs, safer burial practices 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

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

CROSS-CUTTING ISSUES

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. In addition, accelerated development and deployment of MCMs during public-health emergencies may entail significant financial and legal risks, leading, in some circumstances, to the need for indemnification and liability insurance.
- Many of the critical resources for MCM development are scarce, or limited, such as research funding, stored biological samples and biosafety level 4 (BSL-4) containment facilities. Requirements for high-level biocontainment laboratory conditions, for example, pose a significant impediment and may complicate Ebola/Marburg assay development as many assay reagents must be generated in BSL-4 laboratories.
- Preparedness for conducting clinical trials during future outbreaks poses a number of significant challenges, particularly since the location and timing of the next outbreak are unknowns and future outbreaks may be small. To address this issue, longer-term plans may need to be in place for conducting clinical trials over multiple outbreaks and years, and combining data to generate sufficient sample sizes.
- The ability to conduct clinical research may be limited if future outbreaks are consistently small. This will shrink opportunities for investigators to assess new therapeutic agents and vaccines, which is a disincentive for commercial interest in R&D of filovirus MCMs and will likely restrict the number of promising agents that can undergo clinical evaluation.
- Preclinical data are essential for licensing new therapeutics and vaccines via nontraditional regulatory pathways (such as the 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 predicting clinical benefits in

humans based on observed benefits in experimental NHPs remains challenging. In addition, the use of NHP models is constrained by high costs, insufficient standardization and ethical issues, and the need for BSL-4 facilities. Inadequate capabilities in many of the at-risk countries for regulatory and ethical approvals and coordination of multiple research initiatives, may pose additional challenges to conducting clinical research during outbreaks.

- Insufficient data-management capabilities in under-resourced areas, and lack of coordinated mechanisms for data sharing, 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, for example, via the WHO Emergency Use Assessment and Listing (EUAL) procedure or FDA Emergency Use Authorization (EUA).
- Sociocultural and/or political issues may hinder trust in the formal health-care and public-health systems, which could reduce acceptance of filovirus therapeutics or vaccines.

Key needs

- Funding sources (such as public-private partnerships, government agencies and philanthropic organizations), and industry incentives and competitions for non-dilutive funding to encourage innovation and secure private-sector commitments to develop, manufacture and stockpile filovirus MCMs and critical reagents and supplies.
- Strengthened scientific and regulatory capacity within the at-risk regions to enable greater leadership and collaboration throughout the clinical development process for Ebola/Marburg MCMs.
- A clearly defined mechanism for prioritization and coordination of future preclinical and clinical studies, including sharing of biological samples, to optimize the use of limited resources and to expedite the development of filovirus MCMs. This requires international leadership from an authoritative source, such as WHO, to ensure broad-based support, coordination, transparency and collaboration.
- An efficient, interoperable system for collecting data across study sites, reporting to WHO, analysing results and timely sharing of information and outcome data to facilitate evaluation of filovirus MCMs during outbreaks. (The Infectious Diseases Data Observatory's Ebola Data Sharing Platform provides a model for collecting, standardizing and sharing clinical data under the authority of local leadership).
- Standardized and well-characterized assays (to be further defined based on end use), reagents, antibodies, nucleic acids and stocks of challenge strains for R&D of Ebola/Marburg MCMs.
- Detailed planning and preparation (including coordination) for clinical trials to be implemented during future EVD/MVD outbreaks to accelerate the evaluation of MCMs, including: (1) development of key components, such as multicentre trial designs, protocols and consent procedures; (2) availability of mobile laboratories that are compliant with good clinical practice to support diagnostics and clinical biochemistry analysis; (3) obtainment of ethical and

regulatory approvals as far as possible in advance; (4) 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. Strategies for ensuring that stockpile and manufacturing capacities are aligned with anticipated needs should be defined prior to future outbreaks.
- Adequate supplies of licensed filovirus therapeutics and vaccines for rapid deployment during outbreaks.
- Development of material transfer agreements (MTAs) prior to outbreaks to expedite shipping and transfer of clinical samples during outbreaks.
- Operational planning, coordinated by the WHO, to facilitate product-delivery contracts and to prioritize, establish, maintain and deploy global stockpiles of licensed and experimental Ebola/Marburg MCMs.

Knowledge gaps

- Data to refine and standardize 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 that may facilitate evaluation of immune responses in patients with natural immunity to these viruses, mechanisms of viral persistence in “sanctuary” sites in the body, factors influencing the development of post-EVD syndrome and immune correlates of survival.
- Additional research to enable the development of MCMs specifically for Marburg virus; most research to date has focused on Ebola viruses.
- Integrated social science research on sociocultural and behavioural factors pertaining to the development and deployment of socially acceptable Ebola/Marburg MCMs. Strategies for designing socially acceptable field research are also needed.

Strategic Goals and aligned milestones

Strategic Goal 1: to identify sources of private- and public-sector funding and develop appropriate incentives and competitions to promote R&D of Ebola and Marburg MCMs.

Milestones

1. By 2019, develop a public value proposition to support the development and sustainability of Ebola and Marburg MCMs that: (1) articulates the global health security risks of Ebola/Marburg disease; (2) analyses the socioeconomic benefits of accessible and affordable Ebola and Marburg MCMs; (3) recognizes the public-health benefits of effective Ebola/Marburg prevention and treatment in at-risk areas.

2. By 2020, create a funding plan for advancing Ebola and Marburg MCMs toward clinical evaluation, regulatory approval, production, affordability, deployment and public acceptance in at-risk countries.

Strategic Goal 2: to support basic and preclinical research on Ebola/Marburg virology, transmission, pathogenesis, infectivity and immunology to facilitate development of filovirus MCMs.

Milestones

1. By 2019, generate standardized and well-characterized assays, reagents, antibodies, nucleic acids, and virus stocks to support preclinical and clinical Ebola/Marburg MCM research.

2. By 2020, standardize and refine relevant animal models that adequately recapitulate the clinical hallmarks of human infection and disease from Ebola/Marburg viruses and are suitable for evaluation and licensure of candidate MCMs, via nontraditional regulatory pathways, when clinical efficacy trials are not feasible.

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 (such as, standardized and well-characterized assays [to be further defined based on end use], 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, and equitable access to, limited resources.
- **Develop** a mechanism for publishing negative data from preclinical and clinical studies of Ebola/Marburg MCMs in an online repository (for example, on the WHO or USA National Institute of Allergy and Infectious Diseases websites).
- **Capitalize** on past lessons learned and ensure adequate preparation for clinical trials and field studies of promising MCMs in advance of EVD/MVD outbreaks, to include the following:
    - **identify** stakeholders who have the primary responsibility for developing and implementing clinical evaluations, including study investigators and national research counterparts, with discussion facilitated by international conveners (such as WHO);
    - **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, given that it may be feasible to clinically evaluate only a few MCMs in outbreaks, and recognize the challenge of achieving sufficient coordination and prioritization of studies without stifling creativity;
    - **develop** locally appropriate protocols, consent procedures and scientific and ethics agreements, and obtain approvals from national regulatory authorities (NRAs) as appropriate;

- **promote** broad-based collaboration in planning and organizing clinical trials, for example, by enhancing the involvement of government, health-care providers, public-health and community leaders, industry representatives, ethics committees, NRAs in affected countries and external regulatory agencies;
- **ensure** the eligibility of special populations, such as pregnant women, children and the elderly, in clinical trials (if appropriate, depending on the construct of the MCM) 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 and political issues, such as drawing blood from trial participants and exporting samples for analysis.

Product development

- **Standardize and refine** 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 through nontraditional regulatory pathways.
- **Standardize and characterize** relevant in vitro assays and facilitate rapid sharing of experimental results to enable consideration of investigational products for clinical studies, if appropriate.
- **Conduct ethical and interpretable clinical trials**, when appropriate and feasible, to accelerate the evaluation of MCMs.
- **Develop** plans for rapid development of diagnostics, therapeutics and vaccines specifically for Marburg virus.

Key capacities

- **Enhance** training for local clinical trial personnel during inter-epidemic periods.
- **Ensure** availability of institutional review boards in at-risk countries, during inter-epidemic periods, to facilitate approval of research studies during emergencies.
- **Establish** an interoperable system, during inter-epidemic periods, to enhance capabilities for collecting, reporting, analysing and sharing data from clinical trials and field studies across different sites and outbreaks in resource-limited settings.
- **Strengthen** NRAs and NRA networks in at-risk regions during inter-epidemic periods.
- **Ensure**, during inter-epidemic periods, that pharmacovigilance systems in affected areas are adequate for ongoing monitoring of licensed filovirus MCMs and unlicensed products administered via emergency-use procedures.
- **Establish** a governance body, to oversee management of clinical trials that take place over a span of years, in multiple countries.

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 dialogue with regulators during product development.
- **Promote** plans, including financial support, for adequate manufacturing, stockpiling and supply chains for the deployment of filovirus MCMs and critical supplies in at-risk areas.
- **Support** the development of affordable pricing mechanisms to promote accessibility of Ebola/Marburg MCMs in low- and middle-income at-risk countries. (Note: according to the WHO, an "affordable and fair" price is one that can reasonably be paid by patients and health budgets and that simultaneously sustains research and development, production and distribution within a country).

DIAGNOSTICS

Primary challenges, key needs and knowledge gaps

Primary challenges

- Ebola/Marburg diagnostic testing is critical for patient management (for example, 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, such as nucleic acid detection via automated real-time reverse transcriptase polymerase chain reaction (rRT-PCR) assays for identification of EVD/MVD cases; (2) laboratory-based molecular, serologic, antigenic and virologic assays for case follow-up and clinical management; (3) genomic analysis of Ebola/Marburg viruses, such as using portable real-time sequencing devices for surveillance, epidemiologic analysis and accurate diagnosis of circulating viruses.
- 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.
- 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 health-care providers, if the suspect case is being treated with routine (non-isolated) care; (3) delayed outbreak detection and response; (4) delayed initiation of antiviral therapy (this may be more important as effective therapies are developed).
- Laboratory infrastructure, diagnostic capability and adequately trained personnel in at-risk areas is 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. Many of these obstacles can be addressed by ongoing support of deployable field laboratories, as needed during future outbreaks, although maintaining this capacity also involves a number of challenges and requires resources and commitment.

- Differentiating EVD and MVD from other diseases that present with similar symptoms (for example, 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; (3) epidemiologic control via genomic analysis of cases and transmission chains; (4) biosurveillance of suspected wild animal reservoirs.
- Diagnostic tests that can be performed using inactivated specimens in lower biosecurity level laboratories (not requiring BSL-4 conditions). Regulatory clearance of standardized and validated EVD/MVD diagnostic assays, such as via the FDA's premarket notification 510(k) process or European conformity (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 (such as, 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 and epidemiologic analysis during outbreaks;
    - minimal requirements for laboratory infrastructure, sensitive sample handling (including cold-chain maintenance) prior to analysis, molecular biology expertise, electrical power, temperature-sensitive reagents, PPE for specimen handling and specialized laboratory equipment—to enable deployment in remote locations;
    - automated technologies and low-risk alternatives to obtaining specimens, such as oral swabs and capillary blood sampling, or alternative methods for performing venipunctures, including for post-mortem diagnosis (which is particularly important for safe burial practices);
    - infectivity testing, such as for risk evaluation of potential exposures, assessment of patients on discharge from treatment centres 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 (such as accurate testing to determine appropriate disposition of suspect cases);
    - diagnostic algorithms for high-prevalence (outbreak) and low-prevalence (surveillance) settings that are 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 (such as 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 (for example, Lassa virus in West Africa) to facilitate wider usage.

- Standardization and validation of diagnostic methodologies to enable comparability of data from different studies and diagnostic assays, using WHO international standards (when available) as calibrators, and reported in units/ml.
- Safe repositories of well-characterized clinical and preclinical specimens (with detailed companion data) for diagnostic test development, along with clear mechanisms and protocols for who has ownership of the specimens and how they can be accessed and used. Global governance is needed for management of such repositories.
- 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 and Marburg infection to assess the performance of testing options in different situations and patient populations, such as patients with low viral loads (that is, those who are very early in the clinical course or close to the point of recovery).

Strategic Goals and aligned milestones

Strategic Goal 1: to evaluate existing diagnostic assays for Ebola virus infection and develop recommendations to standardize diagnostic testing during future Ebola outbreaks.

Milestones

1. By 2019, convene an expert working group (facilitated by WHO) to identify one current PCR-based diagnostic assay to serve as a frontline test during future Ebola outbreak investigations and set a standard for interpreting cycle threshold (Ct) values.

2. By 2020, identify one currently available serologic assay or platform for diagnosing Ebola virus infections (acute and convalescent) during future outbreaks, and develop guidelines for interpreting results.

3. By 2020, create well-characterized and standardized panels for evaluating and comparing different serologic assays and different PCR-based assays for Ebola virus infection, and conduct comparative studies to identify the most robust assays among currently available methodologies.

4. By 2021, complete any field studies necessary to support regulatory clearance of at least two validated PCR-based diagnostic tests.

5. By 2022, obtain regulatory approval of at least two validated rapid and inexpensive PCR-based diagnostic tests for Ebola virus infection, using blood, other body fluids, or tissue specimens.

Strategic Goal 2: to support the continued development of rapid and reliable diagnostic methodologies for Ebola and Marburg virus infections.

Milestones

1. By 2019, revise the current TPP for Ebola diagnostics to include all relevant Ebola and Marburg virus species and diagnostic use cases.

2. By 2020, develop improved metagenomics methodologies, including software to support molecular epidemiology, to enhance the use of field-based whole-genome sequencing during outbreaks.

3. By 2020, develop a multiplex assay for diagnosing filovirus infections, including Marburg virus, aligned with optimal and desirable test characteristics identified in the revised Ebola/Marburg diagnostics TPP.

Strategic Goal 3: to strengthen laboratory infrastructure and capacity to enable rapid evaluation of diagnostic specimens during future Ebola/Marburg outbreaks.

Milestone

1. By 2019, convene an expert working group, with WHO oversight, to develop plans (including identifying funding) for enhancing in-country diagnostic laboratory capacity in at least two at-risk countries (for example, Democratic Republic of the Congo, Uganda, West African countries) over the next five years, with the potential for expanding capacity in all at-risk countries in Africa.

Strategic Goal 4: to stimulate research into novel diagnostic approaches, including infectivity testing, prognostic biomarker analysis and alternatives to single Ebola/Marburg assays (such as broad testing panels, platforms, or multiplex assays) for ongoing use between outbreaks.

Milestone:

1. By 2021, convene an expert working group, to meet in 2021 and then annually thereafter, to review data on new targets for filovirus diagnostic tests, with summaries of these reviews

published in the open scientific literature or through another publicly available platform, such as the WHO website.

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 and Marburg infection.
- **Generate** well-characterized and standardized panels for evaluating and comparing different diagnostic assays for detecting Ebola virus infection.
- **Research and characterize** 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.
- **Develop** improved metagenomics methodologies to enhance the use of field-based whole-genome sequencing during outbreaks.
- **Explore** new diagnostic approaches that may enhance EVD/MVD diagnostic testing (for example, by measuring infectivity, allowing earlier detection of infection, shortening turnaround time to results and/or predicting survival).

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 detect all relevant Ebola and Marburg virus species.

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.
- **Enhance** in-country diagnostic laboratory capacity to provide early warning for EVD/MVD outbreaks and enhance case detection.
- **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 and MVD survivors.
- **Generate and update** new EVD diagnostic screening algorithms for high-prevalence (outbreak) and low-prevalence (surveillance) settings as additional diagnostic tests become available.

THERAPEUTICS

Primary challenges, key needs and knowledge gaps

Primary challenges

- Efficacy data are lacking for therapeutic agents against EVD/MVD, particularly among special populations (such as, children, pregnant women, immunocompromised patients), patients with late-stage disease and EVD/MVD survivors with viral persistence.
- Ethical issues in therapeutic clinical trials need to be addressed, particularly regarding the assignment of patients to control groups (such as, best available standard of care); advance discussion may be needed to identify potential trial designs that provide flexibility and scientific validity for future outbreaks.
- Outbreaks often occur in areas with limited available staff or staff that lack experience in the many issues involved with EVD management, such as cold-chain requirements, shipping constraints, steps in establishing treatment units and understanding of research protocols. These issues reflect the instability of outbreak geography, which is a major challenge.

Key needs

- Development of a TPP that identifies optimal and desirable characteristics of EVD/MVD treatment interventions to guide the development of safe, effective treatment approaches that are appropriate to the medical capabilities in the region and that consider the context of therapeutic delivery and feasibility.
- Safe and effective therapies for patients with EVD/MVD that improve survival, decrease morbidity and sequelae and reduce the potential for relapse or late transmission among survivors.
- Safe, effective and non-invasive (for example, oral) methods for PEP to prevent EVD/MVD following exposure to filoviruses, to protect health-care workers, family, caregivers and burial teams, and to reduce transmission during outbreaks.

Knowledge gaps

- Clinical data on the safety, tolerability and efficacy of investigational treatments (for example, mAb114, ZMapp, remdesivir, favipiravir and Regn 3450-3471-3479), particularly in special populations, such as pregnant women, immunocompromised persons and children.
- Clinical data on the safety and effectiveness of administering combinations of treatment agents (such as a monoclonal antibody [mAb] with a direct-acting antiviral agent).
- 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. Mechanisms for determining how to measure efficacy of PEP would also be useful.
- 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 and MVD survivors, based on clinical evaluations of novel agents.
- Research to characterize biomarkers (such as, 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 be needed to better define therapeutic targets, enhance the design of therapeutic clinical trials and improve clinical care (for example, through risk stratification and patient triage).
- Additional research on the potential role of broadly protective filovirus immunotherapies. Priority agents include 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 analysing 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.
- 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, antidiarrhoeal agents and non-steroidal anti-inflammatory drugs) 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 and aligned milestones

Strategic Goal 1: to continue to develop and evaluate therapeutic agents to ensure a robust drug-development pipeline for treatment of filovirus infections.

Milestones

1. By 2019, develop a TPP for Ebola/Marburg therapeutics that identifies optimal and desirable characteristics of treatment agents for all relevant Ebola/Marburg virus species.

2. By 2020, complete preliminary safety and pharmacokinetic (PK)/pharmacodynamic (PD) assessments and dosing characterization for at least two promising investigational agents for treatment of infection caused by one or more Ebola/Marburg virus species.

3. By 2020, conduct at least one experimental animal study of combination therapy involving two or more agents for treatment of Ebola virus infection.

4. By 2020, develop at least two candidate therapeutic agents suitable for clinical studies of filovirus infections and ensure availability of sufficient supplies for emergency use during outbreaks.

5. By 2021, complete preliminary safety, PK/PD assessments and dosing characterization for at least two promising investigational agents for treatment of Marburg virus infection.

6. By 2022, conduct clinical efficacy studies of candidate therapeutic agents to obtain data necessary for regulatory approval.

7. By 2025, obtain regulatory approval for at least one therapeutic agent with demonstrated efficacy across different filovirus infections.

Strategic Goal 2: to prioritize investigational therapeutic agents on an ongoing basis that should move forward from preclinical evaluation into clinical trials during future filovirus outbreaks.

Milestones

1. By 2019, develop and implement a process for ongoing (for example, annual) review and assessment of current published and unpublished data for Ebola/Marburg therapeutic agents in the drug-development pipeline to inform prioritization of candidates that should advance to clinical trials.

2. By 2022, design and conduct preclinical studies to allow generation of comparable data for up to five investigational therapeutic agents for treatment of Marburg virus infection, to support prioritization of candidate agents for future clinical trials.

Strategic Goal 3: to improve preparedness for conducting clinical trials of promising therapeutic agents for treatment of filovirus infections during future outbreaks.

Milestones

1. By 2019, develop clinical trial protocols for assessing therapeutic agents and obtain ethics and regulatory approval in at least three countries where future filovirus outbreaks are likely to occur.

2. By 2020, conduct a review of how clinical trials were implemented during the Democratic Republic of the Congo outbreak and identify lessons learned for implementation of trials during future outbreaks.

3. By 2020, perform infrastructure mapping, develop criteria for training, assess training needs for conducting clinical trials in at least three affected countries and develop guidance for clinical trial preparedness training.

4. By 2020, complete clinical trial preparedness training in at least two countries at risk for future filovirus outbreaks.

5. By 2021, identify and assess at least one potential biomarker predictive of filovirus disease outcome to enable the stratification of patients based on likelihood of survival.

Priority areas/activities

Research

- **Continue to research** the safety, tolerability and efficacy of investigational therapies, singly and, when appropriate, in combination, for EVD/MVD, including those evaluated during recent Ebola epidemics. In the absence of outbreaks, this work can include animal studies, PK and PD evaluation, evaluation of dosage, generation of data to allow comparisons between different agents 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 mAbs) with demonstrated efficacy in NHP models for treatment of MVD.
- **Identify and characterize** host biomarkers in patients with early stage EVD/MVD to improve clinical management and predict the likelihood of survival.
- **Conduct** research on the mechanisms of viral persistence in immune-privileged sites to help identify further treatment options.
- **Identify and develop** new therapeutic agents for treatment of post-Ebola syndrome and elimination of viral persistence.

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.

Key capacities

- **Develop** a database of preclinical studies regarding EVD/MVD therapeutic agents.
- **Improve** in-country preparedness for conducting clinical trials during future filovirus outbreaks.

Policy and commercialization

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

VACCINES

Primary challenges, key needs and knowledge gaps

Primary challenges

- Filovirus vaccines are needed for multiple indications, including rapid onset of immunity against a specific outbreak strain and long-lasting immunity against one or more filovirus infections.
- The availability of one or more licensed Ebola vaccines complicates the evaluation of other Ebola vaccine candidates, owing to ethical issues and challenges with clinical 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 (for example, fever and fatigue) 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 individuals.
- Time of onset of effective immunity following vaccination is unclear, which complicates the determination of appropriate vaccination strategies in outbreaks.
- Scepticism of medical interventions and information, 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.

Key needs

- Broad-spectrum filovirus vaccines, or multiple monovalent vaccines capable of inducing cross-reactive antibodies that provide protection against one or more Ebola/Marburg species.
- Establishment of chemistry, manufacturing, and control (CMC) requirements prior to the deployment of vaccines in outbreaks.
- Recommendations regarding vaccination strategies for preventive and reactive use in situations where outbreaks occur in densely populated regions or megacities, where it may be extremely difficult to identify chains of transmission, thereby making ring vaccination more challenging and perhaps less effective as a primary control strategy.
- 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, using WHO international standards (when available) as calibrators, and reported in units/ml for harmonization. In addition, standardization of relevant animal models is needed to enable the extrapolation of data on vaccine-induced immune responses in animals to vaccine-induced immune responses in humans.
- Guidance regarding the use and deployment in outbreak settings of current investigational vaccine candidates.
- Guidance for community sensitization to vaccine acceptance, and promotion within the community as part of broader efforts to promote effective prevention and control measures.
- Guidance regarding the use and deployment during outbreaks in Africa 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. Additional information about the safety and efficacy of these vaccines is needed to generate the appropriate guidance.

Knowledge gaps

- Additional research to identify specific vaccine-induced and infection-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.
- The need for ongoing evaluation of vaccine safety (through clinical trials and post-marketing surveillance) in target populations, to better understand the risk of adverse events in future 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; (3) plans for manufacturing, stockpiling and deployment in field efficacy trials when outbreaks occur.
- Data on the time of onset and 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 and aligned milestones

Strategic Goal 1: to further advance the development of vaccine candidates to enable licensure/registration and prequalification of Ebola, Marburg, or multivalent vaccines for: (1) different indications (such as, rapid onset of immunity against outbreak strains and long-lasting immunity against multiple Ebola/Marburg virus strains); (2) use in special populations (for example, young, pregnant, elderly, immunosuppressed).

Milestones

1. By 2020, convene a scientific conference to review and synthesize data on naturally acquired and vaccine-acquired immunity to Ebola/Marburg disease to enhance understanding of mechanisms of immunologic protection against filovirus infection and inform development of correlates of protection.

2. By 2020, obtain regulatory approval and prequalification of the rVSVΔG-ZEBOV-GP vaccine.

3. By 2023, complete phase 1 and 2 clinical trials of at least one vaccine candidate against Marburg virus or one multivalent vaccine candidate that encompasses multiple filovirus species.

Strategic Goal 2: to support the integration of phase 3 clinical efficacy trials of filovirus vaccine candidates into the public-health response to Ebola/Marburg outbreaks.

Milestones

1. Beginning in 2019, convene an annual independent expert panel to review the available published and unpublished data and prioritize vaccine candidates for clinical evaluation during future Ebola/Marburg outbreaks.

1. By 2020, develop a consensus on clinical trial protocols for assessing new and existing Ebola/Marburg vaccines (including in the context of smaller outbreaks) and obtain ethics and regulatory approval in at least three affected countries where future filovirus outbreaks are likely to occur.

2. By 2021, perform infrastructure mapping, develop criteria for training, assess training needs for conducting vaccine trials in at least three affected countries and develop guidance for clinical trial preparedness training.

3. By 2021, complete preparedness training for conducting vaccine efficacy trials in at least two affected countries that are at risk for future filovirus outbreaks.

Strategic Goal 3: to develop a model of sustainability to ensure ongoing access to filovirus vaccines.

Milestones

1. By 2020, develop plans to maintain Gavi, the Vaccine Alliance's stockpiles of ebola/filovirus vaccines or adequate stockpiles of investigational ebola/filovirus vaccines in advanced development.

2. By 2023, establish manufacturing capabilities to ensure ongoing production and provision of licensed and prequalified Ebola/Marburg vaccines to at-risk countries.

Priority areas/activities

Research

- **Determine** the mechanisms of humoral and/or cell-mediated immune protection.
- **Identify** correlates of protection (such as, across vaccine platforms) that 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 scepticism toward vaccines and other medical interventions, and concerns related to participation in research involving filovirus vaccines.

Product development

- **Continue to 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

- **Improve** in-country preparedness for conducting clinical vaccine trials during future filovirus outbreaks.
- **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 licensed and unlicensed 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.
- **Develop** guidance for community sensitization to vaccine acceptance, and promotion within the community.

BACKGROUND INFORMATION

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