

WHO R&D Blueprint

A WHO-Strategic Research Agenda for Filovirus Research and Monitoring (WHO-AFIRM)

WHO-AFIRM Strategy Roadmap 2021-2031

DRAFT version 3.0

WHO reference number

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R&D Blueprint

Powering research
to prevent epidemics



About this roadmap

This roadmap is based on the draft roadmap and baseline analysis XXX, the research roadmap for DRC, the xxxxxx.

All elements were updated with evidence as of June 7, 2022.

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Executive Summary

Since the emergence of Ebola virus disease (EVD) in West Africa in 2013 the world has seen a constant surge of EVD outbreaks in Central and Western African countries. This increased reporting of EVD is probably due to enhanced surveillance and diagnostic technologies that were implemented after the West African 2013-2016 epidemic, and strongly suggest that many previous outbreaks have gone undetected.

In addition, recent discoveries have challenged the current epidemiological model of EVD in which the virus is introduced in a community of naïve individuals via zoonotic spillover. Rather, it is now clear that Ebola virus can persist for several years in immune privileged body sites of disease survivors, and that human-to-human transmission from a survivor to a naïve individual can ignite a new outbreak.

This document describes a long-term global strategy for filovirus research and monitoring. This strategy is based on three principles described in this document, namely, **anticipation**, **reinforcement** and **cure**. The **anticipation** principle intends to foster research areas that may lead to improve our capacity to predict future outbreaks and detect them as early as possible, these research strategies should also enforce the rapid sharing of surveillance data, in particular across endemic countries in which filovirus outbreaks have occurred in the past. This principle also calls for engagement of stakeholders worldwide to transfer technology and support endemic countries in surveillance efforts and capacity building. The **reinforcement** principle is focused on the protection of populations at risk of filovirus diseases, and it is intended to promote the development of filovirus vaccines. It is therefore a call for academic and industry partners to accelerate preclinical and clinical testing of vaccines against filoviruses that pose a public health threat (e. g. Sudan virus, Marburg virus) and to establish research strategies to determine the epidemic potential of poorly



characterized filoviruses. Finally, the **cure** principle intends to foster the development of post-exposure therapies that would help to reduce disease mortality as well as to reduce virus transmission.

The AFIRM strategy is unprecedented as it brings together multiple stakeholders into a common research agenda. No country or public health body will be able to control the next filovirus epidemic alone. The success of this strategy will be based on the coordinated and directed effort supported by scientific discovery. It will also provide support to survivor communities and will engage additional partners as the initiative evolves.

Definition of Terms

Dashboard: The WHO dashboard for R&D Roadmaps is a data visualization tool that consolidates and arranges information to share and monitor progress. It is developed and maintained by the WHO Secretariat and hosted on the WHO website.

Roadmap: A roadmap is a guiding high-level overview describing the initiatives and planned steps an organisation or community needs to take to achieve its stated vision and strategic goals. A roadmap clearly communicates direction, while matching research priority areas with short- and long-term goals and specific solutions to meet the desired milestones.

R&D Blueprint roadmap: An R&D Blueprint roadmap is a framework document laying down a vision, strategic product development and research goals and priority areas for accelerated R&D to prevent and control severe emerging pathogens with epidemic potential.

Roadmap Secretariat: WHO Secretariat for R&D Roadmaps. The Secretariat supports and oversees the roadmapping exercises conducted by external partners to ensure adherence to the present methodology and to provide advice and input, as appropriate.

Strategic goals: Strategic goals are the planned objectives that a roadmap task force aims to achieve over the period of the strategic plan, e.g. over the next year, five years, ten years. Strategic goals determine the long-range direction of the research priority areas identified through a roadmapping process. They should reflect a realistic assessment of the environment, strengths, weaknesses, opportunities and threats and should be based on the stated vision.



Target product profile (TPP): A target product profile is a key strategic document describing the desired R&D outcome for a particular product, e.g. diagnostics, therapeutics and vaccines. By playing a central role in the entire product discovery and development (including effective optimization of product candidates, decision-making within an organization, design of clinical research strategies, and constructive communication with regulatory authorities),ⁱ a TPP is a living reference document for the most current information on the intended product characteristics and features (preferred/optimal/ideal versus critical/minimal/acceptable). **WHO TPPs** describe preferences and minimally acceptable criteria that are shaped by the unmet public health needs in a priority disease area for which WHO encourages development of medical countermeasures.ⁱⁱ WHO TPPs do not remove the need for industry groups to develop their own in-house documents as a guidance for product development plans and they allow for transparency on the degree of alignment between industry or funder TPPs and WHO's preferences.

Vision Statement: The vision statement is a common aspirational declaration that summarises the global health community's mid-term and long-term goals for control of a specific pathogen. Focusing on "what" and "when", the vision statement serves as a source of motivationⁱⁱⁱ and provides guidance and direction for choosing current and future courses of action.



Abbreviations and 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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The R&D Blueprint for action to prevent epidemics

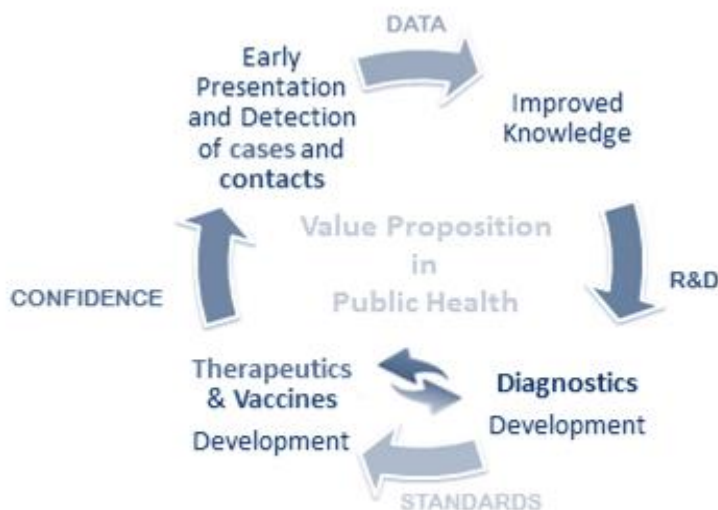
The R&D Blueprint for action to prevent epidemics^{iv} is a global strategy and preparedness plan to address highly infectious diseases and strengthen the emergency response by fast-tracking the availability of effective medical technologies that can be brought to patients during epidemics. With a broad global coalition of experts and WHO as convener, the Blueprint encompasses all actions needed to implement critical research in a safe, effective and timely way.

The R&D Blueprint focuses on severe emerging diseases with potential to generate a public health emergency and for which insufficient or no preventive and curative solutions exist, due to market failure or lack of scientific knowledge. The original **list of priority diseases**^v that meet these criteria was agreed at an international consultation held in Geneva in December 2015. This list was revised in January 2017 (Table 1).^{vi}

R&D roadmaps will serve as a cardinal framework to underpin strategic goals, research priority areas and activities to accelerate R&D of the medical countermeasures for each of these priority diseases, from basic research through to late-stage development, licensure and early use of products.

With WHO leadership and coordination, and using the present methodology as their basis, a series of partners will be identified to develop R&D roadmaps for each of the WHO priority diseases.

Figure 1 illustrates the potential public health value that can be derived from a dynamic R&D roadmapping effort and the synergies between each of its components, e.g. targets for diagnostic tests will ideally need to be developed in close understanding with the vaccine targets. This would ultimately allow detection of a vaccine-induced immune response which is different from that induced by natural infection, a concept also known as the DIVA principle (DIVA stands for **Differentiating Infected from Vaccinated Animals**).^{vii}



Introduction

Filoviruses

Viruses belonging to the family *Filoviridae* have been and still continue to be responsible for viral haemorrhagic fever outbreaks in various countries in sub-Saharan Africa. These viruses pose a major public health burden in this area of the world and, due to global air travel, have potential to do so worldwide. The filovirus family comprises 6 genera including *Ebolavirus*, *Marburgvirus*, *Cuevavirus*, *Dianlovirus*, *Striavirus* and *Thamnovirus*. Within the first two genera, Ebola virus (species *Zaire ebolavirus*, EBOV) and Marburg virus (species *Marburg marburgvirus*, MARV) respectively, are responsible for most outbreaks to date and cause severe disease in humans with high case-fatality rates. Due to their high pathogenicity and the general lack of medical countermeasures, handling of filoviruses is restricted to biosafety level 4 (BSL4) facilities.

Ebolaviruses

Besides EBOV, the genus *Ebolavirus* comprises five additional species: *Sudan ebolavirus* (SUDV), *Tai Forest ebolavirus* (TAFV), *Bundibugyo ebolavirus* (BDBV), *Reston ebolavirus* (RESTV) and *Bombali ebolavirus* (BOMV). EBOV and SUDV were first detected in nearly simultaneous outbreaks in northern Zaire (today the Democratic Republic of Congo)



and South Sudan in 1976. Since then, there have been more than 20 outbreaks in Central and Western African countries with the largest Ebola virus disease (EVD) epidemic occurring between 2013 and 2016 in Guinea, Sierra Leone and Liberia. EVD outbreaks are typically initiated by a single spillover from a wildlife source into humans, and are maintained by human-to-human transmission (Kuhn et al., 2020). The wildlife reservoir of EBOV is not known although different species of bats have been proposed (Di Paola et al., 2020). This hypothesis is substantiated by the fact that other filoviruses or filovirus genomes have been detected in bats, and that infectious MARV has been isolated from Egyptian fruit bats (*Rousettus aegyptiacus*) (Amman et al., 2020). Human-to-human transmission of EBOV occurs through direct contact with infected body fluids with the mucosae and skin as main portals of virus entry (Baseler et al., 2017). Caring of sick persons in the household, traditional funerals and exposure in healthcare settings are high-risk factors for EBOV transmission during outbreaks (Dowell et al, 1995., Roels et al 1999). After infection, EBOV replicates primarily in macrophages and dendritic cells (DCs) at the mucosae and skin, which likely participate in the dissemination of EBOV to the tissue-draining lymph nodes (Lüdtke et al., 2017). Once the virus is disseminated, it can infect many other cell types including hepatocytes, endothelial cells and resident macrophage-like cells such as Kupffer cells and microglia (Geisbert et al 2003.,). After an incubation period of 2-21 days, EVD initiates with nonspecific symptoms followed, in severe cases, by a systemic disease characterized by multiorgan involvement, electrolyte imbalance, endothelial disruption, coagulation abnormalities, immune dysregulation and, in many cases, shock and death. Bleeding, including hematemesis, hematuria and melena is observed in a discrete number of cases (Rougeron et al., 2015). Recent research demonstrates that, after recovery, EBOV may persist in immune privileged body sites for months or even years. The molecular mechanisms of persistence are not known, although resident macrophages have been suggested to play a role as EBOV cell reservoirs (Zeng et.al, 2017). Infectious EBOV has been detected months after recovery in the central nervous system, the ocular fluid and semen (Diallo, et al., 2016; Chungtai, et al., 2016,), and weeks after recovery in breast milk (Sissoko et al., 2017). Importantly, relapse in long-term survivors has also been demonstrated, and molecular epidemiology data indicate that recent outbreaks may have been initiated through direct infection from a survivor into a naïve individual (Blackley et al., 2016). These findings have chief implications for public health measures as we will discuss in this document.

Currently, there are two licensed EBOV vaccines, both based on vectored vaccine platforms. There are no specific post-exposure treatments, although monoclonal antibody therapy has shown promising results in clinical trials (Mendoza et al., 2016). In addition to EBOV, some other members of the *Ebolavirus* genus are highly pathogenic for humans. These include Sudan virus (SUDV) and Bundibugyo virus (BUDV) with case-



fatality rates ranging between 42 – 65 % and 34 – 44 % respectively (Rougeron et al., 2015,). There is only one case known of Tai Forest virus (TAFV) infection in humans, which was a non-lethal case (Le Guenno et al., 1995). Reston virus (RESTV) is the only ebolavirus that is not endemic in sub-saharan Africa. It has been detected primarily in the Philippines and does not seem to be pathogenic for humans, although seroconversions have been observed (Geisbert, T. W, 2015). Finally, Bombali virus (BOMV) genomes -but not infectious virus- has been detected in *Chaerephon pumilus* and *Mops condylurus* bats in Sierra Leone and Kenya (Goldstein et al., 2018). Its putative pathogenicity in humans is unknown.

Marburgviruses

The genus *Marburgvirus* consists of one species, *Marburg marburgvirus* and is represented by two viruses, namely, Ravn virus (RAVN) and Marburg virus (MARV) (Kuhn, 2013). Since the discovery of MARV during two simultaneous outbreaks in 1967 in Germany and Serbia, there have been sporadic outbreaks in sub-Saharan Africa with reports of imported cases to the Netherlands and the USA in 2008 (Languon, 2019).

Marburg virus disease (MVD) outbreaks occur at random intervals and have been, in some instances, associated to activities in caves (e. g. mining, tourism) where *Rousettus aegyptiacus* bats roost (Amman et al., 2015). Infected bats shed virus in saliva and urine and there is evidence showing that MARV persists in organs such as the spleen and liver of these bats (Amman et al., 2015; 2020 Schuh et al., 2017). The largest MVD outbreak so far was recorded in 2005 and occurred in Uige, Angola with 374 total cases and an 88 % case fatality rate, one of the highest case fatality rates recorded for a filovirus outbreak (6-Bausch et al., Amman et al., 2020).

Similar to EVD, transmission occurs when individuals come into contact with infectious bodily fluids (Feldmann et al., 2017)

MARV has a tropism similar to that of EBOV and targets multiple cell types including DCs, monocytes, macrophages and Kupffer cells, which are the initial targets of infection (Hensley et al., 2011). Infected cells migrate and, in the process, facilitate the dissemination of the virus to the lymphatic system and to target organs such as the spleen and liver via the circulatory system (Messaoudi et. al., 2015).

The incubation period for MVD varies between 2-21 days before the onset of symptoms (Cooper et al., 2018). The early stage of MVD is characterized by non-specific symptoms such as headache, myalgia, fever and chills. The next stage occurs between day 2 and 5 after symptom onset and is characterized by gastrointestinal symptoms



such as abdominal pain, nausea and vomiting, respiratory symptoms such as chest pain and neurological symptoms such as confusion, delirium and seizure (Rougeron et al 2015., Shifflett and Marzi 2019). Between day 5 and 7 after the onset of symptoms, the severity of the disease increases and symptoms can include oedema, petechiae, visceral and mucosal haemorrhage with some patients developing a maculopapular rash (Shifflett and Marzi, 2019; Cooper et al., 2018). In the last stage, patients can experience convulsions, confusion, multiorgan failure and coma (Shifflett and Marzi, 2019).

Not much is known about MVD survivors due to the sporadic nature and remote locations of MVD outbreaks, which makes survivor monitoring and follow-up difficult. Studies have shown the existence of post-MVD complications (Cooper et.al, 2018) and the presence of sequelae such as myalgia, arthritis, conjunctivitis and psychosis in survivors of MVD (Martini G.A, 1973; Shifflett & Marzi, 2019). The long-term effects of the persistence of MARV in survivors are yet to be conclusively determined.

As opposed to EBOV, there are currently no licensed nor approved vaccines against MARV. There are however promising candidates based on vectored vaccine platforms.

Vision

Improve the availability and accessibility of robust methods to detect, control and cure EVD and MVD:

1. Establish prediction methods to anticipate future outbreaks and develop additional rapid and accurate diagnostics for Ebola/Marburg virus infection to inform outbreak identification and monitoring, case detection, treatment and clinical trials;
2. Accelerate the development of additional safe and effective vaccines to prevent EVD/MVD and stop filovirus transmission in human populations.
3. Establish additional safe and effective treatment and post-exposure prophylaxis (PEP) to reduce morbidity and mortality from EVD/MVD;



Aim

The aim of this research roadmap is to establish a set of research priorities for filovirus diseases during the next decade.

The critical knowledge gaps are enumerated and research priorities are identified including critical steps to proceed in order to accomplish short- and medium-term goals as detailed in this document.

Input from various stakeholders including scientists, medical professionals and policy makers during expert global consultations led by the WHO R&D Blueprint have been taken into account.

This **R&D Blueprint roadmap** is a concise, comprehensive document laying down a vision and strategic goals towards accelerated R&D to prevent and control diseases caused by filoviruses.



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 at random intervals in low-income countries. In addition, accelerated development and deployment of medical countermeasures (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 the development of filovirus vaccines, therapeutics and diagnostic tools 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 also pose a number of significant challenges, particularly since the location and timing of the next outbreak are unknown 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 reduce opportunities for investigators to assess new therapeutic agents, vaccines and diagnostic methods, 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 Listing (EUL) 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.

Key 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. This also includes animal models to determine the pathogenicity of poorly characterized filoviruses (e. g. Bombali virus, Lloviu virus, Tai Forest virus).



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.

Prediction models and diagnostic tools to prevent and tackle future filovirus outbreaks.

STRATEGIC GOALS

ANTICIPATION: Research Strategies to prevent and control future Filovirus outbreaks

REINFORCEMENT: Research strategies to develop and evaluate additional vaccines

CURE: Foster research to improve standard of care and the development and evaluation of treatments and of post-exposure therapies



ANTICIPATION: Research strategies to prevent and control Future Filovirus outbreaks

Rationale

Since the emergence of EVD in West Africa in 2013 several outbreaks of EVD and MVD have been detected in sub-Saharan Africa. This strongly suggests that: i) both diseases are endemic and several western and central African countries, ii) outbreak detection is positively correlated with improved surveillance networks that were implemented after the 2013-2016 EVD epidemic and, iii) the size and extension of outbreaks can be controlled if existing tools are adequately implemented and if new ones are developed and evaluated.

Therefore, there is a need to improve and strengthen the surveillance system for early detection and response to VHF outbreaks in at risk areas, to better understand the epidemiology and risk factors and the ecology of filoviruses and, to strengthen the country capacities for safe handling, diagnosis and reporting of filoviruses diseases.

Strategic goals

1. To enhance coordination on research across endemic countries by establishing a WHO-coordinated multi-country research network program. Prevention of future outbreaks will require big data complex models and multi-country coordination. Data to be collected must include not only ecological data on putative reservoirs but also socioeconomics data (e. g. healthcare, seasonal events). This networks should also facilitate open access to data, including sequencing data and existing diagnostic pipelines.
2. To strengthen efforts to develop and evaluate additional diagnostics tools, including filovirus rapid tests and prognostic biomarker analysis and to expand research related to genomic sequencing.
3. In order to achieve (1) and (2), laboratory capacity needs to be strengthened in filovirus endemic countries. Capacity should include tools for diagnostics but also for



serosurveillance and clinical investigation of cases. This capacity should result in expanded ecology studies and sero-surveillance studies with assays that can discern specific filoviruses.

4. To develop a network for survivor follow-up and where possible the sharing of data to enable immunological and genetic characterization of survivors, vaccinees and asymptomatic infections. Research priorities in the 'Anticipation' area should include the study of virus persistence mechanisms.
5. To engage social sciences stakeholders promote grassroots campaigns and increase community engagement with the goal of encouraging appropriate outbreak behaviours and to develop a tool for monitoring common misperceptions and risk behaviour.

Milestones

1- By 2025, develop a WHO-coordinated network that spans countries where filovirus outbreaks have occurred as well as partner countries, to facilitate the sharing of i) biological samples, ii) ecological and genomic data.

2- By 2025, develop novel multiplex diagnostic assays that enable the detection of different filoviral species. Additionally, compile data from currently available diagnostic tests, standardize protocols and develop guidelines for result interpretation. Develop a framework for the testing, validation, standardization and comparison of novel assays.

3- By 2025, Explore diagnostic tests based on different platforms that include multiple targets and that can be used on different biological samples.

4- By 2030, develop a plan to improve laboratory infrastructure and potentially the construction of a reference diagnostic laboratory capable of handling BSL-4 samples in outbreak prone countries.



REINFORCEMENT: Research strategies to develop and evaluate additional vaccines

Rationale

Filovirus outbreaks occur at random intervals and, with the exception of Ebola virus, there are no licensed vaccines against filoviruses. However, there are candidates in the pipeline for Marburg and Sudan viruses, and some have now entered human safety and immunogenicity trials. Ecological and outbreak data collected during the last two decades as well as improved laboratory capacity in endemic areas also facilitates outbreak management and vaccine clinical trials. In this scenario, the main goals will be:

Strategic goals

- 1- To understand filovirus short-term and long-term immune responses to natural infection and vaccination. This knowledge would allow immunobridging of future filovirus vaccines, improved clinical trial design and better understanding of correlates of protection.
- 2- To establish a platform trial design for vaccines against Marburg and Sudan virus
- 3- To setup a WHO-coordinated consortium including regulators, developers and members of academia to accelerate the development of filovirus vaccines. Such future vaccines need to be deployable (outbreak-ready) as well as preventive. Multivalent filovirus vaccines would be preferred.
- 4- In order to achieve (3), different vaccine platforms need to be tested that incorporate different targets with the goal of developing multivalent vaccines.
- 5- To compile data on the duration of protective immunity after vaccination with ERVEBO® and identify the correlates of protection involved to facilitate faster evaluation of promising vaccine candidates against other filoviruses.



6- Engage funding agencies to promote vaccine development and assay standardization.

Milestones

- 1- By 2025, complete clinical trials for vaccine candidates against Marburg and Sudan virus.
- 2- By 2025, obtain licensure for at least one vaccine against Marburg virus or Sudan virus.
- 3- By 2030, develop a broad-spectrum filovirus vaccine that is low cost, efficacious and safe.

CURE: Foster the development of post-exposure therapies

Rationale

The EVD epidemic in West Africa highlighted the need to develop filovirus-specific post-exposure therapies. In addition to saving human lives, the development of these therapies could greatly contribute to public health by reducing the infectiousness period in EVD patients. Importantly, the West African epidemic also underscored the inequality between endemic countries and northern countries in the treatment of filovirus diseases. These inequalities resulted in significant differences in case-fatality rates (CFR) in patients treated in West Africa compared to patients treated in Europe and the US. The **cure** approach intends to foster the development of filovirus post-exposure therapies as well as to make these therapies and protocols universally available.

Strategic goals



- 1- To establish a common, publicly available reference protocol for the treatment of filovirus diseases. There is an important knowledge gained from previous epidemics, which show for example that risk factors for severe disease (viral loads, organ failure) can be modified. There is an urgent need to share this knowledge and standardize treatment across medical caretakers globally.
- 2- To accelerate the development and testing of filovirus post-exposure therapies
- 3- To obtain, compile and compare data on the safety, efficacy and tolerability of currently available therapeutics and evaluate the benefit of combinations thereof.
- 4- To create tools and networks to enable better surveillance of survivors including regular sampling and assessment of blood, semen etc. where possible in order to facilitate the early detection of sequelae.
- 5- To evaluate laboratory-measured molecular biomarkers that can predict clinical outcomes and that can inform on the efficacy of therapeutic interventions.
- 6- To foster research on immunotherapies that can be used as post-exposure therapies and that are capable of eliminating viral sequelae.
- 7- To develop guidelines and establish rigorous procedures for supportive care taking into account the economic capacity of the affected countries.

Milestones

- 1- By 2024, assess the safety, efficacy, pharmacokinetics and pharmacodynamics of drugs intended for therapeutic use.
- 2- By 2025, identify and develop therapeutic agents against Marburg virus and conduct preliminary investigational studies to determine their efficacy.
- 3- By 2025, determine the contribution of different viral epitopes to pan-ebolavirus responses and foster more research on the development of pan-filoviral antibodies.
- 4-
- 5- By 2024, establish a system for the exchange of data obtained from pre-clinical studies.

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- ^{vii} FAQ: DIVA vaccines and diagnostics. In: Epizone/FAQ [website]. The Netherlands: EPIZONE European Research Group (ERG); (no date) (<http://www.epizone-eu.net/en/Home/show/FAQ-DIVA-vaccines-and-diagnostics.htm>, accessed 25 February 2017).