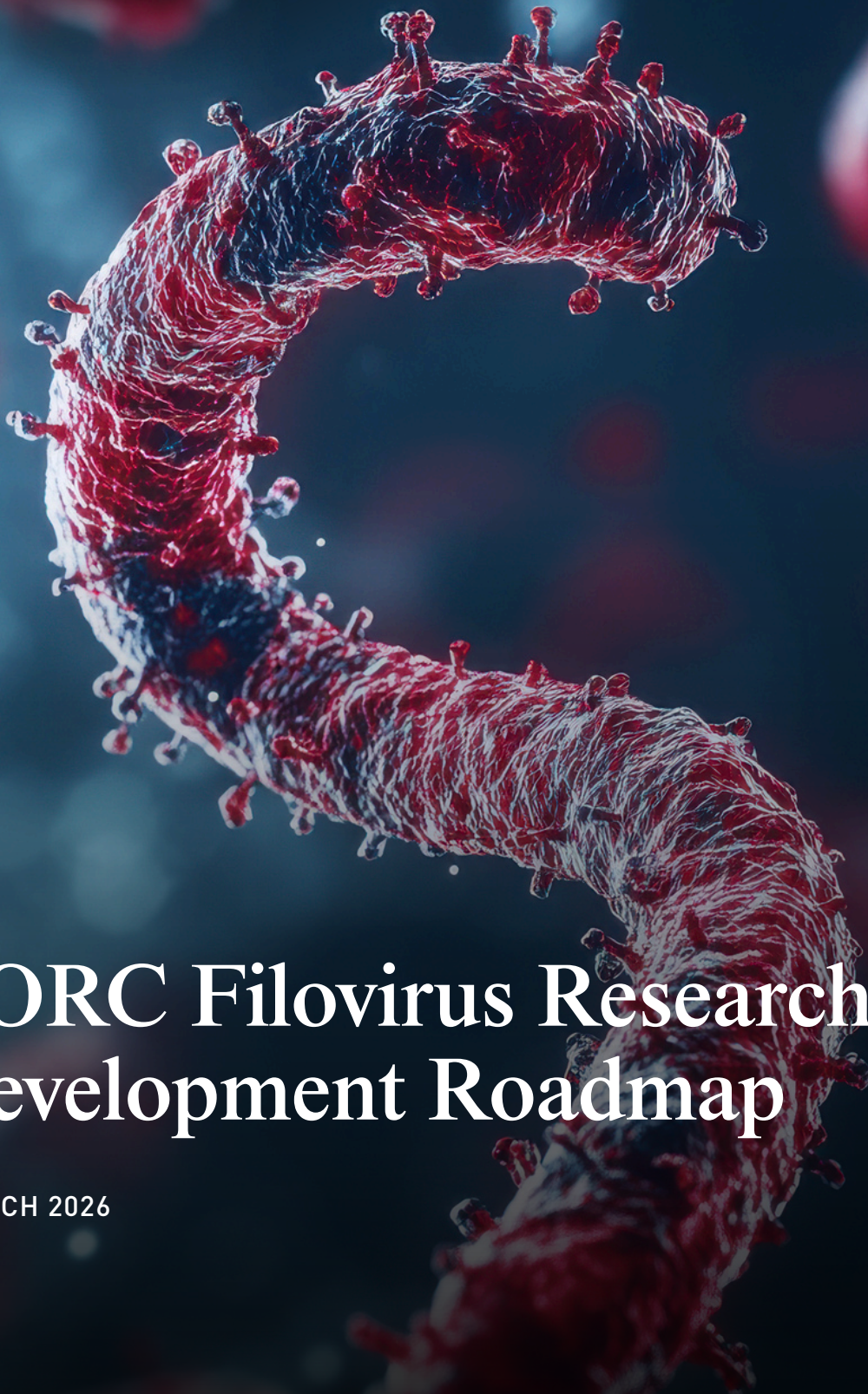




World Health
Organization



CORC Filovirus Research & Development Roadmap

3 MARCH 2026



R&DBlueprint

Powering research
to prevent epidemics

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EMERGENTES **Inserm**

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Abbreviations

Ag-RDT : antigen rapid diagnostic test

ANRS MIE : French National Agency for Research on HIV and Emerging Infectious Diseases

BDBV: Bundibugyo virus

BSL: Biosafety Level

CORC: Collaborative Open Research Consortia

EBOV: Ebola virus

MARV: Marburg virus

R&D : Research and Development

RESTV: Reston virus

SUDV: Sudan virus

TAFV: Taï Forest virus

WHO: World health organization

Preamble

In recent decades, the global epidemiological landscape has been marked by an increasing frequency and geographic spread of infectious disease outbreaks. In this context of heightened epidemic risk, strengthening research capacities and international collaboration is essential to improve preparedness and enable rapid responses to emerging health threats.

To support this objective, the World Health Organization has identified a set of priority pathogen families with epidemic and pandemic potential and promotes research strategies that focus on these groups. As part of this approach, Collaborative Open Research Consortia (CORCs) have been established to foster coordinated scientific efforts, facilitate open data sharing, and accelerate the development of medical countermeasures and public health interventions.

The *Filovirus* CORC focuses on R&D blueprint WHO priority pathogens and prototype pathogens from the *Filoviridae* family, including Ebola virus and Marburg virus, which cause severe viral hemorrhagic fevers and recurrent outbreaks. Coordinated by ANRS Emerging Infectious Diseases, the Filovirus CORC aims to identify key research priorities and guide the development of knowledge and tools needed to strengthen preparedness and response to future filovirus outbreaks. The Filovirus CORC has been tasked to update the WHO AFIRM strategy roadmap 2021-2031 provided by the MARVAC consortium, with significant achievements such as the development of standardized CORE protocols for filovirus vaccine and therapeutic trials, accelerated deployment of candidate vaccines during outbreaks, and strengthened global collaboration between research institutions, health authorities, and affected communities.

Scope

This *Filovirus* research and development roadmap outlines the key scientific priorities and operational considerations required to strengthen preparedness and response to filovirus disease outbreaks. It presents the current thematic landscape and state of knowledge on filoviruses, highlighting major findings, emerging trends, and critical data gaps that need to be addressed to advance the field. It builds on substantial work already undertaken by researchers, public health agencies, and international organizations—including the WHO and partner networks—to ensure continuity with existing evidence, tools, and strategic frameworks.

The roadmap also identifies existing operational assets that support research and outbreak response efforts, examines the principal challenges facing the filovirus research community, and defines strategic objectives to guide future scientific activities and collaboration. In addition, it considers several transversal considerations that cut across research domains — social sciences, issues of equity and access to knowledge, tools, and medical countermeasures. Across the five working groups, additional structural constraints and shared scientific needs consistently emerged. These cross-cutting challenges shape the feasibility, comparability, and overall impact of filovirus research and preparedness efforts across all priority families and their associated CORCs. Five dedicated working groups were convened to structure collective expertise and ensure comprehensive coverage of the scientific and operational priorities. Each group was coordinated by a designated lead and composed of multidisciplinary experts contributing their knowledge across the key thematic areas: virus ecology, diagnostics, pathophysiology and disease models, vaccines, and treatments.

The virus Ecology working group was coordinated by Ahidjo Ayouba, with contributions from Kofi Bonney, Karifa Kourouma, Benjamin T. Vonhm, Sanaba Boumbaly, Almudena Mari Saez, Sung Joon Park, Alpha Kabinet Keita, Vincent Cicculi, and Armelle Pasquet-Cadre.

The diagnostics working group, led by Eddy Kinganda Lusamaki, brought together Bolarinde Lawal, Cathy Roth, Gavin Harris, Apiyo Paska, Yonas Tegegn Woldemariam, Anaïs Legand, Luisa Enria, Vincent Cicculi, and Armelle Pasquet-Cadre

The Pathophysiology and Disease Models Working Group was coordinated by Hervé Raoul, with the participation of Lisa Hensley, Dave Safronetz, Logan Banadyga, Ngiambudulu Francisco, and Simon Funnell, Mélanie Nguyen-Marzin, and Armelle Pasquet Cadre

The Vaccines working group, under the leadership of Beth Ann Coller, included Alex Lehrer, Sylvain Baize, Mathieu Mateo, Sandhya Talasila, Deborah Watson Jones, Sylvain Faye, Yann Le Duff, Bruce Kirenga, Daniela Manno, Paul Scott, Philip Renatus Krause, Meena Murmu, and Armelle Pasquet-Cadre.

Finally, the Treatments working group was coordinated by Alexandra Calmy, with contributions from Amanda Rojek, Elizabeth Higgs, Rafael Delgado, Placide Mbala Kingebeni, Denis Malvy, Marie Jaspard, Beatrice Serra, Jamie Harper, Thomas Moench, Andre Siqueira, Ann Kelly, Armand Sprecher, Frédérique Jacqueroz Bausch, Tom Fletcher, Tara Nyhuis, Pauline Vetter, Esther Sterk, Mélanie Nguyen-Marzin, and Armelle Pasquet Cadre.

By establishing a shared understanding of research priorities and needs, this roadmap aims to support coordinated actions and informed decision-making among stakeholders, as well as funding organizations. Its development was made possible thanks to the collective engagement of experts. Their diverse yet complementary areas of expertise created the scientific depth and operational insight required to build a coherent, forward-looking roadmap. This multidisciplinary collaboration has been instrumental in ensuring that the roadmap reflects both the complexity of filovirus research and the practical realities of outbreak preparedness and response.

Executive summary

Filoviruses remain a significant global health threat, particularly in resource-limited settings, where surveillance, research, and funding have been insufficient since the 2013–2016 Ebola epidemic in West Africa, which caused over 11,000 deaths. Additional filoviruses, such as Bombali virus, Taï Forest virus, and Bundibugyo virus, remain poorly characterized, and their potential risk to human populations is not fully understood. Given the ongoing and evolving risk of filovirus outbreaks, urgent global collaborative efforts are required, including the establishment of the Filovirus Collaborative Open Research Consortium and active engagement of WHO Member States, research institutions, and funding organizations. These initiatives have led to the creation of this roadmap, which provides a coherent and actionable framework for guiding research priorities, fostering coordinated global efforts, and supporting timely, evidence-based decision-making to mitigate future filovirus threats.

This filovirus research and development roadmap is structured around five thematic areas, each playing a central role in advancing scientific understanding and enhancing preparedness and response to filovirus disease outbreaks. The division into thematic areas reflects the multiple approaches required to address the complexity of filoviruses, including their diverse biological characteristics, modes of transmission, and multifactorial patterns of spread within human populations. While each thematic area has a specific focus, many factors intersect across themes, and several elements are relevant to all areas, highlighting the strong interconnections within the filovirus research landscape. Furthermore, building public trust and addressing sociocultural barriers are critical components for effective interventions, and these considerations must be integrated across all thematic areas to reinforce global capacity to anticipate, detect, and control filovirus outbreaks.

In this context, the Top 10 research priorities offer a clear synthesis of the entire roadmap. They translate the scientific, operational, and societal insights of all working groups into a coherent agenda:

1. Achieve and sustain licensure of vaccines for filovirus targets

- Advance clinical development of additional filovirus vaccine candidates, including SUDV and MARV vaccines, leveraging EBOV licensure experience to guide development pathways.
- Explore pan-filovirus vaccines including multivalent and next-generation approaches, with early down-selection criteria based on regulatory feedback, harmonized immunogenicity, and functional assays
- Apply immunobridging to support product development when feasible supported by validated correlates of protection, harmonized assays
- Validate filovirus-specific immune correlates of protection and durability benchmarks to inform booster dose strategies
- Maintain outbreak-ready clinical trial platforms (e.g., SOLIDARITY), including pre-approved protocols, trained teams, and interoperable data systems
- **Ensure inclusion of vulnerable and complex populations** (children, pregnant women, high-risk groups) through adaptive trial designs and ethical frameworks enabling early, disaggregated data
- Establish resilient manufacturing and supply ecosystems for filovirus vaccines
- **Reinforce and diversify therapeutic options to complement and reinforce vaccination options, particularly in potential exposure scenarios**

2. Design therapeutics targeting under-researched viruses

Monitor, develop and evaluate monoclonal antibodies and antiviral agents for all filoviruses

- Investigate host-directed therapies to modulate immune responses or block viral replication
- Target viral persistence and sanctuary sites in survivors and in treated patient's cohorts

3. Build Experimental Models to Understand Immune and Pathological Mechanisms

- Develop intermediate animal and in vitro models
 - Identify immune signatures linked to disease severity
 - Differentiate protective from pathogenic immune responses
- In vitro, study the dynamics of filoviruses in susceptible bat species to study viral shedding, distribution in different organs

4. Monitor Patient and survivors Cohorts to Understand Immunity and Viral Persistence

- Assess safety, effectiveness, duration of protection, immune response, and viral persistence sites

- Use simplified sampling strategies to reduce patient burden
- Document risks of flare-ups due to viral persistence in survivors

5. Advance Research on Zoonotic Transmission

- Intensify efforts to identify natural reservoirs and transmission pathways
- Develop serological and molecular tools for ecological surveillance
- Rethink sampling methods, species prioritization, and analytical approaches to overcome current limitations
- Develop and implement effective early warning systems (EWS) to enable the timely detection of potential filovirus circulation and to support coordinated surveillance activities.
- In the wild, perform longitudinal surveys in selected at-risk areas in Africa where filoviruses repeatedly occurred in the past to cope with seasonality;
- In the wild, in selected bat species, perform longitudinal ecological monitoring via the use of marking systems.

6. Strengthen Diagnostic and Field Laboratory Capacity

- Reinforce coordination and rapid deployment of mobile laboratories
- Ensure timely results for surveillance and patient management by supporting Ag-RDT development
- Develop and validate serological and PCR tests suitable for field use
- Develop sensitive, high throughput and low cost multiplex serology, PCR and multiplexed sequencing approaches for early characterisation
- Harmonize serological and functional assays across countries to support immunobridging, correlates of protection, and cross-trial comparability
- Strengthen reagent repositories and ensure alignment with WHO International Standards to support vaccine evaluation and regulatory decision-making

7. Improve Social Acceptability of Medical Interventions

- Study public perception and acceptance of vaccines and treatments
- Identify strategies to enhance community engagement and adherence
- Define indicators to guide and adapt communication efforts
- Integrate early and continuous community engagement into vaccine and drug development and deployment strategies, especially for complex populations

8. Reinforce Inter-Epidemic Preparedness and Coordination

- Maintain operational capacity between outbreaks to prevent loss of momentum
- Support local networks and expertise with a continuity-based approach
- Align biomedical research with social sciences, public health, and field actors
- Expand trial networks: Scale beyond anchor sites to additional national institutes with lab and cold chain capacity

- **Establish rapid data-sharing agreements** across ministries, research institutions, and global partners. Align regulatory, ethical, and operational pathways to enable rapid activation of vaccine trials during outbreaks

9. **Advance Therapeutic Evaluations and accelerate Clinical Trial Approvals**

- Standardize Protocols to Generate Clinical Evidence
- Implement pan-filovirus CORE protocols with pre-approvals to ensure reactive, consistent feasibility, safety and efficacy data
- Define optimized clinical supportive care and support training
- Build and sustain infrastructure in risk areas
- Strengthen reliance-based regulatory mechanisms (e.g., WHO EUL, AVAREF) to accelerate evaluation of vaccines and therapeutics during outbreaks
- Harmonize immunogenicity endpoints and assay standards to support rapid, comparable evidence generation

10. **Increase Visibility of Research to Mobilize Sustainable Funding**

- Foster interdisciplinary and interinstitutional collaboration
- Position research as a central pillar of epidemic preparedness and response
- Highlight the need for sustained investment in vaccine platforms, manufacturing capacity, and cold-chain resilience as core components of epidemic preparedness

Introduction

Filoviruses are enveloped, negative-sense RNA viruses that belong to the family *Filoviridae* within the order of *Mononegavirales*. They are further classified into eight genera. We will focus on the two that contain human-pathogenic viruses: *Orthoebolavirus*, *Orthomarburgvirus*. . Based on genomic organization and similarity of conserved genes, member species are further segregated into several species. Notably, among the human-infecting filoviruses, Ebola virus (EBOV), Sudan virus (SUDV), Bundibugyo virus (BDBV), and Tai Forest virus (TAFV) are members of the genus *Orthoebolavirus*, while Marburg virus (MARV) belongs to the genus *Orthomarburgvirus*.

EBOV (species *Orthoebolavirus zairense*) and MARV(species *Orthomarburgvirus marburgense*) are responsible for most outbreaks to date and cause severe disease in humans with high case-fatality rates.

EBOV has caused large outbreaks in West and Central Africa (Guinea, Sierra Leone, Liberia, Democratic Republic of the Congo). SUDV outbreaks have occurred mainly in Sudan and Uganda, while BDBV has been reported in Uganda and the Democratic Republic of Congo. TAFV caused a single documented human infection in Côte d'Ivoire. MARV has emerged in Angola, Rwanda, the Democratic Republic of Congo, Uganda, and Kenya. RESTV, detected in the Philippines and Vietnam, can infect humans but has not caused clinical disease.

Infections caused by filoviruses typically present as severe viral hemorrhagic fevers. Early symptoms include fever, fatigue, muscle pain, and sore throat, and can progress to hemorrhage, multi-organ failure, and shock. EBOV, SUDV, BDBV, and MARV are associated with particularly high pathogenicity and mortality rates.

While therapeutic options for filovirus diseases remain limited, important progress has been made in developing treatments that can be rapidly deployed during outbreaks. However, these advances are largely specific to EBOV, and significant gaps persist across the broader filovirus family, where no comparable countermeasures exist for most viruses.

Virus ecology

1. Thematic and state of knowledge

Since 1967 for Marburg virus disease (MVD) and 1976 for Ebola virus disease (EVD), there have been 17 MVD and 42 EVD outbreaks worldwide respectively, mostly in sub-Saharan Africa, with variable case fatalities, depending on the filovirus. Drivers of these outbreaks remain very composite and include multiple factors such as trade, travel, wild game consumption, failures of medical procedures, weakness in human health infrastructures, etc (1). Although the drivers are not fully understood, the trend is towards an increase in the number and frequency of outbreaks over time (Figures 1&2). However, we cannot exclude the improvement of awareness, detection tools, surveillance and reporting systems. Molecular evolution modelling of filoviruses using Bayesian inference estimated their Most Recent Common Ancestor (MRCA) back to 10,000 years ago, while for *Othoebolavirus zairense*, the MRCA is dated only to 50 years ago (2), compatible with its highest pathogenicity to its novel human and non-human primates hosts.

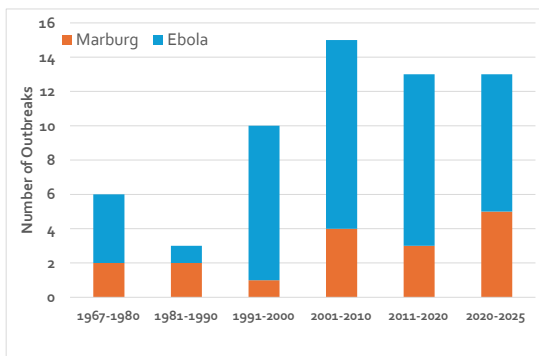


Figure1: Trend of filoviruses (Ebola and Marburg viruses) outbreaks, by decades.

Adapted from raw data of WHO and CDC, accessed 9th January 2026.

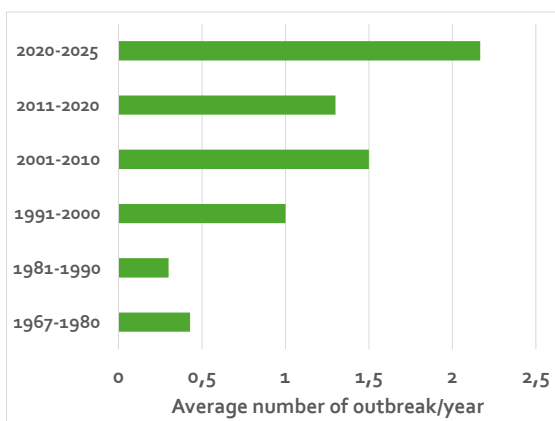


Figure 2: average filovirus outbreak per year since 1967. Same source as in Figure1.

The reservoir host(s) and the ecology of filoviruses remain an open question, especially for Orthoebolaviruses. While for Orthomarburgviruses, there is a consensus in the scientific community to consider the Egyptian rousette bat (*Rousettus aegyptiacus*) as the natural host of the virus, for EBOV, the question remains unanswered.

This section addresses the interactions between filoviruses, their host organisms, and the environment, with the aim of identifying key knowledge gaps in filovirus ecology and outlining potential mitigation pathways. Two major gaps remain central to advancing ecological understanding:

- **What is the reservoir species of filoviruses?**
- **What are the outbreaks drivers?**

2. Key Findings, Emerging Trends, and Data Gap

Reservoir of Filoviruses

For MARV, as mentioned above, the natural host of virus is very likely *R. aegyptiacus*. The virus has been detected, at molecular level and by serology, in different parts of Africa by different teams and link with MVD outbreaks humans visiting caves where *R. aegyptiacus* roosts has been established and MARV was detected in multiple instances in *R. aegyptiacus* (3–6). This species, existing in two different subspecies, is widely distributed in sub-Saharan Africa, from South Africa to the eastern part of the continent, in Kenya; and in West Africa up to Guinea (7). For MARV, as mentioned above, the natural host of virus is very likely *R. aegyptiacus*. The virus has been detected, at molecular level and by serology, in different parts of Africa by different teams and link and link with MVD outbreaks humans visiting caves where *R. aegyptiacus* roosts has been established and MARV was detected in multiple instances in *R. aegyptiacus* (3–6). This species, existing in two different subspecies, is widely distributed in sub-Saharan Africa, from South Africa to the eastern part of the continent, in Kenya; and in West Africa up to Guinea (7).

For orthoebolaviruses and more specifically the viruses infecting humans and non-human primates, bats are the primary suspects. For example, genetic material of EBOV has been detected in three frugivorous bat species (*H. montrosus*, *E. franqueti* and *M. torquata*) in an investigation during EVD outbreaks in Gabon and Congo between 2001 and 2003 (8). The authors sampled more 1,000 specimens from bats (630 specimens), birds and small mammals around carcasses of chimpanzees and gorillas, victims of virus. This is the unique example of positive detection of a small fragment (<500 bp) of viral genetic material of EBOV in bats. Since then, thousands of bats sampled throughout sub-Saharan Africa (South Africa, the Democratic Republic of Congo, Kenya, Cameroon, Guinea, Gabon, etc.), including during outbreaks, detected no EBOV RNA in blood and swabs (9–11). Nevertheless, RNA of another orthoebolavirus, Bombali virus (species *Orthoebolavirus bombaliense*), have been readily detected in Sierra Leone and Guinea in West Africa and Kenya and Mozambique is East Africa in two bats species, *Chaerephon pumilus* and *Mops condylurus* (12–15). Inversely, varying prevalence of antibodies to Ebola virus antigens have been detected by different groups in different genera of bats throughout Africa, Asia and even Australia using different methodologies (16–21). In other animal species, including wild ungulates and apes, viral RNA

has been detected in carcasses during outbreaks and antibodies in serum/plasma samples from live animals such as pigs, dogs, or wildlife killed for bushmeat (20,22–25). Since no Ebola virus RNA has been detected in these animals, except the RESTV in Philippines macaques, the more likely explanation is that mammals, and non-human primates the first of them, are rather victims than reservoirs of Ebola viruses (26). Finally, beside bats as putative reservoirs of Ebola virus, a paradigm change has occurred following the outbreak of 2021 in Guinea which showed evidence that a human survivor can be at a start of a novel outbreak years after an outbreak had been declared over (27). Survivors to Ebola virus diseases should thus be considered, to some extent, as potential reservoirs of the virus. In this case it will be important to use social sciences research methods to study survivors ‘social networks’ and develop a participatory approach to address the social and moral implications of human resurgences.

Table 1: summary of currently known potential Filoviruses reservoirs.

Genera	Reservoir	Evidence:	RNA	Ab
<i>Marburg Marburgvirus</i>	<i>R. aegyptiacus</i>		+++	+++
<i>Orthoebolavirus zairense</i>	Fruit bats			
	<i>H. monstrosus</i>		±	++
	<i>E. franqueti</i>		±	++
	<i>M. torquata</i>		±	++
	Other genera/species		-	++
	<i>H. sapiens sapiens</i>		±*	++
	Other mammals		±**	+
<i>Orthoebolavirus bombaliense</i>	Insectivorous bats			
	<i>C. pumilus</i>		+	+
	<i>M. condylurus</i>		+	+
	<i>Other species</i>		-	±
Other Orthoebolavirus	various species		-	±

*: in survivors; **: in carcasses

There are two main hypotheses to explain the difficulty of identifying Filovirus reservoirs, except Orthomarburgvirus.

- Methodological issues.** The detection tools used are not sensitive enough. This is very unlikely because the PCR approaches used are highly sensitive and able to detect down to less than 10 copies/ microliter of extract. Another possibility is the sampling methods. Several teams working on wildlife, especially on bats, avoid lethal sampling, and rather take oral and rectal swabs and viral shedding might not be sufficient, or absent, or transient to the viral biology, especially in bats.
- Targeted hosts are not the right ones:** investigators of filovirus reservoirs have been focusing on mammals, and very rarely on arthropods. Given the large host spectrum of

the *Mononegavirales* order and the recent MRCA of filoviruses, some authors are now not excluding the possibility that filoviruses descend from some plant viruses, necessitating a small animal (insect?) as intermediate host before adaptation to a mammalian host (for example a bat). This hypothesis has the advantage of explaining the high seroprevalence of IgG directed against Ebola virus glycoproteins in areas where no outbreak has ever been registered.

Hence, after half a century (1976-2026) since the first EVD outbreak and after 60 years since the first MVD outbreak, there is a real need to develop new research pathways to study the reservoirs of filoviruses, apart from the orthomareburgviruses. To this end, we need to combine reservoir search and the drivers of outbreaks.

Drivers of filovirus outbreaks : As mentioned in the section above, there is a trend towards an increase in the number and frequency of filovirus outbreaks, mainly in Africa. Since 2000, there is, on average, at least one filovirus outbreak per year. This trend can be explained by the improvement of surveillance, detection and reporting systems in various African countries. The increasing number of outbreaks can also be explained by ecological factors including climate change, land use change, human population growth associated with changes in human/wildlife interactions, and human behaviours/activities.

Hence, anthropogenic activities, particularly industrial and artisanal mining, should be considered a major determinant of filovirus emergence. Mining induces rapid land-use changes, habitat fragmentation, and creation of artificial roosting and sheltering sites for bats and other wildlife. In parallel, mining-related human mobility and settlement increase interfaces between humans, wildlife, and potential viral reservoirs.

Filling the gaps : Two main knowledge gaps have been identified. The first is the identification of the reservoirs of filoviruses. In this regard, it is crucial to go beyond bats. It has been shown that different bat species can be successfully infected *in vitro* with various filoviruses from different species, including MARV and EBOV. Bats are thus susceptible to infection and survive it. Despite fifty years of efforts, the definitive demonstration is missing. Actions proposed to address knowledge gaps :

1. In the wild, test additional species, including arthropods and ectoparasites of bats and other mammals living in areas where filovirus outbreaks have occurred in the past;
2. In the wild, perform longitudinal surveys in selected at risk areas in Africa where filoviruses repeatedly occurred in the past to cope with seasonality;
3. In areas where longitudinal studies are conducted, perform socio-ecological studies assessing how long-term environmental transformations, such as (plantations, poaching, mining activities, extensive agriculture, livestock production, eco-tourism) may influence animal species presence, absence and distribution.
4. In humans, establish cohorts of filovirus survivors to study the immunity and the virology to understand viral dynamics, including in immune privileged sites. Moreover, in identifying survivors, it is crucial to distinguish between symptomatic and pauci-symptomatic cases.

5. In the wild, in selected bat species, perform longitudinal ecological monitoring via the use of marking system. This will allow to monitor the movements of these flying mammals, ideally more than a year;
6. In vitro, study the dynamics of filoviruses in susceptible bat species to study viral shedding, distribution in different organs at the relation of these parameters in association with sex, age, gestational status;
7. Model outbreak risks based on ecological AND robust field and laboratory data

3. Operational Assets

Example of projects and Networks that could be leveraged, connected, or scaled to accelerate progress. include:

ZOOSURSY project : it covers seventeen African countries : funded by the European Union to enhance research, diagnostics, and policy to reinforce national veterinary services, improve wildlife and livestock surveillance, harmonise diagnostic practices, and build operational capacity for early detection of high-risk pathogens at the human–animal–environment interface. Led by WOAHA, in collaboration with CIRAD, IRD, Institut Pasteur, the Helmholtz Institute for One Health, and the University of Helsinki, the project fosters One Health collaboration. The project enables rapid mobilisation of wildlife surveillance teams, supports ecological investigations (including bats and other potential reservoirs), strengthens diagnostic capacity in affected regions, and facilitates data-sharing between veterinary and public-health sectors.

The **CONTAGIO network**, funded under the French “PEPR Santé Globale” programme and coordinated by a consortium of leading French research institutions (including Inserm, CNRS, Institut Pasteur, IRD, and several universities), is designed to build a **national and international research infrastructure dedicated to anticipating, detecting, and responding to emerging infectious threats**. The CONTAGIO network can rapidly activate expert networks, support genomic and ecological investigations, mobilise modelling teams, facilitate data-sharing, and connect national research capacities with international partners.

- The **Pasteur Network**, coordinated by the **Institut Pasteur**, is a global alliance of more than 30 public health and research institutions across five continents, dedicated to strengthening surveillance, laboratory capacity, and scientific collaboration on infectious diseases. The network integrates expertise in virology, epidemiology, entomology, genomics, and social sciences. The network can mobilized laboratory teams, deploy diagnostic capacity, support genomic sequencing and field investigations, and facilitate datasharing across countries. Its longstanding presence in Africa and other highrisk regions makes it a critical platform for early detection, coordinated response, and accelerated research during filovirus emergencies
- ANRS MIE partner sites and PRISME in Africa

4. Key challenges

The lives of humans and animals, whether wild or domestic, are interconnected; however, in some context these relationships go beyond interaction and constitute forms of entanglement.

Anthropological work on hemorrhagic fever has highlighted that human and animal lives may be mutually constituted and cannot be easily separated or understood in isolation. These reciprocal processes of shaping of lives unfold across social, ecological and material domains (28)

Human - animal relationships thus exist along a gradient of mutuality. They might be more or less intimate, regular or sporadic, and take diverse forms, mediated by different material conditions and motivated by a range of social, economic and ecological factors. Despite this, relatively few studies that describe and analyze potential context of viral transmission with the level of granularity required to capture these dynamics. Beyond understanding modes of contact, and drivers of filoviruses outbreaks, virological fundamental research may benefit of anthropology understanding of contextualized analysis, as it can provide essential insights into how contact, transmission, and viral spillover are produced and understood (29).

From this perspective, interactions between human - bats (among other animals) cannot be reduced solely to notions of biological risk. Human - bats lives might involve play, livelihood strategies, economic means, health practices and religious or symbolic meanings (30,31) However, risk communication and prevention campaigns have often reshaped local perceptions of these relationships, sometimes framing specific animal species as threats or “villains” (32). Such framing may oversimplify complex social realities and contribute to some population 's groups' stigma.

5. Strategic Objectives

Short-Term Priorities (0–12 months)

The development of Early Warning Systems based on the integration of ecological, environmental, and human indicators is recommended. Such systems should aim at detecting weak signals preceding human outbreaks and rely on continuous data collection, risk modelling, and predefined alert thresholds to trigger preventive actions.

Milestone: A simple and effective early warning system (EWS) will be developed and progressively implemented to enable the timely detection of potential filovirus circulation and to support coordinated surveillance activities.

Expected outputs:

- Operational EWS prototype
- Standardized indicators and alert thresholds
- Initial datasets to trigger preventive actions

Medium-Term Priorities (1-3 years)

Filovirus ecology investigations should evolve toward an integrated and longitudinal surveillance framework combining wildlife (bats, arthropods, and other mammals), environmental drivers, and human populations. This includes ecological monitoring,

serological and virological surveys, and structured follow-up of filovirus survivor cohorts as part of the ecosystem

Milestones:

1. Cohorts of filovirus survivors will be established to investigate long-term immunity and viral persistence, including viral dynamics in immune-privileged sites.
2. Additional species will be investigated to broaden the understanding of potential reservoirs and transmission pathways. Arthropods and ectoparasites associated with bats and other mammals living in areas where filovirus outbreaks have previously occurred will be collected and tested.
3. Longitudinal surveys will be conducted in selected high-risk areas in Africa where filovirus outbreaks have repeatedly occurred in the past, allowing the investigation of seasonal patterns and environmental drivers of viral circulation.
4. The dynamics of filoviruses in susceptible bat species will be investigated, focusing on viral shedding, tissue distribution across organs, and their relationship with host biological factors such as sex, age, and gestational status.

Expected outputs:

- Longitudinal datasets on viral circulation
- Characterization of wildlife reservoirs and transmission pathways
- Insights into ecological and seasonal drivers of filovirus emergence
- Data to inform predictive models and risk assessment

Long-Term Priorities (+5 years)

Data generated through integrated surveillance should feed directly into predictive models and public health decision-making processes. The objective is to transform filovirus ecology research into an operational tool for anticipation, preparedness, and risk mitigation rather than post-outbreak response alone.

Milestones:

1. Integration of surveillance data into predictive models for outbreak anticipation.
2. Development of decision-support systems for public health authorities.
3. Full operationalization of the EWS with continuous data streams, automated alerts, and real-time risk assessment.
4. Translation of research outputs into evidence-based preparedness and response strategies.

Expected outputs:

- Operational predictive modelling platforms
- Decision-support tools for public health
- Evidence-based outbreak mitigation strategies

Diagnostic

1. Thematic and state of knowledge

Currently, diagnosis relies on a combination of direct detection of the virus using molecular and antigenic methods, as well as indirect detection through serological methods, with an emphasis on point-of-care (POC) tools deployable in higher risk areas of sub-Saharan Africa. The tests are classified as BSL-4 for initial handling due to the high risk, but inactivation protocols allow processing under BSL-2 conditions. According to WHO guidelines (updated December 2024), confirmation is based on blood, serum or plasma samples (collected on EDTA) as well as oral swabs on deceased patients. While assays have been developed for EBOV or MARV allowing quick characterization, gaps remain for neglected filoviruses and for early detection before symptom onset. (33–40)

Axe	Description and examples	key challenges
Molecular detection	Methods based on viral RNA, the standard for early and quantitative detection (viral load). High sensitivity).(41) Real-time RT-PCR (RT-qPCR) e.g., RealStar Filovirus Screen RT-PCR Kit detects EBOV, SUDV, BDBV, TAFV, RESTV and MARV in <2 hours).	Issues: genetic variability of viruses, need for specialized equipment (thermocyclers).(42–45) Costs, maintenance and specific environment requirements
Antigen assay	Rapid tests for viral antigens (NP, VP40, GP) in blood or oral swabs (including from cadavers).(39,46) Lateral flow assays (LFAs) such as the ReEBOV Antigen Rapid Test (EUA 2015 for EBOV).	Specificity >99%, but lower sensitivity in the late phase. Limited availability for MARV and other filoviruses.(47,48)
Serological detection	Antibody detection (IgM for the acute phase, IgG for epidemiological surveillance). Useful during the convalescent phase or serosurveys in human/wild animals during interepidemic periods, or investigations involving survivors.(49–51) Capture IgM/IgG ELISA (e.g., kits for EBOV).	Limitations: temporal window (IgM detectable after 5–7 days), false positives in areas with outbreak history.(52)
Advanced and integrated methods	Integration of technologies for multiplexing on point-of-care (POC) (GeneXpert, Biofire, ...) or with high throughput, integrating serology on Luminex or MSD platforms or NGS.(50,51,53) with tangible impact on public health response; microarray for 16 haemorrhagic pathogens...(54)	Cost, requirement for BSL-3/4 facilities, maintenance, supply chain

2. Key Findings, Emerging Trends, and Data Gap

Filovirus diagnostics have made significant advances in recent years, aiming to make tools faster, decentralized, and suitable for field settings, although many gaps remain.

RT-qPCR remains the reference method for confirming infections with orthoebolaviruses and orthomarburgvirus, due to its high sensitivity and proven field use, notably in mobile laboratories and through inactivation protocols that allow sample processing at BSL-2.(55)

Existing platforms rely on (i) open PCR platforms and (ii) semi-automated closed PCR platforms. While the open PCR are less costly, they might be more complicated to decentralize closer to field as opposed to semi-automated closed PCR platforms that can be decentralized more easily despite the cost and the need to make it available for most filoviruses. (43,56). In addition, waste management challenges are not always anticipated in remote areas.

Rapid antigen tests based on lateral flow immunoassays show high specificity but variable sensitivity, often insufficient for routine use, and no rapid test has yet achieved regulatory approval for filoviruses (39,46) (57) Furthermore, genomic surveillance and viral sequencing (NGS and RNA seq) have become essential for monitoring virus evolution, pathogen discovery, understanding transmission chains, and detecting new strains, but sequencing capacity still needs to be improved and sustained in high risk countries despite progress with the COVID-19 pandemic (58–60). Serological tests, particularly IgM and IgG, remain poorly standardized and difficult to interpret, although they are essential for epidemiology and detection of past cases often missed.

Innovative technologies such as CRISPR/Cas biosensors and isothermal LAMP tests offer strong potential for portable and rapid diagnostics suitable for rural or low-resource settings, but they still require rigorous clinical validation and protocol standardization.

Gaps

The absence of standardized sample banks, low tool interoperability, lack of sustainable funding, and loss of capacity between outbreaks compromises epidemic preparedness. These gaps lead to delays in case detection, potential silent transmission, incomplete epidemiological monitoring, and late deployment of control measures such as contact tracing and ring vaccination where relevant, highlighting the urgent need to develop reliable rapid tests, molecular biology and sequencing infrastructure, and robust validation strategies to improve filovirus surveillance and outbreak management.(61) Another critical point concerns less-studied filoviruses: most existing diagnostic tests focus on EBOV, SUDV, and MARV, and there are few or no validated diagnostics for other emerging filoviruses, creating a risk of delayed detection and limiting effective epidemiological surveillance(55). In addition, filovirus sequencing remains expensive, and targeted NGS syndromic approaches should be developed to allow rapid early characterization. Finally, the trust in patients/ communities has emerged across epidemics as a challenge, particularly with novel approaches and may need to be addressed to allow early and reliable detection of the viruses in the community.

3. Operational Assets

Resource / Platform	Geographical scope	Key capabilities	Emergency response	Optimal effectiveness contexts
Global Outbreak Alert and Response Network (GOARN)	Global	Mobilization of experts, laboratory teams, logistics, deployment of mobile labs	Activation via WHO within 48–72 hours; multi-agency coordination; support for regulatory compliance	Early outbreak phase; countries with limited capacity; multi-country hotspots
Africa CDC – Pathogen Genomics Initiative (PGI)	Africa (West, Central, East, Southern hubs)	Genomic sequencing, bioinformatics, variant monitoring, standardized pipelines	Transport of inactivated samples to reference labs; activation of bioinformatics networks	DRC, Guinea, Uganda, Sierra Leone; inter-epidemic genomic surveillance
GeneXpert TB/HIV Network	Africa, Asia, Latin America	Decentralized rapid PCR testing; existing modules in primary healthcare centers	Emergency supply of Ebola cartridges; integration into national diagnostic algorithms	Rural and remote areas; rapid confirmation without new infrastructure
FIND (Foundation for Innovative New Diagnostics)	Global	Independent evaluation; analytical and clinical validation; support to manufacturers	Accelerated evaluation of PCR/LAMP/Ag-RDT; support for WHO EUL submission	Validation during inter-epidemic periods; controlled introduction of new diagnostics
WHO Emergency Use Listing (EUL)	Global	Accelerated regulatory pathway enabling procurement by UN agencies	Pre-submission dossier preparation; expedited review; post-market surveillance	Rapid large-scale deployment; procurement via UNICEF/UNOPS
Go.Data (WHO)	Africa, Asia, South America	Case and contact management; integration of lab data; real-time analytics	Integration of PCR/Ag-RDT data; rapid staff training; interoperability with DHIS2	Field operations; transmission chain monitoring
Mobile laboratories (MSF, EU, CDC)	Globally deployable	On-site PCR diagnostics; mobile BSL-3 modules; rapid staff training	Deployment within 24–72 hours; setup in low-infrastructure areas	Rural epicenters; limited hospital capacity; hard-to-reach settings
National/Regional Sample Banks / MOHS–UKHSA Ebola Biobank	Endemic countries + WHO networks	Reference standards; validation panels; access to inactivated samples	Secure storage; sharing via MTAs; support for inter-laboratory validation	Inter-laboratory standardization; EQA; inter-epidemic validation
ECOWAS / Africa CDC – Logistics Hubs	West Africa / Pan-African	Supply chain management; stockpiling; cross-border distribution	Activation of regional stockpiles; delivery of reagents; deployment of mobile teams	Cross-border outbreaks; supply chain disruptions
ARTIC Network	Global	Real-time viral genome sequencing; standardized protocols and primer schemes	Provision of primers, protocols, training, technical support	Outbreak response; field NGS deployment; preparedness
ZOO-SURSY Project	West, Central, East, Southern Africa	Strengthening zoonotic surveillance; early detection; wildlife investigations	Capacity building; field investigations; training	Inter-epidemic surveillance; One Health preparedness
East African Community (EAC) Mobile Laboratory Network	East Africa	PCR/qPCR/ELISA diagnostics; mobile BSL-2/3 labs; genomic surveillance; training	Rapid deployment of mobile labs for detection and response	Remote, resource-limited settings; cross-border surveillance; high-risk One Health environments

4. Key challenges

The effective implementation of research and diagnostic efforts for orthoebolaviruses and orthomareburgviruses faces multiple barriers, particularly in resource-limited settings or during outbreaks. Infrastructural and logistical challenges include the limited availability of laboratories equipped and certified to handle highly infectious samples, as safe sample manipulation requires BSL-3 or BSL-4 facilities, biosafety cabinets, and specialized equipment, which are often lacking in at-risk countries (59). Sample transport and storage requirements further complicate operations, with strict mandates for low-temperature storage, triple packaging, and compliance with international regulations. On the human and organizational side, shortages of trained and experienced personnel, coupled with the need to maintain biosafety and adhere to standard operating procedures, constrain the rapid expansion of

diagnostic capacity, even with the deployment of mobile or semi-automated laboratories (62–64).

Genomic approaches, such as next-generation sequencing (NGS), are essential for rapid characterization of viral strains (65), monitoring of mutations (66) and guiding the development and deployment of molecular diagnostics, therapeutic and vaccines. However, access to sequencing platforms, high costs, lack of trained bioinformaticians, and limited computational infrastructure often hinder the timely use of NGS during outbreaks. In addition, during an outbreak, they should be considered alongside epidemiological data which are not always easier to gather on time (67,68). Furthermore, delays in data sharing, ethical concerns, and regulatory barriers may prevent genomic information from being rapidly disseminated and integrated into public health responses (59,69,70)

Limited availability of clinical samples, particularly during the early stages of outbreaks, further hampers assay validation and the development of rapid diagnostic tools. Rapid antigen-detection tests (Ag-RDTs), while potentially useful for point-of-care screening, face additional limitations including lower sensitivity compared with RT-PCR, variable performance in field conditions, and insufficient data for newly emerging species, complicating their interpretation and implementation (71,72). Moreover, the development pipeline for filovirus Ag-RDTs remains extremely limited because the market is considered unprofitable by most manufacturers, who face high development and regulatory costs with little commercial return, resulting in very few companies willing to invest in such diagnostics (33,40). Social and dynamics also play a key role: fear of infection, stigma, mistrust of authorities and external medical research, or reluctance to undergo testing can reduce sample availability and delay diagnosis, ultimately impeding outbreak containment (73,74).

Finally, regulatory, financial, and data-sharing constraints can delay research efforts and the uptake of new diagnostics, while ongoing security issues or political instability in outbreak regions may further impede both laboratory operations and field investigations (59,73,75)

5. Strategic Objectives

Short-Term Priorities (0–12 months) - Focus: Rapid deliverables, feasibility assessments, and foundational systems.

- The operationalization of below priorities should integrate primarily national and regional laboratories of areas at higher risk, as they urgently need to be equipped for baseline diagnostic with available tools and their relative biosafety materials, and standardized SOPs. Therefore, formalized national diagnostic algorithms tailored to local operational realities and integrated within regional reference laboratory networks will not only be developed but also ensure high impact research.
 - ⇒ These frameworks standardize testing strategies, improve equitable access to diagnostics across different regions, and optimize the use of specialized laboratories
- Improve surveillance in remote areas at risk by integrating innovative approaches such as AI to enhance data collection and/or to empower the yield of current diagnostic

(serological, PCR and sequencing panels targeting all known filovirus in humans, animals and environment)

⇒ To allow accurate data collection and narrow laboratory syndromic diagnosis and to ensure immediate minimum detection capacity and reduce reliance on external laboratories during early outbreak phases.

• **Launch community-engagement frameworks** through participatory design and social-science assessments.

⇒ *This increases community trust and prevents resistance to testing when outbreaks occur.*

• **Develop and validate simplified sampling tools** such as dried blood spots, ambient-temperature swabs, inactivation buffers for both human and animals, as well as **low-cost POC assays** PCR, LAMP/CRISPR assays, Ag-RDTs, sequencing approaches in open platforms

⇒ *These tools expand diagnostic reach to remote settings and reduce logistics costs.*

• **Establish rapid data-sharing agreements** across ministries, research institutions, and global partners.

⇒ *identify reticence factors and accompanying countries because fast information flow accelerates detection of transmission patterns, and the epidemics response by facilitating therapeutic and vaccination. This should be built on previous developed pre-agreement and procedures.*

• **Develop harmonized regulatory pathways** to fast-track approval of diagnostic tools during outbreaks

⇒ *Streamlined regulation shortens deployment timelines for essential tests.*

Medium-Term Priorities (1–3 years)

Focus: Validated outputs, field-ready tools, operational platforms.

• **Validate multiplex PCR assays and next-generation sequencing tools** using standardized biobank samples

⇒ *This improves diagnostic accuracy, fills gaps for filovirus species lacking assays, and enhances animal surveillance and virus ecology studies, enabling rapid species identification to activate appropriate care pathways and accelerate the launch of therapeutic trials.*

• **Enhance and expand multiplex serology platforms's targets to cover the broad family of filoviruses in both human, animal and environmental samples**

⇒ *This enhances virus ecology studies and surveillance by detecting past exposure, informing vaccination strategies, and supporting evaluation of protective*

immunity in populations, enabling targeted public health interventions and rapid response planning.

- **Deploy decentralized diagnostic and sequencing platforms;** portable PCR, LAMP/CRISPR assays, Ag-RDTs, to rural clinics and mobile units.
to rural clinics and mobile units, integrating non-invasive, low-risk methods suitable for safe use even in post-mortem settings. Attention should also be paid to developing thermostable, long-shelf life assays for such decentralized use.

- Develop POC approaches for patient biological follow-up and identify earlier biomarkers that could suggest infection
 - ⇒ *physiopathological and modelling studies may help to draw profiles for early detection, and even in eumonctory organs where the virus is latent or when virus detection is challenging*

- Develop models for sustainable national diagnostic systems including training, equipment, and long-term support
 - ⇒ *this will allow countries that may be newly affected and anticipate any global spread*

- **Create a networked, ethically governed biobanking system with early-outbreak sample-sharing agreements.**
 - ⇒ *A stable sample supply allows rapid test validation (diagnostics, treatment, vaccine) and supports local research capacity. Building collaboration and regular assessments or exercises with these biobanks should be prioritized*

- **Implement genomic surveillance tools, guidelines and pipelines,** with routine sequencing, bioinformatics training, and integration into outbreak dashboards.
 - ⇒ *Genomic data enables early identification of pathogen, transmission hotspots. This also allows better understanding of outbreak dynamics, zoonotic origin, diagnosis ajustment and countermeasures developement*

- **Scale community-engaged testing pilots** involving local health workers and civil-society partners.
 - ⇒ *Locally anchored approaches improve participation, reduce stigma, and increase uptake.*

- **Operationalize regional logistics systems** with pooled procurement, reagent stockpiles, and rapid deployment teams.
 - ⇒ *Stronger supply chains minimize stock outs and improve preparedness for surges in demand.*

Launch regular EQA proficiency test enrolling laboratories with those located in higher risk area in priority.

- ⇒ *This will allow to keep level of awareness and preparedness during interepidemic periods*

Long-Term Priorities (3+ years)

Focus: System integration, policy adoption, and sustainable scale-up.

- **Integrate validated diagnostics into national surveillance programs**, including routine testing in health facilities, cross-border monitoring, and One-Health animal/human systems.
 - ⇒ *Integration of diagnosis into routine surveillance promotes early detection and coordination of control measures at the regional level.*
- **Establish sustained financing mechanisms**; regional manufacturing partnerships, advanced market commitments, or donor-supported procurement lines, to guarantee long-term access to diagnostics.
 - ⇒ *Stable financing guarantees long-term availability and reduces dependence on emergency funding.*
- **Embed social and behavioral science approaches into diagnostic policy and workforce training.**
 - ⇒ Addressing behavioral drivers improves acceptance, informed consent, and testing adherence.
- **Evaluate long-term impact** and refine policies to ensure equitable diagnostic access across regions and population groups.
 - ⇒ *Continuous evaluation supports evidence-based policy improvements and reduces inequities. In addition, survivors continued follow-up and serological surveys to assess population susceptibility or protection should be considered.*

Physiopathology and Disease Models

1. Thematic and state of knowledge

Current knowledge on filovirus pathogenesis indicates that infection begins at mucosal surfaces or through skin breaches, where macrophages and dendritic cells serve as initial targets and subsequently disseminate the virus to lymph nodes and major organs(76). Disease progression is driven by uncontrolled viral replication and a strong yet ineffective inflammatory response(77), shaped by well-characterized immune-evasion strategies: VP35 suppresses RIG-I-mediated interferon induction, orthoebolaviruse VP24 and orthomarburgviruse VP40 block STAT1 nuclear import, and the GP glycoprotein disrupts tetherin activity and cytokine signaling(78).

Systemic involvement extends beyond classical hepatic, splenic, and renal injury to include gastrointestinal, pulmonary, and neurological manifestations(76,79), while severe disease is marked by a hemorrhagic syndrome now better characterized through clinical features such as, laboratory biomarkers, and mechanistic insights into vascular leakage and coagulopathy.

Viral persistence in survivors, documented in immune-privileged sites such as the eye(80), CNS, and testes as well as organs like the liver and placenta, is increasingly characterized through longitudinal cohorts, targeted sampling, and molecular and immunologic profiling. A diverse array of animal models—including rodents, ferrets, humanized mice, and non-human primates—supports countermeasure evaluation, with NHP intensive-care models now enabling more controlled, clinically relevant studies at least for model pathogens.

2. Key Findings, Emerging Trends, and Data Gap

Recent research has clarified how infection initiates at mucosal or cutaneous entry points, spreads through macrophages and dendritic cells, and progresses to systemic organ involvement accompanied by strong but dysregulated immune responses. Yet determinants of tissue tropism, duration of persistence, and correlates of clearance versus recrudescence remain incompletely understood. However standardized biomarker panels and predictive thresholds remain lacking(81).

Filoviral proteins such as VP35, VP24, VP40, and GP are well characterized for their roles in immune evasion, while the diversification of animal models—including ferrets, humanized mice, and collaborative cross strains—complements traditional rodent and non-human primate systems(80,82–84). Complementing these systems, new approach methodologies such as organoids, organ-on-chip platforms, and organotypic cultures incorporating immune components offer human-relevant tools to investigate persistence, immune-privileged tissues, survivor outcomes, and patient-specific responses, strengthening the bridge between mechanistic insights and clinical translation. This system will also help avoiding the systematic use of animal models(85–87).

Also, the field still lacks an animal model that reliably recapitulates either long-term viral persistence or episodes of recrudescence since actual models are 100% lethal. These two issues are deeply intertwined, without a model capable of maintaining low-level infection over time, it remains difficult to study the mechanisms that trigger viral reactivation. Extending follow-up of surviving animals in high-containment facilities may eventually reveal such models, but this approach is logistically demanding, which reinforced the value of developing organoid and microphysiological systems specifically tailored to immune-privileged sites such as the eye, CNS, and testes.

Alongside this central gap, additional research needs persist, including the development of robust tools for neglected filoviruses (Sudan, Bundibugyo, Taï Forest, and Ravn viruses), clarification of the cytokine programs and cell types that distinguish survival from severe disease, identification of transcriptional and chromatin regulators shaping host responses, improved understanding of early disease stages including incubation and initial immune sensing, and deeper exploration of co-infections and their impact on disease severity and treatment outcomes.

3. Operational Assets

Across high-containment networks worldwide, substantial capacity exists to study filoviruses. Yet, critical gaps remain in how these infrastructures connect and translate findings into actionable countermeasures. In Europe, BSL-4 laboratories in France(88), Italy, Hungary, and Sweden—members of ERINHA, the EU research infrastructure dedicated to the study of risk group 4 (RG4) pathogens—combine advanced omics, standardized SOPs, and a broad range of animal and translational models(89), while the UK contributes deep experience with RG4 pathogens and persistence studies. The United States adds large-scale analytical pipelines, CRISPR-based perturbation platforms, spatial multi-omics, and multiple NHP-capable BSL-4 facilities, Canada’s National Microbiology Laboratory integrates CL-3/CL-4 research with deployable outbreak response units and Australia’s CSIRO further strengthens global BSL-4 capacity, while initiatives such as the Global BioLabs database, WHO Collaborating Centres, and GOARN offer coordination, training, and surge support.

Africa provides the essential clinical anchor: survivor cohorts(90), national reference laboratories(91–94), and regional biobanks generate the longitudinal samples and real-time data needed to validate persistence and recrudescence models—resources that no high-containment laboratory can produce alone.

Despite this extensive infrastructure, several structural weaknesses persist. The most pressing is the absence of internationally harmonized standards and reference reagents, without which data generated across laboratories remain difficult to compare. Even with aligned SOPs, biological assays require internal standards to control inherent variability, and global stocks of reference materials are limited. The field still lacks reliable models of long-term persistence and recrudescence, a gap that neither current animal models nor short-term high-containment studies fully address. Survivor cohorts and African biobanks partially fill this void, but sustained investment in organoid and microphysiological systems tailored to

immune-privileged tissues is needed to complement in vivo work. Finally, global coordination mechanisms—such as WHOAFIRM’s long-term research agenda—exist but remain underutilized, and rapid data-sharing frameworks are still unevenly implemented across regions.

4. Key challenges

Despite major scientific advances, physiopathology and disease models about filovirus still face several structural challenges that limit progress toward fully predictive models and actionable countermeasures. High-containment capacity remains unevenly distributed: while Europe, North America, Australia, and the UK host BSL-4/BSL-3 laboratories equipped with advanced omics and CRISPR platforms, endemic regions like Africa lack equivalent infrastructure, which unable local investigation on persistence, recrudescence, and neglected filoviruses. Logistical barriers further complicate research, as safe collection and transport of high-risk specimens—ocular fluid, semen, CSF—require specialized kits, PPE, and cold-chain systems that are difficult to sustain during outbreaks, making survivor-cohort models hard to scale beyond a few well-supported sites. Regulatory frameworks governing international sample transfer, while essential for biosafety and traceability, often slow the circulation of materials needed for multicenter studies, particularly between endemic countries and reference laboratories. At the same time, data remain fragmented across survivor cohorts, animal models, and organoid systems, with limited harmonization of endpoints or eCRFs, hindering interoperability and slowing translation into outbreak-relevant insights. Scientifically, the field still lacks validated animal models for several filoviruses, and many existing rodent models rely on host-adapted strains whose mutations and pathogenic consequences remain poorly understood. Crucially, no current model reliably reproduces long-term infection or recrudescence in immune-privileged sites, and universally lethal systems fail to capture the heterogeneity of human disease. More tractable, ethically sustainable models—alongside deeper investigation of cytokine programs, co-infections, and gene-regulatory mechanisms—are needed to bridge the gap between experimental systems and the complex physiopathology observed in patients.

5. Strategic Objectives

Short term (0–12 months) — priorities and deliverables

- **Set up coordination:** Identify and connect existing labs, survivor cohorts, and networks
- Define a minimal common framework for animal studies: Finalize basic ethical approvals and develop shared SOP elements (sampling procedures, sample types, storage conditions, metadata requirements) to ensure cross-laboratory comparability without imposing a single harmonised protocol.
- **Improve collaboration** between clinical researchers and translational scientists
- Strengthen biomarker mapping
- Begin standardized collection of clinical and laboratory data to characterize hemorrhagic syndromes (coagulation profiles, endothelial markers) and persistence in survivors (ocular fluid, semen, CSF), to ensure harmonized protocols across sites

- Prepare ethical pipelines for sample access: Pre negotiate rapid, ethical, and harmonised access pathways for clinical samples and contemporary isolates, including clauses for secondary use in vaccine/therapeutic protocols.
- Support and structure local biobanks: Reinforce governance, quality control, and sustainability of African biobanks to ensure availability of high-quality materials during and between outbreaks.

Medium term (1-5 years) priorities and deliverables

- **Validate models:** Strengthen animal models and new approach methodologies (organoids, organ-on-chip) to study persistence, recrudescence, and immune dysregulation
- **Develop neglected filovirus tools:** Create reagents and models for neglected filovirus (Sudan, Marburg, Tai Forest, Bundibugyo viruses)
- **Integrate data systems:** Harmonize clinical, laboratory, and cohort data using shared standards to improve interoperability
- **Capacity building:** Train local teams in biosafety, sample handling, and data management; reinforce African reference labs
- Advance physiopathologic studies of host response (immune activation, endothelial dysfunction, coagulation cascades) to identify novel therapeutic targets and validate them in translational models
- **Cross-validate advanced models with transcriptomics:** Use transcriptomic and spatial multiomics data to validate organoids, organonchip systems, and human tissue studies conducted in highcontainment settings

Long term (+5 years) priorities and deliverables

- **Sustain networks:** Maintain standing outbreak-ready platforms linking African clinics with EU/US labs for rapid activation
- **Policy and equity frameworks:** Ensure equitable access to reagents, data, and funding; support local manufacturing of kits and reagents
- **Predictive tools and interventions–:** Establish standardized biomarker panels and thresholds to predict hemorrhagic progression and persistence risk, enabling early intervention and personalized therapeutic strategies
- **Community trust:** Continue survivor follow-up programs with psychosocial support and transparent return of results to reinforce engagement

Therapeutics

1. Thematic and state of knowledge

Current antiviral strategies against filoviruses span monoclonal antibodies, small-molecule antivirals, combination regimens, host-directed therapies, and optimized supportive care, yet major gaps remain across all categories.

Antiviral : Monoclonal Antibodies (mAbs) :

- 2 mAbs are FDA-approved for EBOV (**REGN-EB3/Inmazeb** and **mAb114/Ebanga**) (95,96)
- **MBP134** is in development for SUDV. Although, in nonclinical studies, **MBP134** has been shown to **bind to the glycoproteins of multiple Orthoebolaviruses** and to **confer protective efficacy** in several animal models, including **EVD, SVD, and BDBV disease**. It was not developed for EBOV given the availability of already approved treatments.
- **MBP091** is the lead candidate for MARV, tested in animal models. **MBP091** was **made available and used** under the **PARTNERS** trial framework in Rwanda, in 2024 during the MARV outbreak
- **Despite progress, no “pan-filovirus” antibody exists, and cross-species coverage remains incomplete.**

Classical antivirals (small molecules):

- **Remdesivir** is the most advanced candidate, with extensive use in COVID-19 and filovirus outbreaks (including Rwanda 2024). It shows activity in nonhuman primate models and is considered standard of care in some outbreak settings. Its requirement for intravenous administration represents a limitation on remdesivir’s use
- **Favipiravir** data are, at this stage, weak: oral administration showed no efficacy in a 2018 USAMRIID study, while IV formulations demonstrated partial protection against MARV challenge. Dose and formulation remain unresolved. Additional evidence on safety could be drawn from its approved use for influenza (in Japan since 2014), as well as from its emergency or conditional use during COVID-19 in countries such as India, Russia, and Indonesia. These data may help contextualize its safety profile, even though their relevance to filovirus disease remains uncertain.
- **Obeldesivir** – oral prodrug derived from remdesivir’s parent nucleoside- has shown promise as an oral postexposure prophylaxis in nonhuman primates, with potential applications for both MARV and SUDV but has not been tested for treatment. Given its similarity to remdesivir, its oral route of administration makes it a particularly attractive candidate for further development.

Combination Strategies: Combination regimens (e.g., remdesivir + monoclonal antibodies) have already been used in the field, but systematic data remains limited.

- Strong interest in pairing mAbs with small molecules
- Preclinical synergy observed, but no robust clinical data yet. (97)

- Safety should be considered as acceptable based on COVID-19 experience combining antivirals and antibodies.

Host-Directed Therapies:

- Corticosteroids and sepsis-like interventions have been tested but remain unproven
- Retrospective analyses suggest possible benefit from anti-mediator therapies (anti-TNF, anti-IL1, TLR4 antagonists), but evidence is limited.
- In addition, early studies of host-directed anticoagulant strategies showed partial protection. For example, the tissue factor pathway inhibitor rNAPc2 achieved approximately 33% survival in a nonhuman primate model of EBOVbola viru infection. Subsequent discussions with the license holder suggested that the drug may have been underdosed, as the maximal effective dose had been established in healthy animals rather than in virally challenged models. These findings highlight that modulation of coagulation pathways may have potential but remains insufficiently explored

Supportive Care: Universally recognized as the backbone of treatment(98).

- Standardized supportive care reduces case fatality rates dramatically (from >70% to <40%).
- WHO guidelines are being updated in 2026 with opportunities to define a research agenda for high-value interventions (fluid resuscitation, renal protection, oxygen delivery, infection control). This context could allow the evaluation of adjunctive interventions—such as the role of corticosteroids or the optimal duration of antiviral therapy—thereby broadening the scope of clinical study.

Trials and Protocols:

- The **PREVAIL II** and **PALM** clinical trials provided complementary evidence on therapeutic approaches against EVD:
 - **PREVAIL II:** ZMapp + optimized standard of care (pSOC) vs standard of care alone (oSOC). Mortality reduced to 22% vs 37%, with 91% likelihood ZMapp was superior
 - **PALM:** ZMapp used as the anchor arm. Mortality was reduced in the Inmazeb (**REGNEB3**) and Ebanga (**mAb114**) arms relative to ZMapp; remdesivir showed comparable outcomes to ZMapp before its arm was discontinued(99)
- **PARTNERS** Protocols provide a single adaptive, multi-arm platform trial framework across filoviruses (EBOV, SUDV, MARV). This design allows simultaneous testing of multiple candidates, harmonization across countries, and pooling of data across outbreaks.

Placebo-controlled designs should be reconsidered in some filovirus outbreaks, particularly in cases where a licensed treatment is available. In the **PARTNERS** framework, patients with **EBOV** systematically receive monoclonal antibodies, whereas in non-EVD outbreaks, a small proportion of participants may be randomised to receive optimised supportive care alone if all control allocations align. However, the acceptability of SoC-only arms varies by country and may pose operational challenges for trial implementation, as well as raising ethical issues.

Except for EBOV, randomization arms should always include remdesivir against mAb alone or in combination with small antiviral molecules.

2. Key Findings, Emerging Trends, and Data Gap

MBP134 and **MBP091** (respectively) are prioritized for SUDV and MARV based on preclinical data and feasibility. But there is limited clinical efficacy data for SUDV and MARV: no Phase III evidence is available, and current efficacy signals derive primarily from nonclinical studies and early phase human safety data. These candidates therefore require confirmation of efficacy in humans through randomized controlled trials. For **favipiravir**, the evidence remains weak and inconsistent, particularly regarding dosing and formulation for filoviruses. Additional data are needed not only for favipiravir but also for other small molecule antivirals, including a better understanding of how monoclonal antibodies may influence viral persistence and the risk of relapse(100). Although favipiravir has an established safety record in other indications—such as influenza (approved by the Japanese regulatory agency in 2014) and its use during COVID19 in countries including India, Russia, and Indonesia—no filovirus-specific safety or efficacy data exist. Priority should therefore be placed on supporting dose finding studies and generating clinical evidence in outbreak settings.

There is still an absence of an universal monoclonal antibody capable of covering all filoviruses, leaving significant gaps for both orthoebolaviruses and orthomarburgviruses. To date, MBP134 is the closest candidate and should be prioritized in all interventional protocols.

High production costs of monoclonal antibodies, raising major issues for large scale manufacturing, sustainable financing, and the need to engage additional funders early in the process. This also raises the broader question of whether developing new mAbs is realistic without parallel work on affordability and access models.

Combination therapies: Preclinical evidence for synergy is extremely limited, with only one study evaluating a variant of MBP134 in combination with remdesivir and no available data for MBP091. While experience from COVID-19 suggests that mAb–antiviral combinations can be well tolerated, no filovirus specific safety data exist to date. Observational data from settings where such combinations have been used (e.g., Rwanda) may provide additional insights, but systematic evaluation of dosing, timing, and safety in outbreak conditions remains lacking.

Position of remdesivir: In the event of future outbreaks of EBOV, remdesivir should now probably be considered the standard, and future trials should be based on this assumption (no randomization arm without offering remdesivir). Key uncertainties remain, including **optimal treatment duration** and whether these questions **require formal clinical evaluation. Safety has been extensively assessed in COVID-19 era.**

Regulatory and operational constraints continue to slow trial initiation. Maintaining operational African partners between outbreaks is essential to ensure readiness. Launching a trial at the first detected cases remains challenging due to PI availability, regulatory approvals, and logistics. “Expanded access” protocols have been valuable for generating safety data and may remain an important tool.

Community engagement must be immediate and embedded from the very start of the trial. Engagement should focus on dialogue around uncertainties, not only on building trust.

Post trial access must be planned in parallel with trial implementation, not as a downstream activity. This includes anticipating procurement pathways, financing, and regulatory alignment

3. Operational Assets

Several existing projects, platforms, and networks established during past filovirus outbreaks could be rapidly leveraged or scaled to accelerate clinical research and access to countermeasures. For example, the PALM trial infrastructure—comprising sites and teams trained in IV monoclonal antibody stockage, reconstitution and delivery, harmonized SOPs, real-time data capture systems, and safety procedures—remains a key asset in the DRC and can be reactivated quickly for EBOV. It also provides a practical mentorship hub to transfer operational expertise to SUDV and MARV trial sites. The PARTNERS protocol, already approved and activated in Rwanda during the 2024 MARV outbreak (with around 10 patients enrolled), and submitted in Tanzania and the DRC, offers a ready-to-deploy therapeutic research platform.

Regional research hubs such as INRB (DRC), Makerere University (Uganda), and several National Public Health Institutes across West and East Africa provide PCR capacity, cold chain and pharmacy staging, community engagement teams, and established regulatory pathways. WHO and Africa CDC further support regulatory facilitation, technical guidance, and crossborder logistics coordination.

However, persistent gaps—outdated guidelines, limited regulatory capacity, and coordination between ethics committees and regulatory authorities, insufficient funding, lack of trained PI identification and fragile site infrastructure—still constrain the rapid and interoperable deployment of these assets during emergencies.

4. Key challenges

Filovirus therapeutics continue to face structural challenges that slow progress from discovery to real-world impact. Outbreaks remain unpredictable and often too short to support adequately powered trials, while site readiness and regulatory activation still vary widely across countries, which create delays. Ethics and approval processes—though necessary—remain a major bottleneck and underscore the need for earlier engagement with regional regulatory bodies such as AVAREF or AMRH to streamline protocol review. Community engagement adds another layer of complexity: rather than aiming for full trust, which is rarely achievable in emergency contexts, the priority is to build durable channels for dialogue that allow concerns to be raised transparently and support participation without coercion before or in between the occurrence of outbreaks.

Scientifically, the evidence base remains thin: combination therapies are underexplored, favipiravir requires dose-finding, and efficacy data and both small molecules and monoclonal antibodies carry risks of viral escape, persistence, or relapse. Treatment duration is still not assessed and specified. Species-specific differences continue to limit translatability, reinforcing

the need for host-directed approaches and for evaluating promising candidates such as obeldesivir in therapeutic—not only prophylactic—settings, including among children and pregnant women.

Finally, access remains a persistent barrier: high production costs, cold-chain requirements, and the absence of post-trial access pathways restrict the deployment of mAbs and IV antivirals in the very settings where they are most needed. Ensuring equitable access will require planning for manufacturing, PK/PD studies and early completion of developmental and reproductive (DART) studies,, and regulatory pathways *before* large trials begin, not after efficacy results emerge.

5. Strategic Objectives

Short term (0–12 months) — priorities and deliverables

- Move from protocol readiness to active enrollment by early planning and implantation activities
- Set up annexes, ethics approvals, PI identification and logistics (including pharmacy) for MARV and SUDV by leveraging existing work—such as previously approved PARTNERS protocols, established trial sites, and regional regulatory networks—so that trials can be activated immediately when the next outbreak occurs
- Secure supply chains: Preposition MBP091 and MBP 134 and remdesivir in outbreakprone regions
- Strengthen supportive care bundles (fluids, oxygen, IPC) to reduce mortality while therapeutics are tested
- **Integrate access considerations upfront to ensure** that pathways for availability, delivery, and affordability are planned from the beginning rather than addressed only at the end of trials
- Deploy strong, early community engagement strategies, not only to support ethical practice but to ensure rapid presentation to care, which is essential for therapeutic efficacy (as demonstrated in the PALM trial). Engagement should: be co designed with communities, be implemented immediately alongside trial rollout, clearly communicate the purpose and benefits of research, counter fears and misconceptions, be adequately budgeted and prepared in advance.
- **Engage governmental, regulatory, and institutional authorities** at local, national, and regional levels to strengthen trust, alignment, and legitimacy across the full ecosystem of actors—not only community groups.
- **Build and mobilize incountry social science capacity**, drawing on existing networks including local academic network to ensure rapid, crosscutting support across trials and therapeutic landscapes, rather than relying on a single social scientist per study.

Medium term (1-5 years) priorities and deliverables

- Generate and consolidate clinical evidence across outbreaks in all populations including children and women in child-bearing age or pregnant and lactating women.

- Emphasize the development of panfilovirus molecules (remdesivir, obeldesivir, MBP134) and strategies including combinations.
- Support cohorts of treated patients to evaluate the impact of treatments and host-directed therapies on viral persistence and relapse prevention.
- **Expand trial networks:** Scale beyond anchor sites (DRC, Uganda, Rwanda...) to additional national institutes with lab, pharmacies, and cold chain capacity
- Negotiate supply and affordability pathways for mAbs and antivirals
- **Continue strengthening national regulatory and ethics capacity**, ensuring rapid, high quality review processes and trust generating oversight

Long term (+5 years) priorities and deliverables

- Validated therapeutics integrated into WHO and national guidelines
- Therapeutic stockpiles incorporated in every at risk country
- **Broader therapeutic classes** (host directed therapies, new antivirals) added once core candidates are validated

Vaccine

1. Thematic and state of knowledge

Clinical development pathways and evaluation platforms

Vaccine development for filoviruses is an area of active research and important progress, but with significant gaps that still exist. Key progress relates to the licensure of two EBOV vaccines : the single-dose recombinant VSV-based vaccine (ERVEBO, rVSV Δ G-ZEBOV-GP) and the two-dose heterologous vaccine regimen consisting on an Adenovirus 26 recombinant vaccine administered as dose one (Zabdeno, Ad26.ZEBOV), followed by a Modified Vaccinia Ankara recombinant vaccine administered as dose two (Mvabea, MVA-BN-Filo). Both products were licensed and received WHO prequalification. However, following the discontinuation of manufacturing of the Ad26.ZEBOV and MVA-BN-Filo regimen when the developer chose to exit the vaccine space, ERVEBO is currently the only EBOV vaccine widely available. Reliance on a single vaccine supplier represents a potential vulnerability for global preparedness and outbreak response and underscores the need to advance additional EBOV vaccine candidates toward licensure.

In contrast to EBOV, vaccine candidates targeting other filoviruses, such as SUDV and MARV, remain at early to intermediate stages of clinical development. However, regulatory experience gained through EBOV vaccine licensure, across multiple development and approval pathways, provides established approaches that can be leveraged, including immunobridging strategies, to support the clinical development and licensure of vaccines targeting these two filoviruses.

Protective immune mechanisms and correlates of protection

Filovirus vaccine development is constrained by an incomplete understanding of the immune mechanisms that confer protection and the immune parameters that best predict vaccine efficacy. In particular, it remains unclear whether survival from filovirus disease induces

protection against subsequent infection with the same filovirus and, if so, how durable such protective immunity is. Defining whether glycoprotein (GP)-specific IgG titers can serve as a reliable proxy for long-term vaccine efficacy, or whether functional immune assays are required, is therefore a critical challenge.

The demonstrated clinical success of passive immunotherapy confirms that antibodies can mediate protection against filovirus infection, as specialized cocktails of anti-filovirus monoclonal antibodies are known to be effective. However, this does not resolve whether immunoassays focused solely on antibody quantity, or even on defined functional profiles, are sufficient to establish a robust and measurable correlate of protection. Moreover, it remains uncertain whether a single correlate of protection can be applied across all filoviruses or whether distinct viruses impose unique immunological requirements. Antibody cross-reactivity between GPs of different filoviruses further complicates the identification of specific immune readouts suitable for use as correlates of protection.

Evidence from both clinical and preclinical studies illustrates this complexity. Dose-ranging nonhuman primate studies of the licensed rVSV Δ G-ZEBOV-GP vaccine demonstrate that EBOV-specific IgG and neutralizing antibodies correlate with protection across a wide range of vaccine doses, supporting a central role for humoral immunity. However, these studies have not defined a robust, prospectively validated protective threshold, despite exploratory post hoc modeling of antibody cutoffs. In humans, early-phase clinical studies of a bivalent ChAdOx1 EBOV-SUDV vaccine have reported induction of binding antibodies, while neutralizing responses to SUDV were limited. However, **clinical efficacy has not yet been demonstrated**, and these immunogenicity findings **should not be directly compared** with protection/correlate data derived from Ervebo NHP studies. Despite an incomplete understanding of the mechanisms of protection for MARV vaccines, evidence from preclinical studies suggest that the level of anti-GP IgG is a better predictor of survival against lethal challenge than neutralizing activity, as observed for VSV based and recombinant GP based vaccines, which aligns with the ability of the non-neutralizing mAb MR228 to confer protection after passive transfer in mice and guinea pigs.

Beyond humoral immunity, analyses from a phase 2 trial of the Ad26.ZEBOV and MVA-BN-Filo regimen indicate that Ebola vaccination induces durable EBOV-specific CD8⁺ T-cell responses with proliferative and cytotoxic phenotypes, and that early innate inflammatory responses are associated with the functional quality of EBOV-specific CD8⁺ T-cell immunity. Unfortunately, it is not known what role these CD8⁺ T-cells play in the context of efficacy in humans as relevant clinical data is missing. Collectively, these findings suggest that correlates of protection for filovirus vaccines are likely multifactorial and filovirus-specific, integrating quantitative and qualitative antibody features with cellular and innate immune components. Defining such integrated, functionally relevant correlates remains a critical priority to enable immunobridging, support multivalent vaccine development, and improve comparability across platforms and pathogens.

Durability of vaccine-induced immunity and immune memory

The persistence of vaccine-induced protection remains a central scientific priority. Nonhuman primate studies of the licensed rVSVΔG-ZEBOV-GP vaccine provide important insights into the durability of vaccine-induced immunity. Although vaccination induces robust and sustained ZEBOV-GP-specific IgG and neutralizing antibody responses, protection against lethal EBOV challenge appears to be time-dependent. High levels of protection are maintained up to approximately 8 months post-vaccination, whereas a reduction is observed around 12 months, despite persistence of measurable antibody titers. These findings suggest that circulating antibodies alone may be insufficient to ensure long-term protection and underscore the need to better characterize immune waning kinetics and qualitative immune attributes.

Recent nonhuman primate studies of a VSV-based Sudan virus (SUDV) vaccine further highlight the complexity of durability across filoviruses. A single-dose VSV-SUDV vaccine confers rapid protection against lethal SUDV challenge, whereas an EBOV-based VSV vaccine elicits cross-reactive antibodies without protection, underscoring the limitations of cross-reactivity and the need for species-specific vaccines and related species-specific assays supporting development. These observations furthermore highlight complications in development of multivalent filovirus vaccines or vaccination strategies eliciting multivalent efficacy profiles using several monovalent vaccines. Modelling analyses from the PREVAC phase 2 trial show that EBOV vaccine-induced antibody responses wane to some extent over time, with platform-specific kinetics and a slower decline following rVSVΔG-ZEBOV-GP vaccination. The PREVAC trial 5-year immunogenicity results for both vaccines in adults and children will be available in 2026. Antibody persistence varies by age, geography, sex, and baseline immunity, highlighting the need to better link immune waning with memory recall and clinical protection to inform booster strategies. Further research is required to establish practical methods to ensure efficacy in previously vaccinated individuals at imminent risk of exposure and to address the complex immune profiles in the context of multivalent filovirus vaccination or exposure.

2. Key Findings, Emerging Trends, and Data Gap

Important progress has been achieved in filovirus vaccine development, particularly with the licensure of EBOV vaccines and the establishment of clinical and regulatory pathways that can be leveraged for other filoviruses. However, reliance on a single widely available EBOV vaccine highlights a vulnerability for preparedness and outbreak response.

Vaccine candidates for SUDV and MARV remain at early to intermediate stages of clinical development, with no licensed products to date. While Phase 1 and 2 studies have generated immunogenicity data, clinical efficacy has not yet been demonstrated, and licensure-enabling evidence is lacking.

Current approaches increasingly rely on immunobridging and standardized immunogenicity assessments, supported by WHO International Standards and global laboratory networks. At the same time, available evidence indicates that immune protection is complex and likely involves both humoral and cellular responses.

However, major data gaps remain. There is no validated correlate of protection or defined immune threshold, and it remains unclear whether antibody responses alone are sufficient to predict protection. The durability of vaccine-induced immunity is not fully understood, with evidence suggesting that antibody persistence does not necessarily ensure long-term protection.

Additional uncertainties relate to cross-reactivity and cross-protection between filoviruses, which complicate the development of multivalent vaccine strategies. Data are also limited for specific populations, including children, pregnant women, and individuals with comorbidities, as well as for previously vaccinated individuals at risk of re-exposure.

Finally, operational gaps persist, particularly in access to biological samples and reference reagents, which remain limited and constrain assay development, standardization, and comparability across studies.

3. Operational Assets

Clinical trial platforms for outbreak-ready vaccine evaluation

Several MARV and SUDV vaccine candidates have generated promising Phase 1 data and are progressing through Phase 2 clinical development, although no vaccines are yet licensed. In this context, outbreak-capable clinical trial infrastructures represent a critical enabling resource for timely vaccine evaluation in emergency settings.

The SOLIDARITY trial is a Phase 2/3 cluster-randomized ring vaccination study designed for rapid deployment during Filovirus outbreaks, using immediate versus delayed vaccination of contacts and contacts of contacts of laboratory-confirmed cases. The platform was activated during the 2022 Sudan virus outbreak in Uganda as the Tokomeza trial, although enrollment did not occur before outbreak resolution, and was reactivated in January 2025 during a subsequent outbreak. In 2025, the Tokomeza trial enrolled 131 participants before outbreak termination, with immunogenicity follow-up ongoing in a subset of participants.

Building on this experience, the SOLIDARITY platform provides a harmonized, regulator-approved, clinical trial framework that can be leveraged and scaled across multiple at-risk countries, supporting rapid trial activation, interoperable data generation, and regulatory-aligned evaluation of Filovirus vaccine candidates, including SUDV and MARV, during outbreak responses.

Reference materials and infrastructure to Support Vaccine Development and Immunogenicity Assessment

WHO International Standards (IS) are available at www.nibsc.org to support vaccine development against EBOV (15/262), SUDV (24/124) and MARV (23/146). Evaluated through large multi-center collaborative studies(101), these calibrants increase the harmonization of the quantification of binding and neutralizing antibody activity in human serum/plasma, by allowing results between different studies to be reported in the same unitage, the International Units (IU). These key operational assets therefore facilitate comparison of humoral response induced by different vaccine candidates and support the identification of correlates of protection.

Building on the WHO International Reference Panel for EBOV antibodies (16/344), comprehensive reference panels composed of a large selection of characterized human plasma/sera of varying potencies and relevant negative controls, would further support assay development, validation, technology transfer and performance monitoring, but also the development of secondary calibrant. Sourcing these samples remains extremely challenging, particularly for filoviruses, due to limited access to sufficient volume of clinical samples from vaccinees or convalescent individuals. The Biospecimen Sourcing Initiative (BSI), created by the Coalition for Epidemic Preparedness Innovations (CEPI) in partnership with PATH aligns with the Pandemic Agreement and aims to address this bottle neck and increase collaborative work between local clinical settings, national regulators, testing laboratories and reference material producers to expedite the collection and fair distribution of samples obtained from outbreak survivors. In parallel, the Uganda Virus Research Institute leads the development and technology transfer of serological assays for filoviruses, as part of the CEPI Centralized Laboratory Network (CLN), a global consortium of organizations providing testing capacity to support vaccine evaluation through clinical trials. The reagent resources generated through the BSI and CLN projects could be further leveraged to maximize the use of reference reagents across vaccine development programs and minimize duplication of effort.

Additional reagents such as monoclonal antibodies, antiserum, inactivated viruses and recombinant antigens are available through several repositories or platforms including www.beiresources.org and www.european-virus-archive.com, and commercially. This offer could be enriched by panels of GPs and pseudotyped viruses covering different strains to develop assays that further evaluate the breadth and cross reactivity of vaccine induced immunity. Pseudotyped viruses are powerful tools to quantify neutralizing activity for the development of vaccines and therapeutic, and for seroepidemiological studies and have been produced successfully for(102). These reagents can be produced rapidly and safely at containment level 2 using available GP sequences and do not require complex virus isolation from human clinical samples. As such, they are versatile and reliable reagents which could be deployed in a timely manner during outbreaks. These panels of reagents would ideally be regularly updated to represent previous and currently circulating strains.

Operational challenges often persist in sourcing and accessing these reagents and further effort should be made to strengthen networks between infrastructures, create local distribution hubs, map reagent need, pre-establish legal agreements and streamline supply processes, to maximize rapid access and help build research capacity in countries the most affected by filoviruses outbreaks.

4. Key challenges

Filovirus vaccine development and deployment continue to face several interrelated challenges across scientific, regulatory, and operational domains.

From a scientific perspective, major uncertainties remain regarding correlates of protection, the durability of vaccine-induced immunity, and the respective roles of humoral and cellular responses. The absence of validated immune thresholds limits the use of immunobridging approaches and complicates the design and regulatory evaluation of new vaccine candidates,

particularly for SUDV and MARV. In addition, species-specific immune responses and limited cross-protection between filoviruses constrain the development of multivalent or pan-filovirus vaccine strategies.

From a development and regulatory standpoint, vaccine pipelines for SUDV and MARV remain at early to intermediate stages, with no licensed products currently available. Regulatory fragmentation across countries continues to delay trial initiation and deployment, despite the existence of mechanisms such as WHO Emergency Use Listing (EUL) and regional reliance pathways (e.g. AVAREF), which are not yet systematically embedded in preparedness planning. Early alignment on immunogenicity endpoints, assay standardization, and regulatory expectations remains insufficient.

Operationally, dependence on a limited number of manufacturers, constrained production capacity, and complex cold-chain and logistics requirements limit timely vaccine availability, particularly in resource-constrained and remote settings. Persistent challenges in accessing critical reagents and biological samples further slow assay development, standardization, and comparability across studies.

Finally, challenges related to uptake and implementation remain significant. Vaccine acceptance is strongly influenced by trust, perceived risk, and quality of engagement, while delays in community acceptance can limit the effectiveness of vaccination strategies during outbreaks. In addition, important evidence gaps persist for key at-risk populations, including children, pregnant women, and individuals with comorbidities, which may delay equitable access to vaccination and the development of context-appropriate recommendations.

5. Strategic Objectives

Short term (0–12 months)

1. Advance the clinical development of SUDV and MARV vaccine candidates toward licensure, leveraging EBOV licensure experience to guide development pathways across platforms and candidates.
2. Address critical gaps in immune correlates of protection (thresholds and harmonised assays), functional immunity (neutralisation and Fc-mediated effector functions, where relevant), and durability of immunity (persistence and kinetics of responses, including early predictors of durability).
3. Ensure outbreak-ready activation of the SOLIDARITY platform and complete immunogenicity follow-up in Tokomeza trial.
4. Align emergency and reliance regulatory pathways through coordinated engagement of regulators, ethics committees, and trial stakeholders, and strengthen immediate operational readiness (supply planning, cold chain, surge capacity).
5. Design clinical trials to include all at-risk populations, enabling rapid collection of age- and pregnancy-disaggregated data and early, continuous community engagement to support culturally appropriate participation in research.

Medium term (1–3 years)

1. Implement licensure-enabling clinical development pathways for prioritized SUDV and MARV vaccine candidates, including coordinated Phase 2–3 trial strategies, immune-bridging approaches, and reliance-based regulatory procedures informed by EBOV licensure precedents.
2. Support clinical development of additional vaccine(s) for EBOV in order to minimize the risk of a single product/single manufacturer for a key public health threat and explore options for assessing efficacy with Regulatory Agencies.
3. Validate filovirus-specific immune correlates of protection and durability benchmarks by integrating harmonized humoral, cellular, and innate immune data from multi-country clinical studies, supported where relevant by non-clinical models, to inform booster, dose-optimization, and platform-selection strategies.
4. Expand and operationalize the SOLIDARITY platform across additional at-risk countries, with standardized protocols.
5. Encourage reagents and clinical samples sharing through repositories to generate additional reference reagents that support assay development, validation and calibration against the established WHO International Standards.
6. Advance regional regulatory harmonization through systematic use of reliance mechanisms (e.g. WHO EUL, AVAREF), early alignment on immunogenicity endpoints and assay standards, and strengthened national regulatory and pharmacovigilance capacity.
7. Embed systematic inclusion of vulnerable populations (children, pregnant women, and other high-risk groups) into clinical trials and post-deployment studies, supported by adaptive trial designs, ethical frameworks (e.g. PREVENT), and co-developed, context-specific vaccination strategies.

Long term (3+ years)

1. Achieve and sustain licensure of SUDV and MARV vaccine candidates, and embed platform-based, EBOV-informed development pathways into preparedness planning to enable rapid adaptation, lifecycle management, and deployment of next-generation or multivalent filovirus vaccines.
2. **Embed validated immune correlates of protection and durability benchmarks** into regulatory guidance and policy frameworks to support sustainable licensure and lifecycle management of monovalent first-generation vaccines. Use validated correlates of protection to test feasible strategies to achieve multivalent immunity using first- or next-generation filovirus vaccine products. Assess the feasibility of prophylactic multivalent filovirus immunization (e.g., EBOV+MARV as a single product or as separate vaccines)
3. **Institutionalize outbreak-capable clinical trial, laboratory, and data infrastructures** as standing preparedness assets, with durable governance, financing mechanisms, and equitable global access to reagents and standards.

4. **Institutionalize harmonized regulatory and platform-based approval pathways** within global and regional preparedness planning, enabling rapid authorization, updating, and deployment of filovirus vaccines during outbreaks.
5. **Establish resilient manufacturing and supply ecosystems** for filovirus vaccines, including diversified production capacity, cold-chain resilience, and stockpiling strategies aligned with outbreak-response needs.
6. **Institutionalize equity-by-design approaches across filovirus vaccine R&D, regulation, and deployment**, ensuring affordability, inclusivity, sustained community partnership, and trust before, during, and after outbreaks.

Transversal considerations

Filovirus research must integrate cross-cutting principles that address social, ethical, and systemic challenges to ensure effective, equitable, and sustainable outcomes. These considerations span all research domains—from ecology and diagnostics to therapeutics and vaccines—and require coordinated, multidisciplinary approaches.

1. Social sciences

Filovirus research spans ecology, pathophysiology, diagnostics, therapeutics, and vaccines, yet its impact depends on integrating biological insights with social, behavioral, and governance considerations. Outbreaks emerge from complex human/animal/environment interactions, where local practices, perceptions, and cultural norms directly influence exposure risk. Rapid social investigations provide early guidance, but sustained ethnographic research is essential to capture temporal, social, and contextual variability, informing ethically sound and effective interventions.

Biological studies of host responses, immune activation, endothelial dysfunction, coagulation, and tissue repair, identify therapeutic targets and guide diagnostic development. Because animal models are scarce and ethically sensitive, human samples are often critical for advancing filovirus research. However, collecting these samples requires culturally adapted consent processes and trust-building strategies to ensure ethical and feasible participation. Stigma, mistrust, and fatigue can impede participation across diagnostics, clinical trials, and vaccine studies, directly affecting data quality, uptake, and outbreak control.

Diagnostics, therapeutics, and vaccines face common social constraints: fear, misinformation, and low confidence in authorities limit testing, trial enrollment, and vaccination. Evidence from filovirus outbreaks shows that embedding social scientists and anthropologists into research teams, co-designing protocols with communities, ensuring transparent communication, and involving local leaders substantially improves participation, adherence, and acceptance(103).

This requires a **multi-layered approach** that engages communities, policymakers, and healthcare workers at every stage of the research cycle.

- **Community engagement and participatory design**

- Develop **co-designed frameworks** with affected communities to ensure research aligns with local needs, values, and priorities. This includes involving community leaders, survivors, and civil society organizations in the design of surveillance systems, diagnostic strategies, and clinical trials.
- Implement **social science assessments** to identify barriers to participation, such as stigma, mistrust of healthcare systems, or cultural beliefs about disease transmission. These insights should inform communication strategies and intervention design.
- **Behavioral and anthropological research**
 - Conduct **ethnographic studies** to understand how filovirus outbreaks affect social dynamics
 - Investigate **risk perception and misinformation** to develop targeted communication to promote adherence to public health measures, such as testing, isolation, and vaccination.
 - Study the **psychosocial impact** of filovirus infections on survivors and their families, including long-term mental health effects, social reintegration challenges, and economic consequences. These findings should inform support programs and policy recommendations.
- **Capacity-building and local ownership and foster cross-regional collaboration** among social scientists to share best practices and adapt successful strategies to different cultural and epidemiological settings.

A fully integrated roadmap therefore links ecological surveillance, pathophysiology, diagnostic strategies, therapeutic development, and vaccination through cross-cutting social and governance engagement. Interdisciplinary collaboration ensures that interventions are biologically effective, ethically robust, and socially acceptable, strengthening preparedness and response while addressing the complex interplay of trust, acceptability, and community engagement across all stages of filovirus research

2. Equity and access in filovirus research: an integrated perspective

Equity and access must be central to filovirus research to ensure that scientific advancements benefit all populations, particularly those in low-resource and high-risk settings.

Resource disparities pose a major barrier to equity. Advanced pathophysiological tools (organoids, CRISPR, spatial omics), diagnostics, and laboratory infrastructures are concentrated in high-income settings, while outbreak-prone regions often face limited research capacity. Developing affordable, simplified assays, portable diagnostics, and decentralized platforms, along with equitable funding models that support local laboratories and shared infrastructures, is essential to reduce dependency and ensure timely, context-relevant data generation. Diagnostics should be integrated into national health systems and validated filovirus diagnostics should be available in healthcare facilities, particularly in remote and high-risk areas.

Similar considerations apply to therapeutics and vaccines: prioritizing deployable candidates, ensuring compassionate use frameworks, and designing study protocols adapted to local norms strengthen both access and trust.

Strengthening sustainable financing and manufacturing is crucial, as is establishing long-term financing mechanisms and supporting local manufacturing. Policy and governance frameworks should also promote equitable data and sample sharing by establishing ethically governed biobanking. Furthermore, access equity requires strengthening regulatory harmonisation and advocating for regional and global alignment of regulatory processes, such as the WHO Emergency Use Listing (EUL) and the African Vaccine Regulatory Forum (AVAREF), to accelerate approvals for diagnostics, therapeutics and vaccines.

Vulnerable population (including children, adolescents, pregnant women, people living with HIV, malnourished individuals, and people with disabilities), are often underrepresented in research and face heightened exposure during outbreaks. Equity requires their systematic inclusion across trials, surveillance, and vaccination strategies, guided by ethical frameworks, culturally adapted consent, and context-sensitive engagement. Transparent communication, integration of social and behavioral sciences, and codesign with communities are critical to improving uptake and adherence for diagnostics, clinical trials, therapeutics, and vaccines alike.

Overall, achieving equity in filovirus research demands integrated, interdisciplinary approaches that address structural, social, and operational barriers. Embedding social and behavioral sciences, strengthening local capacities, and aligning research and intervention strategies with community priorities ensure that scientific advances are not only biologically effective but also ethically sound, accessible, and socially acceptable, ultimately enhancing outbreak preparedness and response in the regions most affected.

3. Cross cutting Issues

Across the five working groups, several issues consistently emerged as structural constraints and shared scientific needs. These cross-cutting challenges affect the feasibility, comparability, and impact of filovirus research and preparedness activities across all priority families and their associated CORCs.

- **Survivor cohorts** : Survivors have become central actors in filovirus ecology, physiopathology, and countermeasure development. Virus ecology indicates that survivors may act as secondary reservoirs, capable of reintroducing the virus into human populations. From a physiopathological perspective, there is a need to better understand viral persistence in immune-privileged sites and the mechanisms of recrudescence. In addition, the development of therapeutics, vaccines, and diagnostics depends on well-structured survivor cohorts to validate biomarkers, assess viral clearance, and evaluate medical countermeasures.

Recommendation:

Establish, harmonize, and sustain survivor cohorts through robust ethical frameworks and efficient logistical pipelines.

- Access to samples, biobanking, and regulatory bottlenecks : All working groups identified major constraints in obtaining, storing, and sharing clinical, ecological, and environmental samples. Regulatory delays continue to limit international sample transfers. At the same time, ecological studies require longitudinal wildlife sampling, and countermeasure development depends on access to contemporary isolates and standardized reference materials.

Recommendation:

Develop harmonized, ethical, and rapid mechanisms for sample access and biobanking, particularly in endemic regions.

- Standardization and interoperability of data, protocols, and models : A lack of standardization remains a major barrier across research domains. There is limited availability of internationally validated reference reagents, while sampling and testing protocols vary across studies. In addition, countermeasure development relies on reproducible animal and organoid models, which are not yet sufficiently harmonized.

Recommendations:

Define minimal common frameworks for standard operating procedures (SOPs), metadata, study endpoints, and reference panels to ensure comparability and accelerate translation. Establish pre-negotiated agreements to enable rapid and real-time sharing of surveillance, genomic, and clinical data among ministries of health, research institutions, and international partners.

Conclusion

The five working groups provide a comprehensive overview of the scientific, operational, and societal challenges that continue to shape filovirus research and preparedness. The updated roadmap shows that progress has been substantial across all thematic areas: ecological surveillance has expanded, physiopathology has clarified early infection and immune-evasion mechanisms, countermeasures have advanced with licensed monoclonal antibodies and vaccines, and diagnostic capacity has improved through faster, more deployable tools. These advances have translated into concrete operational gains. Recent responses have been faster, better coordinated, and more effective than in previous decades, with quicker case detection, earlier deployment of mobile laboratories, and accelerated activation of clinical trial platforms and preventive interventions, as highlighted in multiple WHO outbreak reviews.

Yet the working groups also converge on the persistent gaps that still constrain filovirus preparedness—uncertainty around reservoirs, incomplete understanding of viral persistence, limited tools for non-EBOV viruses, uneven laboratory capacity, and the need for harmonised assays and interoperable data systems. Social sciences emerge as an essential integrative component across all groups. They illuminate how human–animal interactions influence spillover risk, how survivors face stigma and barriers to follow-up, and how community perceptions shape the acceptance of diagnostics, vaccines, and therapeutics. They also provide the frameworks needed to sustain engagement, guide communication strategies, and ensure that research and interventions remain grounded in local realities.

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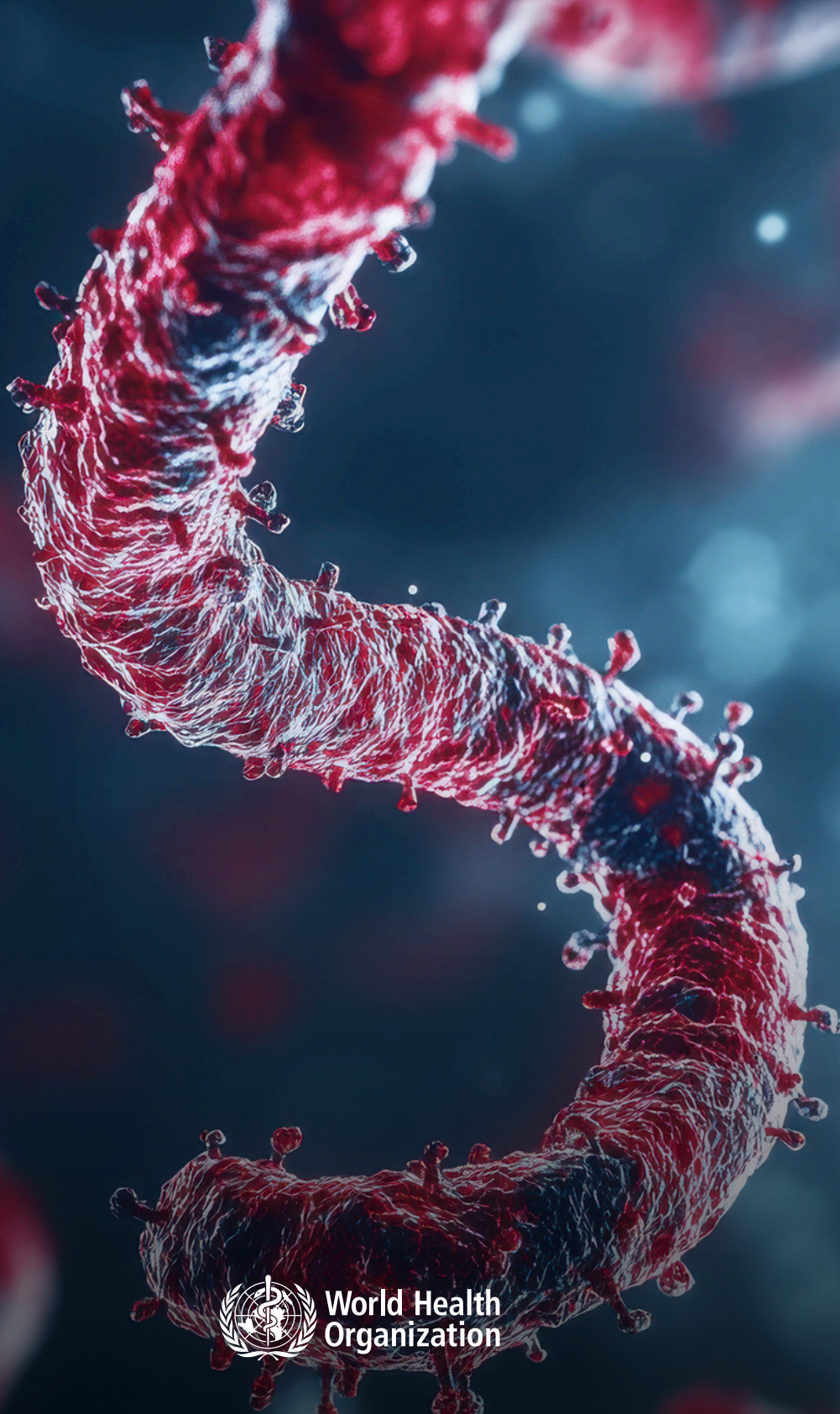
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