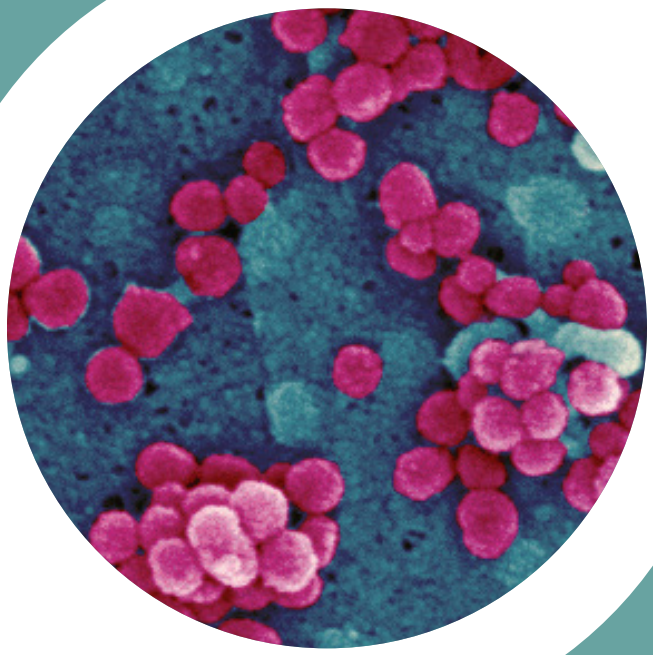
A Research and Development Roadmap for Lassa Fever



2024 Update

CIDRAP

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Contents

Acronyms and Abbreviations

ACEGID	African Center of Excellence for the Genetics of Infectious Diseases
AMRH	African Medicines Regulatory Harmonisation Programme
AVAREF	African Vaccine Regulatory Forum
BSL	Biosafety level
CD8+ T cells	Cytotoxic T lymphocytes that express CD8 glycoproteins on their surface
CEPI	Coalition for Epidemic Preparedness Innovations
CRISPR	Clustered regularly interspaced short palindromic repeats
DART	Development and reproductive toxicity
EBS-LASV	VSV-based vaccine that encodes LASV glycoproteins
EQA	External quality assessment
EVD	Ebola virus disease
GPC	Glycoprotein complex
INO-4500	DNA-based vaccine for LASV developed by Inovio
LASV	Lassa virus
mAb	Monoclonal antibody
MCM	Medical countermeasure
mRNA	Messenger RNA
MV-LASV	Measles-virus vector vaccine for LASV
NHP	Non-human primate
NRA	National regulatory authority
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PPE	Personal protective equipment
R&D	Research and development
RDT	Rapid diagnostic test

RT-PCR	Reverse transcriptase polymerase chain reaction
rVSV	Recombinant vesicular stomatitis virus
rVSVΔG-LASV-GPC	rVSV vaccine for LASV that encodes LASV glycoproteins
SORMAS	Surveillance Outbreak Response Management and Analysis System
TPP	Target product profile
UHC	Universal Health Coverage
VHF	Viral haemorrhagic fever
WAHO	West African Regional Health Organization
WALC	West Africa Lassa Fever Consortium
WHO	World Health Organization
VSV	Vesicular stomatitis virus

Definition of Roadmap Terms

Barriers: Inherent obstacles or technical challenges that may influence the likelihood of success at various stages of coronavirus vaccine development; identifying such barriers helps inform the nature and scope of activities designed to achieve the research and development (R&D) outcomes.

Gaps: Key unresolved issues or limitations in knowledge that are critical to the development of new vaccines and that can be addressed through targeted R&D activities.

Strategic Goals: Long-range high-level research priorities that the roadmap's actions are intended to address during the stated timeframe.

Milestones: Actions deemed necessary to achieve the roadmap's strategic goals; the milestones include target dates for completion and reflect SMART (specific, measurable, achievable, realistic/relevant, and time-sensitive) criteria, to the degree feasible.

Additional Research Priorities: Further topics and issues that are relevant to the achievement of the strategic goals, but are either not high enough priority to be considered milestones or not sufficiently specific or time-bound to be identified with SMART criteria.

Overview

Note: This updated roadmap is an adaptation of an original work titled, "*Lassa Fever Research and Development (R&D) Roadmap: Advanced Draft*" Geneva: World Health Organization (WHO); January 2019 (WHO 2019). Licence: CC BY-NC-SA 3.0 IGO. This adaptation was not created by WHO and WHO is not responsible for the content or accuracy of this adaptation. The original edition shall be the binding and authentic edition.

Roadmap purpose: To provide a 6-year framework for identifying the vision, underpinning strategic goals, and priority areas and activities—from basic research toward advanced development, licensure, manufacture, acceptance and deployment, and assessment—for accelerating the collaborative development of medical countermeasures (MCMs)—diagnostics, therapeutics, and vaccines—against Lassa fever.

Lassa fever is a zoonotic disease caused by Lassa virus (LASV) and is endemic in several West African countries, including Guinea, Liberia, Nigeria, and Sierra Leone. Populations in other countries in West Africa (i.e., Benin, Burkina Faso, Ghana, Côte d'Ivoire, Mali, and Togo) also are at risk for Lassa fever, based on the identification of sporadic cases or outbreaks and serologic surveys demonstrating evidence of prior LASV infection in some people in those areas (Fichet-Calvet 2009, Gibb 2017, Günther 2000, Mylne 2015, Pigott 2017, Yadouleton 2020). LASV exhibits marked genetic heterogeneity. To date, seven distinct lineages of LASV have been identified across West Africa (Figure 1). Strains were traditionally categorized into four distinct phylogenetic lineages—three in Nigeria (lineages I through III) and one in the Mano River Union countries of Guinea, Liberia, and Sierra Leone (lineage IV) (Bowen 2000). More recently, however, new LASV lineages have been identified in Mali and Côte d'Ivoire (lineage V), Nigeria (lineage VI), and in Benin and Togo (lineage VII) (Garry 2023, Manning 2015, Whitmer 2018, Yadouleton 2020).

LASV is a zoonotic virus that is found in rodents with frequent spillover events to human populations. *Mastomys natalensis* (i.e., the Natal multimammate rat, which also is known as the multimammate mouse) has long been considered the sole natural reservoir of LASV, but additional rodent reservoirs (e.g., *Mastomys erythroleucus, Hylomyscus pamfi, Mus baoulei* pygmy mice, and others) recently have been discovered and may

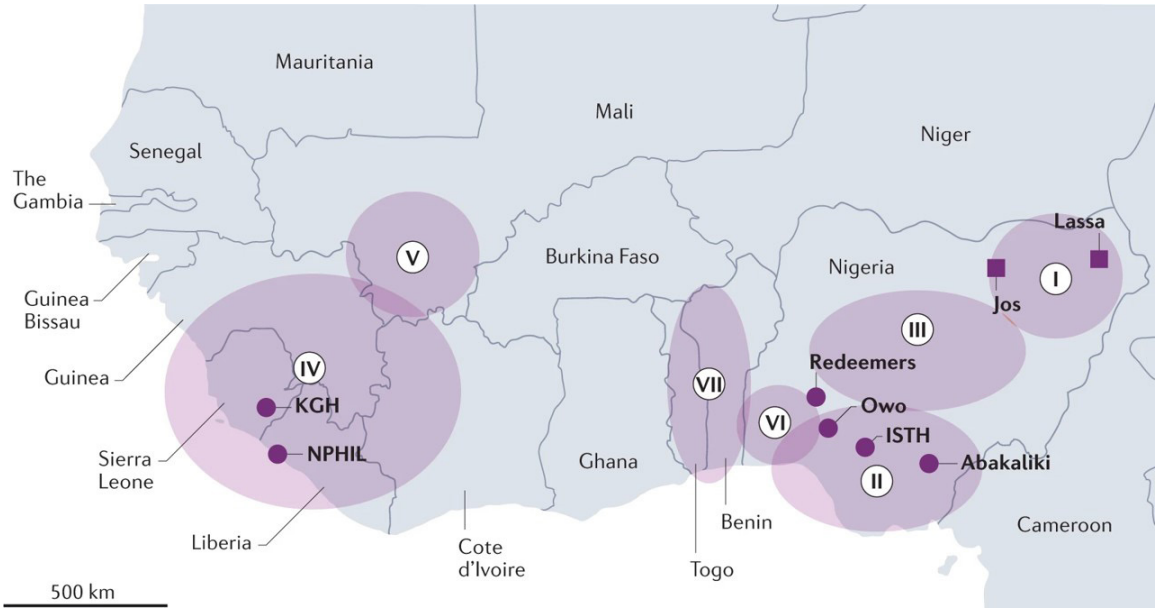

Figure 1. Distribution of Lassa fever cases in West Africa by lineage (Garry 2023). The ovals that are labelled with Roman numerals I–VII represent the approximate ranges of the seven different LASV lineages. Printed with permission from Dr. Robert Garry, October 2023.

affect the distribution of Lassa fever (Adesina 2023, Bangura 2023, Olayemi 2016, Yadouleton 2019). Primary transmission of the virus from animal hosts to humans typically occurs via exposure to excreta (urine or feces) or blood from LASV-infected rodents, through consumption of contaminated food or water, or via aerosolization. Person-to-person and laboratory transmissions occur to a lesser extent and result from direct contact with the blood, tissue, urine, feces, or bodily secretions from an LASV-infected individual; reuse of contaminated medical equipment (e.g., needles and syringes); or contact with contaminated surfaces and items around an infected patient. Person-to-person transmission through sexual contact is also suspected (Thielebein 2022). Mother-to-child transmission has been described, both vertical transmission in utero and possibly through breast milk (Greenky 2018).

Although public health officials often cite annual case estimates of 100,000 to 300,000 LASV infections and 5,000 to 10,000 deaths across West Africa, these numbers are extrapolations from a single longitudinal study conducted more than 35 years ago in Sierra Leone (McCormick 1987). A more recent report, which used a machine-learning framework applied to a mechanistic mathematical model of infection dynamics, suggests that about 900,000 LASV infections occur each year across West Africa, with Nigeria accounting for more than half (Basinski 2021). The true public health burden of Lassa fever, however, remains unknown and represents a crucial gap in understanding the relative impact of Lassa fever in the affected West African countries. In a number of areas, Lassa fever surveillance data are limited and/or biased because they typically have been collected in conjunction with biomedical research projects located where the disease already is recognized to be endemic or are based on cases who seek medical care, which leads to underrepresenting case incidence, even for severe disease (Dalhat 2022). An exception is Nigeria,

which implemented a nationwide electronic case-based surveillance system—Surveillance Outbreak Response Management and Analysis System (SORMAS) through which Lassa fever is now reported. Seroprevalence studies in endemic and non-endemic areas have identified high numbers of previously unrecognized infections, suggesting that the disease burden is greater than previously recognized (Grant 2023a, Safronetz 2017, Sogoba 2016). Recent surveillance reports have observed substantial increases in the number and geographic spread of cases in the last few years, particularly in Nigeria, although this may be in part due to improved case reporting (Dalhat 2022).

LASV infection causes a wide spectrum of clinical manifestations; an estimated 80% of people with LASV infection have no or mild symptoms (and hence their cases often are unrecognized and unreported), while the remaining 20% progress to severe and life-threatening disease requiring hospitalization (WHO 2017a). The case-fatality rate for hospitalized patients is often quoted as approximately 20%, but actually may be as high as 30% to 60%, depending on how acute cases are defined (Asogun 2012, Dahmane 2014, Duvignaud 2021, Shaffer 2014). Maternal and perinatal mortalities are disproportionately higher (Okogbenin 2019) and delivery by caesarean section may expose healthcare workers to the virus and lead to nosocomial outbreaks. Among survivors, the most common long-term sequela of Lassa fever is sensorineural hearing loss, which appears to occur in up to one-third of patients (Mateer 2018). The onset of Lassa fever is gradual and nonspecific, with an incubation period ranging from 2 to 21 days; thus, distinguishing Lassa fever from other febrile illnesses that occur in West Africa such as malaria, typhoid, yellow fever, dengue, and Ebola virus disease (EVD) can be challenging, particularly early in the clinical course.

In 2016, WHO designated Lassa fever a priority disease for epidemic preparedness as part of its *R&D Blueprint for Action to Prevent Epidemics* (WHO 2016) because Lassa fever is associated with significant morbidity and mortality, occurs in epidemic patterns that can be disruptive to society, and effective MCMs are generally not available. At the outset of the WHO R&D Blueprint Initiative, pathogen-specific R&D roadmaps were considered an integral component of the program. In 2022, WHO revised its strategy for epidemic/pandemic preparedness, with a renewed focus on entire classes of viruses or bacteria rather than individual pathogens (WHO 2023a). However, pathogen-specific roadmaps are still highly valuable to inform future directions and investments in preparedness for pathogens with epidemic potential. Furthermore, when considering epidemic preparedness for the Arenaviridae family overall, LASV is an ideal prototype virus for developing medical countermeasures against Old World arenaviruses (Hastie 2023). Thus, defining research priorities for Lassa fever is an important adjunct step to the current prototype-pathogen approach for pandemic preparedness.

An advanced draft of the Lassa Fever R&D Roadmap was published on the WHO website in January 2019 (WHO 2019). The roadmap included a set of strategic goals and milestones for generating Lassa fever diagnostics, therapeutics, and vaccines. In August 2023, Wellcome convened a workgroup of 20 experts (six from countries affected by Lassa fever, nine from Europe, and five from the US) to review the 2019 roadmap and generate an updated set of research priorities for promoting development of Lassa fever MCMs by 2030. The expert working group reviewed drafts of the revised document in the fall of 2023 and early 2024. The updated research priorities outlined in this document reflect scientific developments over the past 5 years and consensus opinion of

the group. Many of the experts involved in the 2023 meeting were also part of the roadmap development taskforce that generated the initial roadmap in 2018.

The scope of R&D addressed in the roadmap ranges from basic research to late-stage development, licensure, manufacture, deployment, and early use of MCMs aimed at human populations to prevent and control Lassa fever outbreaks and endemic disease. The roadmap is organized into four main sections: cross-cutting issues (for areas that apply to more than one MCM category), diagnostics, therapeutics, and vaccines. (*Note*: These topics are not presented in order of public health priority.) Each section of the roadmap includes barriers (inherent obstacles or technical challenges that may influence the likelihood of success for development of Lassa fever MCMs) and gaps (key needs or unresolved limitations in knowledge that are critical to the development of new Lassa fever MCMs). These are followed by strategic goals and milestones, which build on the gaps and barriers and are focused on achievements for the next 6 years that are necessary for moving Lassa fever MCMs forward. Each section also includes additional ongoing priorities that should be considered for MCM R&D.

Other aspects of public health preparedness and response, in addition to R&D for diagnostics, therapeutics, and vaccines, are critical to successful Lassa fever prevention and control, but are outside the scope of this document. Examples include understanding zoonotic transmission from rodents to humans; programs and activities to prevent zoonotic transmission, such as rodent control (Clark 2021, Mariën 2019); access to high-quality personal protective equipment (PPE) for healthcare workers; implementation of adequate infection prevention and control practices in healthcare settings; improved specialized care for pregnant women with Lassa fever, particularly for delivery and surgical needs; adequate infrastructure to deploy MCMs (such as cold-chain maintenance); and availability of guidelines to reduce nosocomial transmission, including care for pregnant women. Additionally, rodent vaccination with anti-Lassa fever vaccines is a promising and innovative approach to reduce the incidence of Lassa fever in hyperendemic areas as part of an overarching One Health disease control strategy (Hansen 2023, Nuismer 2020). A self-disseminating cytomegalovirus (CMV)-vector vaccine has been developed to vaccinate *Mastomys natalensis* against Lassa virus. A small-scale trial batch of the candidate vaccine was immunogenic in inoculated animals, transmissible to naïve co-housed cagemates, and reduced Lassa virus infection and excretion after challenge at highly significant levels (University of Plymouth 2022).

Vision

Robust MCMs to detect, control, treat, and prevent Lassa fever that are readily available and accessible for use in at-risk areas for both endemic and outbreak-related disease. These MCMs include: (1) rapid and accurate, point-of-care or near-patient diagnostics for Lassa fever; (2) safe and effective treatment and post-exposure prophylaxis (PEP) for Lassa fever; and (3) safe and effective vaccines to prevent disease, disability, and death from Lassa fever and stop person-to-person transmission of LASV.

Cross-Cutting Issues

Barriers and Gaps

Barriers

- The diversity of LASV strains and their propensity to evolve over time complicate the development of effective MCMs for Lassa fever. In addition, the different LASV lineages may vary in their pathogenicity, virulence, and disease manifestations; therefore, research needs to be completed in parallel for the different lineages, particularly in animal models but also in the field (Anderson 2015, Beitzel 2019, Hallam 2018, Siddle 2018, Stein 2021).
- Changes in environmental conditions due to land use and climate change have the potential to increase the risks of LASV spillover from the peridomestic rodent reservoir, leading to changes in LASV transmission patterns and more frequent Lassa fever outbreaks (Klitting 2022). Increased transmission facilitates ongoing evolution of the virus, resulting in further genetic changes that may affect the utility of MCMs. Increased LASV transmission, as a result of more frequent spillover events, may result in further genetic changes to LASV strains that could affect MCM development, including diagnostic tests and vaccine composition and efficacy.
- Maximum biologic containment is required for research involving LASV and may pose a barrier to R&D of Lassa fever MCMs, as certain materials must be generated or tested under the highest biosafety level (BSL-4) conditions (Aloke 2023, Emperador 2019, Saito 2023).
- Other important barriers continue to exist for conducting LASV research in animal models, including the following (Arnason 2020, Lukashevich 2013, Sattler 2020, Tang-Huau 2019): (1) animal model research using LASV must be done under BSL-4 biocontainment and a limited number of BSL-4 facilities are available, resulting in backlogs for animal research use; (2) the difficulty and costs in procuring animals, particularly non-human primates (NHPs); and (3) increased regulations, restrictions, and ethical concerns regarding animal research, especially for NHPs (Carvalho 2018).

- West Africa continues to struggle with low and inadequate in-country clinical, laboratory, research, public health, and regulatory capacity, particularly since the 2014 to 2016 EVD epidemic (McPake 2019).
- A number of important barriers exist with regard to conducting clinical trials of novel therapeutic agents and vaccines for Lassa fever in the endemic area. Examples include (Penfold 2023, Salami 2022, Shaffer 2019): (1) the lack of accurate disease burden estimates to guide the selection of clinical trial sites; (2) challenges in identifying and equipping clinical sites with the administrative, research, clinical, and laboratory infrastructure and workforce capacity to conduct clinical trials; (3) the lack of dependable water and electricity sources, which hinders clinical care, laboratory services, and safe storage of therapeutics and vaccines; (4) the remote and sometimes politically unstable nature of certain endemic areas, which can make clinical research difficult; (5) issues in excluding vulnerable populations from clinical trials (such as pregnant women, children, and immunocompromised persons), although they are at risk, or even at increased risk, of mortality from Lassa fever; and (6) challenges in patient recruitment owing to socioeconomic constraints and misconceptions or suspicion regarding the purposes of Lassa fever human subjects research.
- Sharing of clinical samples, virus isolates, and other materials for LASV research is hampered by national and international policies, such as those outlined in the Nagoya protocol, which can limit the ability to conduct research for Lassa fever MCMs (CBD 2011, Ribeiro 2018).

Gaps

- Funding for Lassa fever research is insufficient, and economic incentives to invest in such research are not readily apparent, as the disease is endemic in under-resourced areas of West Africa (Akpede 2018, Torreele 2023). Development of a sustainable value proposition, expansion of international philanthropic-public-private partnerships, and generation of innovative strategies (such as industry incentives and competitions for non-dilutive funding) are needed to secure funding to complete development, licensure, manufacture, deployment, and use of affordable Lassa fever MCMs (Torreele 2023). Furthermore, promotion of in-country leadership and engagement in affected countries is critical for successful R&D of Lassa fever MCMs (Oyebanji 2023).
- Efforts are needed to better characterize the incidence of Lassa fever to determine the design of clinical trials. The *Enable* Lassa research programme, which is conducting prospective cohort studies in Benin, Guinea, Liberia, Nigeria (three sites), and Sierra Leone, is aimed at assessing and characterizing the incidence of Lassa fever and LASV infection in different countries through a coordinated governance structure and a harmonized study protocol (Penfold 2023). Results of this effort will provide critical information about Lassa fever and will inform future Phase 2b or 3 clinical trials for Lassa fever vaccine candidates.
- Owing to the genetic diversity and ongoing evolution of LASV strains, a coordinated, transparent, multinational system is needed for procuring, storing, and sharing LASV isolates from across West Africa for use in MCM development (Oloniniyi 2018). Reverse genetic

systems may facilitate availability of diverse LASV strains (Beitzel 2019).

- Standardized and well-characterized assays (to be further defined based on end use), reagents, antibodies, nucleic acids, and stocks of LASV challenge strains are needed for R&D of MCMs for Lassa fever, including the availability of diagnostic assays for use in epidemiologic research, surveillance activities, and clinical trials of therapeutics and vaccines for Lassa fever.
- The determinants of LASV infection and disease severity in West Africa, particularly pathogen versus host factors, have not been well-characterized. Additional data are needed to better understand Lassa fever disease severity (asymptomatic, mild, and severe) and Lassa fever–associated sequelae by LASV lineage, geographic area, and other population demographics (Penfold 2023, Simons 2022). The *Enable* Lassa research programme noted above will be useful in addressing some of these issues (Penfold 2023).
- Although progress has been made in recent years on developing animal models for Lassa fever, particularly for several small animals including outbred guinea pigs and mice, important issues still need to be addressed, such as: (1) determining appropriate experimental design (e.g., challenge strain[s], route of challenge, timing of challenge, and challenge dose) for testing MCMs in animals; (2) ensuring availability of laboratory reagents and appropriate collections of genetically modified small animals; and (3) the need for small-animal models that accurately recapitulate the pathogenicity and clinical effects of LASV in humans, including infection caused by different LASV strains (Lukashevich 2013, Salami 2019, Sattler 2020, Stein 2021, Tang-Huau 2019). Small-animal models can be used to identify promising MCM candidates using surrogate viruses at lower levels of biocontainment, with further research involving LASV to be conducted under BSL-4 conditions (Sattler 2020).
- Ongoing and sustainable epidemiologic studies and surveillance infrastructure and capacity are needed to determine Lassa fever incidence and LASV infection seroprevalence in affected countries over time using standardized, highly sensitive and specific diagnostic tests with uniform testing algorithms and case definitions across affected countries (Rohan 2022).
- LASV infection is believed to cause profound suppression of innate and adaptive immune functions, involving weak or delayed Type 1 interferon (IFN-1) and pro-inflammatory cytokine responses in the early stages of illness (Brisse 2019, Murphy 2022, Saito 2023). Additional research is needed to determine how immune suppression occurs in severe cases of Lassa fever, as well as the mechanisms of viral clearance and recovery, which could have implications for LASV therapeutics and vaccines (Murphy 2021).
- Development of optimal therapeutic agents and vaccines will require additional research to: (1) understand how Lassa fever develops following LASV infection and the reasons for the substantial variation in disease severity, (2) further characterize both cell-mediated and humoral immune responses, (3) identify factors influencing the development of permanent sequelae, and (4) determine mechanisms of viral persistence in immunologically protected body sites.
- Other key gaps that need to be addressed include the following:

- Ensuring a sufficient workforce of clinical, laboratory, research, public health, and regulatory personnel in West Africa who are qualified by education, training, and experience (McPake 2019).
- Further characterization of the clinical course of Lassa fever in pregnancy and definition of a core set of outcomes for maternal Lassa infection to facilitate data harmonization (Kayem 2020).
- Early and recurrent communication between product developers and the appropriate national regulatory authorities (NRAs), including those in affected West African countries, to obtain clarity and guidance on regulatory pathways, requirements, and other considerations for new Lassa fever MCMs during the pre-licensure and post-licensure periods.
- Enhancement of good clinical practice capabilities, as well as capacity for data reporting and analysis to support collaborative clinical research, including methods for collecting, standardizing, and sharing clinical data (Shaffer 2019).
- Prioritization of Lassa fever therapeutics and vaccines that should be moved forward into clinical trials versus those that need additional preclinical research or those that are not be suitable for additional evaluation in clinical trials.
- Increased infrastructure and capacity for post-marketing surveillance of safety and effectiveness for licensed Lassa fever therapeutics and vaccines (once available).
- Clarification regarding strategies to promote technology transfer for Lassa fever MCMs to at-risk areas (Kagame 2022).
- Identification of effective community engagement strategies for prevention, detection, and treatment of Lassa fever.
- Social science research to: (1) assess the socioeconomic impact of Lassa fever, (2) understand how best to engage the West African population (including vulnerable groups) to promote awareness and sensitization about Lassa fever symptoms and prevention programs, (3) encourage participation in clinical trials, (4) determine community attitudes and barriers toward novel treatments or vaccination, and (5) identify the best mechanisms of community engagement to ensure successful implementation of vaccination programs or acceptance of novel therapies. Such research should be prioritized and initiated early to combat vaccine hesitancy and promote community trust and engagement.
- Ecologic research and modelling to assess the impacts of climate, environmental, demographic, and socioeconomic changes occurring in West Africa on the rodent reservoirs, which will improve forecasting for Lassa fever and inform MCM R&D (such as identifying additional clinical trial site locations) (Adesina 2023, Gibb 2017, Klitting 2022, Pigott 2017, Smither 2021).
- Research to understand the psychosocial drivers and impact of the disease including stigma and psychiatric morbidity.

Strategic Goals and Aligned Milestones

Strategic Goal 1.1: Strengthen the clinical, laboratory, public health, and regulatory capacity in endemic areas for Lassa fever to: (1) promote awareness and education about Lassa fever through community engagement; (2) improve early and accurate diagnosis; (3) promote optimal case management and clinical care; (4) provide readiness for conducting clinical trials and other field studies applicable to MCM development; (5) expand and strengthen surveillance efforts; and (6) allow assessment, licensure, and regional (i.e., in Africa) manufacturing of new MCMs for Lassa fever.

Milestone 1.1.a: By 2024, share initial findings from the *Enable* Lassa research programme, which is aimed at assessing and characterizing the incidence and clinical features of Lassa fever in five West African countries.

Milestone 1.1.b: By 2024, determine design methodologies for conducting phase 3 clinical trials for Lassa fever therapeutics and vaccines in West Africa.

Milestone 1.1.c: By 2024, establish operational site readiness for conducting multi-country phase 3 clinical trials for vaccines and therapeutics in West Africa. This effort should build on key lessons learned and capacity strengthening via prior research investments in the West African subregion.

Milestone 1.1.d: By 2024, conduct community-based studies to inform development of strategies that (1) promote awareness about Lassa fever and the potential benefits to local communities of surveillance activities and clinical research and (2) improve vaccine acceptance and community participation in clinical trials.

Milestone 1.1.e: By 2024, establish ongoing mapping of and engagement with key in-country and regional government authorities across West Africa (such as through the West African Regional Health Organization [WAHO]) to promote harmonization of Lassa fever case definitions and clinical trial methodologies across the subregion.

Milestone 1.1.f: Develop and implement a strategy for technology transfer of Lassa fever MCM manufacturing to one or more countries in Africa to promote local manufacturing capability and support equitable access to Lassa fever MCMs.

Strategic Goal 1.2: Promote mechanisms to further integrate Lassa fever detection, prevention, and control efforts into existing government and healthcare systems.

Milestone 1.2.a: By 2024, engage civil society organizations in West African countries to inform healthcare integration and advocacy approaches for Lassa fever prevention and control.

Milestone 1.2.b: By 2025, develop plans to support integration of Lassa fever prevention and control efforts into existing primary/universal healthcare systems in affected countries, such as through the WHO Universal Health Coverage (UHC) Compendium (WHO 2023b) and the WHO UHC Service Package Delivery & Implementation Tool (WHO 2023c).

Milestone 1.2.c: By 2025, develop an advocacy strategy to secure funding commitments from West African national governments for prevention and control of Lassa fever and other viral hemorrhagic fevers.

Strategic Goal 1.3: Support research to improve understanding of LASV virology, pathogenesis, and immune response in humans and animal models through providing the necessary research tools.

Milestone 1.3.a: By 2024, have available necessary standardized and well-characterized assays, reagents, antibodies, and nucleic acids.

Milestone 1.3.b: By 2025, establish benchmark parameters (e.g., challenge strain[s], route of challenge, timing of challenge, and challenge dose) for preclinical evaluation of MCMs in animal models.

Milestone 1.3.c: By 2026, explore the possibility of creating a coordinated multinational system for ongoing procurement, storage, standardization, and sharing of diverse LASV isolates from across affected West African countries to be used in R&D of Lassa fever MCMs that takes into consideration issues related to the Nagoya Protocol.

Milestone 1.3.d: By 2026, refine relevant animal models for multiple LASV lineages to support basic science research and subsequent preclinical evaluation (to include development and reproductive toxicity [DART] studies) of Lassa fever MCMs.

Milestone 1.3.e: By 2026, explore alternatives to NHPs for evaluating Lassa fever vaccines and therapeutics.

Strategic Goal 1.4: Improve understanding of the epidemiology, behavioral science, and ecology of LASV in West Africa.

Milestone 1.4.a: By 2025, convene a strategic meeting to revise the current clinical case definition of Lassa fever based on current epidemiologic data.

Milestone 1.4.b: By 2025, design and implement plans for expanding and strengthening Lassa fever surveillance, including genomic surveillance, to obtain accurate and up-to-date epidemiologic data and clinical data (including sequelae).

Milestone 1.4.c: By 2026, develop and implement plans to initiate multi-country epidemiologic studies of Lassa fever among pregnant women to further determine the course of maternal, perinatal, and neonatal illness and to identify appropriate clinical endpoints to inform trial design for studies involving pregnant women.

Milestone 1.4.d: By 2026, develop and implement plans to initiate multi-country epidemiologic studies of Lassa fever in children to further determine the pediatric course of illness and to identify appropriate clinical endpoints to inform trial design for studies involving children.

Milestone 1.4.e: By 2026, convene a group of behavioral scientists to formulate a plan for integrating interdisciplinary behavioral science research into development and implementation of Lassa fever MCMs.

Milestone 1.4.f: By 2027, conduct additional research to further investigate LASV animal reservoirs in different West African countries to determine the potential for geographic spread of the virus to new areas, which could (1) impact human disease patterns and incidence, thereby strengthening the need for Lassa fever MCMs, (2) lead to identification of additional clinical trial sites for studying Lassa fever MCMs, and (3) inform modeling predictions to determine future endemic/epidemic risk.

Priority Areas/Activities

Research

Continue to conduct basic science research on the immunology and pathogenesis of LASV infections (including the timing and duration of viremia and the mechanisms of immune suppression following infection) to inform the development and appropriate use of MCMs for LASV infection and Lassa fever.

Continue to further characterize the determinants of LASV infection and disease severity in West Africa, particularly in relation to pathogen versus host factors and taking into account variability in pathogenesis based on LASV strain diversity.

Conduct clinical research to improve understanding of viral shedding among asymptomatic persons and those with mild or sub-acute infection, particularly in relation to the potential for human-to-human transmission.

Conduct clinical research to understand the effect of asymptomatic or mildly symptomatic infection on long-term sequelae, such as hearing loss.

Continue to refine and standardize animal models over time, based on circulating lineages, for assessment of promising Lassa fever therapeutic and vaccine candidates.

Continue to conduct ongoing research and surveillance to obtain accurate and up-to-date epidemiologic data on Lassa fever incidence and LASV seroprevalence over time by lineage, geographic area, and other population demographics and to assess the impact of certain Lassa fever MCMs, such as vaccines.

Continue to conduct research on ecologic issues influencing the natural reservoirs for LASV to better forecast disease occurrence in human populations.

Conduct social science research for Lassa fever to assess socioeconomic impact and determine effective community engagement strategies, as well as strategies for acceptability of novel treatments and vaccines.

Conduct research to assess the psychosocial impact of the disease, such as stigma on health-seeking behavior and determining effective interventions.

Product development

Promote early and recurrent communication between developers and appropriate NRAs for clarity and guidance on the regulatory pathways, requirements, and other considerations for Lassa fever MCM development.

Develop guidance for prioritizing Lassa fever therapeutics and vaccines that should be moved forward into clinical trials versus those that need additional preclinical research or those that are not be suitable for additional evaluation in clinical trials.

Consider developing a business model for generating Lassa fever MCMs. This effort could involve engagement of West African initiatives that foster local cooperation, such as the Manu River Union.

Key capacities

Continue to build capacity and workforce (including in-country technical leadership) for conducting clinical trials of new therapeutics and vaccines for Lassa fever in endemic areas and **create** an enabling environment for retention of the relevant personnel.

Create international partnerships to fund, support, and promote enhanced laboratory, clinical, and surveillance capacities and infrastructure for detection of LASV infection and Lassa fever in endemic and at-risk areas of West Africa.

Strengthen regulatory capacity in areas at risk for Lassa fever (such as through the African Vaccine Regulatory Forum [AVAREF] or the African Medicines Regulatory Harmonisation Programme [AMRH]) to enhance the ability of in-country NRAs to work with researchers and product developers toward evaluating and licensing Lassa fever MCMs and to clarify roles and responsibilities.

Develop good clinical practice capabilities, including standardized data collection and sharing methods to facilitate clinical research into potential therapeutic agents and vaccines for Lassa fever.

Strengthen infrastructure and capacity for post-marketing surveillance of safety and effectiveness of licensed Lassa fever therapeutics and vaccines (once available).

Conduct a feasibility study to determine whether (1) a maximum (BSL-4) biocontainment laboratory is needed in one or more Lassa fever-endemic countries to advance development of Lassa fever MCMs and (2) sustainable resources are available to build, staff, and maintain such a facility.

Policy and commercialization

Explore methods (such as priority review vouchers) to incentivize developers to perform R&D for Lassa fever MCMs.

Ensure access to regulatory guidance, oversight, review, and authorization from appropriate NRAs for Lassa fever MCMs.

Promote plans for adequate manufacturing and robust supply chains for subsequent deployment and use of Lassa fever MCMs in endemic and at-risk areas.

Continue to explore strategies for dealing with issues on sharing of biologic specimens and other materials as outlined in the Nagoya Protocol.

Support the development of affordable pricing mechanisms to promote accessibility of LASV MCMs in low- and middle-income at-risk countries. (*Note*: According to WHO, an "affordable and fair" price is one that can reasonably be achieved by patients and health budgets and simultaneously sustains research and development, production, and distribution within a country.)

Promote policies that support communities involved in clinical trials and in the provision of relevant data.

Diagnostics

Barriers and Gaps

Barriers

- LASV strain variability poses major challenges for Lassa fever diagnostic assay development and validation (Emperador 2019, Mazzola 2019, Raabe 2017a, Wiley 2019). For example, the high genetic diversity of LASV strains may result in false negative results for older polymerase chain reaction (PCR) tests, and few pan-LASV PCR tests have been developed (Mazzola 2019). LASV antigen tests may also show some variation in lineage sensitivity (Mazzola 2019).
- Differentiating Lassa fever from other conditions with similar presenting symptoms (e.g., malaria, typhoid, yellow fever, dengue, and EVD) poses challenges in clinical care and management of patients with febrile illness in West Africa (Mazzola 2019, Raabe 2017a). Antimalarial and antibiotic therapies usually are given first, and Lassa fever is considered only after patients fail to improve, which can lead to delays in diagnosis, treatment, isolation, and contact follow-up (Murphy 2021). Another complicating factor is that patients may present with co-infections (e.g., malaria and Lassa fever), and some existing case definitions for Lassa fever require exclusion of other diseases.
- Lassa fever may mimic early pregnancy symptoms such as malaise, nausea, and vomiting. Even when severe Lassa disease presents with seizures, bleeding, and sepsis, these symptoms could be mistaken for obstetric complications, such as eclampsia, obstetric hemorrhage, and obstetric sepsis. Misdiagnosis is therefore common in pregnancy, and contributes to the high maternal and perinatal mortality from Lassa fever and to nosocomial LASV infections in healthcare workers.
- The broad disease spectrum, which encompasses asymptomatic LASV infection through severe Lassa fever, and the associated variations in viremia levels, immune responses, and symptoms pose challenges for diagnostic tests and the timing of their use (Mazzola 2019). No single reference test (i.e., a gold

standard) currently exists to definitively determine which patients have Lassa fever (Raabe 2017a).

- Diagnostic testing for Lassa fever using blood, serum, or tissues from symptomatic individuals poses safety and logistical challenges for collection, handling, and transport of specimens in low-resource areas. In addition, the utility of noninvasive techniques and evaluation of specimens such as saliva and urine for the diagnosis of acute Lassa fever is not clear.
- A limited number of facilities exist for confirmatory laboratory diagnosis and treatment of Lassa fever in an area comprising over 5 million square kilometers. This can lead to prolonged delays in diagnosis and initiation of therapy, as well as delayed implementation of infection control measures and public health interventions (Dhillon 2018). While some efforts have been made to enhance laboratory and diagnostic capacity, building infrastructure requires (1) dedication and ongoing commitment, (2) prioritization in relation to other competing public health needs, and (3) sustained resources from international partners and national health ministries in affected countries (Naidoo 2020).
- PCR-based molecular assays, such as reverse transcriptase PCR (RT-PCR) are commonly used for diagnosing Lassa fever; however, PCR testing is not readily available in many endemic areas, which poses a significant barrier for diagnostic testing (Boisen 2018, Happi 2019, Mazzola 2019, Raabe 2017a).
- Different clinical sites use different diagnostic testing algorithms, which creates challenges for comparing data from different sites.

Gaps

- Point-of-care or near-patient-care tests could solve many of the logistic challenges with diagnosing Lassa fever (Dhillon 2018). Also, widespread use of rapid diagnostic tests (RDTs) at the point of care could aid in early diagnosis. RDTs refer to diagnostics categorized by performance characteristics rather than the specific test platform. They have relatively short performance times, are designed to detect pathogen-specific antigens or nucleic acid sequences, provide results to inform clinical decision making, and allow for point-of-care testing (Rabold 2023). Two RDTs (one for lineage IV Lassa strains and one that is a pan-Lassa RDT) have recently been evaluated in field studies with promising results (Boisen 2018, Boisen 2020). Further research, however, is needed to evaluate the performance of these tests at the point-of-care and to definitively establish the utility of these RDTs for earlier diagnosis of Lassa fever.
- Continuing improvements are needed in clinical and laboratory capacity for diagnosis of Lassa fever in West Africa. Capacity enhancement should ensure that more referral hospitals in endemic and at-risk areas have the capability to perform point-of-care or near-patient diagnostic testing for Lassa fever, including (1) a high index of suspicion and tools to enable differential diagnosis; (2) the availability of diagnostic tests; (3) the skills and mechanisms to appropriately collect, transport, process, and test specimens; and (4) the ability to interpret test results. Such hospitals will need guidance, equipment, and training of personnel for required diagnostic methodologies, enhanced biosafety practices, quality standards (including WHO International Standard/reference materials),

and quality control methods, such as external quality assessments (EQAs) (Mazzola 2019). Additionally, more in-country reference laboratories are needed for confirmatory testing. Finally, building and sustaining mobile laboratory capacity should be considered for use in remote or peripheral health districts for use during outbreaks.

- Further efforts are needed to address or clarify the following issues:
    - Developing a target product profile (TPP) for Lassa fever diagnostics that takes into account the need for point-of-care testing and detection of multiple LASV strains (Emperador 2019).
    - Defining clear diagnostic criteria and case definitions (for suspect, probable, and confirmed Lassa fever cases that can be used in different geographic populations and across the different LASV lineages) for clinical management of patients, clinical trials, and surveillance activities.
    - Determining the role of LASV in causing febrile illness when multiple pathogens are detected in the same patient. Such information is important for understanding the differential diagnosis of Lassa fever and the relative contribution of LASV in causing febrile disease.
    - Ensuring access to a large reference panel for assay validation, to be comprised of qualified acute and convalescent samples from across West Africa and representing the multiple LASV lineages (Mazzola 2019).
    - Obtaining more detailed understanding of LASV kinetics across a range of sample types to allow further refinement of diagnostic assays (Mazzola 2019).
    - Determining a gold standard test for validation of Lassa fever candidate diagnostic assays (Boisen 2018, Boisen 2020, Takah 2019).
    - Generating guidance, such as an agreed upon diagnostic testing algorithm, on forward deployment and best practices for using rapid and confirmatory tests to diagnose Lassa fever.
    - Generating guidance on testing of alternative specimen types (such as seminal fluid) for viral persistence in Lassa fever survivors (Thielebein 2022).
    - Determining the utility of multiplex assays that can simultaneously detect LASV and other important pathogens, such as Ebola and Marburg viruses (Mazzola 2019, Yao 2021).
    - Researching clustered regularly interspaced short palindromic repeats (CRISPR)-based platforms for rapid, point-of-care diagnosis of Lassa fever (Barnes 2020).
- Diagnostic tests are needed that can accomplish the following:
    - Allow accurate diagnosis across the full disease spectrum, ranging from asymptomatic LASV infection to advanced Lassa fever.
    - Can be performed using inactivated specimens in lower biosecurity level laboratories (i.e., not requiring BSL-4 conditions).
    - Can detect diverse LASV strains in a timely manner. In addition to antigen- and antibody-based RDTs, these include

improved molecular detection methods such as industry-standard RT-PCR assays and all-in-one cartridge-based PCR systems that can be used with and without molecular diagnostic laboratory infrastructure, respectively (Emperador 2019).

- Ongoing molecular characterization of LASV isolates from both rodent reservoirs and humans is needed to map the geographic distribution of various strains across West Africa and to continually monitor genetic changes in LASV strains over time so that diagnostic assays can be updated and refined as needed (Garry 2023, Wiley 2019). Additionally, a system is needed for communicating sequencing results to key stakeholders.

Strategic Goals and Aligned Milestones

Strategic Goal 2.1: Enhance early diagnosis of acute LASV infection by promoting and continuing to develop and evaluate affordable point-of-care or near-patient immunologic- and nucleic acid–based assays.

Milestone 2.1.a: By 2024, generate a TPP identifying essential and desirable characteristics to guide the development of Lassa fever diagnostic assays, including multiplex assays, for detection of the multiple LASV lineages and detection of other common pathogens that cause febrile illness, taking into account the need for point-of-care testing.

Milestone 2.1.b: By 2024, initiate additional analytic testing of one or more promising candidate diagnostic assays that align with the TPP (when available).

Milestone 2.1.c: By 2025, expand availability of clinical samples and facilitate timely access by creating a sustainable, multinational virtual reference repository of clinical samples representing the multiple LASV lineages, with samples to be collected and maintained in the countries of origin. Samples would be used for analytic testing of candidate diagnostic assays.

Milestone 2.1.d: By 2026, conduct at least one field validation study in multiple countries of a point-of-care Lassa diagnostic assay to evaluate test performance and confirm utility.

Milestone 2.1.e: By 2026, determine the most appropriate diagnostic standard, ideally to be used across the at-risk countries (potentially using a combined standard), for assay development and for determining performance of candidate diagnostic assays.

Milestone 2.1.f: By 2028, promote and support regulatory clearance/market authorization by a relevant stringent regulatory agency for at least one new validated multi-lineage Lassa fever point-of-care or near-patient diagnostic assay that is aligned with the TPP.

Strategic Goal 2.2: Continue to engage a multinational network of laboratories in West Africa for conducting field trials of promising diagnostic assays for Lassa fever.

Milestone 2.2.a: By 2024, build on previous efforts of engaging with field laboratories and other clinical sites for studying diagnostic assays and conduct a standardized needs assessment at sites that are suitable for future research.

Milestone 2.2.b: By 2025, complete training as identified by the needs assessment and obtain resources necessary to enhance preparedness for conducting field studies of future Lassa fever diagnostic assays, including establishing appropriate study design protocols.

Milestone 2.2.c: By 2026, implement routine EQA monitoring of Lassa fever diagnostic testing at selected laboratories in at-risk countries.

Strategic Goal 2.3: Develop clinical guidance and appropriate algorithms for using Lassa fever diagnostic assays.

Milestone 2.3.a: By 2025, develop best practices on forward deployment and use of Lassa fever point-of-care, near-patient-care, and laboratory-based tests in endemic-disease and outbreak situations, to include vetted and widely agreed-upon diagnostic algorithms (Boisen 2018, Boisen 2020).

Milestone 2.3.b: By 2026, create a process for continually reviewing best practices and refreshing diagnostic algorithms as needed.

Priority Areas/Activities

Research

Continue to determine performance characteristics for promising new assays for Lassa fever diagnosis and **develop** appropriate standards, including rapid evaluation of assays against existing samples (from biobanks or other repositories).

Conduct field evaluation of new diagnostic tests for Lassa fever, including assessment of test performance using non-invasive specimens such as saliva, oral swabs, and urine.

Perform ongoing molecular characterization (i.e., sequencing) of LASV strains to assess genetic changes geographically and over time so that diagnostic assays can be updated and refined as needed.

Improve understanding of viral kinetics across different clinical sample types.

Conduct additional clinical research to evaluate diagnostic assays using different types of clinical specimens for assessing persistence of infection in immunologically protected sites.

Conduct clinical research to improve understanding regarding the role of LASV in causing febrile illness when multiple pathogens are detected in the same patient.

Product development

Continue to develop, evaluate, and validate Lassa fever point-of-care or near-patient immunologic- and nucleic acid–based RDTs that are affordable and can capture (1) the full spectrum of disease associated with LASV infection and (2) the wide genetic diversity of LASV strains in endemic and at-risk areas.

Develop multiplex diagnostic assays that can distinguish between specific fever-related illnesses to allow differentiation of Lassa fever from other infectious diseases, such as EVD, that present with similar symptoms (if feasible and as a long-term goal).

Continue to explore the role of CRISPR-based platforms for rapid, point-of-care diagnosis of Lassa fever.

Key capacities

Create mechanisms and protocols for collecting, shipping, and sharing of clinical samples.

Build on progress by the African Center of Excellence for the Genetics of Infectious Diseases (ACEGID) at Redeemers University in Nigeria, to promote ongoing molecular characterization (i.e., sequencing) of LASV strains across endemic and at-risk areas.

Construct a communication infrastructure and plan to notify key stakeholders of sequencing results, especially about the evolution of LASV strains and the identification of additional LASV lineages.

Continue to build laboratory infrastructure and workforce capacity in affected countries.

Policy and commercialization

Provide guidance on testing of alternative specimen types for viral persistence in Lassa fever survivors.

Promote adequate access to point-of-care diagnostic assays across the West African subregion, particularly as new and improved assays are developed.

Therapeutics

Barriers and Gaps

Barriers

- Ribavirin is considered part of the standard of care for treatment of Lassa fever and is widely utilized in West Africa, although data supporting its use are limited and are based on one clinical trial conducted more than 35 years ago (McCormick 1986) and several additional retrospective cohort studies (Cheng 2022, Eberhardt 2019). Because ribavirin is widely recommended, challenges exist with conducting randomized clinical trials involving this medication versus placebo (Bourner 2023, Salam 2021).
- The high cost of treatment in low-resource countries in West Africa limits access and thus contributes to the disease burden.
- Infection prevention and control infrastructure, practices, and governance are weak across healthcare facilities in West African countries where Lassa fever is endemic. Limited supplies of PPE and other infection prevention commodities hinder case management.
- Specific challenges for clinical trials of candidate therapeutics in the endemic area include (Bourner 2023, Merson 2021) (1) early signs and symptoms of Lassa fever resemble a number of other infectious diseases that occur in areas at risk for Lassa fever; (2) difficulties in rapidly and accurately diagnosing Lassa fever for prompt initiation of treatment, which may affect evaluation of efficacy in clinical trials; (3) the need to involve multiple diverse health centers in conducting trials; (4) the wide variability in quality of supportive care across health centers, which makes comparison of therapies difficult; and (5) social and ethical issues in recruiting patients for clinical trials involving placebo versus ribavirin, given that ribavirin is included in the standard of care.
- Stigma associated with the disease presents challenges in clinical trial recruitment and the willingness of patient to seek medical care.

Gaps

- A TPP for Lassa fever therapeutic agents, identifying essential and desirable characteristics, is needed to guide the development of promising treatment approaches (WHO 2018). The West Africa Lassa Fever Consortium (WALC) recently held a consultation to inform development of a TPP for Lassa fever therapeutics (Danwafor 2023). The TPP will be completed by the Viral Haemorrhagic Fevers (VHF) group at WHO.
- Existing studies involving the efficacy of ribavirin may be at serious risk for bias (Cheng 2022). Additionally, ribavirin may actually be harmful for patients with mild Lassa fever (Eberhardt 2019, Salam 2021). Furthermore, a recent pharmacokinetic study suggests that the mode of action for ribavirin may be immunomodulation rather than antiviral, calling into question the rationale for high ribavirin doses that are associated with significant toxicity (Groger 2023). These studies indicate that randomized clinical trials are needed to compare ribavirin with other promising therapeutic agents to definitively address whether or not ribavirin is efficacious against Lassa fever (Bourner 2023). One exploratory controlled randomized clinical trial on the pharmacokinetics, tolerability, and safety of favipiravir compared to ribavirin for the treatment of Lassa fever has recently been completed in West Africa, but results are not yet available (Bernhard Nocht Institute for Tropical Medicine 2023).
- Currently, two different dosing regimens are used for ribavirin therapy in non-pregnant patients (the McCormick regimen and the Irrua regimen); however, limited information is available on the pharmacokinetics of ribavirin in animal models or humans for treating Lassa fever (Salam 2022). Since future clinical trials will likely at least initially involve ribavirin as a comparator and part of the standard of care, the dosing for ribavirin needs to be standardized (Bourner 2023).
- The following agents are being considered for further evaluation in clinical trials as outlined in a prepositioned phase 2/3 platform clinical trial protocol for Lassa fever therapeutics that was recently developed by WALC (Bourner 2023).
    - Favipiravir has been shown to protect against LASV lethal challenge in guinea pigs (Safronetz 2015) and has also been used successfully to treat cynomolgus macaques against Lassa fever (Rosenke 2018).
    - A cocktail of three monoclonal antibodies (mAbs), named Arevirumab-3, has been shown to protect cynomolgus macaques at advanced stages of disease (Cross 2019, Mire 2017). Efforts, however, are needed to reduce the costs related to its production and deployment (Cross 2019). Similarly, a recent study showed that combinations of two or three broadly neutralizing mAbs (Arevirumab-2 or Arevirumab-3) protected 100% of cynomolgus macaques against challenge with two of the major lineages of LASV (lineages II and III) when treatment was initiated at advanced stages of disease (Cross 2023). However, Arevirumab-3 protected only 40% of macaques infected with lineage VII when treatment was administered more than 7 days post-exposure, suggesting increased virulence of this strain (Woolsey 2024).
    - A small molecule inhibitor, LHF-535 (which is an analog of an earlier small molecule

[ST-193]), has shown promising results in animal models (Cashman 2022, Madu 2018) and a phase 1 clinical trial of LHF-535 has demonstrated an acceptable safety profile (Amberg 2022).

- Another small molecule inhibitor, ARN-75039, has also shown promise in guinea pigs, alone or in combination with favipiravir (Westover 2022).

- Clinical trial data are needed on the safety, tolerability, and efficacy against the multiple LASV lineages for these promising Lassa fever therapies, potentially using ribavirin as the comparator (Bourner 2023). A platform phase 2-3 clinical trial (the INTEGRATE study) is scheduled to begin in 2024 to evaluate efficacy of available drugs for treating Lassa fever (Irrua Specialist Teaching Hospital 2023, Irrua Specialist Teaching Hospital 2024). Understanding the disease kinetics and the efficacy of treatment at various stages of disease progression are important considerations when conducting such clinical trials.

- Additionally, it may be worthwhile to study new agents in combination with each other or with ribavirin. For example, a combination of ribavirin and favipiravir may be of clinical benefit (Oestereich 2016, Raabe 2017b), as may a combination of ARN-75039 and favipiravir (Westover 2022). Also, adjuvant drugs such as dexamethasone in combination with ribavirin or other drugs may be worth exploring.

- Other agents have demonstrated activity against LASV and deserve further preclinical testing in animal models (Hansen 2019, Joseph 2022) to obtain data on efficacy for the multiple LASV lineages, pharmacodynamics, pharmacokinetics, barriers to resistance, and dose and regimen selection. Preclinical data on treatment effectiveness by time of treatment initiation also are needed for these agents. Convalescent plasma has been considered as a potential therapy; however, availability is limited and maintaining lot-to-lot consistency is a challenge, making this strategy less practical (Grant 2023b).

- Additional research would also be of value to identify broad-spectrum agents for Lassa fever and to examine therapeutics in the R&D pipeline for other viral pathogens that also may protect against Lassa fever (i.e., drug repurposing) (Kim 2019). Such approaches may assist with funding, logistics, and technical aspects of research, and provide long-term market potential.

- Currently, no evidence supports the use of ribavirin as PEP therapy for exposure to LASV (WHO 2017a). Additional data are needed to inform the development of guidance on the use of PEP and the most appropriate agents to administer to prevent Lassa fever following exposure (Grant 2023b).

- Efforts are needed to ensure that pregnant women and children have opportunities to participate in clinical trials of Lassa fever therapeutics (Couderc- Pétry 2020, Olayinka 2022).

- Clinical evaluations of novel agents are needed to identify therapeutic options for eliminating persistent virus in the urine and semen of Lassa fever survivors.

- Patients may benefit from optimal supportive care independent of treatment with specific Lassa fever therapeutic agents. Key research areas include obtaining data on the safety and efficacy of supportive care approaches for Lassa fever to inform best-practice guidelines, such as ideal fluid, electrolyte, and blood pressure management; proper

blood oxygen saturation; prompt diagnosis of organ dysfunction; appropriate triage of other secondary complications; and judicious use of empiric antibiotics and antiparasitics, antiemetics, antidiarrheal agents, and vitamin K. Clinical evaluation of various aspects of supportive care should focus on patients in endemic areas to avoid extrapolating from conclusions based on patient outcomes in high-income countries.

- In addition to improving supportive care, operational research is needed to determine optimal approaches for supportive care coupled with the use of therapeutic agents to reduce overall case-fatality rates once new therapeutic agents become available.

Strategic Goals and Aligned Milestones

Strategic Goal 3.1: Generate good clinical practice guidelines for optimizing supportive care of Lassa fever patients to promote consistency of treatment across clinical trial sites.

Milestone 3.1.a: By 2024, convene an expert working group (including clinical-care providers) to share current evidence and identify gaps to inform evidence-based good clinical practice guidelines for supportive care of patients with Lassa fever.

Milestone 3.1.b: By 2025, develop good clinical practice guidelines for supportive care of patients with Lassa fever through a consensus-driven process.

Milestone 3.1.c: By 2026, disseminate the guidelines and conduct outreach to clinicians, including training on implementation of the guidelines, as needed.

Milestone 3.1.d: By 2026, provide infrastructure support in selected sites (e.g., necessary intensive care unit equipment) to allow guideline implementation.

Strategic Goal 3.2: Assess promising therapeutic agents for the treatment of Lassa fever through randomized clinical trials.

Milestone 3.2.a: By 2024, develop ethical guidelines and appropriate inclusion criteria for participation in clinical trials of Lassa fever therapeutics of populations that are exceptionally vulnerable to disease, such as pregnant women and children.

Milestone 3.2.b: By 2024, share findings from completed clinical trials on the pharmacokinetics, pharmacodynamics, tolerability, and safety of favipiravir and ribavirin for the treatment of Lassa fever.

Milestone 3.2.c: By 2024, establish standardized dosing of ribavirin for clinical trials, based on recent data.

Milestone 3.2.d: By 2026, conduct early clinical research on investigational drugs (such as favipiravir, Arevirumab-3, LHF-535, and ARN-75039), host-directed therapies, and selected combination therapies to determine their pharmacokinetics/pharmacodynamics, safety profiles, and optimal dosage regimens.

Milestone 3.2.e: By 2026, create a process for determining which drugs to include in phase 2/3 trials, given the limited resources for conducting such trials.

Milestone 3.2.f: By 2028, complete at least one randomized phase 2/3 clinical efficacy trial involving investigational drugs (such as favipiravir, Arevirumab-3, LHF-535, and/or ARN-75039), host-directed therapies or combination therapies in comparison with ribavirin (or the current standard of care).

Milestone 3.2.g: By 2029, bring to market at least one new drug for treatment of Lassa fever that is affordable, appropriate for use in a variety of healthcare settings, and is readily available in affected countries.

Milestone 3.2.h: By 2029, develop guidance for using PEP therapy, based on results of earlier clinical efficacy trials.

Strategic Goal 3.3: Continue to expand the R&D pipeline for Lassa fever therapeutics over time.

Milestone 3.3.a: By 2024, finalize a TPP that identifies essential and desirable characteristics to guide the development of novel Lassa fever therapeutics (Danwafor 2023, WHO 2018).

Milestone 3.3.b: By 2025, expand screening efforts to identify (1) additional novel broad-spectrum antivirals that are effective against LASV, (2) host-directed therapies, and (3) other biologicals for LASV treatment.

Milestone 3.3.c: By 2028, complete preclinical evaluation for at least two additional novel therapeutic agents for the treatment of Lassa fever that are aligned with the TPP.

Milestone 3.3.d: By 2029, obtain safety, pharmacokinetics/pharmacodynamics, and possibly preliminary efficacy data through clinical trials for at least one promising additional Lassa fever therapeutic agent that is aligned with the TPP.

Priority Areas/Activities

Research

Continue to research the safety, tolerability, and efficacy of investigational therapies for Lassa fever via preclinical animal studies, and determine which of these therapies warrant further evaluation through clinical trials.

Conduct future clinical trials for the most promising therapeutic candidates (including early trials in affected countries) to determine dose regimen and assess safety, tolerability, and efficacy.

Assess therapeutic options for eliminating persistent LASV in the urine and semen of Lassa fever survivors.

Explore the potential for linking Lassa fever clinical trials for therapeutics with other disease initiatives, such as other clinical trial networks.

Product development

Continue to "mobilize stakeholders from both the public and private sector, and different forms of financing, around the shared objective of developing and making available Lassa fever drugs for the communities in West Africa" (Torreele 2023).

Develop, clinically evaluate, and license safe and effective therapeutic agents for the treatment of Lassa fever that are broadly active against the multiple lineages of LASV, particularly as new lineages are discovered over time.

Continue to explore drug repurposing options for identifying candidate therapies for treatment of Lassa fever.

Continue to develop broad-spectrum antivirals that can be used for Lassa fever as well as for other viruses (such as segmented or negative-sense RNA viruses).

Key capacities

Promote enhancements to the healthcare delivery systems in affected areas to improve and standardize clinical management and supportive care of Lassa fever patients, including the ability to provide critical care (such as through establishment of additional strategically positioned referral centers for management of critically ill patients).

Policy and commercialization

Develop treatment and guidance for LASV PEP as new therapies become available.

Generate updated guidance on the role, dosing, and duration of therapy for using ribavirin, depending on outcomes of future clinical studies.

Develop approaches to ensure that therapies for Lassa fever are readily available and affordable in affected countries.

Vaccines

Barriers and Gaps

Barriers

- The high genetic and phenotypic diversity of the different LASV lineages poses a significant challenge for LASV vaccine R&D, since cross-protection following natural infection has been observed for some but not all lineages (Buck 2022, Heinrich 2020, Sullivan 2020, Ugwu 2022). Pan-LASV vaccines that incorporate multiple immunogens or conserved immunogens are needed to assure protection against all lineages (Aloke 2023, Andersen 2015, Buck 2022, Garry 2023, Ibukun 2020, Ugwu 2022).
- The LASV surface glycoprotein complex (GPC), which is the sole protein on the virus surface, mediates viral attachment and cell entry and, therefore, has been a primary target for vaccine development. Structural analyses indicate that the GPC is densely glycosylated, which shields it from the binding of neutralizing antibodies; glycan-shield penetration is required for antibody activity (Brouwer 2022, Gunn 2022, Ibukun 2020, Li 2022, Murphy 2021, Sommerstein 2015, Zhu 2021).
- Neutralizing immune responses against the LASV GPC following natural infection are either weak or nonexistent, which creates challenges for identifying appropriate antibody targets (Li 2022).
- Recombinant GPC immunogens may be necessary to neutralize LASV (particularly across lineages); however, they are relatively unstable because the GPC trimer tends to break down into monomeric subunits after expression (Brouwer 2022, Gunn 2022).
- Preliminary evidence suggests that cellular immunity could play a dual role in LASV infection, which creates potential challenges for LASV vaccine development. T-cell immune responses appear to be critical for immune protection and survival from Lassa fever, but in in some circumstances, T-cell responses may also trigger further LASV-related pathogenicity and possibly contribute to long-term sequelae

such as sensorineural hearing loss (Murphy 2021, Saito 2023).

- Vaccine clinical efficacy trials typically require a large investment of resources, which is a significant barrier to LASV vaccine development. A recent scoping review of clinical trials for LASV vaccine candidates provides progress to date in conducting clinical trials for LASV vaccine candidates (Sulis 2023). Four vaccine candidate vaccines have entered clinical trials: a DNA-based vaccine (INO-4500), a live attenuated measles-virus vector vaccine (MV-LASV), a recombinant vesicular stomatitis virus (rVSV) (rVSVΔG-LASV-GPC), and a VSV-based vaccine that encodes LASV glycoproteins (EBS-LASV) (Sulis 2023, Tschismarov 2023). Most of these vaccines have been assessed in phase 1 clinical trials; however, a phase 2 trial for rVSVΔG-LASV-GPC is being initiated in West Africa (International AIDS Vaccine Initiative 2023). Clinical development for INO-4500 was recently discontinued because the vaccine regimen did not meet the selection criteria put forth by the funder (the Coalition for Epidemic Preparedness Innovations [CEPI]) for further evaluation (Inovio 2022).
- Several additional vaccine candidates are in preclinical development (Isaac 2022, Melnik 2022, Murphy 2022, Saito 2023), including candidates using mRNA-based platforms (CEPI 2022, Hashizume 2023, Ronk 2023). Efforts are needed to continue to move these candidate vaccines through preclinical evaluation to determine if they are suitable for clinical trials.
- The variable incidence of Lassa fever disease and sporadic nature of Lassa fever outbreaks creates challenges for planning and implementing clinical efficacy trials (Sulis 2023). For example, conducting trials during periods of low Lassa fever incidence will necessitate longer follow-up of clinical trial participants (Sulis 2023), which can add logistical challenges and increase costs. Conducting clinical trials during outbreaks may be needed to achieve statistical significance, although additional preparedness is required in advance, including manufacturing sufficient quantities of candidate vaccines and obtaining emergency use authorizations (Salami 2020).
- The lack of ongoing systematic estimates for Lassa fever incidence and LASV seroprevalence creates challenges in monitoring the impact of vaccination on the public health burden of disease.
- Practical limitations and complex logistics exist for sustainable manufacturing, stockpiling, and deployment of LASV vaccines (e.g., trained personnel to administer the vaccines, vaccines that require multiple-dose regimens, cold-chain storage requirements) pose additional barriers to vaccine development (Aloke 2023). Features such as single-dose regimens, temperature stability of the product, and alternative modes of administration (e.g., oral, nasal, transdermal) will facilitate the use of safe and effective vaccines in low-resource countries where LASV is endemic (WHO 2017b).
- A major hurdle to the deployment of LASV vaccines is affordability. A practical necessity for LASV vaccine R&D will be low-cost vaccines that can be delivered in sustainable, community-based vaccination programs (Salami 2019).

Gaps

- Additional needs for vaccine clinical efficacy trials include the following:

- Correlates of protection to provide surrogate markers for vaccine-induced immunogenicity and prevention of infection, symptomatic illness, severe disease, disease sequelae, and death (Sulis 2023, Ugwu 2022).
- Well-defined endpoints for LASV vaccine efficacy trials (e.g., clinical disease, infection, or correlates of protection) and diagnostic algorithms (Salami 2020).
- Strategies to determine the duration of protection for vaccine candidates during the clinical trial process, since vaccines should ideally be targeted for preventive use and, therefore, should offer protection across at least several years (Salami 2020).
- Since cross-protection against different circulating LASV strains is a critical element of a successful LASV vaccine, phase 2 clinical studies should assess how the immune response elicited by candidate vaccines cross-reacts with different Lassa strains (Heinrich 2020, Salami 2020).
- Evidence suggests that LASV infection is a significant underlying cause of maternal, perinatal, and neonatal mortality in LASV-endemic areas (Kayem 2020). Researchers have, however, been reluctant to include pregnant women in vaccine clinical trials unless robust safety data are available from early phase 1/2 studies (Salami 2022). Furthermore, high-quality safety data on reproductive toxicity in preclinical animal models are needed to support including pregnant women in LASV vaccine clinical efficacy trials (Salami 2020).

- Additional critical basic science and translational research needs for enhancing understanding of the immune response to LASV infection and facilitating generation of pan-LASV vaccines include the following:
  - Further research to determine the relative roles of cellular and humoral adaptive immunity in protecting against LASV infection and disease to inform future vaccine antigen/platform designs (Hallam 2018, LaVergne 2022, Murphy 2022, Sakabe 2020), particularly with regard to generating cross-protective immunity against the different LASV lineages (Heinrich 2020, Sullivan 2020).
  - Additional research to clarify the potential dual role (protective and pathogenic) of immune responses induced by LASV infection or potentially LASV vaccines (Mantlo 2019, Murphy 2021, Saito 2023).
  - Efforts to better understand the pathogenic mechanisms of Lassa fever-associated sequelae, particularly hearing loss, to inform development of safe and effective vaccines.
  - Further research on the structural biology of LASV to elucidate optimal antigen or epitope compositions and configurations for enhancing the immunogenicity and protective efficacy of LASV vaccines (Brouwer 2023, Hastie 2019, Li 2022, Rowaiye 2022).
  - Most survivors of Lassa fever are believed to have lifelong cellular immunity (e.g., via CD8+ T cells) to the infecting LASV strain (Hallam 2018, LaVergne 2022, Murphy 2022), but additional research is needed to clarify durability and breadth of protection following natural infection.

- Additional needs related to vaccine policy include the following:
    - One vaccine may not be suitable for all uses, and guidance on vaccination strategies for different vaccines will ultimately be needed. LASV vaccines with different characteristics, such as durability and risk profiles, may be needed for:
        - » Diverse populations in endemic areas (e.g., residents of all ages, women of childbearing age, and healthcare workers).
        - » Different use cases, including long-term preventive use in endemic areas and short-term reactive use in outbreaks.
        - » Different endpoints, such as preventing infection and transmission of the virus versus protecting against severe disease and death.
- Further research is needed to determine the mechanisms of and the differences between naturally acquired immunity (such as among Lassa fever survivors and individuals with asymptomatic LASV infection) and vaccine-induced immunity.
- Mathematical modelling may be useful in estimating the potential impact of LASV vaccines and in simulating various epidemiologic scenarios that may affect vaccine use, particularly when paired with more accurate incidence data from additional epidemiologic studies and surveillance activities.

Strategic Goals and Aligned Milestones

Strategic Goal 4.1: Facilitate clinical evaluation, regulatory review, licensure, and authorization of LASV vaccine candidates, particularly for candidates that are currently in the clinical development pipeline.

Milestone 4.1.a: By 2024, review and revise as appropriate the TPP for Lassa fever vaccines.

Milestone 4.1.b: By 2024, complete the characterization of vaccine safety and immunogenicity through phase 1 clinical trials in affected and non-affected countries for at least two of the most promising LASV candidate vaccines.

Milestone 4.1.c: By 2024, harmonize clinical endpoints (e.g., infection, asymptomatic illness, clinical disease, and severe clinical disease), diagnostics, and case definitions for LASV phase 3 vaccine efficacy trials in healthy adults.

Milestone 4.1.d: By 2024, initiate engagement with appropriate regulatory agencies in affected countries to clarify strategies for approval of LASV vaccine candidates.

Milestone 4.1.e: By 2025, create a plan for vaccine clinical efficacy trials to be conducted specifically during outbreaks, including determining requirements and mechanisms to obtain Emergency Use Listings of candidate vaccines for at-risk populations.

Milestone 4.1.f: By 2025, conduct reproductive toxicity studies, as required, in preclinical animal models for at least two promising LASV vaccine candidates to determine the suitability of including pregnant women in vaccine efficacy trials.

Milestone 4.1.g: By 2028, identify correlates or surrogates of protection that can be used to predict vaccine-induced protection against LASV infection, disease, severe disease, and disease sequelae in humans. Correlates of protection may be specific to each vaccine antigen/platform construct and may not necessarily be generalizable across different vaccines.

Milestone 4.1.h: By 2028, complete phase 3 clinical efficacy trials for at least one promising LASV vaccine candidate.

Milestone 4.1.i: By 2029, obtain regulatory approval for at least one LASV vaccine that can be used in children and other high-risk groups, and is aligned with the TPP for use in Lassa fever endemic and at-risk areas.

Strategic Goal 4.2: Conduct additional preclinical or translational research to accelerate the development of new LASV vaccines that protect against multiple LASV lineages.

Milestone 4.2.a: By 2027, complete preclinical evaluation in animal models for additional candidate LASV vaccines for safety, immunogenicity, and efficacy, and identify the most promising candidates to advance into clinical trials.

Milestone 4.2.b: By 2027, conduct additional research to clarify the roles of cellular and humoral immunity in generating protection against LASV infection and disease to inform vaccine antigen/platform design.

Milestone 4.2.c: By 2028, further investigate optimal antigen targets and configurations for broadly protective LASV vaccines through structural biology research.

Milestone 4.2.d: By 2028, complete additional research to clarify the potential dual role (protective and pathogenic) of immune responses induced by LASV infection or potentially LASV vaccines.

Priority Areas/Activities

Research

- **Incorporate** assessments of the duration of protective immunity for candidate LASV vaccines into clinical trial study designs. Such research will determine which vaccines are most suitable for preventive use and will inform vaccination strategies for different LASV vaccines.
- **Conduct** mathematical modelling to estimate the potential impact of LASV vaccines and to simulate various epidemiologic scenarios that may affect vaccine use, particularly when paired with more accurate incidence data from ongoing and additional epidemiologic studies and surveillance activities.
- **Conduct** research to determine the mechanisms of and the differences between naturally acquired immunity and vaccine-induced immunity.
- **Conduct** research to further clarify durability and breadth of protection following natural infection with LASV.
- **Conduct** research to identify causes of hearing loss in survivors of Lassa fever to inform issues around vaccine safety.

Product development

- **Collect**, **summarize**, and **publicly share** up-to-date information on the progress of LASV vaccine R&D, such as through the creation of a publicly available, online technology landscape for LASV vaccines that are in preclinical or clinical development.
- **Determine** the stability of different vaccine types and formulations in field conditions in at-risk areas.
- **Continue to develop, clinically evaluate, and license** safe and effective LASV vaccines that protect against the multiple LASV lineages for preventive or reactive/outbreak use.

Key capacities

- **Establish and maintain** stockpiles of LASV vaccines for use during large Lassa fever outbreaks.
- **Improve** ongoing surveillance capabilities in endemic areas to assess the impact of vaccination campaigns once vaccines become available.
- **Support** capacity-building to enable researchers to conduct vaccine clinical efficacy studies in affected areas of West Africa.

Policy and commercialization

- **Develop** an implementation research plan that crosses endemic and at-risk areas and that addresses vaccine acceptability and policy implications.
- **Provide** guidance on optimal vaccination strategies for various target populations, geographic areas, and epidemiologic scenarios once LASV vaccines are available.
- **Continue to assess** issues around vaccine hesitancy in affected communities.

- **Develop** guidance for community sensitization to vaccine acceptation and promotion within the community.
- **Ensure** that approved or licensed LASV vaccines are affordable and easy to use in at-risk and endemic areas. Ease-of-use strategies include single-dose regimens (or regimens with only a few doses), temperature stability, and alternative modes of administration (e.g., oral, nasal, transdermal).
- **Develop** strategies for stockpiling and distribution of limited vaccine stocks, especially in situations where conflicting demands on the vaccine supply may exist.

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