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# Lassa Fever Research and Development (R&D) Roadmap

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**R&D**Blueprint

Powering research  
to prevent epidemics

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## ABBREVIATIONS & ACRONYMS

AMRH	African Medicines Harmonization Initiative
AVAREF	African Vaccine Regulatory Forum
BSL-4	biosafety level 4
EVD	Ebola virus disease
LASV	Lassa virus
MCM	medical countermeasure
NHP	nonhuman primate
NRA	national regulatory authority
PCR	polymerase chain reaction
PD	pharmacodynamic
PEP	post-exposure prophylaxis
PK	pharmacokinetic
PPE	personal protective equipment
R&D	research and development
RDT	rapid diagnostic test
TPP	target product profile
WHO	World Health Organization

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## ACKNOWLEDGMENTS

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**Roadmap purpose:** to provide a 10-year framework for identifying the vision, underpinning strategic goals and prioritizing areas and activities (from basic research towards 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.

## INTRODUCTION

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 the region (that is, Benin, Burkina Faso, Côte d'Ivoire, Ghana, Mali and Togo) also appear to be at risk for Lassa fever, based on the identification of occasional sporadic cases and serologic surveys demonstrating evidence of prior LASV infection in some people in those areas. LASV exhibits marked genetic heterogeneity, and at least five different LASV lineages have been identified. LASV isolates from Nigeria generally fall into lineages I, II and III, while isolates from the Mano Union River countries (Guinea, Liberia and Sierra Leone) usually fall into lineage IV. Recently, a fifth LASV lineage has been identified for isolates from Côte d'Ivoire and Mali, and two additional lineages have been proposed in Nigeria and Togo. *Mastomys natalensis* (that is, the multimammate mouse, which is also known as the multimammate rat), has long been considered the sole natural reservoir of LASV, but additional rodent reservoirs (*M. erythroleucus* and *H. pamfi*) have recently been discovered and may affect the distribution of Lassa fever. Primary transmission of the virus from animal hosts to humans typically occurs via exposure to excreta (urine or faeces), or blood from LASV-infected rodents. Person-to-person and laboratory transmissions occur to a lesser extent and result from direct contact with the blood, tissue, urine, faeces, or bodily secretions of an LASV-infected individual, reuse of contaminated medical equipment, or contact with contaminated surfaces and items close by an infected patient. Modelling information indicates that, in natural settings in Sierra Leone, the contribution of human-to-human transmission is approximately 20%, with most cases arising from super-spreaders.

Although public-health officials often cite annual case estimates of 100 000 to 300 000 LASV infections and up to 5000 deaths, these numbers are extrapolations from a single longitudinal study conducted more than 30 years ago in Sierra Leone. The true public-health burden of Lassa fever is unknown and this represents a crucial gap in understanding the relative impact of Lassa fever in the affected West African countries. Existing Lassa fever surveillance data are limited and/or biased because they typically have been collected in conjunction with biomedical research projects located in areas where the disease is already recognized as endemic. In contrast, seroprevalence studies in non-endemic areas have suggested high numbers of previously unrecognized infections, and more recent surveillance reports have observed substantial increases in the number and geographic spread of cases. Thus, the true

incidence and spatial distribution of Lassa fever may be significantly underestimated. LASV infection causes a wide spectrum of clinical manifestations; an estimated 80% of people with LASV infections have none or mild symptoms (and hence their cases are often unrecognized and unreported), while the remaining 20% may progress to severe and life-threatening disease requiring hospitalization. Among survivors, the most common long-term sequela of Lassa fever is sensorineural hearing loss. The onset of Lassa fever is gradual and nonspecific with an incubation period ranging from 3–21 days; hence, it is clinically difficult to distinguish Lassa fever from other febrile illnesses that occur in West Africa, such as malaria, typhoid, yellow fever, dengue and Ebola virus disease (EVD).

The R&D roadmap for Lassa fever is an integral component of the World Health Organization (WHO) [R&D Blueprint](#) initiative for accelerating research and product development of MCMs to enable effective and timely emergency response to infectious disease epidemics. LASV is identified in the Blueprint's list of "priority pathogens" (defined as pathogens that are likely to cause severe outbreaks in the near future and for which few, or no MCMs exist). The Blueprint calls for the creation of R&D roadmaps, for the priority pathogens, to align and stimulate R&D of new or improved countermeasures, such as rapid diagnostic assays, novel therapeutics and vaccines. Furthermore, the Blueprint considers product R&D for all three of these categories of MCMs to be a high priority for Lassa fever. 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 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). The strategic goals and milestones identified in the roadmap are focused on key achievements for the next 10 years; the roadmap milestones will be tracked over time, with periodic assessment of progress and updating, as needed.

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. Examples include: understanding zoonotic transmission from rodents to humans; programmes and activities to prevent zoonotic transmission (such as rodent control); access to high-quality personal protective equipment (PPE) for health-care workers; implementation of adequate infection prevention and control practices in health-care settings; development of adequate capacity (in terms of workforce, equipment and infrastructure) at strategic locations in endemic areas for optimal clinical case management; adequate infrastructure to deploy MCMs (such as cold-chain maintenance), and availability of guidelines to reduce nosocomial transmission. Many of these issues are beyond the scope of the R&D roadmap, but need to be addressed as part of a broader public-health control strategy.

## VISION

**Ready availability and accessibility of robust MCMs to detect, control and prevent Lassa fever, for use in at-risk areas for both endemic and outbreak-related disease. These MCMs include: (1) rapid and accurate, near-patient diagnostics for Lassa fever; (2) safe and effective treatment and post-exposure**

**prophylaxis (PEP) for Lassa fever; (3) safe and effective vaccines to prevent disease, disability and death from Lassa fever and to stop person-to-person transmission of LASV.**

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## CROSS-CUTTING ISSUES

### Primary challenges, key needs and knowledge gaps

#### Primary challenges

- The diversity of LASV strains and propensity of these strains 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, which necessitates that research be completed in parallel for the different lineages, particularly in animal models.
- Maximum biologic containment is required for LASV and may pose an impediment to R&D of Lassa fever MCMs, as materials must be generated and/or tested under the highest biosafety level (BSL-4) conditions.
- The development of animal models for R&D of Lassa fever MCMs is associated with a number of issues, including: (1) a limited number of BSL-4 facilities and limited space within those facilities, resulting in backlogs for animal research use; (2) the difficulty and costs in procuring animals, particularly nonhuman primates (NHPs); (3) increased regulations, restrictions and ethical concerns regarding animal research, especially for NHPs; (4) the need to address animal welfare issues, such as identification of euthanasia criteria; (5) determining appropriate experimental design (for example, challenge strain, route of challenge, timing of challenge and challenge dose); (6) the need to better understand the adequacy of current animal models and clarify whether or not additional animal models are required. Some of these issues necessitate downselection of MCM candidates from rodent models prior to conducting further research in NHPs under BSL-4 conditions; however, these decisions are complicated by inherent limitations of the rodent models.
- The absence of diagnostic assays to distinguish between acute illness, prior infection and response to vaccination hinders Lassa fever patient management, disease surveillance efforts, epidemiologic research on LASV infection and disease in West Africa and clinical research on promising Lassa fever treatments and vaccines.
- West Africa continues to experience the loss of physicians and scientists to more lucrative jobs elsewhere, and this weakens in-country clinical, laboratory, research, public-health and regulatory capacity. The 2014 to 2016 EVD epidemic in this region also resulted in further workforce reductions owing to the deaths of numerous health-care workers, including those with Lassa fever expertise. In addition, the infrastructure necessary for optimal clinical case management is often lacking.
- 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 the under-resourced West African region. Development of a sustainable value proposition, international philanthropic public-private partnerships and innovative methods, are needed to secure funding to complete development, licensure, manufacture, deployment and use of affordable Lassa fever MCMs.
- A number of important obstacles exist with regard to conducting clinical trials of novel therapeutic agents and vaccines for Lassa fever in the endemic area. Examples include: (1) 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) lack of dependable water and electricity sources, which hinder 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 special 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; (6) challenges in patient recruitment owing to socioeconomic constraints.

- Insufficient and/or ineffective community awareness, sensitization and education programmes needed to strengthen community participation and ownership for the prevention, detection and treatment of Lassa fever.

### **Key needs**

- Funding sources (such as public-private partnerships, government agencies and philanthropic organizations) and industry incentives and competitions for non-dilutive funding to encourage innovation and secure private-sector commitments to develop, manufacture and stockpile critical LASV MCMs.
- Standardized and well-characterized assays (to be further defined based on end use), reagents, antibodies, nucleic acids and stocks of LASV challenge strains 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. This work should use WHO international standards, when available, as calibrators, reported in international units to harmonize assay results. A number of important issues will need to be addressed in developing and sharing these tools, such as issues regarding intellectual property and ethical concerns.
- Ongoing availability of current circulating LASV strains as reference samples for MCM development.
- Epidemiologic studies and ongoing surveillance infrastructure and capacity 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.
- A sufficient workforce of clinical, laboratory, research, public-health and regulatory personnel in West Africa who are qualified by education, training and experience.
- Early and recurrent communication between product developers and the appropriate national regulatory authorities (NRAs), including those in West Africa, 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.
- Efforts to design clinical efficacy trials in affected areas that are ethical, interpretable and feasible. Researchers should explore the potential for conducting clinical trials before considering alternative regulatory pathways for licensure (such as the United States Food and Drug Administration's Animal Rule). (Note: early clinical trials do not necessarily need to be conducted in affected areas.)



- Enhanced 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.
- Prioritization of Lassa fever therapeutics and vaccines that should be moved forward into clinical trials versus those that need additional preclinical research.
- Increased infrastructure and capacity for post-marketing surveillance of safety and effectiveness for licensed Lassa fever therapeutics and vaccines (once available).
- Clarification regarding the potential for, and possible strategies to, promote technology transfer to at-risk areas for Lassa fever MCMs.
- Identification of effective community engagement strategies for prevention, detection and treatment of Lassa fever.

### **Knowledge gaps**

- Additional research on animal models is needed to: (1) identify, or adapt, refine and validate relevant animal models (for example, guinea pig, common marmoset and macaque models) for the multiple LASV lineages; (2) define their role in supporting basic research on the pathogenesis and immunology of Lassa fever and Lassa fever-associated sequelae; (3) allow evaluation of new Lassa fever MCMs. In addition, efforts should be considered to establish benchmark parameters (for example, challenge strain, route of challenge, timing of challenge and challenge dose) for testing in animals.
- A better understanding of the natural history of Lassa fever is needed to inform R&D of MCMs. In addition, viral shedding in asymptomatic individuals, or those with mild or subacute infection, is not established and this may contribute to human-to-human transmission, particularly at the community level.
- Further research is needed on the pathogenesis and immunology of LASV infections (including the timing and duration of the viremic phase) to support the development and appropriate use of MCMs for LASV infection and Lassa fever. (For example, detailed knowledge of the innate, cell-mediated and humoral immune responses that constitute protective immunity against Lassa fever, is needed to identify specific vaccine-induced immune responses that can serve as biomarkers for clinical protection against Lassa fever and predict the level of vaccine efficacy).
- The determinants of LASV infection and disease severity in West Africa, particularly pathogen versus host factors, have not been well-characterized. More 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.
- Successful R&D, deployment and assessment of MCMs depend on current and accurate descriptive epidemiologic information on Lassa fever incidence and LASV seroprevalence by lineage, geographic area and other population demographics. Detailed information about Lassa fever incidence, and LASV seroprevalence by geographic area, is needed to identify communities with and without ongoing transmission within the endemic countries of West Africa.
- Ecologic research and modelling are needed to assess the impacts of climate, environmental, demographic and socioeconomic changes occurring in the rodent reservoir in West Africa, which will improve forecasting for Lassa fever.

- Social science research is needed to: (1) assess the socioeconomic impact of Lassa fever; (2) understand how best to engage the West African population (including special populations) to promote awareness and sensitization about Lassa fever symptoms, and prevention programmes, participation in clinical trials and acceptance of Lassa fever MCMs.

### Strategic goals and aligned milestones

**Strategic Goal 1:** to strengthen the clinical, laboratory, public-health and regulatory infrastructure and workforce in the endemic area for Lassa fever to: (1) promote awareness and education about Lassa fever; (2) improve capacity for early and accurate diagnosis; (3) promote optimal case management and clinical care, including the availability of critical care and enhanced supportive care in strategically located health-care facilities; (4) provide capacity for conducting clinical trials and other field studies applicable to MCM development; (5) allow assessment, licensure and policy decisions for new Lassa fever MCMs.

#### Milestones

1. By 2019, convene a workshop about Lassa fever for key in-country national government authorities (public health, regulatory and others) to promote their engagement in, and ownership of, Lassa fever prevention and control efforts in West Africa, including MCM development.
2. By 2019, convene an expert working group (including clinical-care providers) to develop and publish evidence-based guidelines for supportive care of patients with Lassa fever.
3. By 2019, initiate a multinational training programme in West Africa to enhance preparedness for conducting field evaluations and clinical trials in areas targeted for future Lassa fever research.
4. By 2020, initiate a long-term training programme aimed at improving laboratory, clinical and public-health capacity for responding to microbial threats across West Africa. This effort can build and expand upon existing advanced-degree training programmes.
5. By 2020, establish a harmonized regional research plan across multiple countries in West Africa for improving epidemiologic understanding of Lassa fever in West Africa, enhancing development of Lassa fever MCMs and conducting implementation research for Lassa fever vaccines and therapeutics.

**Strategic Goal 2:** to improve understanding of the current epidemiology and ecology of LASV in West Africa.

#### Milestones

1. By 2019, formalize a coordinated programme for conducting molecular characterization of LASV isolates from several locations in West Africa, with open sharing of results.
2. By 2020, complete at least one multi-centre study to define the seroprevalence of LASV antibody and to characterize the disease burden (both hospital- and community-based) of Lassa fever across key regions of West Africa.

3. By 2025, complete the identification of LASV reservoirs in different West African countries, perform spatial and longitudinal surveys on rodent populations and initiate investigations on the hosts' genome.

**Strategic Goal 3:** to develop a sustainable value proposition and identify funding sources to promote R&D, availability and accessibility of Lassa fever MCMs.

#### Milestones

1. By 2020, develop a public-value proposition to effectively advocate for the development and sustainability of Lassa fever MCMs that: (1) articulates the potential threat of LASV infection; (2) outlines the social and economic benefits of generating accessible and affordable Lassa fever MCMs; (3) details the positive impact on health systems in affected areas.
2. By 2020, create a funding plan for moving Lassa fever diagnostics, therapeutics and vaccines towards clinical evaluation, licensure/approval, acceptance and sustainable access.

**Strategic goal 4:** to support basic science research to improve understanding of LASV virology, pathogenesis and immune response in humans and animal models.

#### Milestones

1. By 2022, generate standardized and well-characterized assays, reagents, antibodies, nucleic acids and stocks of LASV challenge strains to facilitate R&D of Lassa fever MCMs using WHO international standards, when available, as calibrators.
2. By 2022, refine and standardize relevant animal models for the multiple LASV lineages, to support basic science research on pathogenesis and immunology of Lassa fever, and preclinical and clinical evaluation of Lassa fever MCMs.

### Priority areas/activities

#### Research

- **Conduct** basic research on the immunology and pathogenesis of LASV infections (including the timing and duration of viremia) to inform the development and appropriate use of MCMs for LASV infection and Lassa fever.
- **Determine** the innate, cell-mediated and humoral immune responses that contribute to protective immunity against Lassa fever through animal models, or study of disease, in infected individuals.
- **Further characterize** the determinants of LASV infection and disease severity in West Africa, particularly in relation to pathogen versus host factors.
- **Conduct** clinical research to improve understanding of viral shedding among asymptomatic persons and those with mild or subacute infection, particularly in relation to the potential for human-to-human transmission.
- **Generate** research tools to promote R&D of MCMs for Lassa fever (for example, standardized and validated assays, reagents, antibodies, nucleic acids and stocks of LASV challenge strains) that use WHO international standards, when available, as calibrators.

- **Refine and standardize** animal models for assessment of promising Lassa fever therapeutic and vaccine candidates.
- **Explore** possible strategies for conducting clinical efficacy trials in affected areas that are ethical, interpretable and feasible, or identify alternative approaches for assessing the efficacy of new LASV vaccines and therapeutics, in coordination with the appropriate NRAs.
- **Ensure** the eligibility of children and pregnant women in clinical trials, if appropriate, depending on the construct of the MCM, to evaluate the safety, dosage and toxicity of experimental LASV MCMs.
- **Conduct** ongoing research and surveillance to obtain accurate and up-to-date epidemiologic data on Lassa fever incidence and LASV seroprevalence by lineage, geographic area and other population demographics, and to assess the impact of certain Lassa fever MCMs, such as vaccines, over time.
- **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 treatments and vaccines.

#### **Product development**

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

#### **Key capacities**

- **Ensure** adequate infrastructure, workforce and capability for conducting clinical trials of promising Lassa fever therapeutics and vaccines in the endemic area.
- **Strengthen** regulatory capacity in areas at risk for Lassa fever (such as, through the African Vaccine Regulatory Forum [AVAREF] or the African Medicines Regulatory Harmonization Initiative [AMRH]), to enhance the ability of in-country NRAs to work with researchers and product developers towards 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.
- **Create** strategies to promote community awareness, sensitization and education to strengthen community participation and ownership for the prevention, detection and treatment of Lassa fever.

#### **Policy and commercialization**

- **Establish** a sustainable value proposition and **secure** funding to complete development, licensure, manufacture, deployment and use of affordable Lassa fever MCMs.

- **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.
- **Support** the development of affordable pricing mechanisms to promote accessibility of LASV MCMs in low- and middle-income at-risk countries. (Note: according to the WHO, an “affordable and fair” price is one that can reasonably be achieved by patients and health budgets and that simultaneously sustains research and development, production and distribution within a country).
- **Develop** models for, and plans to, coordinate use of new MCMs, as they become available, to optimize their impact, efficiency and cost-effectiveness.
- **Clarify** potential for, and possible strategies to, promote technology transfer for Lassa fever MCMs.

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## DIAGNOSTICS

### Primary challenges, key needs and knowledge gaps

#### Primary challenges

- LASV strain variability poses major challenges for Lassa fever diagnostic assay development and validation.
- Differentiating Lassa fever from other conditions with similar presenting symptoms (for example, malaria, typhoid, yellow fever, dengue and EVD) poses challenges in clinical care and management of patients with febrile illness in West Africa. Antimalarial and antibiotic therapies are usually 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. Another complicating factor is that patients may present with co-infections (such as malaria and Lassa fever) and some existing case definitions for Lassa fever require exclusion of other diseases.
- 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. No single reference test (that is, a gold standard) currently exists to definitively determine which patients have Lassa fever.
- In Lassa fever survivors, the virus may persist for extended periods in immunologically protected sites, such as the kidney and gonads, which can result in secondary transmission. The presence and levels of virus in these immunologically protected sites typically are unknown.
- Diagnostic testing for Lassa fever using blood, serum, or tissue from symptomatic individuals poses safety and logistical challenges for collection, handling and transport of specimens in under-resourced 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 a region comprising over five million square kilometres. 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. 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; (3) sustained resources from international partners and in-country national health ministries.

#### Key needs

- Clarification regarding the use cases for different Lassa fever diagnostic assays, since the corresponding performance, validation and regulatory approval requirements may differ depending on whether the test will be used for differential diagnosis, confirmation of diagnosis, preclinical and clinical R&D of therapeutics and vaccines, or surveillance activities. For example, it may be desirable to have a screening test that is highly sensitive and a confirmatory test that is highly specific.
- A target product profile (TPP) for Lassa fever diagnostics, identifying optimal and desirable characteristics to guide the development of promising diagnostic assays.

- 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.
- Assays that allow accurate diagnosis across the full disease spectrum, ranging from asymptomatic LASV infection to advanced Lassa fever.
- Diagnostic tests that can be performed using inactivated specimens in lower biosecurity level laboratories (not requiring BSL-4 conditions).
- Lassa fever near-patient diagnostic assays, with adequate sensitivity, that detect genetically diverse LASV strains in a timely manner. In addition to antigen- and antibody-based rapid diagnostic tests (RDTs), these include improved molecular detection methods such as industry-standard real-time polymerase chain reaction (PCR) assays and all-in-one cartridge-based PCR systems that can be used with and without molecular diagnostic laboratory infrastructure, respectively.
- A gold standard test for validation of Lassa fever candidate assays.
- Access to a large reference panel comprised of qualified acute and convalescent samples from across West Africa and representing the multiple LASV lineages for assay development, qualification, validation and ongoing assay performance.
- Continuing improvements 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 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; (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. 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 in outbreaks.
- Guidance on forward deployment and best practices for using rapid and confirmatory tests to diagnose Lassa fever.
- Guidance on testing of alternative specimen types (such as seminal fluid) for viral persistence in Lassa fever survivors.

**Knowledge gaps**

- Additional field validation data are needed to assess performance characteristics of Lassa fever diagnostic assays against the multiple lineages of LASV that can be found across West Africa.
- 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 diagnostics assays can be updated and refined as needed. Additionally, a system is needed for communicating sequencing results to key stakeholders.

- Further research is needed to better understand 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.

### Strategic goals and aligned milestones

**Strategic Goal 1:** to enhance early diagnosis of acute LASV infection by promoting and continuing to develop and evaluate affordable near-patient immunologic- and nucleic acid-based assays.

#### Milestones

1. By 2019, generate a TPP identifying optimal and desirable characteristics to guide the development of Lassa fever diagnostic assays for detection of the multiple LASV lineages.
2. By 2020, create a multinational virtual reference repository of clinical samples representing the multiple LASV lineages, with samples to be collected and maintained either regionally, or in the countries of origin.
3. By 2020, initiate analytic testing of promising candidate diagnostic assays, which align with the TPP, through well-characterized serologic and virologic panels that represent the different LASV lineages.
4. By 2021, conduct multinational field studies of at least two candidate near-patient diagnostic assays (nucleic acid-based or immunologic) that align with the TPP.
5. By 2022, obtain regulatory clearance/market authorization by a relevant regulatory agency for at least one new validated multi-lineage Lassa fever near-patient diagnostic assay that is aligned with the TPP.

**Strategic Goal 2:** to create a multinational network of laboratories for conducting field trials of promising diagnostic assays for Lassa fever.

#### Milestones

1. By 2019, identify multiple sites for conducting field trials of promising LASV diagnostics and develop a standardized needs assessment tool.
2. By 2019, conduct a standardized needs assessment in each of the field sites.
3. By 2020, complete training and obtain resources necessary to enhance preparedness for conducting field studies.

**Strategic Goal 3:** to develop clinical guidance on the further deployment and best practices for using current assays for the diagnosis of Lassa fever.

#### Milestones

1. By 2023, complete implementation research to guide public-policy decision-making.



## Priority areas/activities

### Research

- **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 noninvasive specimens such as saliva, oral swabs and urine.
- **Perform** molecular characterization (that is, sequencing) of LASV strains to assess genetic changes geographically, and over time, so that diagnostic assays can be updated and refined as needed.
- **Conduct** 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

- **Generate** a TPP for Lassa fever diagnostics.
- **Define** use cases for Lassa fever diagnostic assays, including for screening and confirmatory diagnostic purposes and for conducting clinical trials of therapeutics and vaccines.
- **Build** biobanks of reference samples for validation of Lassa fever diagnostic assays via prospective studies using standardized methods.
- **Establish** a gold standard test for definitive diagnosis of Lassa fever and validation of other candidate assays.
- **Develop, evaluate and validate** Lassa fever near-patient immunologic- and nucleic acid-based RDTs that are affordable and can capture: (1) the full spectrum of disease associated with LASV infection; (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 that present with similar symptoms, if feasible and as a long-term goal.

### Key capacities

- **Create** mechanisms and protocols for collecting, shipping and sharing of clinical samples.
- **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.
- **Establish** a network of LASV surveillance laboratories that can perform ongoing molecular characterization (that is, sequencing) of LASV strains isolated from rodents and humans, over time and by geographic region, in endemic and at-risk areas.
- **Construct** a communication infrastructure and plan to notify key stakeholders of sequencing results, especially as regards the evolution of LASV strains and the identification of additional LASV lineages.

### Policy and commercialization

- **Create** Lassa fever diagnostic algorithms and case definitions, and revise them as new diagnostic methods become available.
- **Provide** guidance on testing of alternative specimen types for viral persistence in Lassa fever survivors.
- **Develop** guidance on forward deployment and use of Lassa fever RDTs and confirmatory assays in endemic-disease and outbreak situations, taking into consideration the occurrence of other febrile illnesses that may vary by geographic area.

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## THERAPEUTICS

### Primary challenges, key needs and knowledge gaps

#### Primary challenges

- Supportive care and ribavirin are common therapies used for Lassa fever. Ribavirin, a broad-spectrum antiviral, appears to be most effective in reducing mortality from Lassa fever if given within the first six days of illness and when administered intravenously rather than orally. Scant efficacy data are available for ribavirin, however, and its significant cost and difficulty in procurement present operational challenges for treatment in West Africa.
- Case management and clinical care quality can improve survival rates. Not only does West Africa have an insufficient number of health-care facilities for treatment of Lassa fever, but very few facilities have the capability to provide critical care or enhanced supportive care. In addition, supportive laboratory investigations (for example, full blood count, blood cultures and renal and hepatic function tests) are not routinely available to guide clinical management of patients, as laboratories in health-care facilities are often unwilling to test potentially hazardous samples.
- The high cost of treatment in the setting of low-income countries in West Africa limits access to treatment and hence contributes to the disease burden.
- Infection prevention and control infrastructure, practices and governance are weak across health-care 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: (1) difficulties in rapidly and accurately diagnosing Lassa fever for prompt initiation of treatment (ribavirin or novel therapies) that may affect evaluation of efficacy; (2) wide variability in quality of supportive care across health centres, which makes comparison of therapies difficult; (3) ethical issues in recruiting patients for placebo versus trial drugs. For example, the availability of ribavirin (appearing on the WHO Model List of Essential Medicines) as an off-label widely-used therapy for Lassa fever, despite limited data on its efficacy, raises potential issues for placebo-controlled trials using other therapeutic agents.

#### Key needs

- TPPs for Lassa fever therapeutic agents, identifying optimal and desirable characteristics to guide the development of promising treatment approaches.
- Safe, easily administered and well-tolerated therapeutic agents for treatment of Lassa fever, which are effective against the multiple LASV lineages, including viable treatment alternatives to ribavirin.
- Therapeutic agents or combination therapies that are specifically intended to prevent Lassa fever-associated sequelae, particularly deafness.
- Safe and effective PEP to prevent Lassa fever for high-risk exposure to LASV and guidance on PEP use. Such countermeasures are important tools to protect health-care workers, family caregivers and burial teams, and to reduce transmission.
- Minimum standards for supportive care in West Africa to facilitate the evaluation of new therapies via clinical trials.

**Knowledge gaps**

- Development of optimal therapeutic agents 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; (4) determine mechanisms of viral persistence in immunologically protected body sites.
- Treatment of Lassa fever with ribavirin has been evaluated in only a single non-randomized clinical trial and in field studies using retrospective analyses. Additional data regarding the efficacy of ribavirin at various stages of disease progression are needed, as well as assessment of different administration routes and dosing regimens.
- Several therapeutic agents have demonstrated protection against lethal Lassa fever challenge in animal models (that is, antivirals such as favipiravir, small-molecule inhibitors such as ST-193 and immune-based agents such as convalescent plasma with high titres of neutralizing antibodies and human monoclonal antibodies). However, additional studies of these and other agents in relevant animal models, may be needed before moving to clinical trials to obtain data on efficacy for the multiple LASV lineages, pharmacodynamics (PD), pharmacokinetics (PK), barriers to resistance and dose and regimen selection. Preclinical data on treatment effectiveness by time of treatment initiation are also needed for these agents.
- Further information is needed regarding treatment options and dosing regimens for Lassa fever patients and particularly for infected pregnant women.
- Further research is needed on the efficacy of convalescent blood products (including convalescent whole blood, convalescent plasma, convalescent serum, pooled or high-titre immunoglobulin and polyclonal or monoclonal antibodies) and exchange blood transfusion for the treatment of severely ill Lassa fever patients.
- Additional research would 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 may also protect against Lassa fever. Such approaches may assist with funding, logistics and technical aspects of research, and also provide long-term market potential.
- Clinical trial data are needed on the safety, tolerability and efficacy against the multiple LASV lineages for the most promising novel Lassa fever therapies, used alone or in combination with other therapies, such as ribavirin. Understanding the disease kinetics and efficacy of treatment at various stages of disease progression are important considerations when conducting such clinical trials.
- 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.
- Clinical evaluations of novel agents are needed to identify therapeutic options for eliminating persistent virus in the urine and semen of Lassa fever survivors.
- Research is needed to clarify the clinical and virologic determinants of Lassa fever outcomes and to identify clinical presentation criteria and/or measureable biomarkers that can reliably predict the severity and outcome of illness in infected patients. Identification of such criteria and/or biomarkers, and other methods to quantify viral loads, could lead to evidence-based approaches

to reduce mortality from Lassa fever and may enhance clinical research into new therapeutic agents and PEP countermeasures.

- 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, antidiarrhoeal agents and vitamin K. Clinical evaluation of various aspects of supportive care should focus on patients in the endemic area 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 once new therapeutic agents become available.

### Strategic goals and aligned milestones

**Strategic Goal 1:** to more fully evaluate ribavirin for the treatment of Lassa fever and determine the appropriate role of ribavirin through clinical trials of new therapeutics.

#### Milestones

1. By 2019, conduct a retrospective analysis in endemic areas, to include historical unpublished data, on ribavirin use and outcomes in patients, including pregnant women, and a review of the animal data on safety, toxicity and efficacy of ribavirin.
2. By 2020, conduct a clinical study to obtain additional PK/PD data on ribavirin, to determine an appropriate dosing schedule.
3. By 2020, convene an expert working group, including obstetricians and paediatricians, to develop a consensus document that addresses if, and how, ribavirin will be included in clinical trial designs for novel Lassa fever therapeutics.

**Strategic Goal 2:** to develop, evaluate and license new and improved affordable therapeutic agents for treatment of Lassa fever caused by the multiple LASV lineages.

#### Milestones

1. By 2019, generate a TPP that identifies optimal and desirable characteristics to guide the development of Lassa fever therapeutics, which are broadly active against the multiple lineages of LASV and which address the prevention of sequelae, particularly deafness.
2. By 2020, identify and characterize at least one biomarker predictive of Lassa fever outcome to facilitate clinical efficacy trials of therapeutics.
3. By 2022, complete preclinical evaluation of at least two new therapeutic agents for the treatment of Lassa fever that are aligned with the TPP.

4. By 2023, obtain safety, PK/PD and preliminary efficacy data for at least one promising Lassa fever therapeutic agent that is aligned with the TPP.
5. By 2025, complete phase 3 clinical efficacy trials for at least one promising Lassa fever therapeutic agent that is aligned with the TPP.
6. By 2026, obtain regulatory approval for at least one 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 animal studies, and determine which of these therapies warrant further clinical evaluation.
- **Conduct** clinical trials for the most promising therapeutic candidates (including early trials in affected countries) to determine dose regimen and assess safety, tolerability and efficacy.
- **Research** optimal strategies for supportive care for Lassa fever patients, generate best-practice guidelines and research optimal approaches for combining supportive care with promising therapeutics as new agents become available.
- **Identify, assess and validate** clinical presentation criteria and measureable biomarkers that can reliably predict the severity and outcome of illness in infected patients (such as, quantitative assays to measure LASV load).

### Product development

- **Generate** TPPs for Lassa fever therapeutics.
- **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.
- **Identify** therapeutic approaches for PEP that are broadly active against the multiple lineages of LASV.

### Key capacities

- **Ensure** that a coordinated process is in place to assess promising therapeutic agents, including broad-spectrum agents, and ensure that strategies are created to move them forward.
- **Promote** enhancements to the health-care 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 strategically positioned referral centres for management of critically ill patients).

### Policy and commercialization

- **Develop** a consensus approach for how to address ethical and sociologic issues regarding the role of ribavirin in future clinical trials of new therapeutic agents.
- **Create** guidelines for patient management and minimum standards for supportive care, to facilitate clinical research of novel treatments.
- **Develop** treatment and PEP guidance as new therapies become available.

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## VACCINES

### Primary challenges, key needs and knowledge gaps

#### Primary challenges

- The multiple lineages of LASV present considerable challenges for vaccine development and evaluation.
- The lack of systematic estimates for Lassa fever incidence and LASV seroprevalence creates challenges in designing efficacy studies and monitoring the impact of vaccination on the public-health burden of disease.
- The scientific basis is limited for guiding vaccine research. For example, more information is needed about which biomarkers are associated with Lassa fever immunologic responses and survival.
- One vaccine may not be suitable for all uses. For example, a vaccine for preventive use, or for use in special populations, will likely need to have a relatively low risk profile for adverse reactions, whereas the risk profile may differ if a vaccine is targeted for reactive use in an outbreak. Similarly, a durable vaccine could be most helpful for front-line workers in at-risk areas where the likelihood of exposure over time is high, whereas a vaccine that generates fast-acting immune responses may be more important for use during outbreaks.
- A specific challenge for clinical research on LASV vaccine candidates in the endemic area is the need for a high enough incidence of disease to conduct clinical efficacy trials, which may require implementing trials only during large Lassa fever outbreaks. If clinical trials are planned for implementation during outbreaks, a number of additional challenges will need to be addressed, such as ensuring advance development and regulatory/ethical approval of clinical trial protocols and adequate stockpiles of vaccines. If clinical trials are not feasible, alternative pathways to licensure and policy decision-making will be needed.
- The cost of vaccine, logistics of vaccination and sustainability of vaccine supplies are important challenges in endemic and at-risk countries.

#### Key needs

- Vaccines with many of the optimal and desirable characteristics outlined in the TPP for LASV vaccines and capable of inducing immunity to genetically diverse LASV strains.
- Specific correlates of protection, or causally related surrogates for correlates of protection, to facilitate research on promising LASV vaccine candidates.
- Well-defined end-points for LASV vaccine efficacy trials (for example, clinical disease, infection, or correlates of protection) and diagnostic algorithms and laboratory methods for case verification.
- An assessment of the feasibility of conducting clinical vaccine trials in non-outbreak situations versus conducting trials only during large outbreaks. If clinical trials are conducted primarily when outbreaks occur, then plans and approvals for emergency use of candidate vaccines will need to be in place to ensure research preparedness.
- Guidance for community sensitization to vaccine acceptance and promotion within the community.



- Guidance on vaccination strategies (particularly determining preventive and reactive/outbreak approaches) if, and when, approved LASV vaccines become available.

#### **Knowledge gaps**

- 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.
- Correlates and/or surrogates of protection have not been identified.
- Additional knowledge gaps include: (1) determining the duration of protective immunity for promising vaccine candidates; (2) identifying optimal vaccination strategies for different vaccines in different population groups and geographic areas; (3) measuring the ability of different vaccine types and formulations to remain stable in field conditions in at-risk regions.
- Additional research is needed to better understand the relative contributions of different modes of transmission to better assess the impact of vaccination programmes.
- Social science research is needed to determine: (1) community attitudes and barriers towards vaccination; (2) issues pertinent to vaccine strategy implementation; (3) best mechanisms of community engagement to ensure successful implementation of vaccination programmes.
- 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 1:** through WHO, to develop, evaluate, license and prequalify affordable LASV vaccines that protect against the multiple LASV lineages, for use in Lassa fever endemic and at-risk areas.

#### **Milestones**

1. By 2019, revise the TPP to include both preventive and reactive outbreak-use scenarios.
2. By 2020, complete preclinical evaluation sufficient to progress to human clinical trials for at least three candidate vaccines that align with the TPP and collectively protect against the multiple lineages of LASV.
3. By 2022, further characterize immune responses, following natural infection in humans, to gain insights into potential correlates of protection and/or risk.
4. By 2022, create a plan for licensure pathways for promising LASV candidate vaccines, including addressing options for conducting phase 3 clinical efficacy trials.
5. By 2023, characterize vaccine safety and immunogenicity in the target population for at least two of the most promising candidate vaccines.
6. By 2024, further characterize immune responses following vaccination, to gain insights into potential surrogates of protection to facilitate LASV vaccine research, development and introduction.

7. By 2025, obtain data demonstrating efficacy for at least two promising LASV vaccine candidates through phase 3 clinical trials, if deemed feasible, or through other approaches.
8. By 2026, obtain regulatory approval for at least one LASV vaccine that is aligned with the TPP for use in Lassa fever endemic and at-risk areas.

**Strategic Goal 2:** to identify broad immunization strategies that optimize the potential public-health impact of LASV vaccine.

#### **Milestones**

1. By 2021, define an implementation research plan that crosses endemic and at-risk areas and that addresses vaccine acceptability and policy implications.
2. By 2026, generate vaccination strategies that are consistent with the vaccine attributes for the specific vaccines that become available.

#### **Priority areas/activities**

##### **Research**

- **Determine** the mechanisms of cell-mediated and humoral protective immune responses to LASV vaccines.
- **Identify and standardize**, as feasible, correlates and/or surrogates of protection that are necessary for ongoing research into candidate vaccines and may also be important for vaccine licensure. (Note: it is possible that correlates of protection may differ across different vaccines and a single common one may not be identified).
- **Study** the duration of protective immunity for each type of LASV vaccine.
- **Complete** preclinical evaluation of candidate LASV vaccines for safety, tolerability, immunogenicity, efficacy, correlates of protection and estimation for duration of immunity, and identify the most promising candidates to move forward.
- **Conduct** clinical trials of promising vaccine candidates (including early trials in non-affected areas or in affected areas, as practicable) to determine dose regimen and assess their safety, tolerability, immunogenicity and, if feasible, efficacy in various groups, including special populations.

##### **Product development**

- **Determine** appropriateness of traditional and alternative pathways to licensure for LASV vaccines, as the pathway used will affect development activities.
- **Develop, clinically evaluate and license** safe and effective LASV vaccines, which protect against the multiple LASV lineages, for preventive and reactive/outbreak use.

##### **Key capacities**

- **Establish and maintain** stockpiles of LASV vaccines for use during large Lassa fever outbreaks.
- **Improve** surveillance capabilities in endemic areas to assess the impact of vaccination strategies once vaccines become available.

- **Plan** for clinical vaccine trials to be conducted, including determining the feasibility of conducting trials in non-outbreak versus outbreak settings. If clinical trials are to be conducted primarily when outbreaks occur, then develop advance plans for the emergency use and evaluation of candidate vaccines.

**Policy and commercialization**

- **Provide** guidance on vaccination strategies for various target populations, geographic areas and epidemiologic scenarios once LASV vaccines become available.
- **Develop** guidance for community sensitization to vaccine acceptance and promotion within the community.

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