Lassa Fever Research and Development (R&D) Roadmap

Roadmap purpose: To provide a framework for identifying the vision, underpinning strategic goals, and prioritizing areas and activities (from basic research to advanced development, licensure, manufacture, and deployment) for accelerating the collaborative development of medical countermeasures (MCMs)—diagnostics, therapeutics, and vaccines—against 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; disease occurs both sporadically and as outbreaks. Population studies demonstrating serologic evidence of LASV infection and the presence of occasional sporadic Lassa fever cases in additional West African countries (i.e., Benin, Burkina Faso, Ghana, the Ivory Coast, Mali, and Togo) indicate that other areas of the region also may be at risk. LASV exhibits marked genetic heterogeneity and strains have been phylogenetically placed into four established lineages—three in Nigeria (lineages I-III) and one in the Mano River Union countries of Guinea, Liberia, and Sierra Leone (lineage IV). Three more lineages have been proposed—one in Mali and the Ivory Coast, one found among *Hylomyscus pamfi* rodents in Nigeria, and one in Togo. *Mastomys natalensis* (i.e., the multimammate mouse which also is known as the multimammate rat) has long been considered the sole natural reservoir of LASV, but additional rodent reservoirs (*M. erythroleucus* and *H. pamfi*) recently have 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 feces) 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, feces, or bodily secretions of an LASV-infected individual or reuse of contaminated medical equipment.

Although public health officials often cite annual case estimates of 100,000 to 300,000 LASV infections and up to 5,000 deaths, these numbers are extrapolations from a single longitudinal study conducted over 30 years ago in Sierra Leone. The true public health burden of Lassa fever is unknown and 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 already is recognized to be 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 no or mild symptoms (and often are 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 2 to 21 days; thus, 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 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 topics and issues (for areas that apply to more than one MCM category), diagnostics, therapeutics, and vaccines.

Other aspects of public health preparedness and response, in addition to R&D for MCMs, are critical to successful Lassa fever prevention and control. Examples include understanding the drivers and dynamics of zoonotic transmission from rodents to humans, programs and activities to prevent zoonotic transmission (such as rodent control), access to high-quality personal protective equipment (PPE) for healthcare workers, implementation of adequate infection prevention and control practices in healthcare settings, 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

Robust MCMs to detect, control, 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, accurate, point-of-care diagnostics for Lassa fever; (2) safe and effective treatment, pre-exposure prophylaxis (PrEP), 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 TOPICS AND ISSUES

Current 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, especially for diagnostics and vaccines. 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 certain 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 non-human primates (NHPs); (3) increased regulations, restrictions, and ethical concerns regarding animal research, especially for NHPs; (4) regulations for transport of materials; (5) appropriate experimental design (e.g., challenge strain, route of challenge, timing of challenge, and challenge dose); and (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 down-selection 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.
- The West African region 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 2014-2016 EVD epidemic in this region also resulted in further workforce reductions owing to the deaths of numerous healthcare workers, including those with Lassa fever expertise.
- 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 and 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) 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 impact clinical care and laboratory services, as well as safe storage of therapeutics and vaccines; (4) the remote and sometimes politically unstable nature of the endemic area, 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 skepticism of Western research and medicine.

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

Key needs

- Standardized and validated assays (including assays to compare immunogenicity of different vaccines), reagents, antibodies, nucleic acids, and stocks of LASV challenge strains for R&D of MCMs for Lassa fever, including the availability of validated diagnostic assays for use in epidemiologic research, surveillance activities, and clinical trials of therapeutics and vaccines for Lassa fever.
- 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 utilizing standardized, highly sensitive and specific diagnostic tests with uniform testing algorithms and case definitions across affected countries. These data are needed to better understand the burden of disease and to monitor the effectiveness of Lassa fever MCMs.
- Coordination of preclinical and clinical research for R&D of Lassa fever MCMs.
- 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.
- A determination regarding the feasibility of conducting clinical trials of Lassa fever therapeutics and vaccines, which is needed before considering alternative regulatory pathways for licensure (such as the United States Food and Drug Administration's Animal Rule).
- 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 under the authority of local leadership.
- Prioritization of Lassa fever therapeutics and vaccines that should be moved forward into clinical trials versus those that need additional preclinical research. Head-to-head comparisons of candidate MCMs may be needed to enable these decisions.
- Evaluation of the safety of candidate therapies and vaccines for Lassa fever in animal models prior to clinical trials in vulnerable populations such as pregnant women, children, and immunocompromised persons (including those with HIV infection or malnutrition).
- Increased infrastructure and capacity for post-marketing surveillance of safety and effectiveness for licensed Lassa fever therapeutics and vaccines.
- 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 (e.g., 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; and (3) allow evaluation of new Lassa fever MCMs. In addition, efforts are needed to establish benchmark parameters (such as 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 in order to inform R&D of MCMs.
- 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 are dependent 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 those communities with and without ongoing transmission within the endemic countries in West Africa.
- Ecologic research and modelling are needed to assess the impacts of climate, environmental, demographic, and socioeconomic changes occurring in West Africa on the rodent reservoir to improve forecasting for Lassa fever.
- Social science research is needed to: (1) assess the socioeconomic impact of Lassa fever; and 2) understand how best to engage the West African population (including vulnerable populations) to promote awareness and sensitization about Lassa fever symptoms and prevention programs, participation in clinical trials, and acceptance of Lassa fever MCMs.

Strategic Goals

1. Develop a sustainable value proposition and identify funding sources to promote R&D, availability, and accessibility of Lassa fever MCMs.
2. Improve understanding of the pathogenesis, immunology, and clinical diagnosis of LASV infections to inform the development of MCMs.
3. Support research and surveillance with appropriate sampling methodologies to accurately characterize the current epidemiology and disease burden of Lassa fever in West Africa.

4. 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 healthcare facilities; (4) provide capacity for conducting clinical trials and other field studies applicable to MCM development; and (5) allow assessment and licensure of new MCMs for Lassa fever.

Milestones

[TBD once the strategic goals have been determined.]

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.
- **Generate** research tools to promote R&D of MCMs for Lassa fever (i.e., standardized and validated assays, reagents, antibodies, nucleic acids, and stocks of LASV challenge strains).
- **Refine and validate** animal models for assessment of promising Lassa fever therapeutic and vaccine candidates.
- **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 to enhance the ability of in-country NRAs to work with researchers and product developers toward evaluating and licensing Lassa fever MCMs.
- **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 for 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.
- **Clarify** potential for and possible strategies to promote technology transfer for Lassa fever MCMs.

Schedule of Resources, Coordination, and Implementation

[TBD; will obtain input later in the process.]

Critical Path Analysis

[TBD once the primary activities have been vetted by subject matter experts.]

DIAGNOSTICS

Current 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 (e.g., 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 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. 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.

- 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 (i.e., a gold standard) currently exists to definitively determine who has Lassa fever.
- In Lassa fever survivors, the virus may persist for extended periods of time in immunologically protected sites such as the kidney and gonads. The presence and levels of virus in these immunologically protected sites typically are unknown; thus, this can result in secondary transmission of LASV.
- 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.
- A limited number of facilities exist for confirmatory laboratory diagnosis and treatment of Lassa fever in a region comprising over 5 million square kilometers. This can lead to prolonged delays in diagnosis and initiation of therapy, as well as 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, and (3) sustained resources from international partners and in-country national health ministries.

Key needs

- 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) for clinical management of patients, clinical trials, and surveillance activities.
- 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 point-of-care screening test that is highly sensitive and a confirmatory test that is highly specific.)
- Assays that allow accurate diagnosis across the full disease spectrum, ranging from asymptomatic LASV infection to advanced Lassa fever.
- Lassa fever point-of-care diagnostic assays 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 the West African region and representing the multiple LASV lineages for assay validation.

- 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 both point-of-care and laboratory capability to perform 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, and quality control methods. Additionally, more in-country reference laboratories are needed for confirmatory testing.
- 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.
- If feasible and as a long-term goal, multiplex assays that can detect LASV infection, while simultaneously screening for the presence of other high-consequence pathogens.

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 (i.e. sequencing) 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.

Strategic Goals

1. Promote the development and assessment of affordable, point-of-care, immunologic- and nucleic acid-based Lassa fever RDTs that capture the wide genetic diversity of LASV strains.
2. Develop guidance on forward deployment and best practices for using rapid and confirmatory tests to diagnose Lassa fever.
3. Create a network of laboratories to perform molecular characterization (sequencing) of LASV strains isolated from rodents and humans to assess genetic changes over time and by geographic region in endemic and at-risk areas.

Milestones

[TBD once the strategic goals have been determined.]

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.
- **Perform** 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.

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 point-of-care 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 the 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 (i.e., 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 about 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, which may vary by geographic area.

Schedule of Resources, Coordination, and Implementation

[TBD; will obtain input later in the process.]

Critical Path Analysis

[TBD once the primary activities have been vetted by subject matter experts.]

THERAPEUTICS

Current 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 6 days of illness and when administered intravenously rather than orally; however, scant efficacy data are available for ribavirin and its significant cost and difficulty in procurement present operational challenges for treatment in West Africa.
- Case management and clinical care quality is positively associated with the outcome of Lassa fever (i.e., survival versus death). Not only does West Africa have an insufficient number of healthcare facilities for treatment of Lassa fever but very few facilities have the capability to provide critical care or enhanced supportive care.
- Specific challenges for clinical trials of candidate therapeutics in the endemic area include: (1) delayed presentation of Lassa fever cases to healthcare facilities, which may preclude appropriateness for patient enrollment in clinical research; (2) difficulties in rapidly and accurately diagnosing Lassa fever for prompt initiation of treatment (ribavirin or novel therapies), which may affect evaluation of efficacy; (3) the wide variability in quality of supportive care, which makes the individual evaluation and comparison of therapies difficult; and (4) the availability of ribavirin (appearing on the WHO Model List of Essential Medicines) as an off-label widely used therapy for Lassa fever, which raises potential ethical and sociologic issues for placebo-controlled trials using other therapeutic agents, despite its limitations.

Key needs

- A TPP for Lassa fever therapeutic agents, identifying optimal and desirable characteristics to guide the development of promising treatment approaches.
- Safe, easily administered, well-tolerated, therapeutic agents effective against the multiple LASV lineages, including viable treatment alternatives to ribavirin, for treatment of Lassa fever and prevention of Lassa fever-associated sequelae to improve survival and decrease morbidity and long-term disability.

- Safe and effective PrEP and/or PEP to prevent Lassa fever for high-risk exposure to LASV and guidance on PrEP/PEP use. Such countermeasures are important tools to protect healthcare workers, family caregivers, and burial teams, and to reduce transmission.
- Uniform patient management and minimum standards for supportive care in the West African region 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, and (4) determine mechanisms of viral persistence in immunologically-protected body sites.
- Treatment of Lassa fever with ribavirin has been evaluated in only a single nonrandomized clinical trial and in field studies utilizing retrospective analyses. Additional animal and/or human studies of the efficacy of ribavirin against the multiple LASV lineages and at various stages of Lassa fever disease progression are needed, as well as equivalency trials for alternative administration routes and dosing regimens of ribavirin.
- Several therapeutic agents have demonstrated protection against lethal Lassa fever challenge in animal models (i.e., antivirals such as favipiravir, small-molecule inhibitors such as ST-193, and immune-based agents such as convalescent plasma with high titers of neutralizing antibodies and human monoclonal antibodies); however, additional studies of these and other agents in relevant animal models may be needed before moving into clinical trials to obtain data on efficacy for the multiple LASV lineages, pharmacokinetics, pharmacodynamics, barriers to resistance, and dose and regimen selection. Preclinical data on treatment effectiveness by time of treatment initiation also are needed for these agents.
- Further research is needed on the efficacy of convalescent blood products (including convalescent whole blood, convalescent plasma, convalescent serum, pooled or high-titer immunoglobulin, and polyclonal or monoclonal antibodies) and exchange blood transfusion, for 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 pathogens (such as influenza) that also may protect against Lassa fever. Such approaches may assist with funding, logistics, and technical aspects of research, and 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 the efficacy of treatment at various stages of disease progression are important considerations when conducting such clinical trials.
- Additional data are needed to inform development of guidance on the use of PrEP/PEP and the most appropriate agents to administer to prevent Lassa fever.
- 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 PrEP/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, antidiarrheal agents, and/or 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.

Strategic Goals

1. More fully evaluate ribavirin for treatment of Lassa fever and determine the appropriate role of ribavirin in clinical trials of new therapeutics.
2. Develop, evaluate, and license new and improved affordable therapeutic agents for treatment of Lassa fever and prevention of Lassa fever-associated sequelae, as well as for PrEP/PEP to prevent LASV infection, for the multiple LASV lineages.
3. Determine best strategies for treatment with therapeutic agents and supportive care for Lassa fever patients and develop applicable guidelines.
4. Continue to stimulate research into areas that will enhance prognostic capabilities for Lassa fever, such as use of clinical presentation criteria and/or measurable biomarkers (such as quantitative assays for measuring viral load).

Milestones

[TBD once the strategic goals have been determined.]

Priority Areas/Activities

Research

- **Continue to research** the safety, tolerability, and efficacy of ribavirin, favipiravir, and other 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 and determine best-practice guidelines.

- **Identify, assess, and validate** clinical presentation criteria and/or measureable biomarkers that can reliably predict the severity and outcome of illness in infected patients (such as quantitative assays to measure LASV viral load).

Product development

- **Generate** a TPP for Lassa fever therapeutics.
- **Develop, clinically evaluate, and license** safe and effective therapeutic agents for treatment of Lassa fever that are broadly active against the multiple lineages of LASV.
- **Identify** therapeutic approaches for PrEP/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 (including broad-spectrum agents), and that strategies are created to move them forward.
- **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 and enhanced supportive care.

Policy and commercialization

- **Create** guidelines for patient management and minimum standards for supportive care to facilitate clinical research of novel treatments.
- **Develop** treatment and PrEP/PEP guidance as new therapies become available.
- **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.

Schedule of Resources, Coordination, and Implementation

[TBD; will obtain input later in the process.]

Critical Path Analysis

[TBD once the primary activities have been vetted by subject matter experts.]

VACCINES

Current 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 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 vulnerable populations will likely need to have a relatively low risk profile for adverse reactions, whereas the risk profile may be different if a vaccine is targeted for reactive use in an outbreak situation.)
- 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 will be needed.

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 endpoints for LASV vaccine efficacy trials (i.e., 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 of disease. If clinical trials will be 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 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.
- 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, and (3) measuring the ability of different vaccine types and formulations to remain stable in field conditions in at-risk regions.
- Social science research is needed to determine: (1) community attitudes and barriers towards vaccination, (2) issues pertinent to vaccine strategy implementation, and (3) best mechanisms of community engagement to ensure successful implementation of vaccination programs.
- 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

1. Develop, evaluate, and license affordable LASV vaccines that protect against the multiple LASV lineages for preventive and reactive/outbreak use in Lassa fever endemic and at-risk areas.
2. Identify vaccination strategies that: (1) optimize the potential public health impact of LASV vaccines, (2) consider the regional epidemiology of Lassa fever in at-risk regions, and (3) take into account the vaccine attributes for the specific vaccines that become available.

Milestones

[TBD once the strategic goals have been determined.]

Priority Areas/Activities

Research

- **Determine** the mechanisms of cell-mediated and humoral immune responses to LASV vaccines.
- **Identify** immune correlates of protection that can be used to assess candidate vaccines across different studies.
- **Study** the duration of protective immunity for each type of LASV vaccine and vaccination strategy.
- **Complete** preclinical evaluation of candidate LASV vaccines for safety, tolerability, immunogenicity, efficacy, correlates of protection, and duration of immunity and identify the most promising candidates to move forward.
- **Conduct** clinical trials of promising vaccine candidates (including early trials in affected countries) to determine dose regimen and assess safety, tolerability, and efficacy in various groups, including vulnerable populations.

Product development

- **Determine** appropriateness of traditional and alternative pathways to licensure for LASV vaccines, as the pathway used will impact development activities.
- **Develop, clinically evaluate, and license** safe and effective LASV vaccines that 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 will be conducted primarily when outbreaks occur, then develop advance plans for 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 are available.

Schedule of Resources, Coordination, and Implementation

[TBD; will obtain input later in the process.]

Critical Path Analysis

[TBD once the primary activities have been vetted by subject matter experts.]

BACKGROUND INFORMATION

World Health Organization (WHO) R&D Roadmap Documents and Guidance

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