Lassa vaccine portfolio and clinical development plan

Nadia G. Tornieporth, MD, DTM&H

Accra, 8 November 2018
Outline

• CEPI funded Lassa Fever vaccine portfolio

• Lassa Fever integrated vaccine development

• Ongoing developments and future outlook
CEPI’s initial targets derived from WHO R&D Blueprint

CEPI’s Scientific Advisory Committee chose three initial diseases based on expected Public health impact | Risk of an outbreak occurring | Feasibility of vaccine development

Just in Case Vaccines:

- **MERS-CoV**
  - Affected countries
  - WHO TPP
  - Prophylactic and reactive use

- **Lassa**
  - Prophylactic prioritised

- **Nipah**
  - Reactive use

- **Disease X**
Just-in-Case Vaccines: MERS-CoV, Lassa, Nipah

More than 30 proposals received in first round

Applications from:

• Academic institutions, biotechs, large pharmaceutical companies and Product Development Partnerships
• Broad diversity in vaccine platform technologies
• Proposals from North America, Europe, Africa, Middle East, South East Asia and Australia

New vaccines for a safer world
www.cepi.net
7 partnership agreements signed

<table>
<thead>
<tr>
<th>Disease</th>
<th>Lassa and MERS</th>
<th>Lassa and MERS</th>
<th>Lassa</th>
<th>Nipah</th>
<th>Lassa</th>
<th>MERS</th>
<th>Lassa, MERS, and Nipah</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investment (up to)</td>
<td>$37.5 M</td>
<td>$56.0M</td>
<td>$54.9 M</td>
<td>$25.0 M</td>
<td>$36.0 M</td>
<td>$36.0 M</td>
<td>$19.0M</td>
</tr>
</tbody>
</table>
Objectives of priority pathogen vaccine development

- 5 year funding to advance the most promising vaccine candidates for the three priority pathogens

1. Late preclinical development
   Preclinical Proof of Concept (PoC)

2. Phase I
   Safety and immunogenicity (S & I)

3. Phase II S & I
   final dose and regimen selection

4. Investigational stockpile of 100,000 doses
   Ready for outbreak/efficacy trials
CEPI priority pathogen portfolio

CEPI funds late preclinical through phase II S&I and investigational stockpile generation

More than 30 applications received

- Academic institutions, biotechs, large pharmaceutical companies and product development partnerships
- Wide diversity in vaccine platform technologies
- Proposals from North America, Europe, Africa, Middle East, South East Asia and Australia

Under contract negotiation

* Investment in preclinical only

Lassa
Nipah
MERS CoV

IAVI* rVSVΔG
Inovio DNA
Inovio DNA

Profectus* rVSVNC4ΔG
Themis Measles vector
IDT MVA

Themis* Measles vector
Profectus subunit
UOXF/J ChAdOx1

UOXF/J ChAdOx1
Rep. vector
Rep. vector
Rep. vector

Confidential
# Lassa portfolio – Vaccine profiles

<table>
<thead>
<tr>
<th></th>
<th>Themis</th>
<th>Inovio</th>
<th>IAVI</th>
<th>Replicating vector</th>
<th>Profectus</th>
<th>Non – rep Vector</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technology</strong></td>
<td>Measles virus</td>
<td>DNA + Electroporation</td>
<td>rVSVΔG Live replicating</td>
<td>rVSVNC4ΔG Live replicating</td>
<td>rVSVNC4ΔG Non-replicating</td>
<td>ChAdOx1 Non-replicating</td>
</tr>
<tr>
<td>Lassa transgene</td>
<td>GPC + NP</td>
<td>GPC</td>
<td>GPC</td>
<td>GPC</td>
<td>GPC</td>
<td>GPC</td>
</tr>
<tr>
<td>Josiah strain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose schedule</strong></td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Project status</strong></td>
<td>Preclinical PoC in NHP</td>
<td>Preclinical PoC in NHP</td>
<td>Preclinical PoC in NHP#</td>
<td>Preclinical PoC in NHP#</td>
<td>Immuno in mice</td>
<td>Immuno in mice</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>Vero</td>
<td>E. coli</td>
<td>Vero</td>
<td>Vero</td>
<td>Vero</td>
<td>Suspension cell line</td>
</tr>
</tbody>
</table>

rVSV: recombinant vesicular stomatitis vector  
GPC: glycoprotein precursor  
NP: nucleoprotein  

#Repeat PoC with plaque purified virus
## Lassa vaccine development challenges

<table>
<thead>
<tr>
<th>Knowledge gap</th>
<th>Areas of work</th>
<th>Who?</th>
<th>When?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>• Develop master epi protocol</td>
<td>• CEPI funded consortia/affected countries/WHO</td>
<td>• Data to inform efficacy trial in 2022</td>
</tr>
<tr>
<td></td>
<td>• Conduct cohort studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is an efficacy trial possible?</td>
<td>• Epidemiology</td>
<td>• CEPI funded epi consortia</td>
<td>• Data to inform efficacy trial in 2022</td>
</tr>
<tr>
<td></td>
<td>• Incidence data</td>
<td>• WHO blueprint team</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Case definition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assays, standards and animal models</td>
<td>• Reference sera and antigen</td>
<td>• Assays, standards and animal model working group</td>
<td>Reference material to developers early 2019</td>
</tr>
<tr>
<td></td>
<td>• Animal model development</td>
<td></td>
<td>Animal model development Q4 2019</td>
</tr>
<tr>
<td></td>
<td>• Strain availability</td>
<td></td>
<td>Strains Q4 2019</td>
</tr>
<tr>
<td>Clinical trial capacity in affected</td>
<td>• Map and evaluate trial capacity in W. Africa</td>
<td>• CEPI with partners</td>
<td>• End 2018 ensure site capacity available for S&amp;I studies</td>
</tr>
<tr>
<td>countries</td>
<td>• Build capacity through epi studies</td>
<td>• WHO/CEPI Lassa working group</td>
<td>• Sites available for efficacy trials 2022</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lassa diagnostics</td>
<td>• ELISA and PCR development</td>
<td>• CEPI/FIND/WHO</td>
<td>• Diagnostics validated Q3 2019</td>
</tr>
</tbody>
</table>
Clinical development of Lassa vaccine candidates

Timelines for first clinical trials

- Proactive engagement of affected countries to be briefed on vaccine technology and development plans
- The investigational sites in affected countries will need to be ready
- Epidemiology data on the critical path for trial design
- In close collaboration with WHO (HQ and AFRO) and affected countries
Clinical site mapping in Lassa-affected countries: Significant numbers of clinical sites with good baseline capabilities

- Total mapped sites: 44
- Response rate: 37 out of 44 (84%)
- Assessment of “ready now” sites
- Identification of capacity strengthening priorities across sites
- Operational scores which remain to be validated through site visits
- Focus on vaccine trial capabilities

*Courtesy of Kolawole Salami, MB BS*
Lassa vaccine clinical development plan

**Phase I in EU/US**
- First in Human: Safety and immunogenicity
  - Dose selection

**Epidemiology in W. Africa**
- High incidence areas identified
- Low or unpredictable incidence
  - Occurs in outbreaks

**Clinical trial capacity building**

**Phase IIa safety and immunogenicity trials**
- Conduct clinical endpoint efficacy study in high incidence areas
- Classical licensure pathway
- Develop phase III protocol for outbreak evaluation
- Licensure based on outbreak study
- Consider need for additional S&I trials
- Licensure animal rule/surrogate marker
- Post-licensure effectiveness study in outbreak

**Licensure and introduction**
WHO Lassa Fever Vaccine Target Product Profile (WHO 2017)

- TPP defines two potential scenarios
  1. Preventive use in endemic areas
  2. Reactive use under outbreak conditions

- Ideally safe for all age groups, pregnant/lactating women, immunocompromised populations

- Cross-protection against all clades with VE ≥70%

- Single dose (with booster doses for LT protection)
Efficacy trials of Lassa Vaccines: endpoints, trial design, site selection (WHO workshop April 2018): Gaps

- True disease burden is “highly uncertain” (WHO workshop final report)
  - by lineage
  - potential role of human-to-human transmission
  - the contribution of asymptomatic and mild Lassa infections to LF burden

- No immunological surrogate or correlate of protection

- Diagnostic assays not yet licensed
Efficacy trials of Lassa Vaccines: endpoints, trial design, site selection (WHO workshop April 2018): Gaps (2)

- Well-designed seroprevalence studies and enhanced surveillance, including ecological studies, in West-Africa

- A thorough analysis of the 2018 Nigeria LF outbreak data to better estimate epidemiological drivers and estimates

- Integrated data management systems at the national level and standardization of surveillance tools and data collection across West-African countries

- Standardized, validated assays
Efficacy trials of Lassa Vaccines: endpoints, trial design, site selection (WHO workshop April 2018): Trial endpoints

A randomized placebo-controlled design is preferred if feasible

- Laboratory-confirmed LF of any severity and severe LF illnesses should be co-primary endpoints of a Phase 2b/3 Lassa vaccine trial
  - Linked to a standardized case definition for LF confirmed cases and to the surveillance system of a given country
  - LF incidence rates define sample size
  - Multi-site/multi-season approach

- Secondary/exploratory endpoints
  - Laboratory-confirmed LASV infection, LF-caused mortality, and potential immunological surrogates of protection
Efficacy trials of Lassa Vaccines: endpoints, trial design, site selection (WHO workshop April 2018):

Needs

- More research to assess the true incidence of LF as well as to identify where transmission occurs, to define sites

- Sero-prevalence surveys and longitudinal cohorts to help inform site selection for vaccine trials

- Standardization (e.g. master protocol, LF case definition), and fit-for-purpose instruments (e.g. laboratory assays) required for multi-site trials

- LASV strain sequencing to measure lineage specific protection
Preparing for Lassa vaccine clinical trials with targeted epidemiology studies

• Generate comprehensive and current epidemiological data on Lassa Fever
  • Identify common elements to allow comparability of data

• Inform clinical vaccine (efficacy) trial design

• Inform future vaccine use

• Strengthen site and investigator capacity to conduct clinical trials

• Engage with the community, increase awareness about Lassa
A challenge on many fronts

- No vaccines
- Limited Research Capacity
- No stockpiles
- No plans for delivery

**FY2018**

- Portfolio Established
  - Lassa
  - MERS
  - Nipah
  - Disease X

- Capacity Building Partnerships
  - World Bank
  - EDCTP
  - CARI
  - Industry

- Regulatory Science and Innovation
  - Expanded pre-competitive space
  - Joint development of standards
  - Animal and clinical models
  - Common clinical protocols

- No stockpiles

**FY 2022**

- Vaccines have completed P2
- Research capacity in countries at risk
- Stockpiles in place
- Delivery and dispensing plans in place

- CEPI
How CEPI works
Developing consensus positions together

- CEPI’s aim is to contribute – with its partners and stakeholders – to objectives of the WHO Lassa Fever R&D Roadmap
  - Building on national research plans and existing studies

- CEPI’s portfolio of projects is rapidly expanding
  - Lassa vaccine candidates to enter clinical trials in 2019

- This workshop aims to arrive at a consensus on core protocol elements to enable the launch of epidemiological studies

- CEPI welcomes your expertise
Thank you

Questions?
CEPI’s Board

SAC chair – Helen Rees
JCG chair – Peggy Hamburg
World Bank – Tim Evans
WHO – Peter Salama
CEPI CEO: Richard
Rajeev Venkayya
Joanne Liu
John Nkengasong
David Reddy

Foundation – Trevor Mundel
Sovereign – Norway Tore Godal
Sovereign – Germany Joachim Klein
Sovereign – Japan Ichiro Kurane

Peter Piot
Cherry Kang
Awa Coll-Seck

Jane Halton (chair)
SAC Membership

Helen Rees (Chair)
Wits Reproductive Health and HIV Institute

James Robinson (Vice Chair)
James Robinson Biologics Consulting

Alash’le Abimiku
Institute of Human Virology

Alan D. Barrett
University of Texas Medical Branch

Daniel Brasseur
Consultant

Christian Bréchot
Institut Pasteur

Paula Bryant
US National Institutes of Health

Ralf Clemens
Bill & Melinda Gates Foundation

Inger Damon
US Centers for Disease Control and Prevention

Delese Mimi Darko
Ghana Food and Drug Authority

John Edmunds
London School of Hygiene & Tropical Medicine

George Fu Gao
Chinese Center for Disease Control and Prevention

Christian Happi
African Center of Excellence for Genomics of Infectious Diseases

Penny Heaton
Bill & Melinda Gates Medical Research Institute

Tom Kariuki
Alliance for Accelerating Excellence in Science in Africa

Phil Krause
US Food and Drug Administration

Myron Levine
University of Maryland

Yves Lévy
INSERM

Kathleen Neuzil
University of Maryland

Stanley Plotkin
VaxConsult

Connie Schmaljohn
USAMRIID

Kenji Shibuya
Department of Global Health Policy, University of Tokyo

Peter Smith
London School of Hygiene & Tropical Medicine

Michel De Wilde
Consultant

Non-voting members

Vaseeharan Sathiyamoorthy
World Health Organization

Ali Allouche
Takeda

Kathrin Jansen
Pfizer

Jean Lang
Sanofi Pasteur

Johan van Hoof
Johnson & Johnson
Distribution of clinical trial sites in Lassa affected countries
# Capacity strengthening needs identified

<table>
<thead>
<tr>
<th>Cat. A sites</th>
<th>Cat. B sites</th>
<th>Cat. C sites</th>
<th>Cat. D sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Better access to donor funds and sponsor initiated clinical trials in countries highly endemic for LF</td>
<td>• Qualified scientific and support staff</td>
<td>• Mostly new sites or sites utilised in a previous outbreak</td>
<td>• No information available.</td>
</tr>
<tr>
<td>• Limited investment in facilities to handle investigational products and run containment trials</td>
<td>• ICH audits, ICH- GCP and GCLP training</td>
<td>• Little clinical trial experience</td>
<td>• Declined participation or no response</td>
</tr>
<tr>
<td>• Standard ICH-GCP audits and trainings of staff on GCP and GCLP</td>
<td>• Investment in facilities</td>
<td>• Requires significant investment in human resources and infrastructure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• More exposure to clinical trials and epidemiological studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Confidential**
Lassa outbreak in Nigeria

• From 1st January to 9th September 2018, a total of 2515 suspected cases were reported from 22 states.
• Of these, 504 (including 39 HCWs) were confirmed positive, 10 are probable, 2002 negative.
• 7328 contacts identified.
• 132 deaths in confirmed cases and 10 in probable cases.
• Case Fatality Rate in confirmed cases is 26%