Development of an innovative multivalent mRNA vaccine against HFMD

Consortium by Hilleman Labs

WHO mRNA vaccine meeting, 18-19 March 2024
Hand, Foot and Mouth Disease (HFMD)

**General**
- Highly contagious
- Common in young children
- Group of enteroviruses – coxsackievirus A viruses, enterovirus A71, echoviruses
- Pathogenesis
  - Faecal-oral, direct
  - Replicate in oropharynx
  - Viraemia and dissemination to target organs (CNS, skin)
  - Excreted in pharynx and faeces for weeks

**Symptoms**
- Fever, sore throat, mouth ulcers
- Herpangina vs HFMD
- Blisters on palms of hands and soles of feet
- Symptoms usually appear 3 to 5 days after exposure
- Recurrent HFMD – 0.45%

**Complications**
- Rare neurological complications
- Aseptic meningitis, brain stem encephalitis with neurogenic edema
- In infants and young children (mean age < 2 years old)
- More commonly associated with EV-A71 (0.1-1.1% severe; 0.01-0.03% fatal)
- Long-term neurological sequelae


Additional information:
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References:
Hand Foot and Mouth Disease: A High Incident Disease with Risk Of CNS Complications And Death

**Symptoms (mild cases)**
- Blister-like sores
- Fever
- Eating or drinking less
- Sore throat
- Feeling unwell
- *Most resolve in 7–10 days*

**Symptoms (Central Nervous System complications)**
- Aseptic meningitis
- Cerebella ataxia
- Poliomyelitis-like paralysis
- Acute brainstem encephalitis
- Fulminant neurogenic pulmonary edema
- *May result in death*

**HFMD (all causes)**
- 6% of cases require hospitalization

**HFMD (EV71 confirmed)**
- 18.7% of hospitalized patients develop CNS complications
- 5% of patients with CNS complications die
- 36.9% of hospitalized patients develop CNS complications
- 10.5% of patients with CNS complications die

Koh et. al. *BMJ* 2018
Enteroviruses

- Family of Picornaviridae
- Genus Enterovirus
- Single-stranded positive sense RNA (~7.4kb)
- Capsid proteins VP1 – VP4
- VP1-3 receptor binding, antigenicity
- Non-structural polyprotein processing, replication
- Receptors – SCARB2, PSGL-1, heparan sulfate etc.

Epidemiology of HFMD

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>1,952,435</td>
<td>56</td>
</tr>
<tr>
<td>Japan</td>
<td>358,764</td>
<td>0</td>
</tr>
<tr>
<td>Korea</td>
<td>289,700</td>
<td>0</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>358</td>
<td>0</td>
</tr>
<tr>
<td>Macau</td>
<td>3,402</td>
<td>0</td>
</tr>
<tr>
<td>Singapore</td>
<td>33,663</td>
<td>0</td>
</tr>
<tr>
<td>Vietnam</td>
<td>48,009</td>
<td>1</td>
</tr>
</tbody>
</table>

Hand, Foot and Mouth Disease Situation Update 2017. WHO.
https://apps.who.int/iris/handle/10665/274106
### Disease Burden of HFMD

#### Annual Disability-adjusted Life – Year (DALY) Losses in eight Asian Countries/Regions with 95% Credible Intervals

<table>
<thead>
<tr>
<th>Country or Region</th>
<th>DALY</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>People’s Republic of China (excluding Hong Kong and Taiwan)</td>
<td>75,881</td>
<td>(31,835 to 202,591)</td>
</tr>
<tr>
<td>Hong Kong Special Administrative Region, People’s Republic of China</td>
<td>285</td>
<td>(115 to 767)</td>
</tr>
<tr>
<td>Japan</td>
<td>5,456</td>
<td>(2.290 to 14,589)</td>
</tr>
<tr>
<td>Malaysia</td>
<td>2,723</td>
<td>(1,138 to 7,281)</td>
</tr>
<tr>
<td>Singapore</td>
<td>259</td>
<td>(104 to 748)</td>
</tr>
<tr>
<td>Taiwan, Republic of China</td>
<td>1,084</td>
<td>(435 to 3,052)</td>
</tr>
<tr>
<td>Thailand</td>
<td>3,928</td>
<td>(1,644 to 10,536)</td>
</tr>
<tr>
<td>Vietnam</td>
<td>7,248</td>
<td>(3,042 to 19,414)</td>
</tr>
</tbody>
</table>

  - Total of 94,313 hospitalized HFMD cases
  - HFMD economic burden – US $90,761,749

*BMJ Global Health 2018; 3:e000442*

#### Malaysia: Second Most Common Infectious Disease

- **Total of 94,313 hospitalized HFMD cases**
- **HFMD economic burden – US $90,761,749**

*Ministry of Health Malaysia*
## The HFMD Vaccine Development Landscape

<table>
<thead>
<tr>
<th>Stage</th>
<th>Hillemann PRIOR Asset</th>
<th>Sinovac</th>
<th>Chinese Academy of Medical Sciences (CAMS)</th>
<th>Beijing Vigoo</th>
<th>Enimmune</th>
<th>Medigen</th>
<th>inno.N</th>
<th>Sentinext Therapeutics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus</td>
<td>EV-A71</td>
<td>EV-A71</td>
<td>EV-A71</td>
<td>EV-A71</td>
<td>EV-A71</td>
<td>EV-A71</td>
<td>EV-A71 (bivalent)</td>
<td>EV-A71</td>
</tr>
<tr>
<td>Technology</td>
<td>inactivated whole virus (binary ethylenimine)</td>
<td>inactivated whole virus (formalin)</td>
<td>inactivated whole virus (formalin)</td>
<td>inactivated whole virus (formalin)</td>
<td>inactivated whole virus (formalin)</td>
<td>inactivated whole virus (formalin)</td>
<td>Virus-like Particles (VLP)</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>94.7% year one 95.1% year two</td>
<td>97.40%</td>
<td>90.0% year one 94.8% year two</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registration and target countries</td>
<td>China (licensed 2015)</td>
<td>China (licensed 2015)</td>
<td>China (licensed 2016)</td>
<td>(Taiwan and Vietnam) stated intention to market across ASEAN countries</td>
<td>(Korea)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Vaccine Impact in China

First Inactivated EV-A71 Vaccine Was Approved

- **62.80%** at the end of 2015 (EV-712)
- **37.20%** from 2013 to 2015 (Non-EV-71)
- **32.80%** from 2017 to 2019 (Non-EV-71)

**HFMD: Changes after EV-A71 vaccine was approved (2013-2015 vs 2017-2019)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence rates*</td>
<td>-8.05</td>
</tr>
<tr>
<td>Severe illness rates*</td>
<td>-62.20</td>
</tr>
<tr>
<td>Mortality rates*</td>
<td>-83.78</td>
</tr>
<tr>
<td>Severe / Cases (%)</td>
<td>-58.82</td>
</tr>
<tr>
<td>Death / Cases (%)</td>
<td>-100.00</td>
</tr>
<tr>
<td>Death / Severe Cases (%)</td>
<td>-56.85</td>
</tr>
</tbody>
</table>

### Notes

- Currently mostly monovalent with multi-valent on horizon
- Currently mostly inactivated whole virus with one VLP on horizon
- Currently limited to China with other geographies on the horizon
- Mostly similar characteristics such as:
  - IM route of administration
  - 2 dose, 28 days apart (except Medigen)
  - Adjuvanted (alum hydroxide or phosphate)
  - Efficacy from 90% in year one to >95% in year two

*Adapted: Presentation by Yoke Fun Chan at WHO mRNA meeting, BKK Dec 2023*
Why should we make an innovative combination mRNA vaccine for HFMD?

There is need for a multivalent HFMD vaccine. The classic inactivated whole virus approach does not easily allow for a balanced response. Target Ag are reasonably well defined for enteroviruses making an mRNA candidate feasible.

Processes will allow for reduced cost and time, aiming for low COGs for final product. Access to use of any approved LNP for LMIC is unrestricted. There will be increased mRNA production capacity in the region, especially LMICs.

Further considerations:
- Target population
- Need for sufficient thermostability
- Complexity to optimize various mRNA constructs that come together in 1 final product.
Overview of Project Development Plan & Objectives

1. Research & Pre-clinical
   - Define vaccine strategy
   - Generate and characterize mRNA construct, synthesize and characterize LNP-mRNA
   - Immunogenicity studies to identify RNA construct that elicit neutralizing antibodies

2. CMC Development
   - Drug substance process development
   - Analytical development
   - Drug product formulation development
   - Stability studies
   - GLP Toxicology

3. GMP Production
   - Tech transfer to GMP manufacturing
   - GMP production for clinical studies
   - QC release assays method validation
   - Stability studies

4. Ph 1 Clinical Studies
   - Clinical phase I Studies
Consortium Partners *(indicative)*

Note: Consortium partners as listed above will need further confirmation.
Our capabilities in CMC and preclinical R&D along with GMP manufacturing position us as a key lead for early product development.

**R&D Laboratory for CMC and Preclinical**
- Upstream and downstream process development, drug product development, formulation and analytical development for vaccines and biologics

**GMP Facility for Pilot-scale Manufacturing**
- Drug Substance suites which can be adapted for all platforms, including nucleic acid
- Pilot-scale Drug Product Formulation and Fill & Finish bench-scale lyophilization suite

- Technology transfer from R&D to manufacturing
- Adaptation of new manufacturing condition
- Antigen production

- Delivery system establishment
- Vaccines formulation development
- Manufacturing for safety studies

- Upscale manufacturing GMP
- Critical analytical assay validation

- Fill & Finish
- Established manufacturing process
THANK YOU

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