Hilleman Laboratories

MSD · Wellcome Trust Joint Venture

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

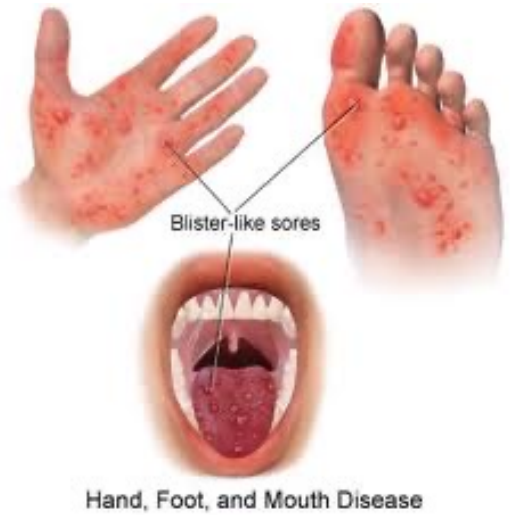
- Fever, sore throat, mouth ulcers
- Herpangina vs HFMD
- Blisters on palms of hands and soles of feet
- Symptoms usually appear 3 to 5 days after exposure
- Recurrent HFMD – 0.45%[4]

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)[1, 2]
- Long-term neurological sequelae[3]

1. *Rev Med Virol* 2019, 29: e2073. 2. *eBiomedicine* 2020, 62: 103078. 3. *Eur J Paediatr Neurol* 2018, 22:763-773. 4. *Emerg Infect Dis.* 2018, 24: 432-442

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



Hand, Foot, and Mouth Disease

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

Koh et. al. *BMJ* 2018

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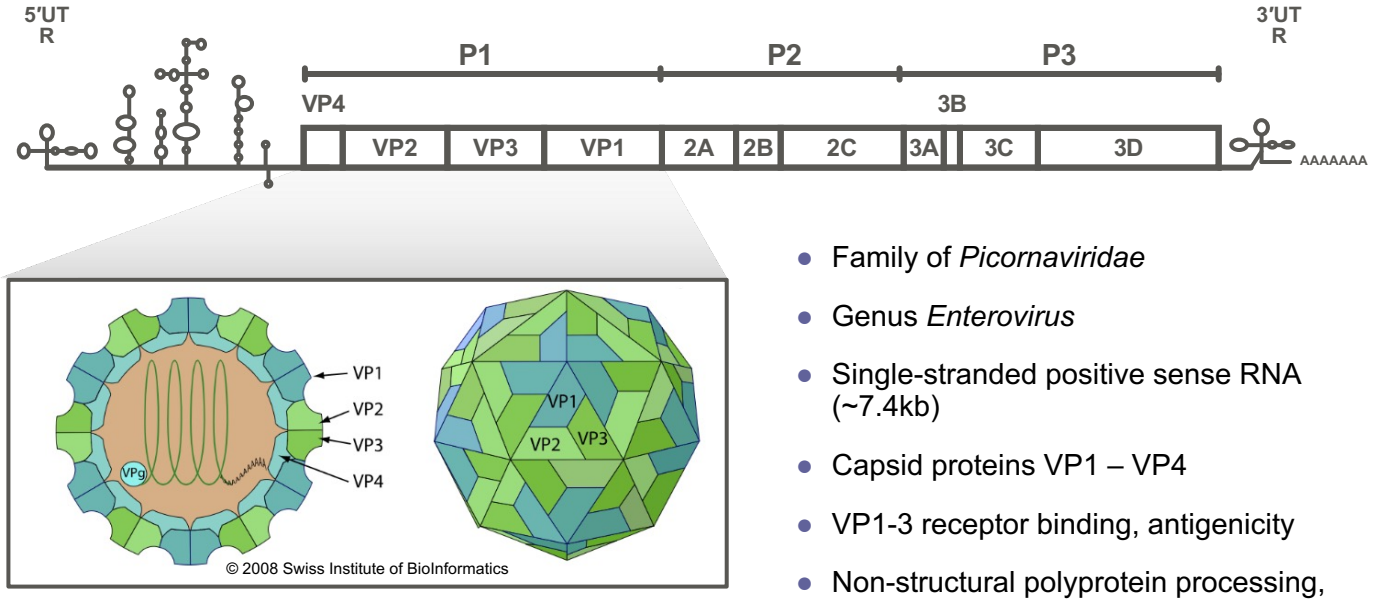
Enteroviruses



Neurology Asia 2010, 16:1-15, https://viralzone.expasy.org/97

- 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

Total Cases of HFMD under WHO Surveillance (2017)

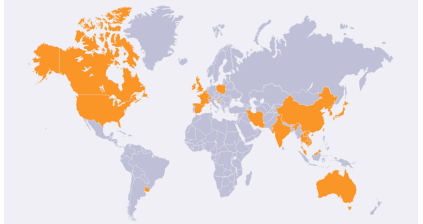
Country	Total	Deaths
China	**1,952,435**	**56**
Japan	**358,764**	**0**
Korea	**289,700**	**0**
Hong Kong	**358**	**0**
Macau	**3,402**	**0**
Singapore	**33,663**	**0**
Vietnam	**48,009**	**1**

Zhu et al. *Current status of hand-foot-and-mouth disease*, 2023

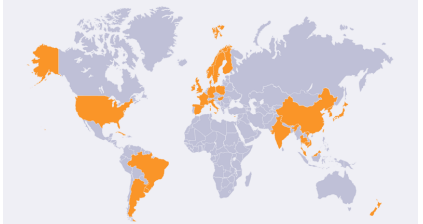
Hand, Foot and Mouth Disease Situation Update 2017. WHO. https://apps.who.int/iris/handle/10665/274106

A: EV-A71

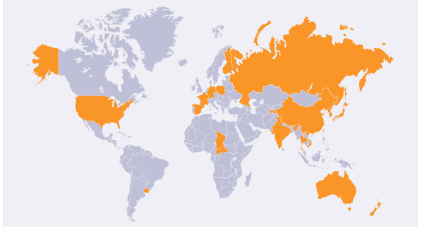
B: CVA16



C: CVA6



D: CVA10



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Disease Burden of HFMD

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

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

- 96,900 (95% CI 40,600–259,000) age-weighted DALYs per annum

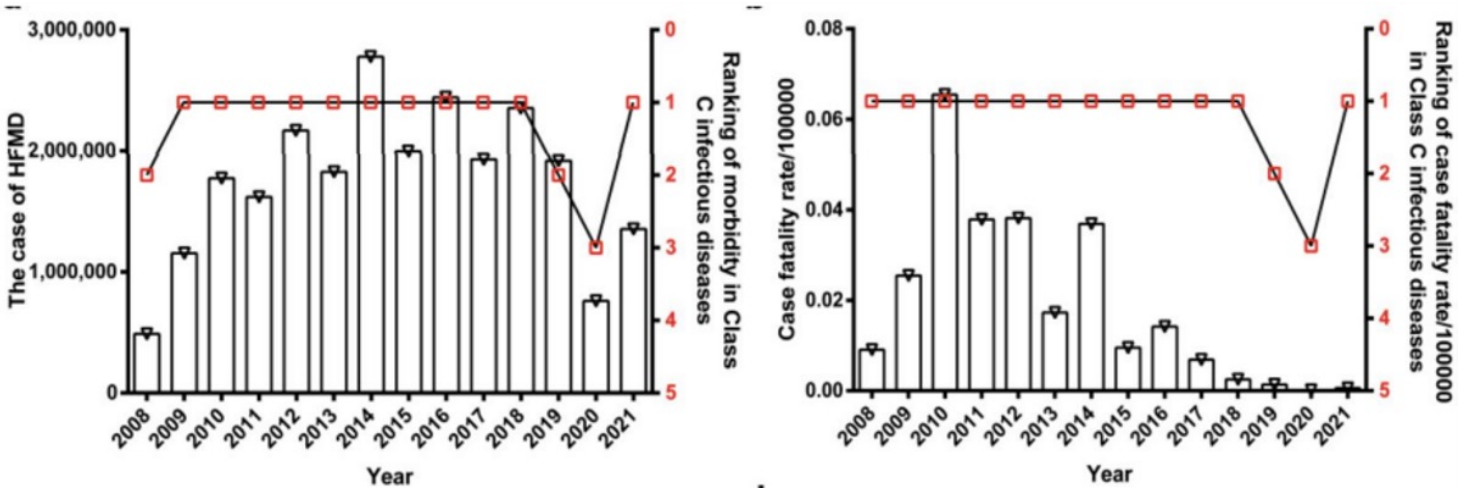
BMJ Global Health 2018; 3:e000442

Vietnam (2016–2017)

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

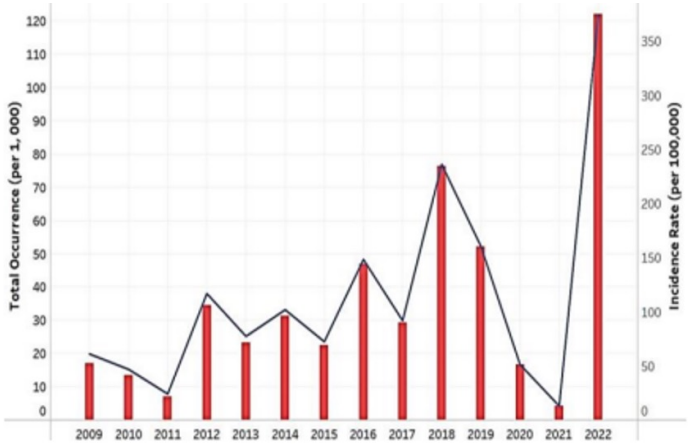
Open Forum Infectious Diseases 2019; 6:ofz284

China: HFMD Morbidity Cases Remained at Approximately 2 Million



Int. J. Mol. SCI. 2023, 24:169

Malaysia: Second Most Common Infectious Disease



Ministry of Health Malaysia

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The HFMD Vaccine Development Landscape

	Hilleman PRIOR Asset	Sinovac	Chinese Academy of Medical Sciences (CAMS)	Beijing Vigoo	Enimmune	Medigen	inno.N	Sentinext Therapeutics
Stage		Licensed	Licensed	Licensed	Phase III	Phase III	Phase I	Phase I
Virus	EV-A71	EV-A71	EV-A71	EV-A71	EV-A71	EV-A71	EV-A71/CV-A16 (bivalent)	EV-A71
Technology	inactivated whole virus (binary ethylenimine)	inactivated whole virus (formalin)	inactivated whole virus (formalin)	inactivated whole virus (formalin)	inactivated whole virus (formalin)	inactivated whole virus (formalin)	inactivated whole virus	Virus-like Particles (VLP)
Efficacy		94.7% year one 95.1% year two	97.40%	90.0% year one 94.8% year two		100%		
Registration and target countries		China (licensed 2015)	China (licensed 2015)	China (licensed 2016)	(Taiwan and Vietnam)	(Taiwan and Vietnam) stated intention to market across ASEAN countries	(Korea)	(Malaysia and Australia)

Currently mostly monovalent with multi-valent on horizon

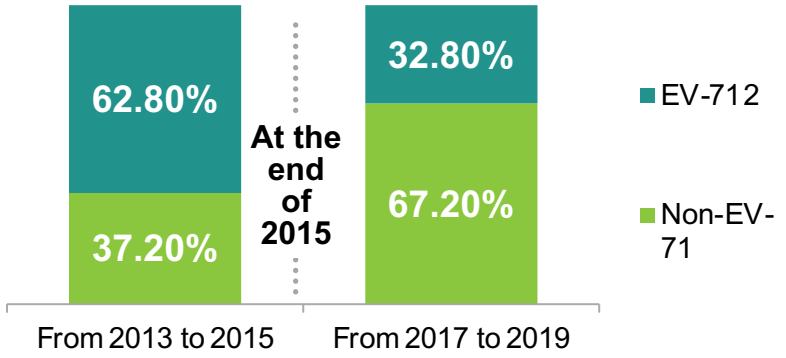
Currently mostly inactivated whole virus with one VLP on horizon

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**

Vaccine Impact in China

First Inactivated EV-A71 Vaccine Was Approved



The Lancet Regional Health – Western Pacific 2022;20: 100370, *Vaccine* 2021, 39: 3319-3323

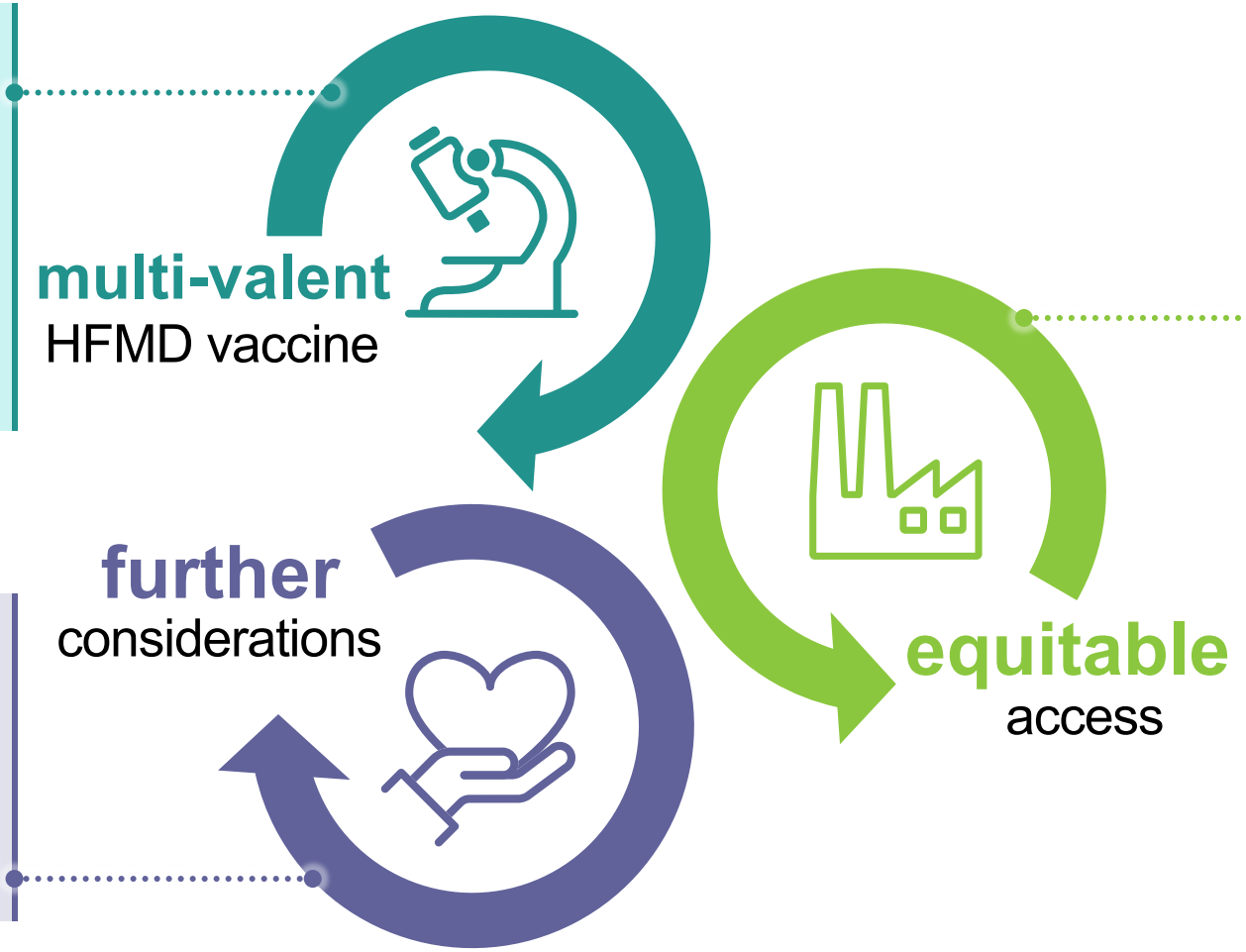
HFMD: Changes after EV-A71 vaccine was approved (2013-2015 vs 2017-2019)

	Change %
Incidence rates*	-8.05
Severe illness rates*	-62.20
Mortality rates*	-83.78
Severe / Cases (%)	-58.82
Death / Cases (%)	-100.00
Death / Severe Cases (%)	-56.85

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.



There are some factors for further consideration, including the **target population**, need for **sufficient thermostability**, and **complexity to optimize** various mRNA constructs that come together in 1 final product.

Processes will allow for **reduced cost and time, aiming for low COGs** for final product

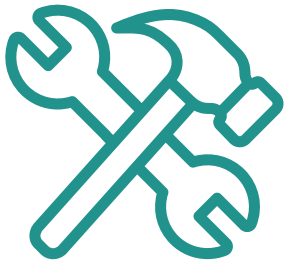
Access to use of any approved LNP for LMIC is unrestricted

There will be **increased mRNA production capacity** in the region, especially LMICs

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

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Consortium Partners *(indicative)*




1 Research & Pre-clinical

2 CMC Development

3 GMP Production

4 Ph 1 Clinical Studies

NUS National University of Singapore

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Genome Institute of Singapore
GIS

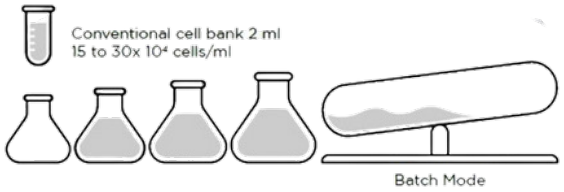
Bioprocessing Technology Institute
BTI

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

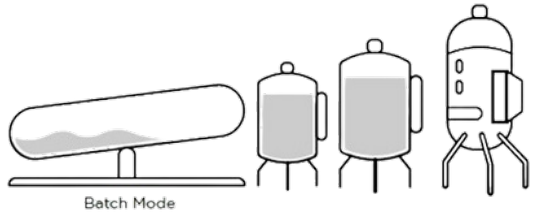
R&D Laboratory for CMC and Preclinical

- Upstream and downstream process development, drug product development, formulation and analytical development for vaccines and biologics



Scale Up

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

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THANK YOU

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