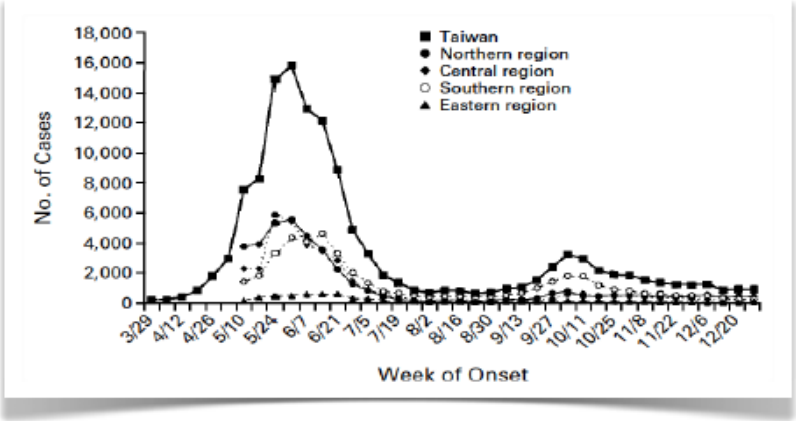
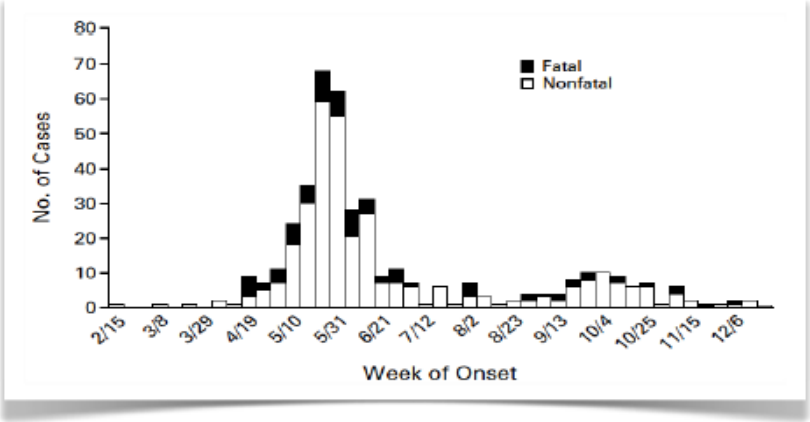
Updates on clinical trials of EV71 vaccine

Kathy Tai
Medigen Vaccine Biologics Corp.（MVC）
September 21,2019

The NEW ENGLAND JOURNAL of MEDICINE

1998 Enterovirus 71 Epidemic in Taiwan





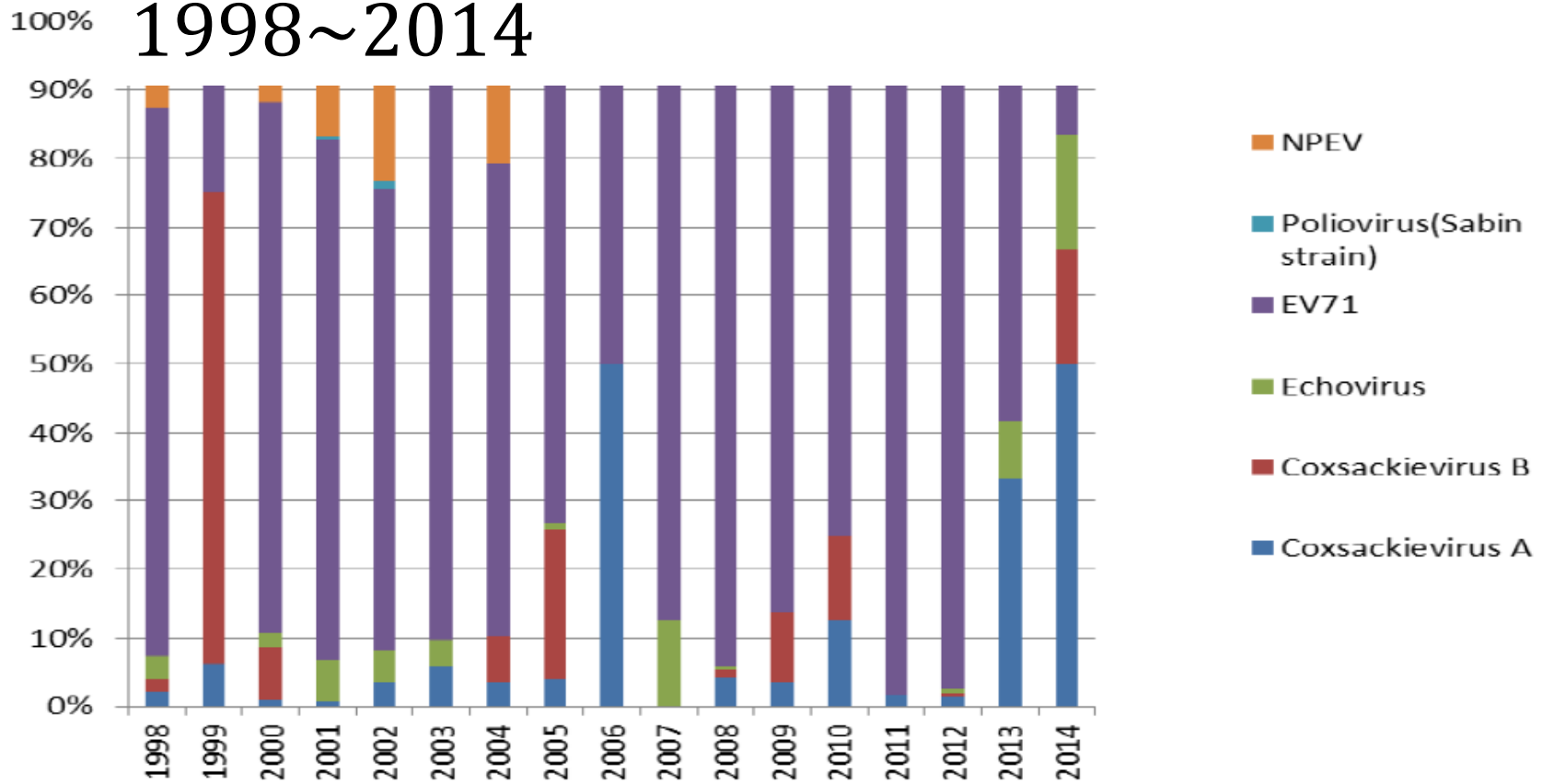
- 405 severe cases, 78 deaths
- Fatality:86% <3 y/o, severe case: 69% < 3 y/o
- Most severe form:
  brainstem encephalitis resulted in cardiopulmonary collapse

Ho M et al N Engl J Med 1999; 341:929-935

Although the number of infection decreased compared to the same period of last year, **the amount of deaths rose.**

In HCM City's Children No1 Hospital, the number of patients hospitalised for the disease has **increased five times in the past three weeks** leaving the hospital overcrowded.

Serotypes of Enterovirus infection with Severe Complications in Taiwan During 1998~2014



EV-A71 contributed to the majority of severe complications

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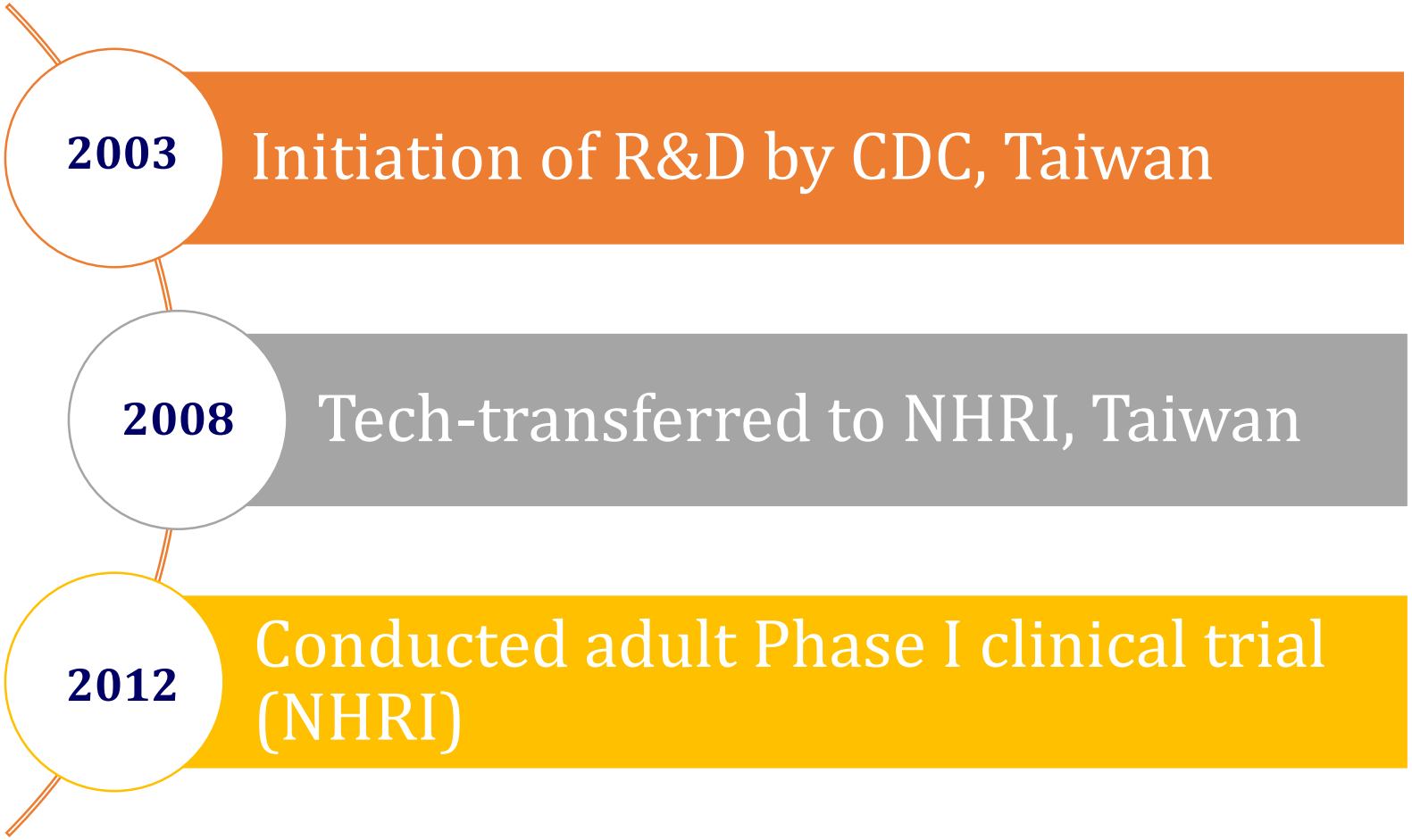
The current stage of six adjuvanted and inactivated EV71 vaccines

Developer	Strain	Antigen Amount	Cell line	Age	Efficacy	Status
CAMS, China	C4	100 U (2 μg)	Human diploid	6-71m	97.4%	Licensed in Dec 2015
Sinovac, China	C4	400 U (1 μg)	Vero	6-35m	94.8%	Licensed in Jan 2016
Vigoo, China	C4	320 U (0.5 μg)	Vero	6-35m	90.0%	Licensed in Mar 2017
Enimmune, Taiwan	B4	1 μg	Vero	2m-6y	ND	Phase III
MVC, Taiwan	**B4**	**2.5 μg**	**Vero**	**2m-5y**	**ND**	**Phase III**
Inviragen (Takeda)	B2	0.3/3 μg	Vero	21-45 yr	ND	Phase I completed

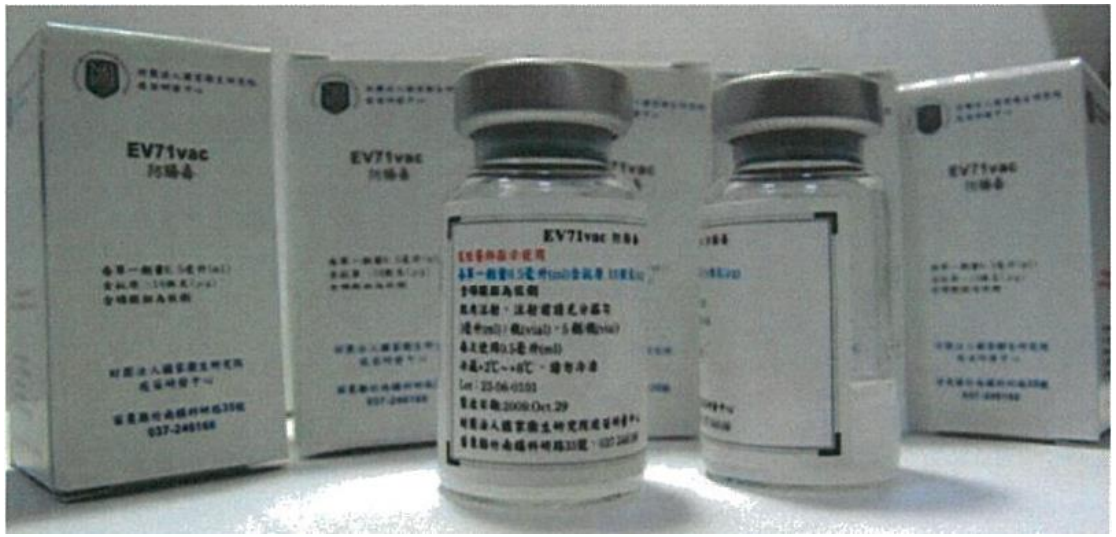
QY Mao, et al. EV71 vaccine, a new tool to control outbreaks of hand, foot and mouth disease (HFMD). Expert Review of Vaccines: 2016 January

Evolutions of Ev71 vaccine

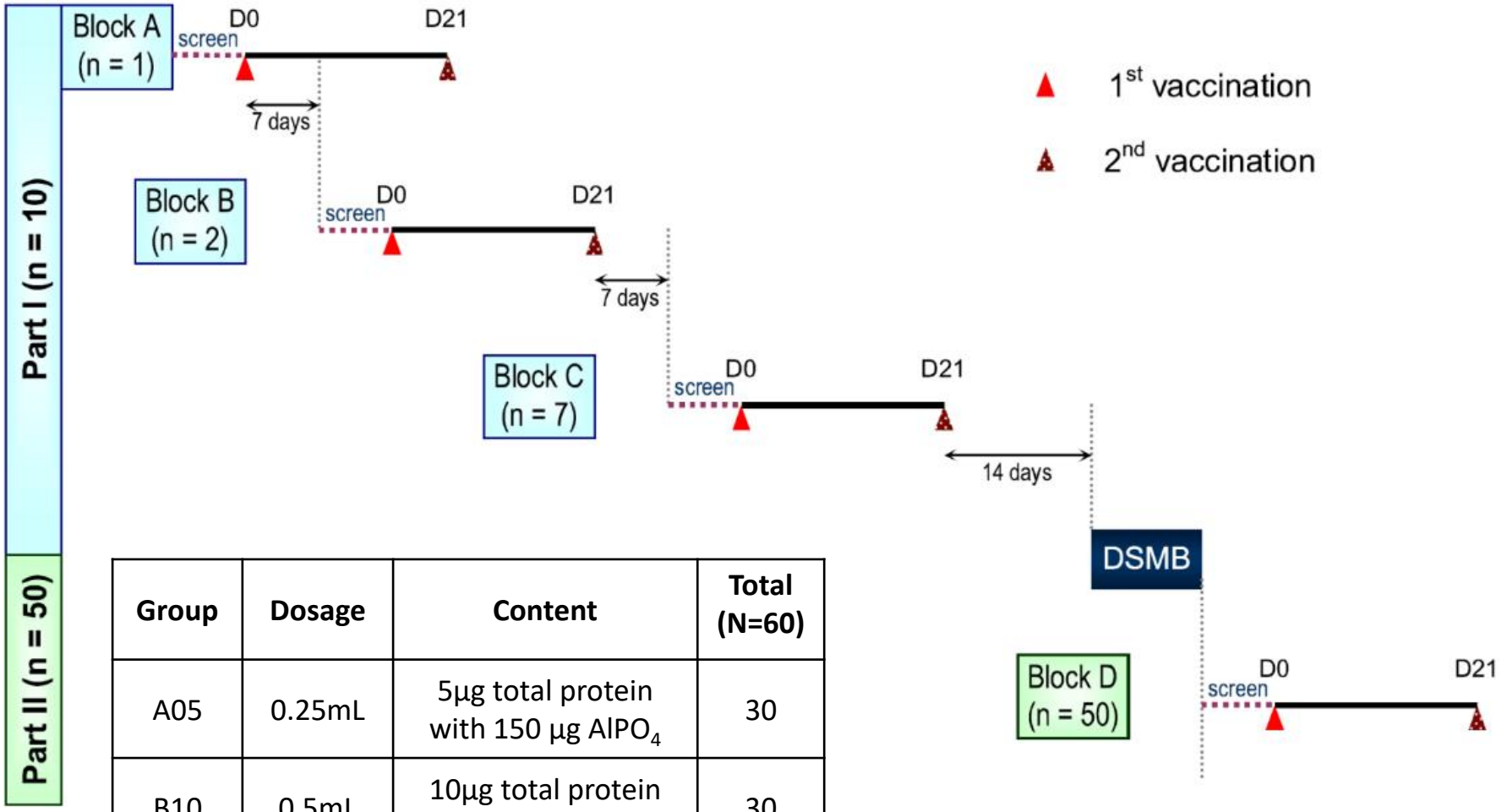


IP for Phase I Study

- Preventive vaccine against EV71-associated disease
- Vaccine strain: EV71 E59 (genotype: B4)
- Formalin-inactivated whole virion
- Dosage form: 10μg total protein with 300μg AlPO4/0.5mL (3mL/vial)



Phase I Study Design



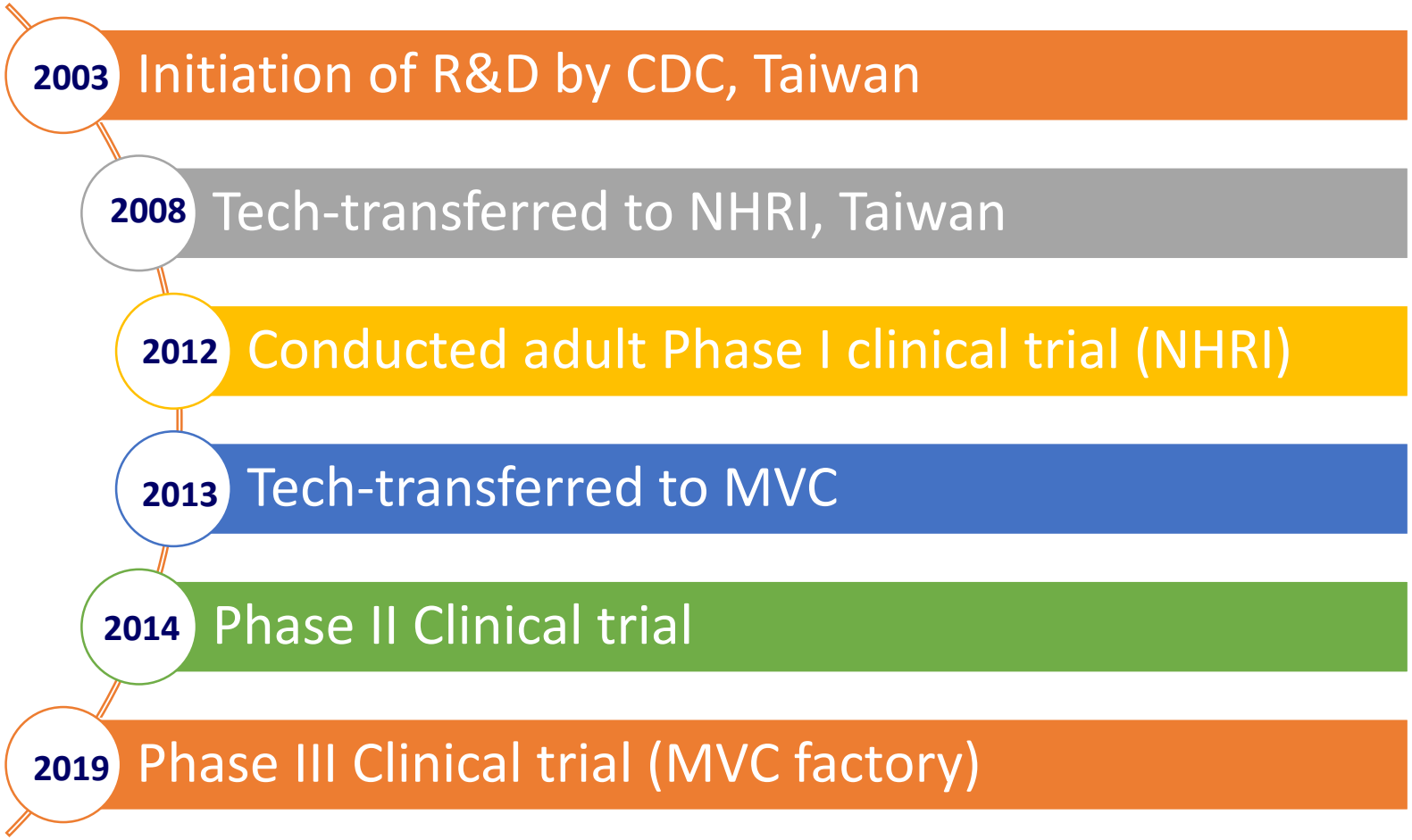
Group	Dosage	Content	Total (N=60)
A05	0.25mL	5μg total protein with 150 μg $AlPO_4$	30
B10	0.5mL	10μg total protein with 300 μg $AlPO_4$	30

Conclusion of Phase I Study

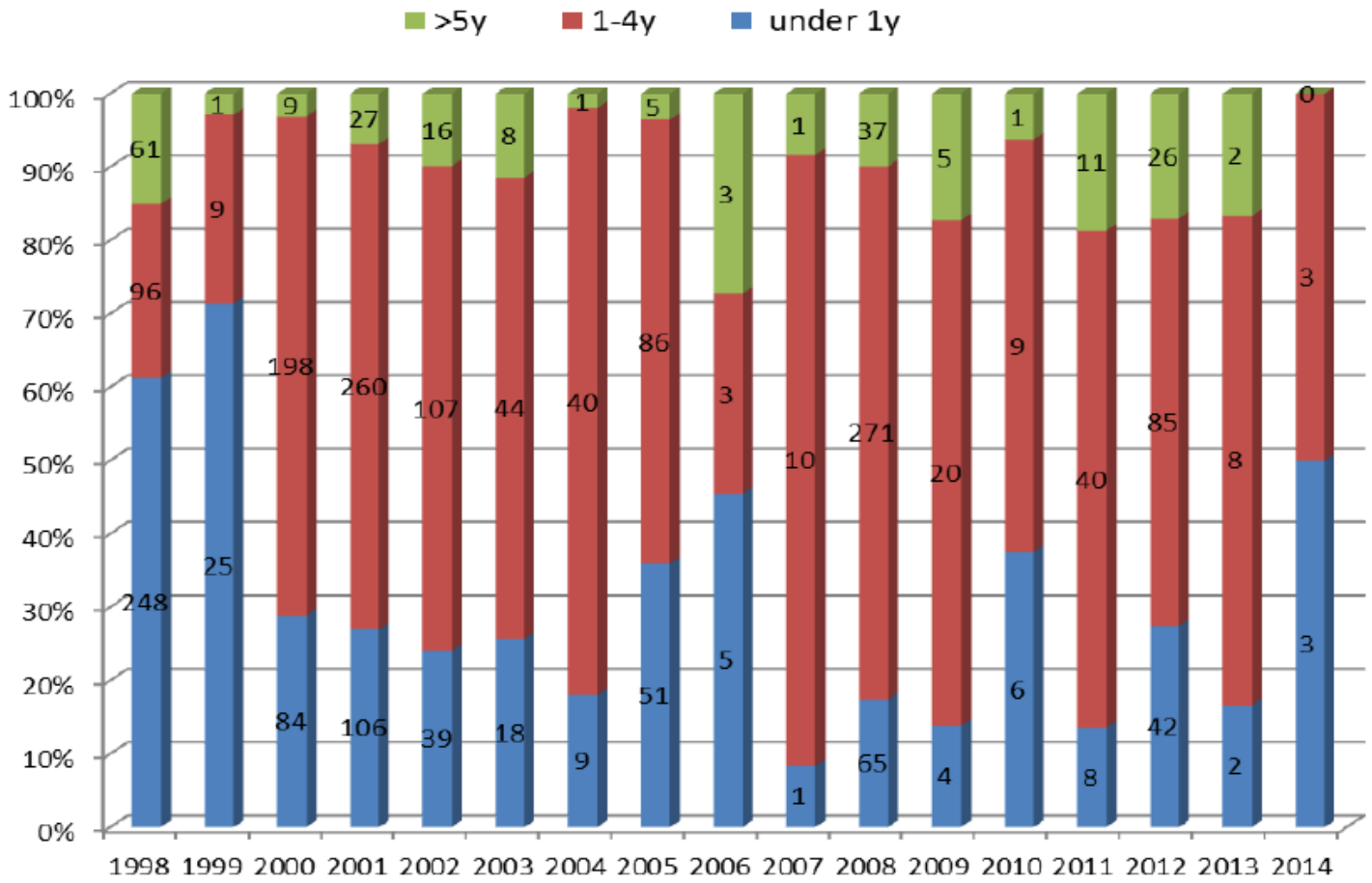
- The solicited ***adverse events*** were mostly ***mild to moderate***.
- No serious adverse event (SAE) was reported during the study period.
- The ***immunogenicity*** of the two dosages (5 mcg, 10 mcg / 0.5ml) were
  - Both ***good*** and not significantly different
- Cross reaction was observed against genotypes B5, B1, and C4a

Ref: Chou, et al. *PloS ONE* 8(11): e79783. Nov. 2013

Evolutions of Ev71 vaccine



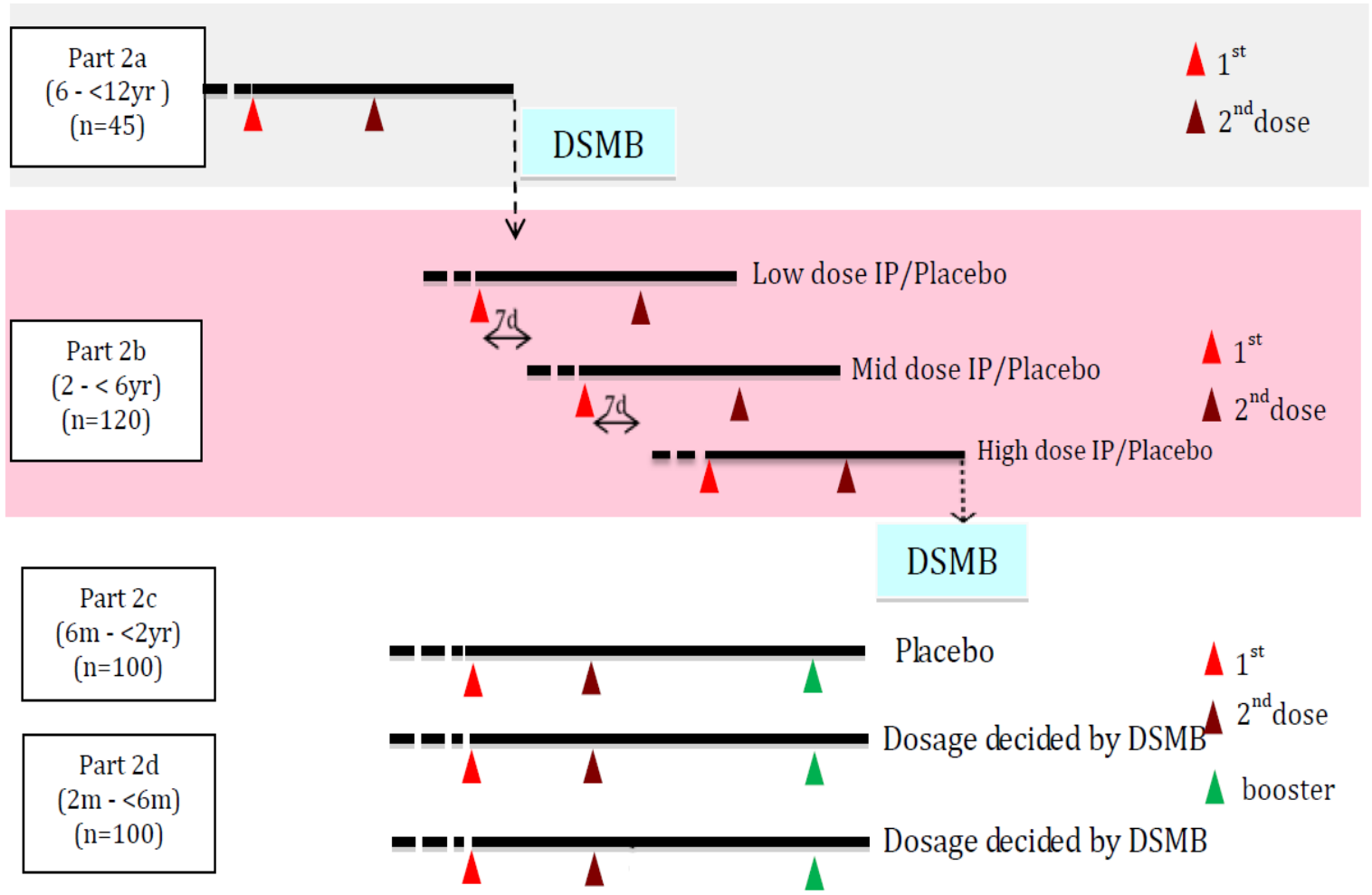
Age Distribution of HFMD With Severe Complications During 1998~2014 in Taiwan



Phase II study

Part	Age	Number of Subjects			Total No.
		LD (1.25µg)	MD (2.5µg)	HD (5µg)	
2a	6 -<12yr	--	----	45	45
2b	2 - <6yr	Vaccine 30 Placebo 10	Vaccine 30 Placebo 10	Vaccine 30 Placebo 10	120
2c	6m -<2yr	Two dosages will be decided by DSMB. The subjects will be randomized to receive either one of the two dosages or placebo in a ratio of 2:2:1.			100
2d	2m -<6m	Two dosages will be decided by DSMB. The subjects will be randomized to receive either one of the two dosages or placebo in a ratio of 2:2:1.			100
				Total patient No.	365

Design of Phase II Study



yr: years; m: months

Solicited Adverse Events after Injection < 7 Days

	Part 2a	Part 2b				Part 2c			Part 2d		
	HD	Placebo	LD	MD	HD	Placebo	MD	HD	Placebo	MD	HD
Local Symptom (%)											
Pain	37.8	13.3	25.0	25.0	31.7	13.3	28.3	21.7	18.6	27.7	12.5
Tenderness	41.1	25.0	30.0	35.0	38.3	15.0	33.3	31.7	23.7	33.6	17.5
Redness	12.2	16.7	21.7	21.7	30.0	26.7	21.7	27.5	25.4	33.6	21.7
Swelling	6.7	3.3	15.0	16.7	18.3	6.7	12.5	15.0	18.6	18.5	14.2
Ecchymosis	1.1	6.7	5.0	5.0	1.7	8.3	1.7	2.5	8.5	4.2	3.3
Induration	4.4	13.3	3.3	13.3	10.0	8.3	11.7	13.3	13.6	20.2	17.5

Solicited Adverse Events after Injection < 7 Days

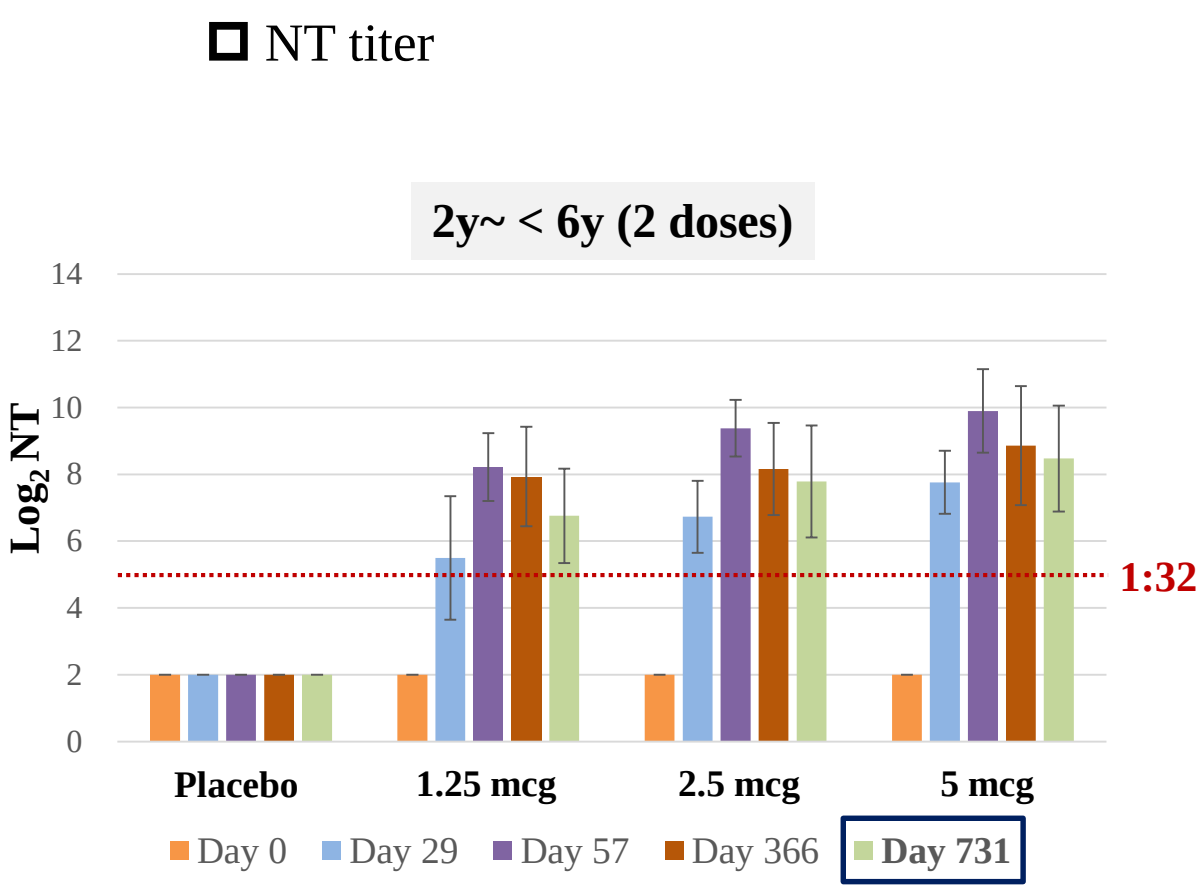
	2a	2b				2c			2d		
	HD	Placebo	LD	MD	HD	Placebo	MD	HD	Placebo	MD	HD
General Symptom	(%)										
Fever	3.3	3.3	3.3	5.0	5.0	6.7	10.0	10.0	5.1	5.0	3.3
Nausea/Vomiting	4.4	5.0	3.3	8.3	3.3	5.0	5.0	3.3	1.7	10.9	5.8
Diarrhea	3.3	5.0	5.0	11.7	1.7	6.7	9.2	9.2	11.9	16.0	6.7
Appetite loss	5.6	5.0	6.7	16.7	3.3	8.3	6.7	8.3	11.9	17.6	15.8
Headache	3.3	3.3	3.3	5.0	1.7	0.0	0.0	0.8	0.0	0.0	0.0
Myalgia	15.6	1.7	3.3	13.3	6.7	0.0	2.5	1.7	0.0	0.0	0.0
Joint pain	4.4	0.0	1.7	3.3	3.3	0.0	1.7	0.0	0.0	0.0	0.0
Fatigue	6.7	6.7	11.7	23.3	11.7	8.3	10.8	13.3	15.3	16.0	13.3
Shivering	1.1	0.0	1.7	0.0	0.0	0.0	0.8	1.7	3.4	5.9	0.8

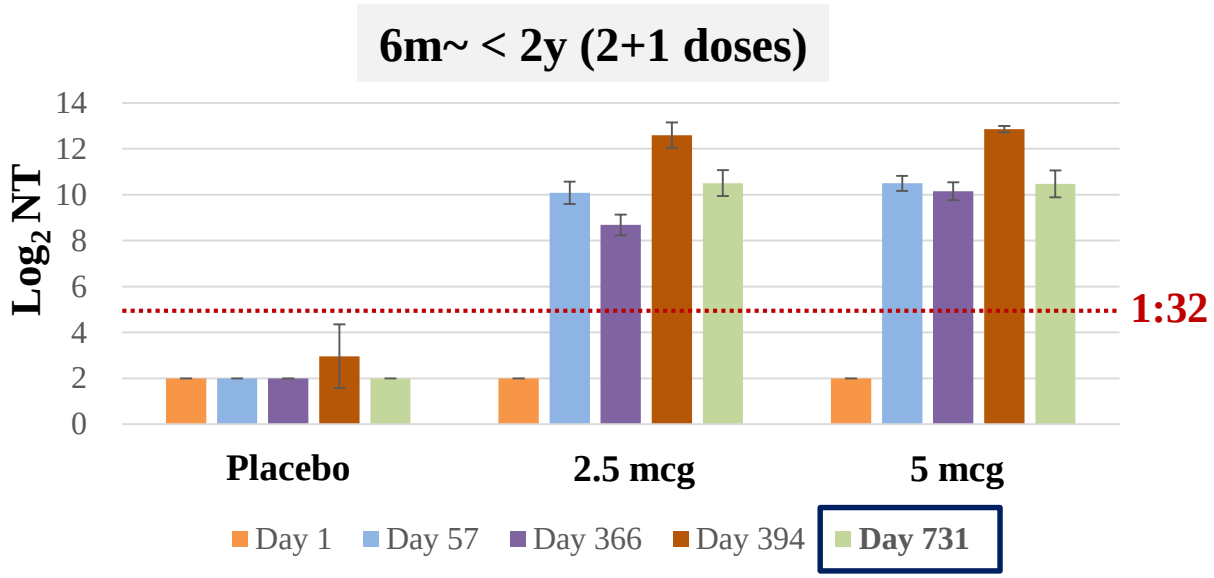
Other Adverse Events - Overall

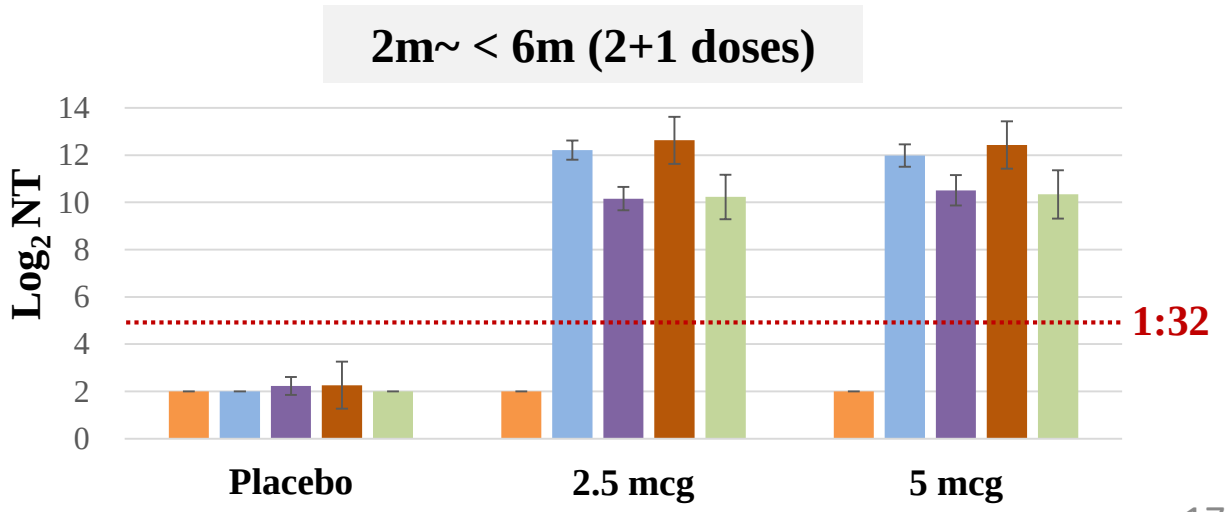
Category	Placebo	Low Dose	Mid Dose	High Dose	Total
AEs	274, 55 (78.6%)	30, 15 (50.0%)	487, 92 (83.6%)	433, 99 (63.9%)	1224, 261 (71.5%)
Related* AEs	0, 0 (0.0%)	3, 2 (6.7%)	9, 4 (3.6%)	4, 4 (2.6%)	16, 10 (2.7%)
'Certain' Related AE	0, 0 (0.0%)	0, 0 (0.0%)	2, 1 (0.9%)	0, 0 (0.0%)	2, 1 (0.3%)
SAEs	10, 7 (10.0%)	0, 0 (0.0%)	27, 15 (13.6%)	23, 11 (7.1%)	60, 33 (9.0%)
Related* SAEs	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)
Grade ≥3 AEs	0, 0 (0.0%)	0, 0 (0.0%)	2, 2 (1.8%)	2, 2 (1.3%)	4, 4 (1.1%)
Related *≥3 AEs	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)
AEs leading to discontinuation^	1, 1 (1.4%)	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)	1, 1 (0.27%)
Related* AEs leading to discontinuation	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)
Death	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)
Death related* to study treatment	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)	0, 0 (0.0%)
*Related= Possible, Probably/Likely, Certain Data in number of events, number of subjects (percentage)					

Immunogenicity results of phase II study

- NT titer







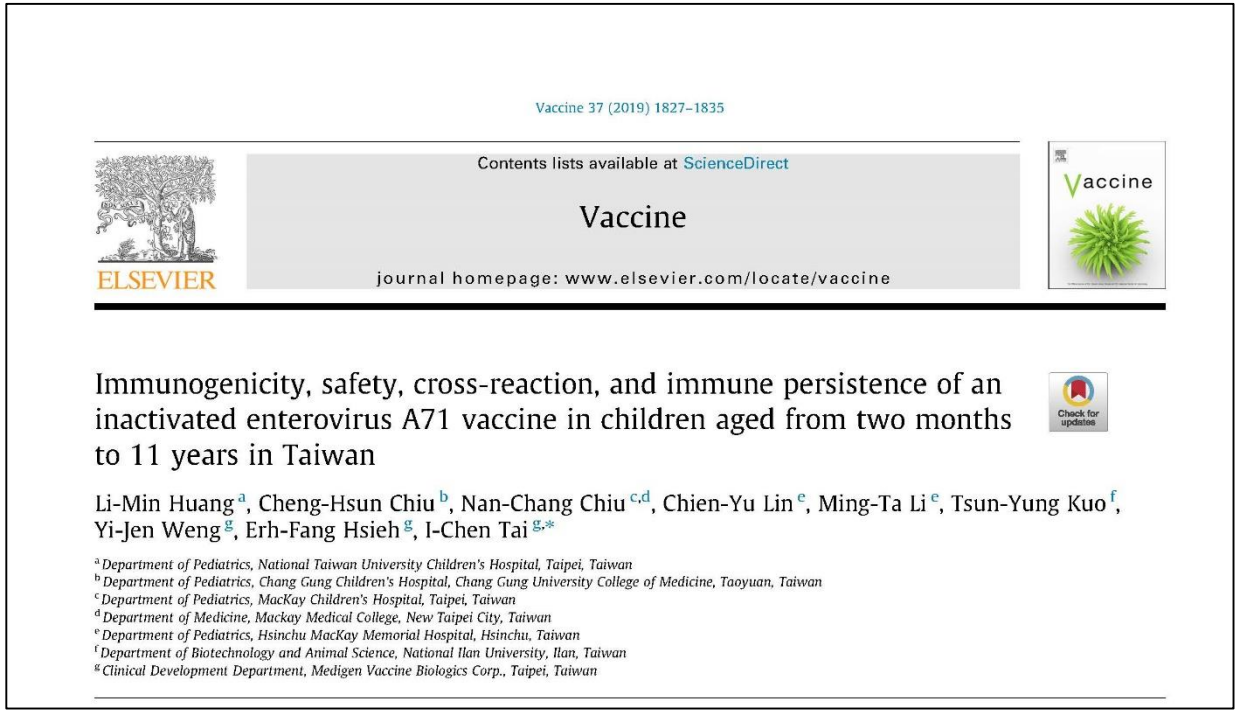
Cross Reaction With Other EV71 Genotypes

Strain	Subjects with 2 doses		LD (1.25mcg)	MD (2.5mcg)	HD (5 mcg)	Placebo
C4a (CN)	Day57	SP Rate (> 1:32)	45.0%	79.2%	81.5%	0%
C4a(VN)	Day57	SP Rate (>1:32)	80%	100.0%	96%	0%
C4a (TW)	Day57	SP Rate (> 1:32)	100.0%	100.0%	100.0%	0%
C4b (TW)	Day57	SP Rate (> 1:32)	100.0%	100.0%	100.0%	0%
B5 (VN)	Day57	SP Rate (> 1:32)	100.0%	100.0%	100.0%	0%
B5 (TW)	Day57	SP Rate (> 1:32)	100.0%	100.0%	100.0%	0%
C5 (VN)	Day57	SP Rate (> 1:32)	100.0%	100.0%	96.0%	0%

Only For subjects with baseline titer <1:8.

Cross Reaction With Other Genotypes

Strain	Seroprotection Rate (%)			
	Placebo	1.25 mcg	2.5 mcg	5 mcg
C4a (TW)	0	100.0	100.0	100.0
C4a (CN)	0	45.0	79.2	81.5
C4a (VN)	0	80.0	100.0	96.0
C4b (TW)	0	100.0	100.0	100.0
B5 (TW)	0	100.0	100.0	100.0
B5 (VN)	0	100.0	100.0	100.0
C5 (VN)	0	100.0	100.0	96.0



Vaccine 37 (2019) 1827–1835

Contents lists available at ScienceDirect

Vaccine

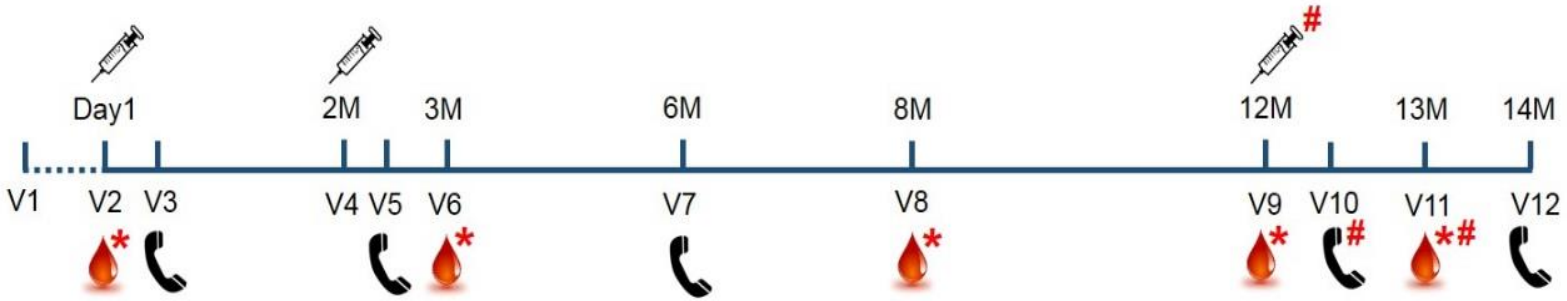
journal homepage: www.elsevier.com/locate/vaccine

Immunogenicity, safety, cross-reaction, and immune persistence of an inactivated enterovirus A71 vaccine in children aged from two months to 11 years in Taiwan

Li-Min Huang[a], Cheng-Hsun Chiu[b], Nan-Chang Chiu[c,d], Chien-Yu Lin[e], Ming-Ta Li[e], Tsun-Yung Kuo[f], Yi-Jen Weng[g], Erh-Fang Hsieh[g], I-Chen Tai[g,*]

[a] Department of Pediatrics, National Taiwan University Children's Hospital, Taipei, Taiwan
[b] Department of Pediatrics, Chang Gung Children's Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan
[c] Department of Pediatrics, MacKay Children's Hospital, Taipei, Taiwan
[d] Department of Medicine, Mackay Medical College, New Taipei City, Taiwan
[e] Department of Pediatrics, Hsinchu MacKay Memorial Hospital, Hsinchu, Taiwan
[f] Department of Biotechnology and Animal Science, National Ilan University, Ilan, Taiwan
[g] Clinical Development Department, Medigen Vaccine Biologics Corp., Taipei, Taiwan

Phase III Design



Population	Healthy infant and children 2m – 6m : 6m – 2y : 2y – 6y = 1:1:1
Study vaccine	EV71vac & placebo =1:1
No. of subject	3200 (Vietnam : Taiwan 3:1)

Vaccination
Blood Sampling
Telephone contact
* Sub-study only
# 2 m ~ < 2 yr only

Thank you for your attention!