



高端疫苗生物製劑股份有限公司
MEDIGEN VACCINE BIOLOGICS CORP

“Current Development Status of EV71 Vaccines”

at

Medigen

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September 15, 2018

Outline

➤ About MVC

- Introduction
- Facility

➤ EV71 Vaccines

- Evolution History
- Development Structure
- Clinical Study Updates
- Obligated Opportunities

Who we are

- The first cell-based vaccine manufacturer in Taiwan, uniquely positioned to serve the vaccine community locally and regionally
- Solid R&D capacity to develop and manufacture cell culture-based vaccines and affordable biosimilars: Dengue, EV71, H7N9 and Palivizumab, to counter local and regional epidemics
- Focused Disease Intervention Strategies aiming at tropical infectious diseases
- Global Networking: partnership with the US NIH/NIAID; collaboration with the US CDC; coalition under the World Health Organization (WHO) to develop affordable Palivizumab, a biosimilar version to Synagis®

What we can offer

- Production capability: cell-based platform, up-scaling production, single-use technology, compliant with PIC/S GMP, EMA
- CMO: from antigen production to fill/finish or importing bulk for fill/finish, to produce finished products
- Manufacturing hub: acting as a regional hub to supply vaccines to Taiwan and Asia-Pacific countries
- China: MVC, a stepping stone for market entry

Our vision

- MVC is geared to serve local epidemic demands, build regional trust and alliances and actively participate in global needs.

- Height : ~26 m
- Total Floor Area : ~12,000 m²
- Features :
 - Fulfills PIC/S GMP and EMA requirements
 - Flexible production (Vaccines & Antibody Drugs)
 - Single-use technology

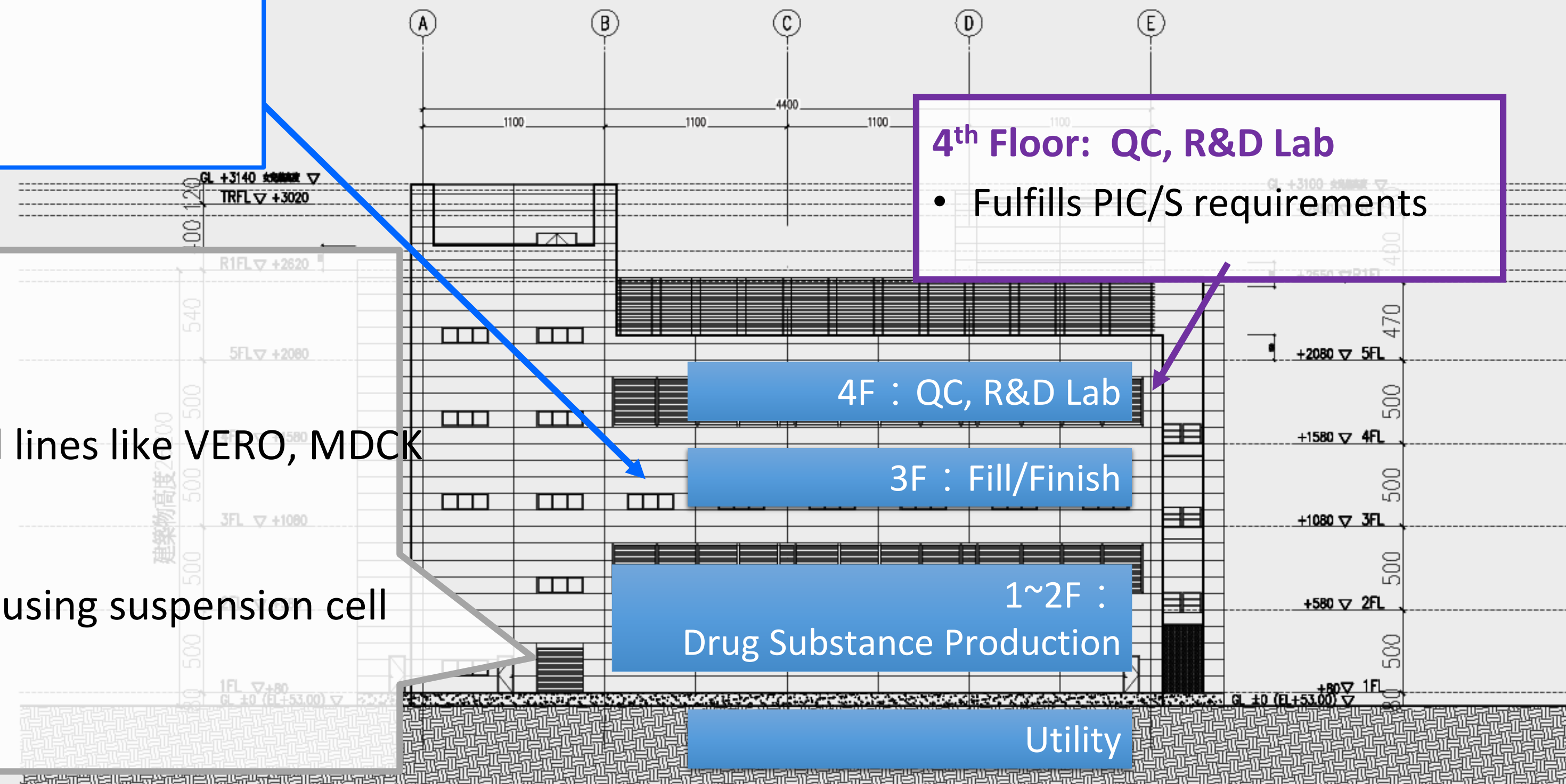


3rd Floor: Fill & Finish

- Bausch & Ströbel Fill & Finish Facility

1st Floor: Drug Substance Production

- **Adherent Cell Culture Production**
Able to manufacture **vaccines** using adherent cell lines like VERO, MDCK
- **Suspension Cell Culture Production**
Able to manufacture recombinant protein drugs using suspension cell lines like CHO

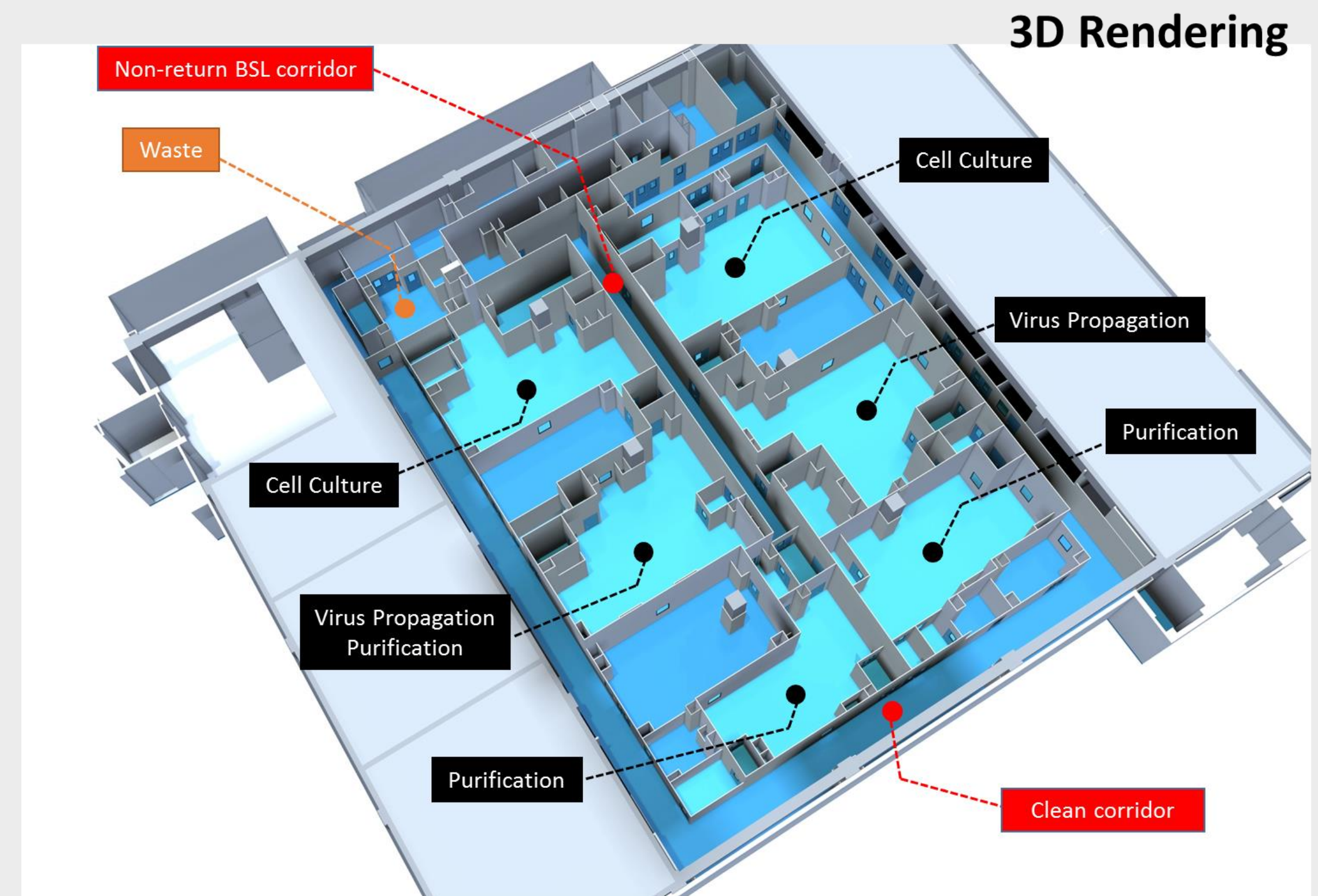


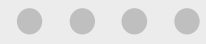
4th Floor: QC, R&D Lab

- Fulfills PIC/S requirements

Drug Substance Production

- **Two production lines:**
 - ✓ Adherent cell culture for vaccines: adjustable to suspension cell culture for seasonal influenza
 - ✓ Suspension cell culture: adjustable pressure system allows switching antibody to vaccine production
- **Upstream production:** Cell Factory, Roller Bottle, TideCell®, stirred-tank bioreactor
- **Downstream production:** column chromatography, adjustable to other systems





➤ **EV71 Vaccines**

- **Evolution History**

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➤ Evolution of virus

Isolated genotypes

A: 1970, California, USA

B: 1972 – 1988, USA & Australia; 1994, Columbia; 1997, Malaysia

C: 1985, USA, Canada, Australia and China

➤ Evolution of vaccine (mattered to Medigen)

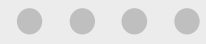


Other EV71 Vaccine Players

Company	Country	Genotype	Cell	Population	Registration status
MVC	Taiwan	B4	Vero	2m-72m	Phase III IND
Adimmune	Taiwan	B4	Vero	6m-72m	Phase III IND
Sinovac	China	C4	Vero	6m-35m	Marketed (in China)
Vigoo	China	C4	Vero	6m-35m	Marketed (in China)
CAMS	China	C4	KMB-17	6m-71m	Marketed (in China)
Inviragen/Takeda	Singapore	B2	Vero	21-45 yr	Phase I completed

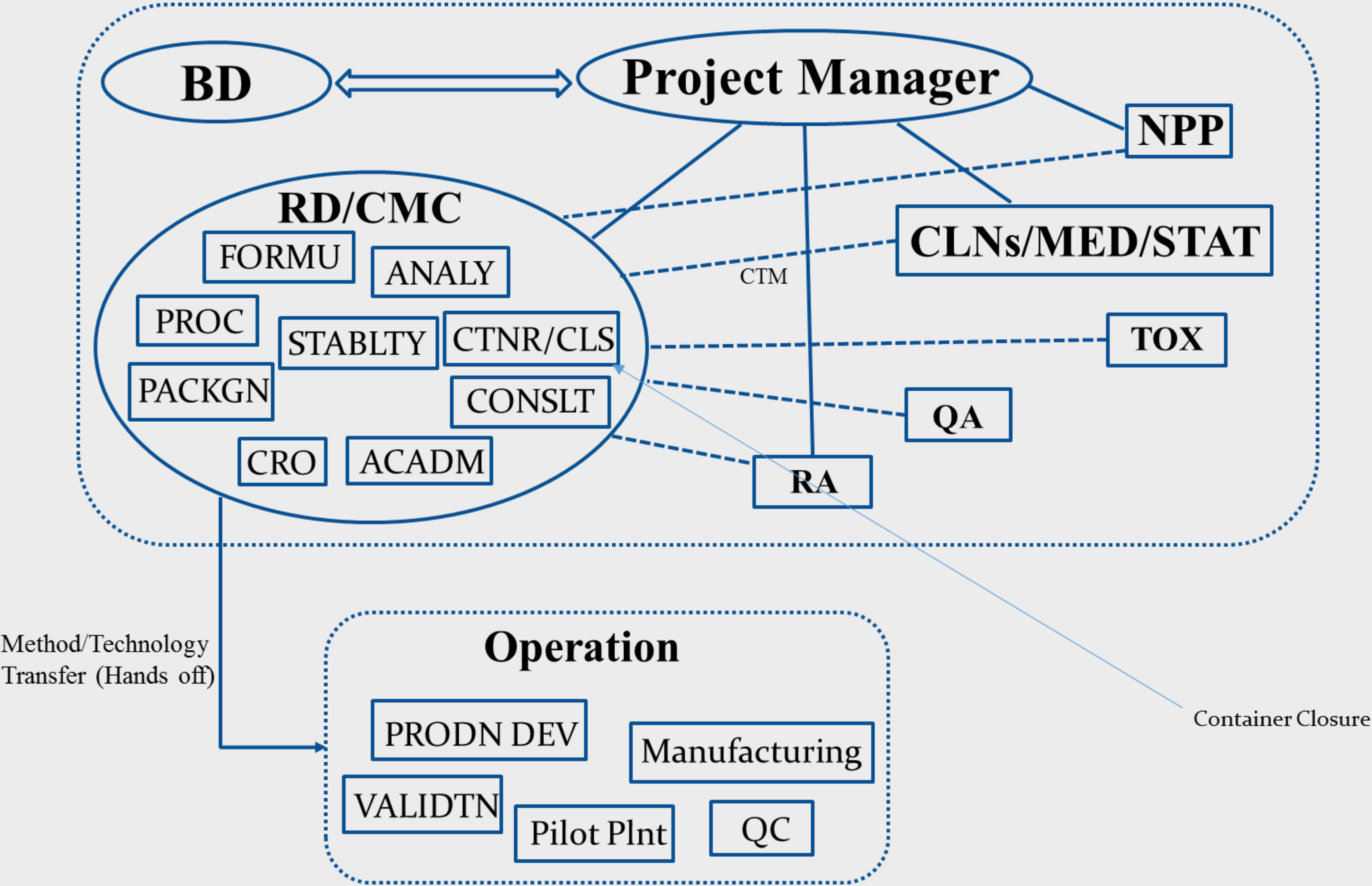
- ◆ World's 1st EV71 vaccine targeting babies as little as **2 months old**
- ◆ **2+1 booster** regime to sustain protection later into life
- ◆ Good **cross reaction** toward **B4, B5, C4a and C5** sub-genotypes circulating in most Asian countries





➤ **EV71 Vaccines**

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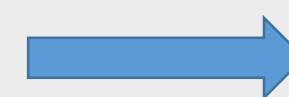
➤ **EV71 Vaccines**

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The Vaccine - EV71Vac®

#13

- **Content:** Formalin-inactivated whole virion with adjuvant AlPO_4
- **Vaccine strain:** EV71 E59 (genotype: B4) produced in Vero cell lines
- **Formulation:**
 - Phase I: Higher total protein with aluminum adjuvant/(0.5mL/0.25mL)
 - Phase II: LD/MD/HD with aluminum adjuvant/(0.5mL)
 - Phase III: MD with aluminum adjuvant/(0.5mL)



Study Phase	Subject no.	Age	Endpoint	Status
Phase I	60	20-60yr	Safety & Immunogenicity	Study completed
Phase II	366	2m-11yr	Safety & Immunogenicity	Study & study extension completed
Phase III	~3000 - 4000	2m-6yr	Efficacy, Safety& Immunogenicity	IND approved (Taiwan) IRB submissions (Vietnam)

- A prospective, randomised, double-blind, placebo-controlled, multicentre study to evaluate the safety and immunogenicity of a newly-developed EV71 vaccine in infants and children aged two months to 11 years (NCT 02200237).
- Participants were divided into four groups according to age:

Group	Age	Subjects	Doses
a	six to < 12 years	45	HD only
b	two to < six years	120	All doses + placebo
c	six months to < two years	100	MD, HD + placebo
d	two months to < six months	100	MD, HD + placebo

Phase II Design - Continued...

Subject Distribution (TVG* Cohort)

Doses	LD	MD	HD	Placebo
Enrolled	30	110	156	70
Completed	30	109	155	69
Discontinued	0	1	1	1
Total Screened	382			
Screen Failure	16			
Total Enrolled	366			

*total vaccinated group

Study Phase	Safety	Immunogenicity
Phase I	<ul style="list-style-type: none">No severe adverse events (SAE) reportedGenerally safe and well tolerated in healthy adults	<ul style="list-style-type: none">Induced significant immune response in healthy adults after 1st vaccinationShowed cross reaction to B1, B5, and C4a strains
Phase II	<ul style="list-style-type: none">No severe adverse events (SAE) reportedGenerally considered no safety concern	<ul style="list-style-type: none">Elicited good immunogenicity after 2 doses of vaccination in subjects -100% seroconversion rate in all vaccine groups against B4 strainShowed cross reaction to C4a, B5 (TW) and B5 (VN) strains in subjectsDetermined MD to be used for next phase development

EV71 Epidemic Genotypes in Asia

#18

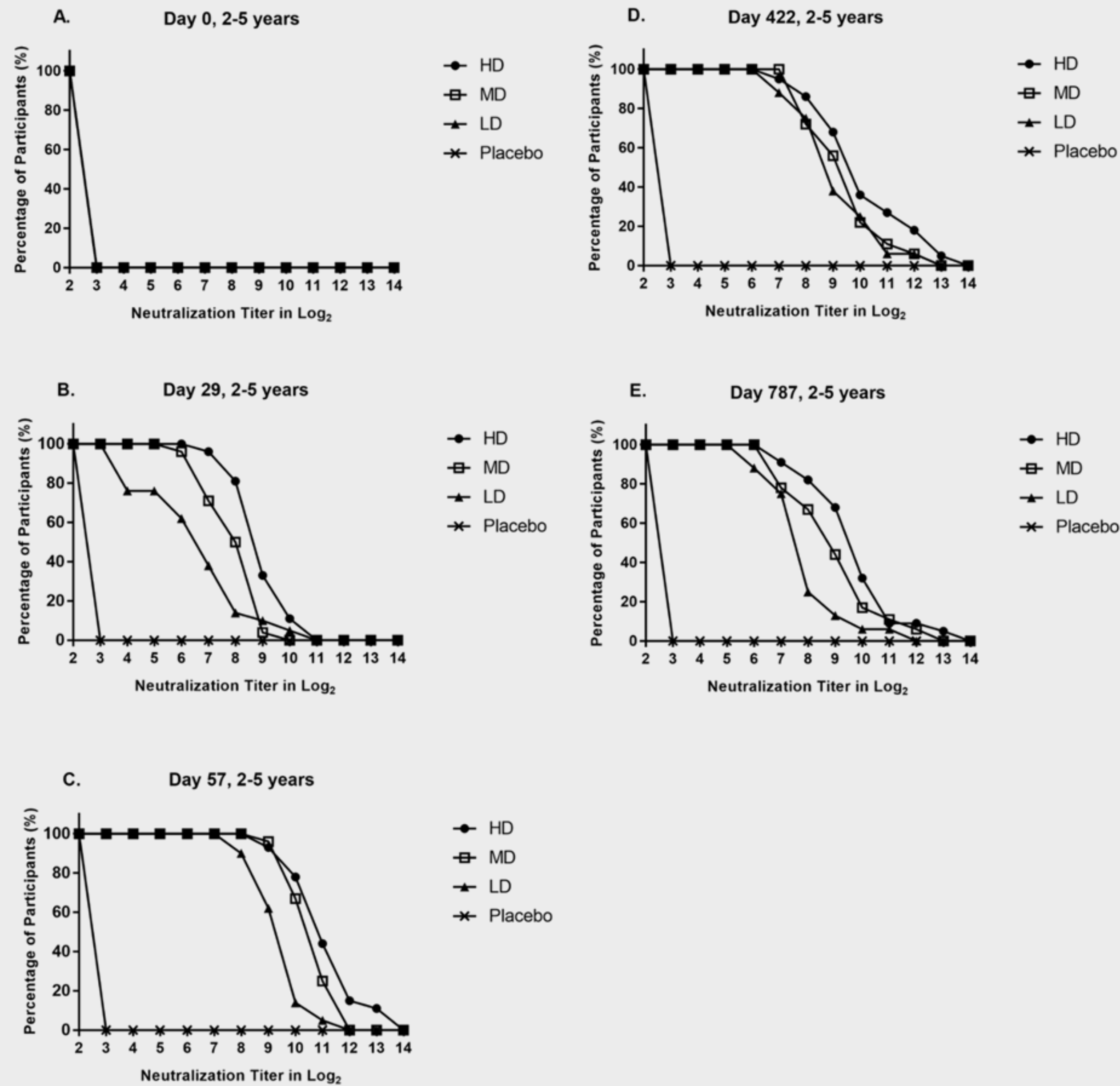
Country	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Japan	C4	C4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Korea	N/A	N/A	N/A	C2,C4	N/A	N/A	N/A	N/A	N/A	N/A
China	C2,C4	C2,C4	A,B5 C4,C2	C2, C4a	C2, C4a	C4a	C4a	C4a	N/A	N/A
Taiwan	C5	B5,C5	B5,C4 C5	B5	C4	C4,B5	B5	B5	N/A	C4,B5
Vietnam	C5	C5	C5	C5	C5	C4,C5	C4,B5	C4,B5	C4,B5	C4,B5
Thailand	C4	C2	C1,C2 C4	B5,C1 C2,C4	N/A	B5	B5	N/A	N/A	N/A
Cambodia	N/A	N/A	N/A	N/A	N/A	N/A	C4a	N/A	N/A	N/A
Malaysia	B5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Singapore	B5	N/A	B5,C2	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Expert Opin. Biol. Ther. (2014) **14**(10)

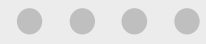
Cross Reaction With Other EV71 Genotypes

Strain	Subjects with 2 doses		LD	MD	HD	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%

Status Summary...Reverse Cumulative Distribution of Part 2b (TVG Cohort; Baseline <1:8)







➤ **EV71 Vaccines**

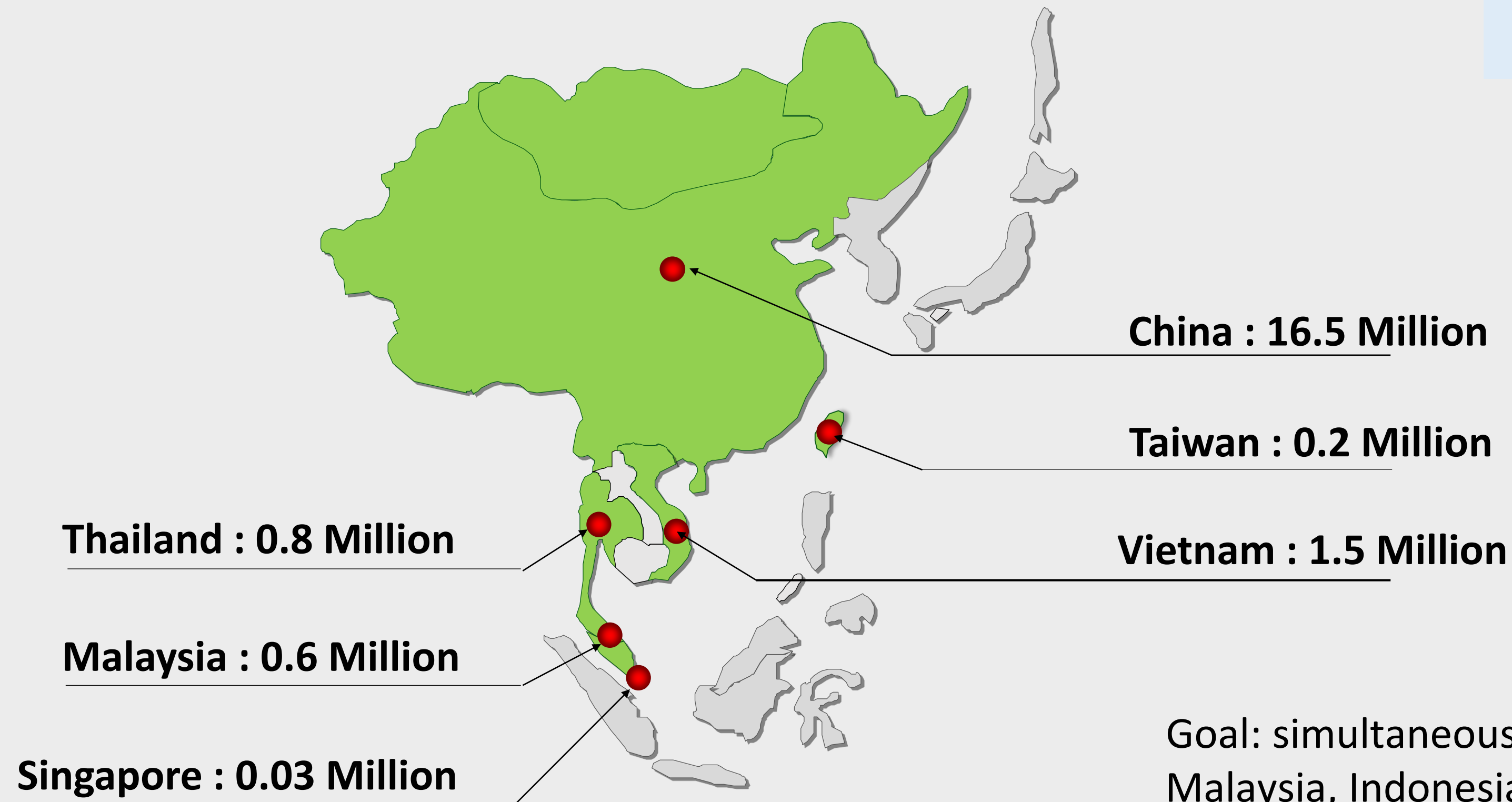
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Obligated Opportunities...babies in need, an astonishing figure

#23

Numbers of newborns for example:
20 million babies/year

- ◆ Target Population: 2 mon ~ 72 mon babies
- ◆ Each Baby receives 2 ~ 3 doses



Goal: simultaneous NDA submissions to Taiwan, Vietnam, Thailand, Malaysia, Indonesia, Singapore, Philippines, and Australia

- The past: proven track record in pre-clinical & clinical studies
- The upcoming: on track to Phase III CT, in Taiwan & Vietnam
- The commitment: MVC is geared to offer a broader value of EV71 vaccine covering babies in need!



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Thank You!

