

Review of the evidence: Vaccine immunogenicity, effectiveness, and impact

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Outline

- ❑ **Inactivated Vero cell-derived vaccines (IXIARO)**
 - Short- and long-term immunogenicity data
- ❑ **Live attenuated SA 14-14-2 vaccine (CD.JEVAX)**
 - Short- and long-term immunogenicity data
 - Effectiveness data
- ❑ **Live attenuated chimeric vaccine (IMOJEV)**
 - Short- and long-term immunogenicity data
- ❑ **Impact of JE immunization programs**

INACTIVATED VERO CELL-DERIVED VACCINES - IXIARO

IXIARO

Short term immunogenicity

Review based on:

- ❑ **9 studies***
 - 2 in JE-endemic countries
- ❑ **Approximately 1400 participants**
 - ~410 children aged 2 months - 17 years

* Kaltenbock et al, 2010; Dubischar-Kastner et al 2012 (abstract); Tauber et al 2007; Schuller et al 2008; Lyons et al 2007; Schuller et al 2009; Kaltenbock et al 2009; Erra et al, 2012; Woolpert et al 2012.

IXIARO

Short term immunogenicity

One month following completion of a 2-dose primary series:

- ❑ High seroprotection rates $\geq 93\%$ in all studies
- ❑ In largest pediatric study in an endemic country* seroprotection rate was $> 99\%$

*Dubischar-Kastner et al 2012 (abstract)

IXIARO

Long term immunogenicity

Review based on:

- ❑ 6 studies with data collected ≥ 1 year post-vaccination***
 - 1 in children/ in JE-endemic country
- ❑ Maximum data collection period 3 years post-vaccination**
 - 1 pediatric and 1 adult study

* Dublischar-Kastner et al 2010; Eder et al 2011; Schuller et al 2008/CDC 2011/European Medicines Agency; Lyons et al 2007; Erra et al, 2014; Valneva – unpublished data.

IXIARO

Long term immunogenicity

❑ Pediatric (endemic area)

- ❑ At 3 years post-immunization, 90% (128 of 142) of children < 17 years were seroprotected
 - >80% children in each age group were seroprotected

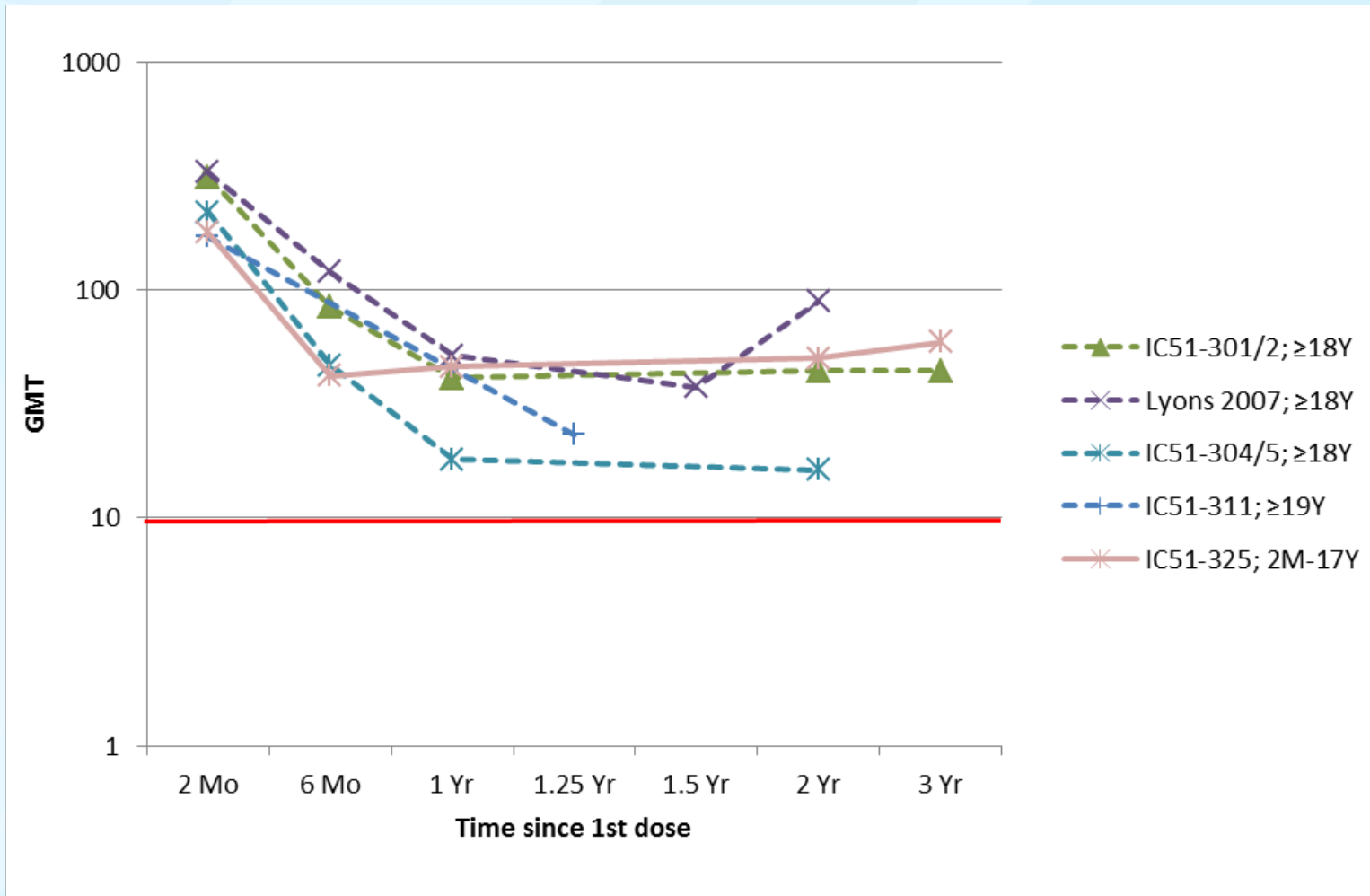
IXIARO

Long term immunogenicity

- ❑ **Adults (non-endemic areas)**
 - Seroprotection rates over time variable by study
 - 12-15 months: 58-100%
 - 2 years: 48-93%
 - 3 years: 85%
 - Manufacturer recommends booster for adults at 12-24 months after primary immunization

IXIARO

Long term immunogenicity



CD.JEVAX

CD.JEVAX

Short term immunogenicity

Review based on:

- ❑ 6 studies with ~ 1,460 participants (all children)*
 - Age range: 8 months – 3 years
- ❑ All CD.JEVAX studies done in JE-endemic countries
- ❑ Older studies from China not included

*Victor et al 2014; Zaman et al 2014; Feroldi et al 2014; Kim et al 2013 (poster); Sohn et al 1999; Chotpitayasunodh et al 2011.

CD.JEVAX

Short term immunogenicity

One month after a single dose:

- High seroprotection rates
 - $\geq 80\%$ in all studies (range: 80–99%)

CD.JEVAX

Long term immunogenicity

Review based on:

- ❑ 3 studies with data collected ≥ 1 year post-vaccination*
- ❑ Maximum data collection period 5.5 years post-vaccination

* Feroldi et al 2014; Clinicaltrials.gov (1 study); Sohn et al, 2008.

CD.JEVAX

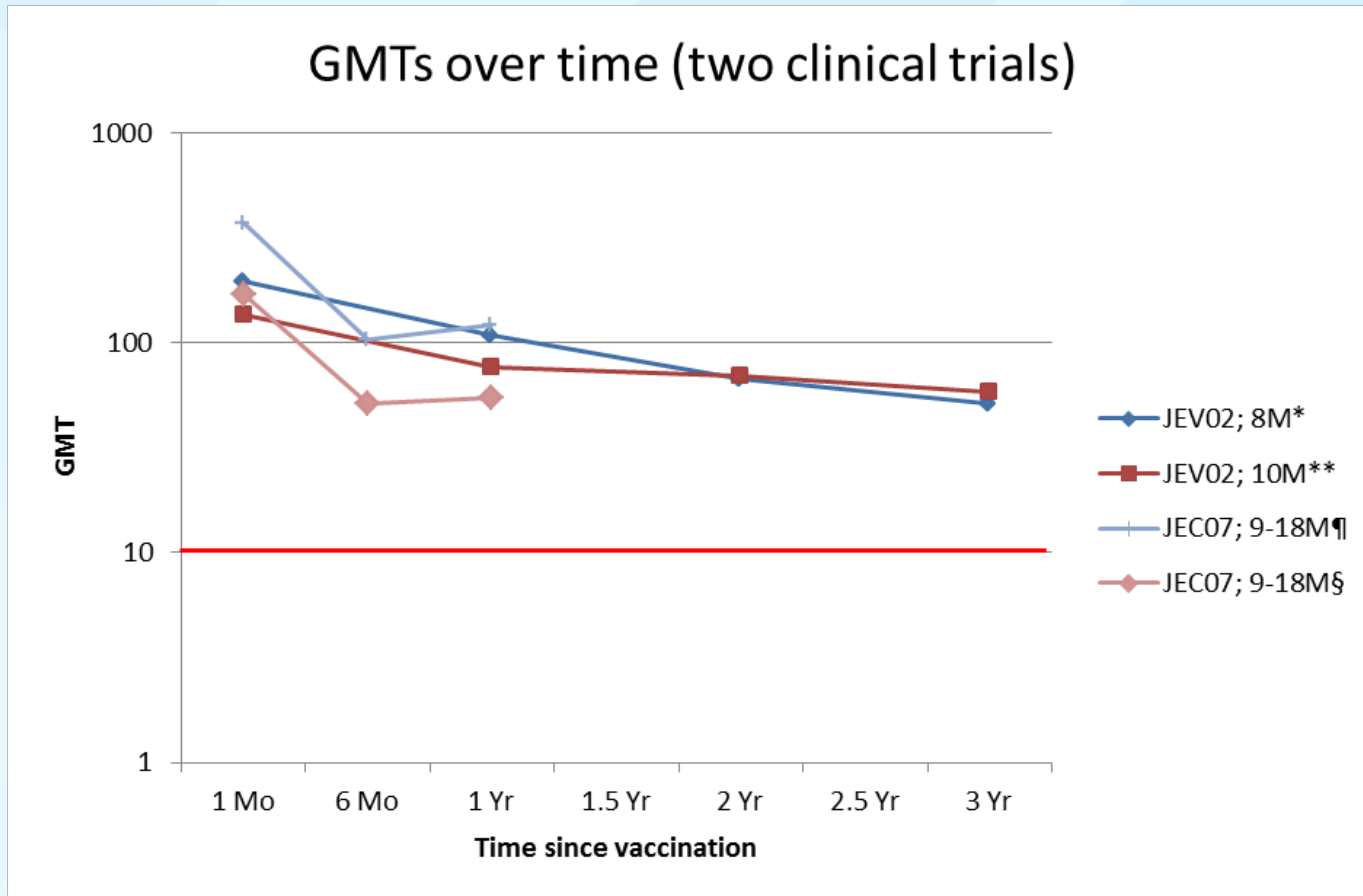
Long term immunogenicity

Seroprotection rates following a single dose:

- Major study (n=243)
 - $\geq 79\%$ at 3 years
- Small observational study (n=69)
 - 90% at 4 years
 - 64% at 5.5 years

CD.JEVAX

Long term immunogenicity



*CD.JEVAX followed by MMR

** MMR followed by CD.JEVAX

¶ PRNT used JE-CV virus and Vero cells

§ PRNT used SA 14-14-2 virus and LLC-MK2 cells

Effectiveness of CD.JEVAX (Case-Control Studies)

Study	Country	Ages @vax	1W-1M	6M	1YR	Up to ~3YR	5YR
Bista 2001	Nepal	1-15Y	99.3% (94.9-100%)				
Kumar 2009	India	1-15Y		94.5% (81.5-98.9%)			
Ohrr 2005	Nepal	1-15Y			98.5% (90.1-99.2%)		
Murhekar 2014	India	16-24M				84% (53-95%)	
Tandan 2007	Nepal	1-15Y					96.2% (73.1-99.9%)

Based on 20-56 cases per study

IMOJEV

IMOJEV

Short term immunogenicity

Review based on:

- ❑ 10 studies*
 - 7 in JE-endemic countries
- ❑ Approximately 2,500 participants
 - ~1900 children aged 9 months – 10 years

*Feroldi et al 2014; Kim et al 2013 (poster); Chokephaibulkit et al 2010; Feroldi et al 2012; Huang et al 2014; Feroldi et al 2013; Torresi et al 2010; Nasveld et al 2010; clinicaltrials.gov (2 studies).

IMOJEV

Short term immunogenicity

One month after a single dose:

- ❑ High seroprotection rates $\geq 81\%$ in all but one study* (range: 81-100%)
- ❑ In largest pediatric study in an endemic country**, $\geq 95\%$ of 1059 children aged 12-18 months were seroprotected

* One small study with inconsistent results (seroprotection rate of 25%)

** Feroldi et al 2012

IMOJEV

Long term immunogenicity

Review based on:

- ❑ 6 studies with data collected ≥ 1 year post-vaccination*
 - 4 in children in JE-endemic countries
- ❑ Maximum data collection period 5 years post-vaccination
 - 1 pediatric & 1 adult study

*Feroldi et al 2014; Feroldi et al 2010/Feroldi et al 2013; Huang et al 2014; Nasveld et al 2010; clinicaltrials.gov (1 study); Sanofi Pasteur unpublished data.

IMOJEV

Long term immunogenicity

Seroprotection rates following a single dose:

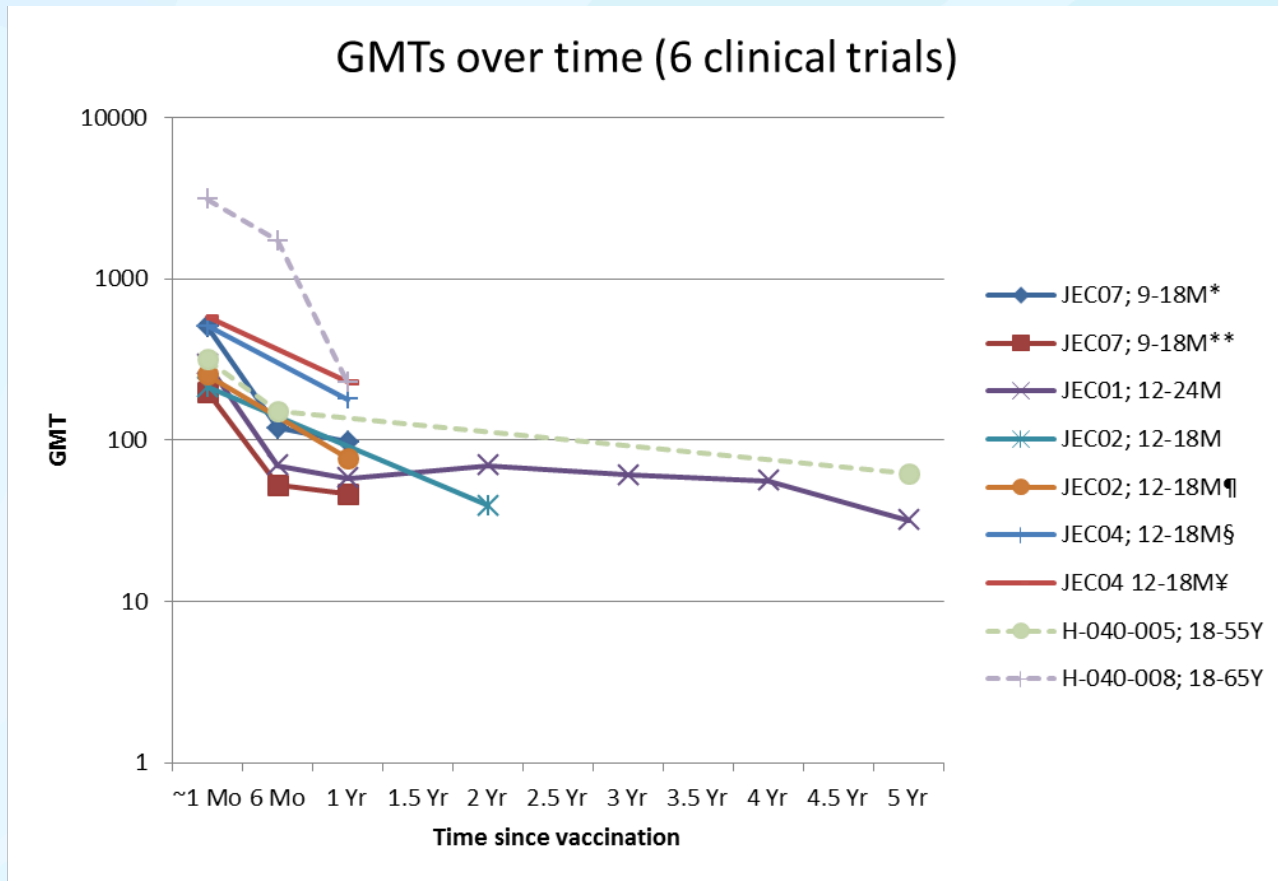
- ❑ Children aged 12-24 months in endemic area
 - 2 years: 80% (2 studies)
 - 5 years: 66% (1 study; 99 of 151 children)

- ❑ Adults in non-endemic area
 - 5 years: 94% (43 of 46)*

*Only 45% of original study population

IMOJEV

Long term immunogenicity



*PRNT used JE-CV virus and Vero cells

**PRNT used SA 14-14-2 virus and LLC-MK2 cells

¶ Subset of full study population

§ IMOJEV followed by MMR

¥ MMR followed by IMOJEV

Conclusions: Short term protection

- All vaccines reviewed provided high ($\geq 80\%$) and comparable levels of seroprotection

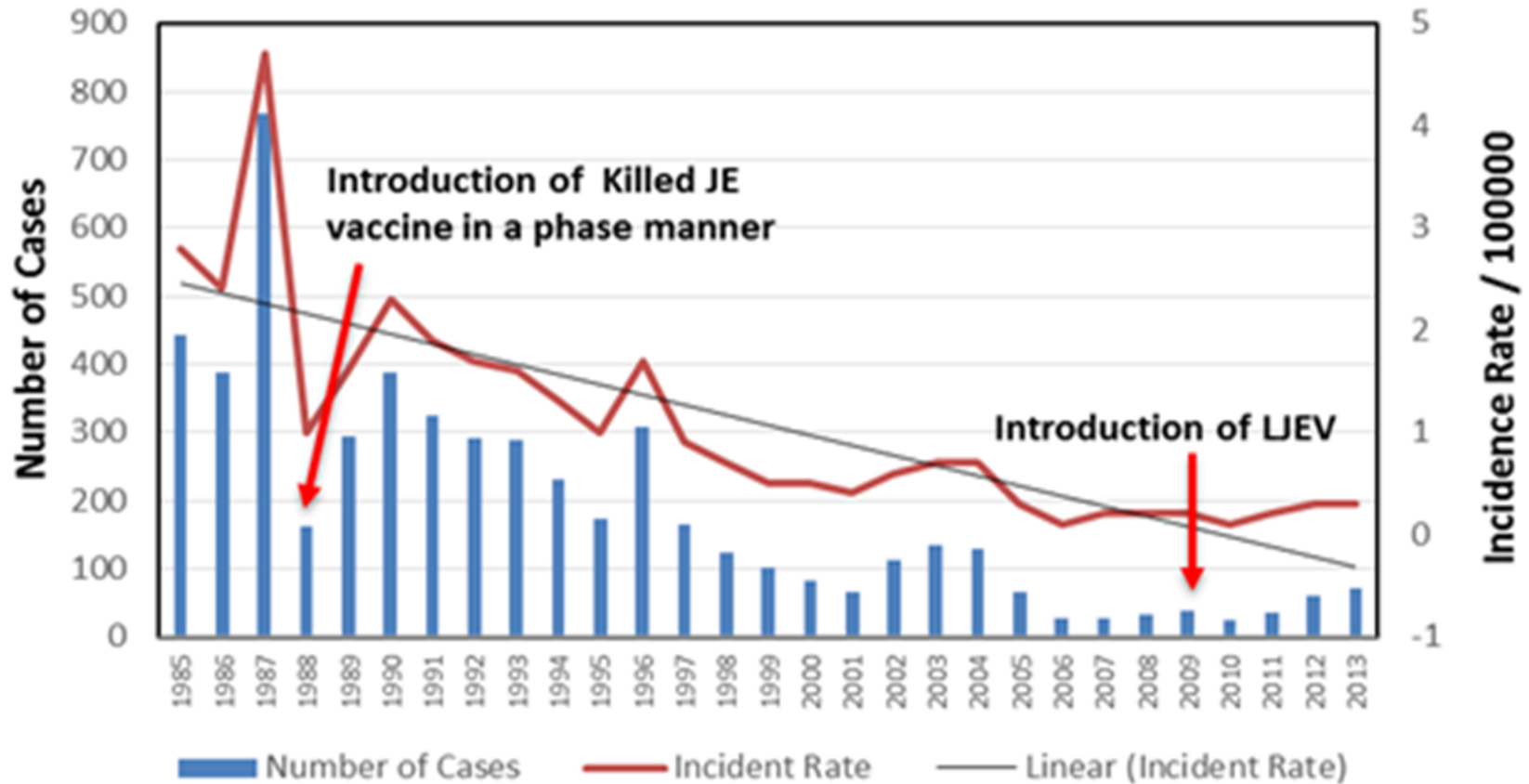
Conclusions: Long term protection

❑ For children in endemic areas

- Limited data available
- Insufficient evidence to indicate booster doses are needed
- Acceptable to use primary schedule and monitor closely
- More data needed to fully assess need for a booster, especially
 - longer periods of follow-up
 - in different transmission settings
 - in routine immunization program use

PROGRAM IMPACT

Impact of JE immunization program: Inactivated mouse brain-derived vaccine and CD.JEVAX used in Sri Lanka



Impact of a JE immunization program: CD.JEVAX in Nepal

	Annual incidence per 100,000		Prevented proportion	Prevented cases
	Pre-campaigns	Post-campaigns		
Lab-confirmed JE	4.6	1.3	72%	891
Acute encephalitis syndrome	17.9	7.5	58%	2,787*

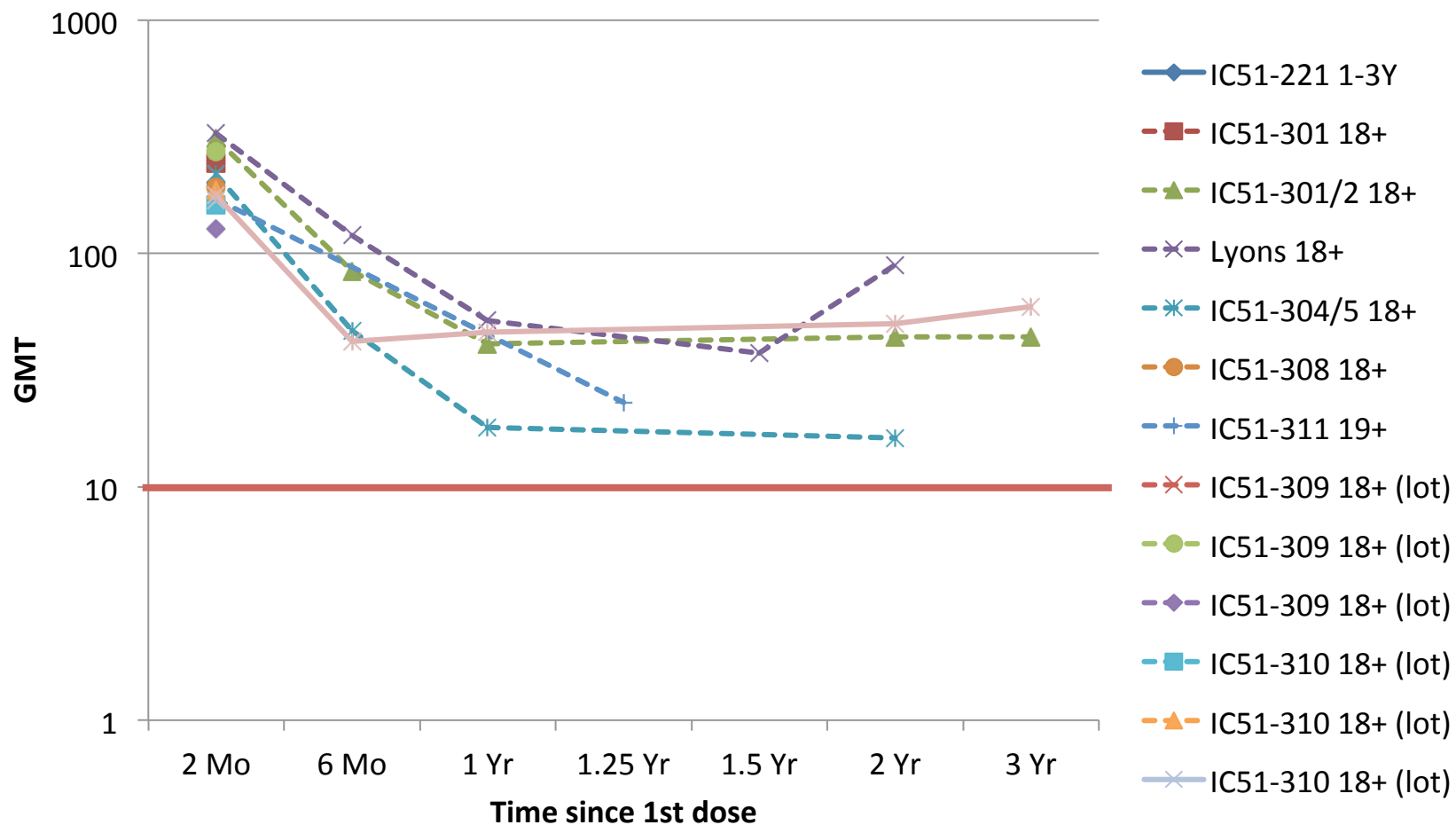
- ❑ Three times as many acute encephalitis disease cases prevented than indicated by the laboratory-confirmed JE cases alone

THANK YOU

EXTRA SLIDES

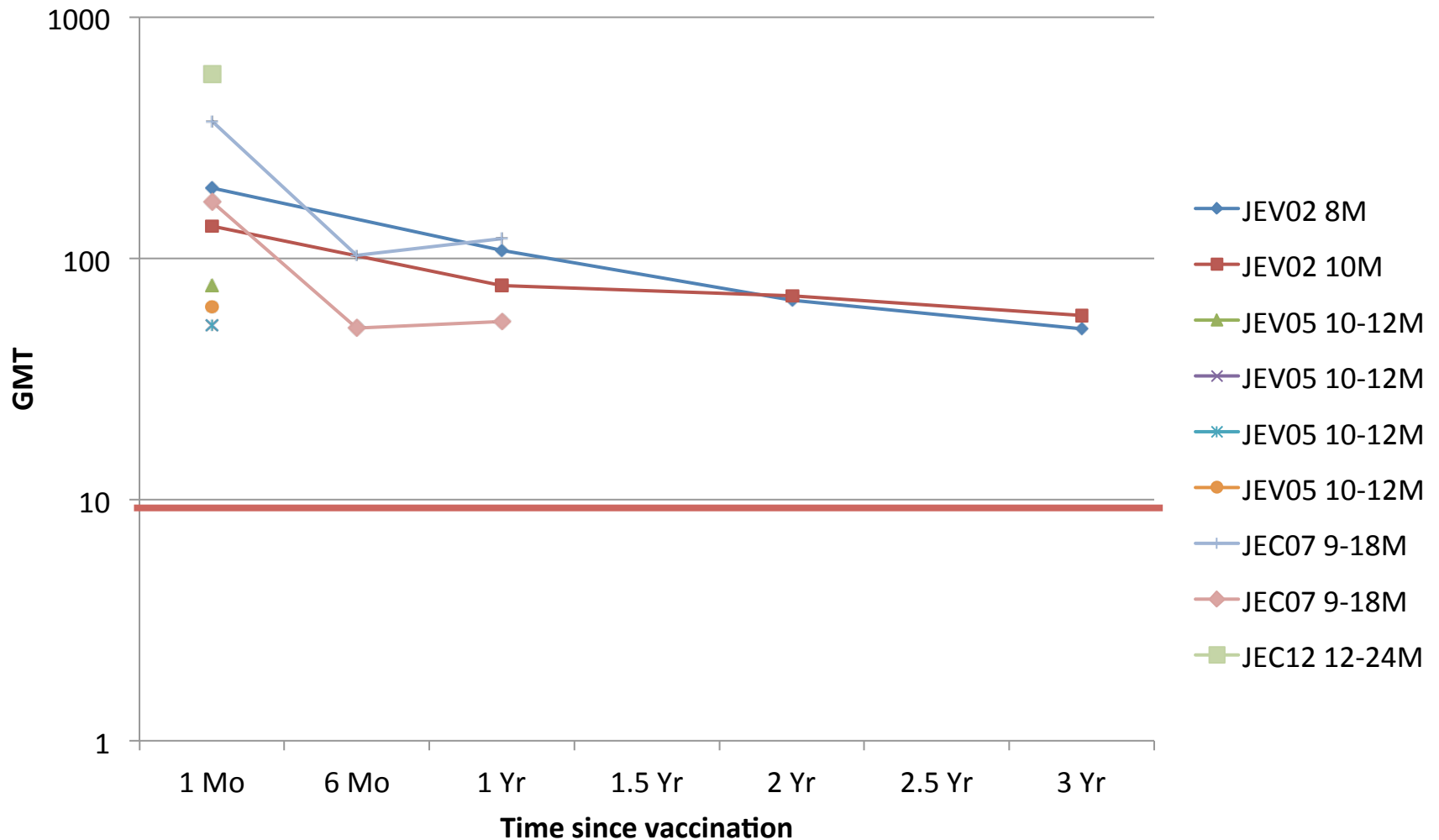
IXIARO - Geometric Mean Titers

Primary series without booster



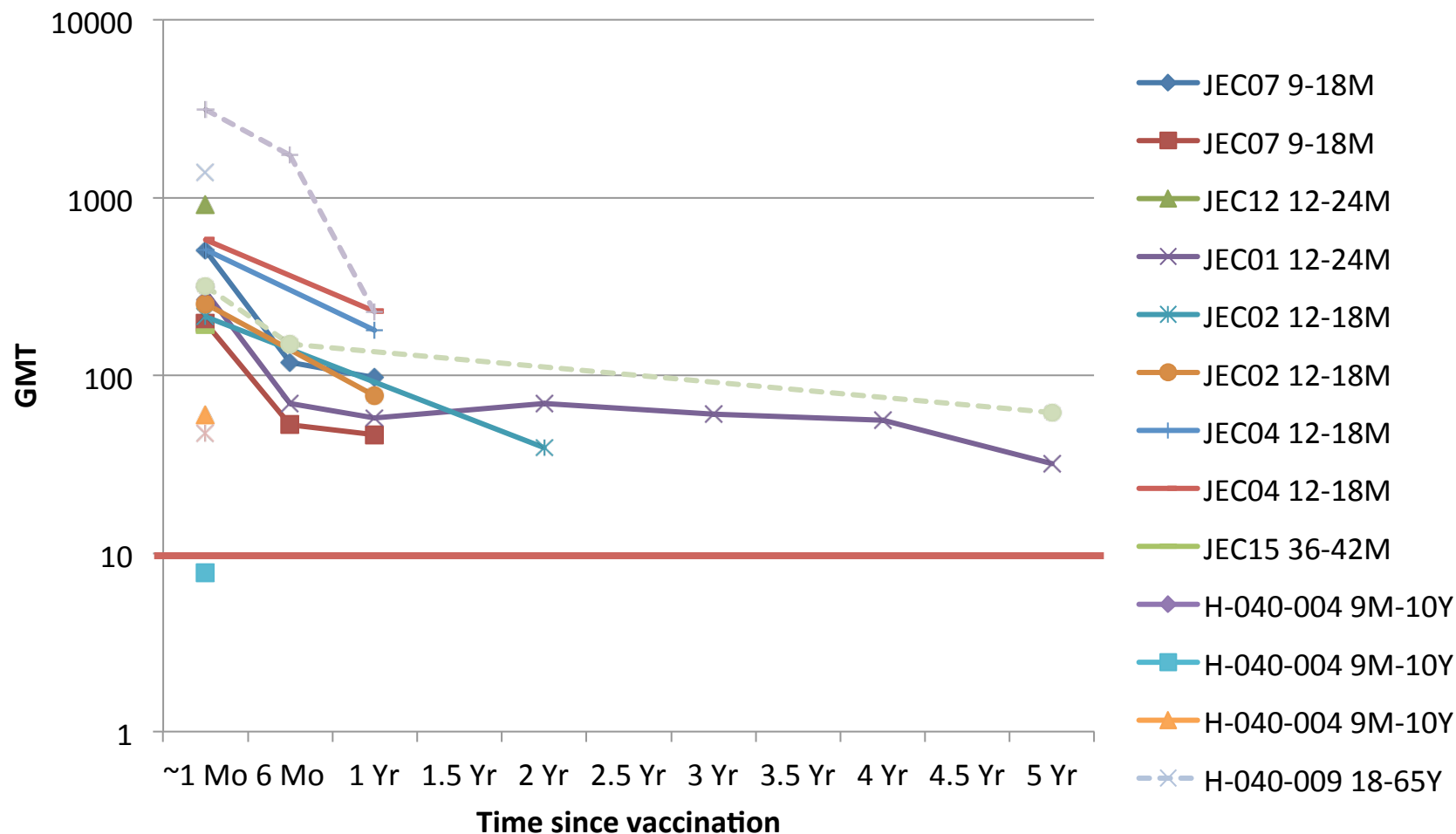
CD.JEVAX – Geometric Mean Titters

Single dose



IMOJEV – Geometric Mean Titters

Single dose



Seroprotection rates - IXIARO

Study ID	Country	Age	N	2M	6M	12M	15M	18M	2Y	3Y
IC51-221	India	1-3Y	24	95.7 (87-104)						
IC51-323	Philippines	2-6M	1869	100 (NR)						
IC51-323	Philippines	6-12M		95 (NR)						
IC51-323	Philippines	1-3Y		97 (NR)						
IC51-323	Philippines	3-12Y		94 (NR)						
IC51-323	Philippines	12-18Y		77 (NR)						
IC51-325	Philippines	2M-17Y	300	100 (NR)	86*** (NR)	89.9 (NR)			89 (NR)	90.1 (NR)
IC51-301	USA, Germany, & Austria	18-80Y	430	98 (NR)						
IC51-301 & 302	Austria, Germany, & Romania	18-86Y	181	99 (96-100)	95 (91-97)	83 (77-88)			82 (76-87)	85 (78-90)
None	USA	18-49Y	25	95 (NR)	100.0 (NR)	100.0 (NR)		90.0 (NR)	87.5 (NR)	
IC51-304/ IC51-305	Germany & Northern Ireland	18-76Y	115	97.3 (94-100)	82.8 (75-89)	58.3 (49-67)			48.3 (39-57)	
IC51-308	Austria & Germany	18Y+	58	98.2 (NR)						
IC51-311	Austria & Germany	19-66Y	198				69.2 (62-75)			33

Seroprotection rates – CD.JEVAX

Study ID	Country	Age	N	28D	6M	1Y	2Y	3YR
JEV01/02	Philippines	8M	70	92.1 (84-97)		90.4 (82-96)	81.1 (72-89)	79.3 (69-87)
JEV01/02	Philippines	10M	173	90.6 (85-94)		86.1 (81-91)	80.7 (75-86)	81.9 (76-87)
JEV05	Bangladesh	10-12M	146	86.3 (80-91)				
JEV05	Bangladesh	10-12M	195	82.1 (76-87)				
JEV05	Bangladesh	10-12M	192	80.2 (74-85)				
JEV05	Bangladesh	10-12M	194	84.5 (79-89)				
JEC07	Thailand	9-18M	150	99.3 (96-100)	97.2 (93.1-99.2)	97.3 (93-99)		
JEC07	Thailand	9-18M	150	97.3 (93-99)	89.0 (82.7-93.6)	87.5 (81-92)		
JEC12	Korea	12-24M	136	99.1 (NR)				

Seroprotection rates – IMOJEV

Study ID	Country	Age	N	28-30d	6 M	1YR	2YR	3YR	4YR	5YR
JEC07	Thailand	9-18M	149	99.3 (96-100)	94.5 (89-98)	88.1 (82-93)				
JEC07	Thailand	9-18M	149	97.2 (93-99)	84.1 (77-90)	76.8 (69-83)				
JEC12	Korea	12-24M	137	100.0 (NR)						
JEC01	Thailand	12-24M	200	96 (92-98)	87 (NR)	82 (NR)	80 (NR)	75 (NR)	74 (NR)	65.6 (NR)
JEC02*	Thailand & Philippines	12-18M	1059	95.0 (93-96)			80.3 (NR)			
JEC02 (subset)	Thailand & Philippines	12-18M	591	100 (99-100)		88.2 (85-91)				
JEC04*	Taiwan	12-18M	110			96.6 (NR)				
JEC04*	Taiwan	12-18M	220			96.8 (NR)				
JEC15	Philippines	36-42M	46	89.7 (76-97)						
H-040-00 4*†	India	9M-10Y	33	100 (NR)						
H-040-00 4*†	India	9M-10Y	33	25 (NR)						
H-040-00 4*†	India	9M-10Y	33	82 (NR)						
H-040-00 9*	USA & Australia	18-65Y	410	99.1 (98-100)						
H-040-00 9*	USA & Australia	18-65Y	410	80.9 (76-85)						
H-040-00 5*	Australia	18-55Y	202 -> 93	99 (96-100)	97 (93-99)	95 (87-99)	90 (81-96)			94 (82-99)
H-040-00 8*†	USA	18-65Y	30	100 (NR)	92 (NR)	92 (NR)				35

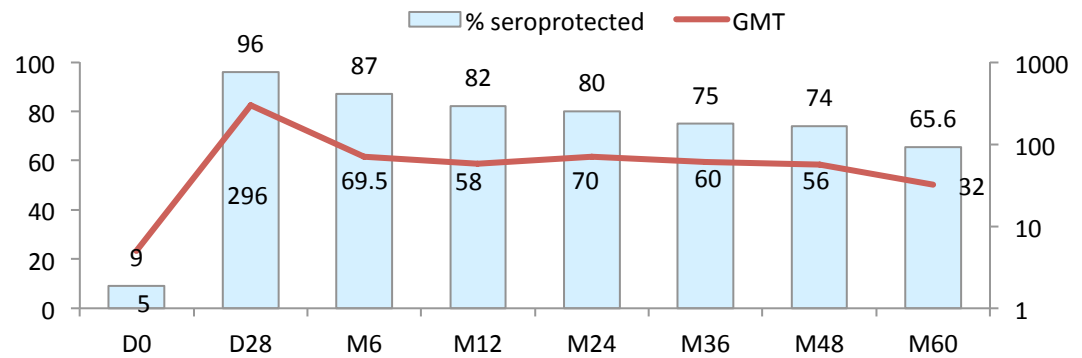
Seroprotection rates (SP%) & GMTs among Bangladeshi recipients of SA14-14-2 vaccine produced in the original facility (“reference lot”) and vaccine manufactured in a new GMP-compliant facility (“GMP lot”)

	n/N	SP%	(95% CI)	GMT	(95% CI)
Original facility					
Reference lot	126/146	86.3%	(79.8-91.0%)	77	(59.6-100.4)
New GMP facility					
“GMP lot” A	160/195	82.1%	(76.1-86.8%)	53	(43-65)
“GMP lot” B	154/192	80.2%	(74.0-85.2%)	53	(42-67)
“GMP lot” C	164/194	84.5%	(78.7-89.0%)	63	(50-78)
Pooled A-B-C	478/581	82.3%	(79.0-85.2%)	56	(50-64)

Immunogenicity after one dose of IMOJEV in naïve toddlers and children primed with MBDV

- **Naïve toddlers**
- n=200; aged 12-24 months
- Sensitivity analysis*
- GMT in protective range at M 60: 32 (24,3-42,1)
- Initial decline is followed by a decrease at a much slower rate.
- The full set analysis (Intent To Treat) show 90,0% (82,8-94,9) seroprotection and GMT 63,8 (48,0-84,7) after five years.

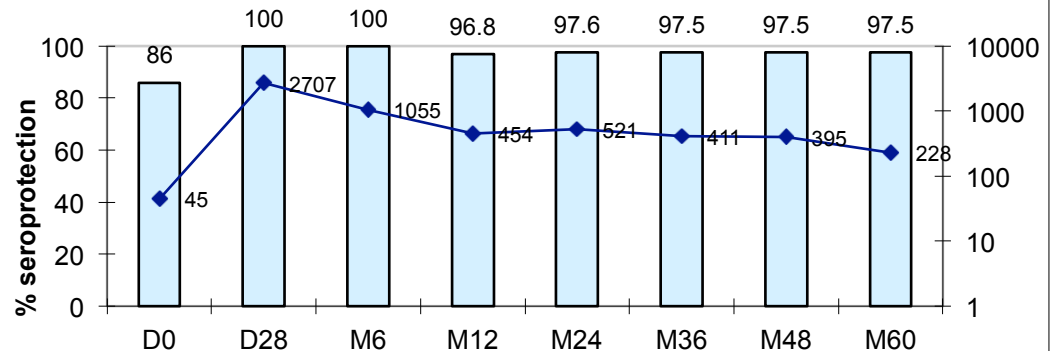
Naïve toddlers single dose



- **Children primed with MBDV**
- n=100; 2-5 years
- Sensitivity analysis*
- IMOJEV® booster effect is demonstrated in subjects primed with MBDV 12 months before
- Very slow decrease after M12.
- Full analysis at Y5: 100% (95,4-100,0) seroprotection and GMT 252 (188-337)

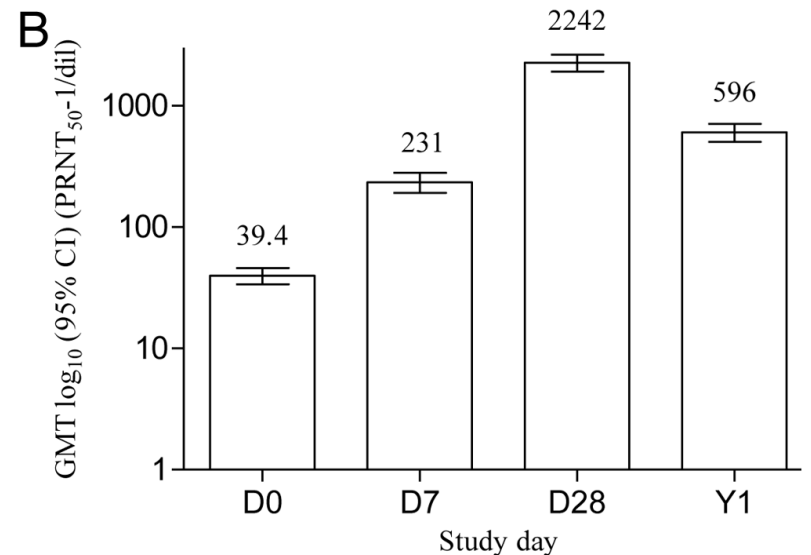
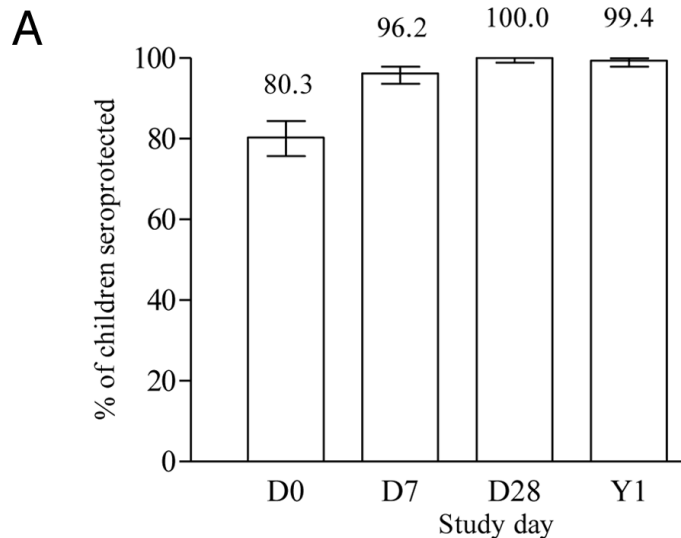
Primed with MBDV

IMOJEV as a booster of MBDV



Ref. Chokephaibulkit K; PIDJ vol29, N°12, 2010; Feroldi E. et al. ACPID 2012, 2014

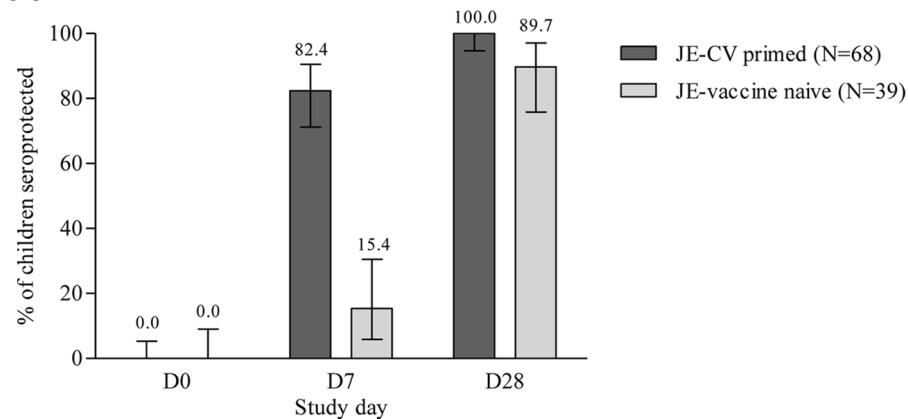
Response to a booster dose of JE-CV at 2 years in children primed with JE-CV: Seroprotection levels (A) and GMT levels (B)



- Response to a booster dose was brisk, with 96% seroprotection rate by 7 days after booster
- High seroprotection rates persisted for 1 year

Response to a booster dose of JE-CV in children primed with JE-CV but seronegative at 2 years versus JE vaccine naïve children: Seroprotection levels (A) and GMT levels (B)

A Seroprotection



B GMT Levels

