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Update on the NIH tetravalent dengue vaccine

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Tetravalent studies in DENV naïve adults

Vaccine	Components:				Potency (log $_{10}$ PFU)
TV-003	DEN1Δ30	DEN2/4Δ30	DEN3Δ30/31	DEN4Δ30	3, 3, 3, 3
TV-005	DEN1Δ30	DEN2/4Δ30	DEN3Δ30/31	DEN4Δ30	3, 4, 3, 3

Healthy adult subjects (18-50 yo) living in Baltimore, Maryland or Burlington, Vermont

All subjects are flavivirus naïve

Single, subcutaneous administration of tetravalent vaccine

Clinical follow-up every other day through day 16

Serum for viremia collected every other day through day 16

Serum for PRNT: Days 28, 56, 90

Clinical summary of adverse events

Adverse event	TV-003 (n=40)	Placebo (n=16)	p-value	TV-005 (n=40)	Placebo (n=16)	p-value
Injection site:						
Erythema	5.0%	6.3%	1.0000	2.5%	0.0%	1.0000
Pain	0.0%	6.3%	0.2857	2.5%	0%	1.0000
Tenderness	5.0%	0.0%	1.0000	0.0%	6.3%	0.2857
Induration	5.0%	0.0%	1.0000	2.5%	0.0%	1.0000
Systemic:						
Fever	0.0%	0.0%	n/a	2.5%	0.0%	1.0000
Headache	45%	25%	0.2300	57.5%	37.5%	0.2397
Rash	**55%**	**0.0%**	**< 0.0001**	**67.5%**	**0.0%**	**<0.0001**
Neutropenia[b]	2.5%	6.3%	0.4935	7.5%	0%	0.5498
Elevated ALT[c]	5.0%	0.0%	1.0000	5.0%	6.3%	1.0000
Myalgia	7.5%	6.3%	1.0000	10.0%	6.3%	1.0000
Arthralgia	0.0%	6.3%	0.2857	0.0%	0.0%	n/a
Retro-orbital pain	5.0%	0.0%	1.0000	7.5%	12.5%	0.6172
Fatigue	20.0%	0.0%	0.0892	32.5%	31.3%	1.0000
Photophobia	0.0%	0.0%	n/a	5.0%	6.3%	1.0000
Elevated PT	2.5%	6.3%	0.4935	5.0%	6.3%	1.0000
Elevated PTT	3.6%	12.5%	0.0779	0.0%	0.0%	n/a
Thrombocytopenia	0.0%	0.0%	n/a	0.0%	0.0%	n/a

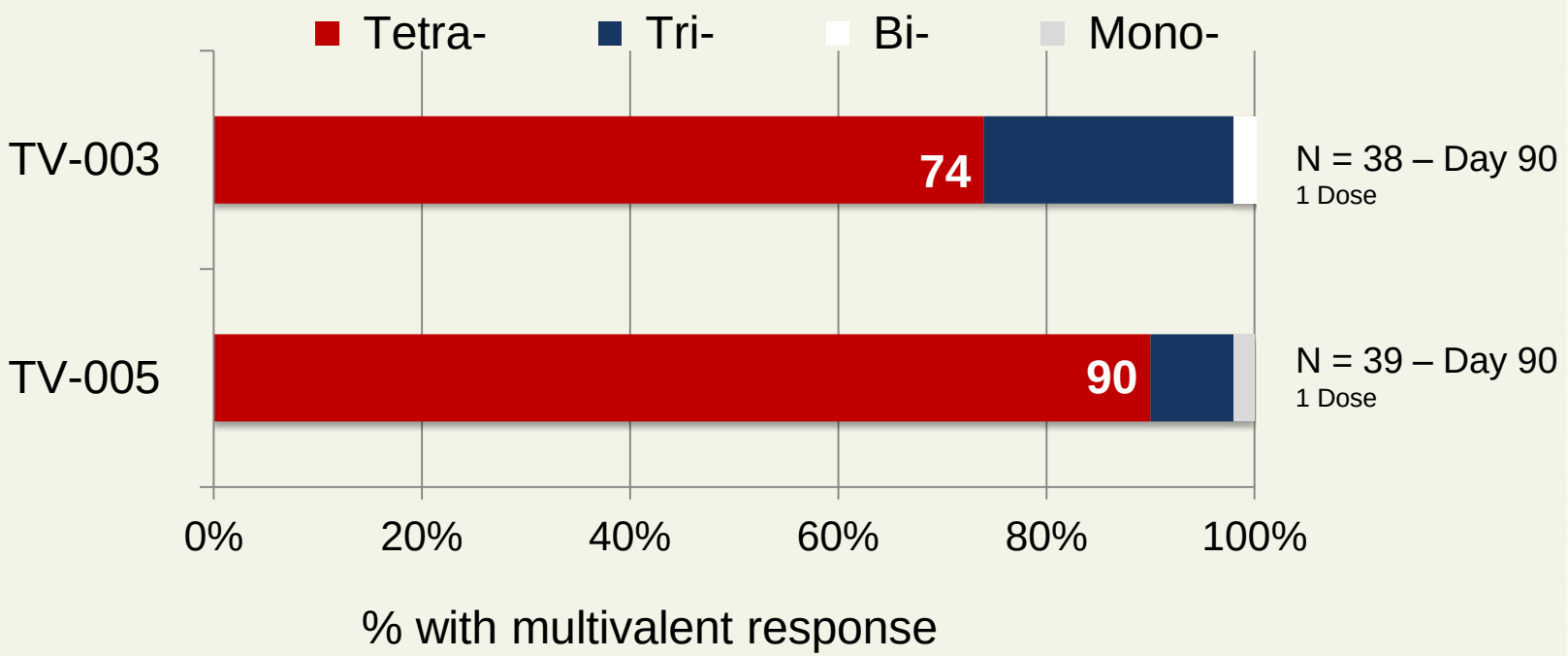
Neutralizing antibody responses

Serum for PRNT: Days 28, 56, 90

TV-003: 3, 3, 3, 3
TV-005: 3, 4, 3, 3

		% seroconverted ($PRNT_{50} \geq 10$)				Mean peak titer (GMT) ($PRNT_{50} \geq 10$)			
Vaccine	N	DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4
TV-003	38	92	**76**	97	100	63	40	85	151
TV-005	39	92	**97**	97	97	35	91	100	205

TV003 & TV005 neutralizing antibody response



A single dose can elicit a tetravalent antibody response in 90% of subjects without previous DENV exposure

Vaccine rash summary

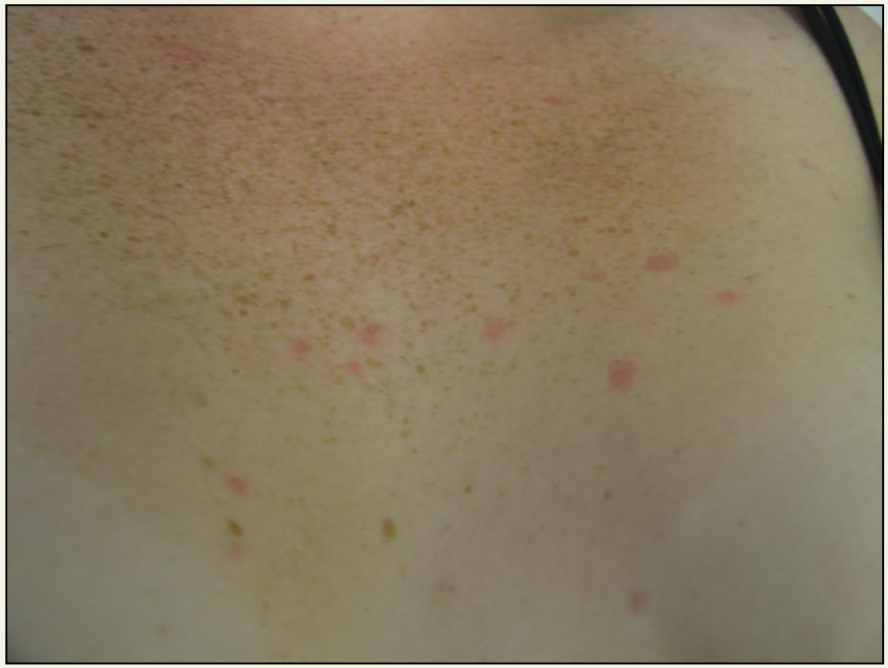
Vaccine	No. with rash	Mean day of onset	Mean duration in days[1]	Rash intensity[2]		
				Mild	Moderate	Severe
TV-003 N = 60	37 (62%)	10.2 ± 0.04	10.6 ± 0.7	37	0	0
TV-005 N = 60	37 (62%)	10.2 ± 0.04	10.0 ± 0.7	36	1*	0

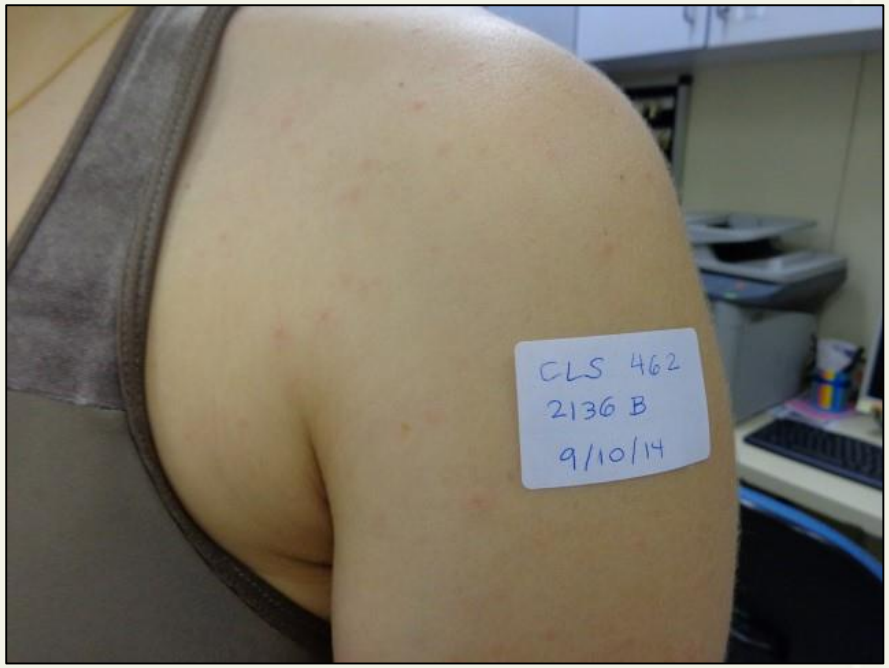
1 Subjects were not seen between Study Day 16 and 21, thus, rashes that were not resolved by Study Day 16 but were resolved at Study Day 21 were given a resolution day of Study Day 21.

2 Mild: Rash is present but asymptomatic
Moderate: Rash is present and asymptomatic (pruritis/pain) but does not interfere with normal function
Severe: Rash is present and interferes with normal function

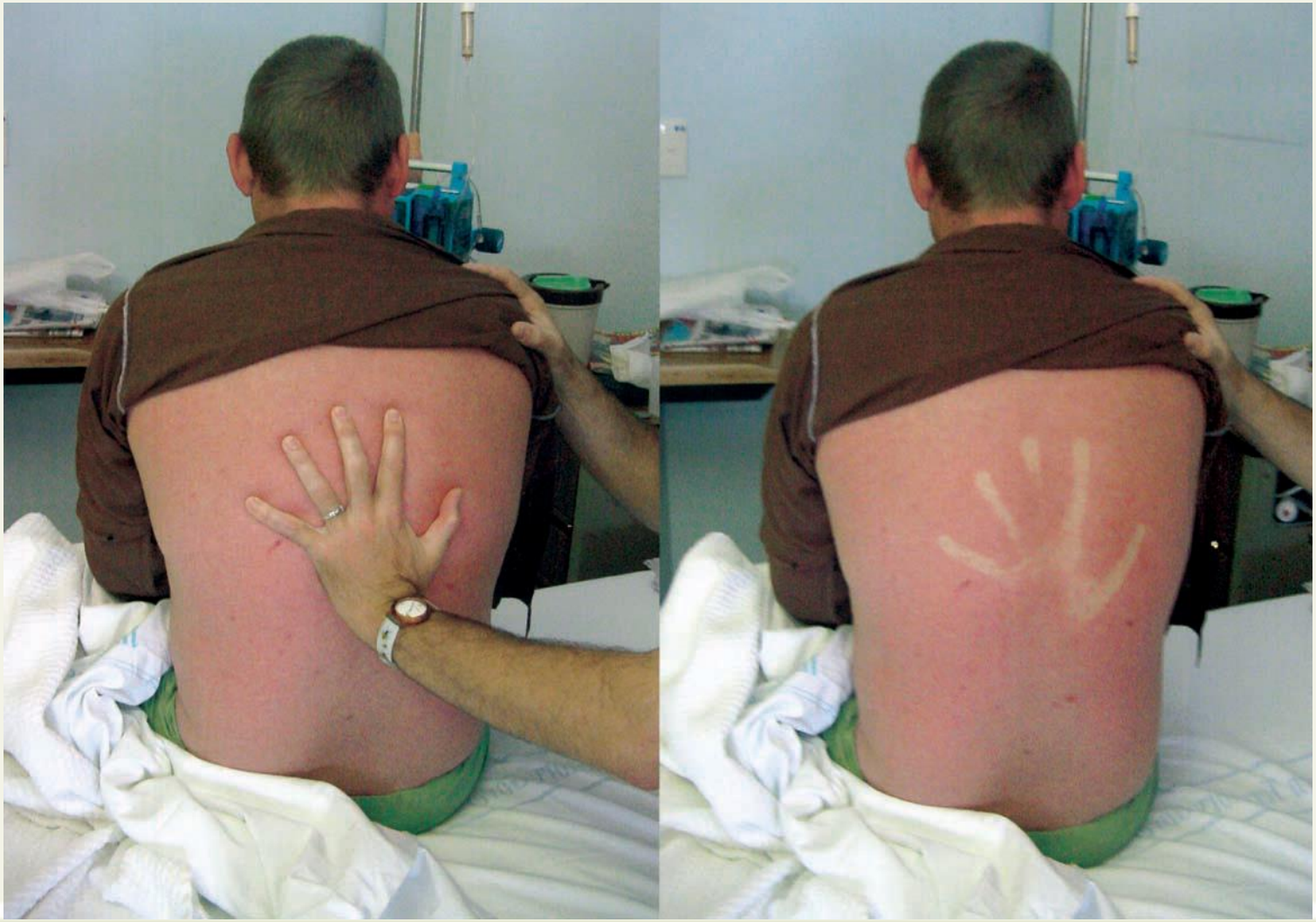
* Mildly pruritic, no medication was taken.

Vaccine-associated rash - asymptomatic



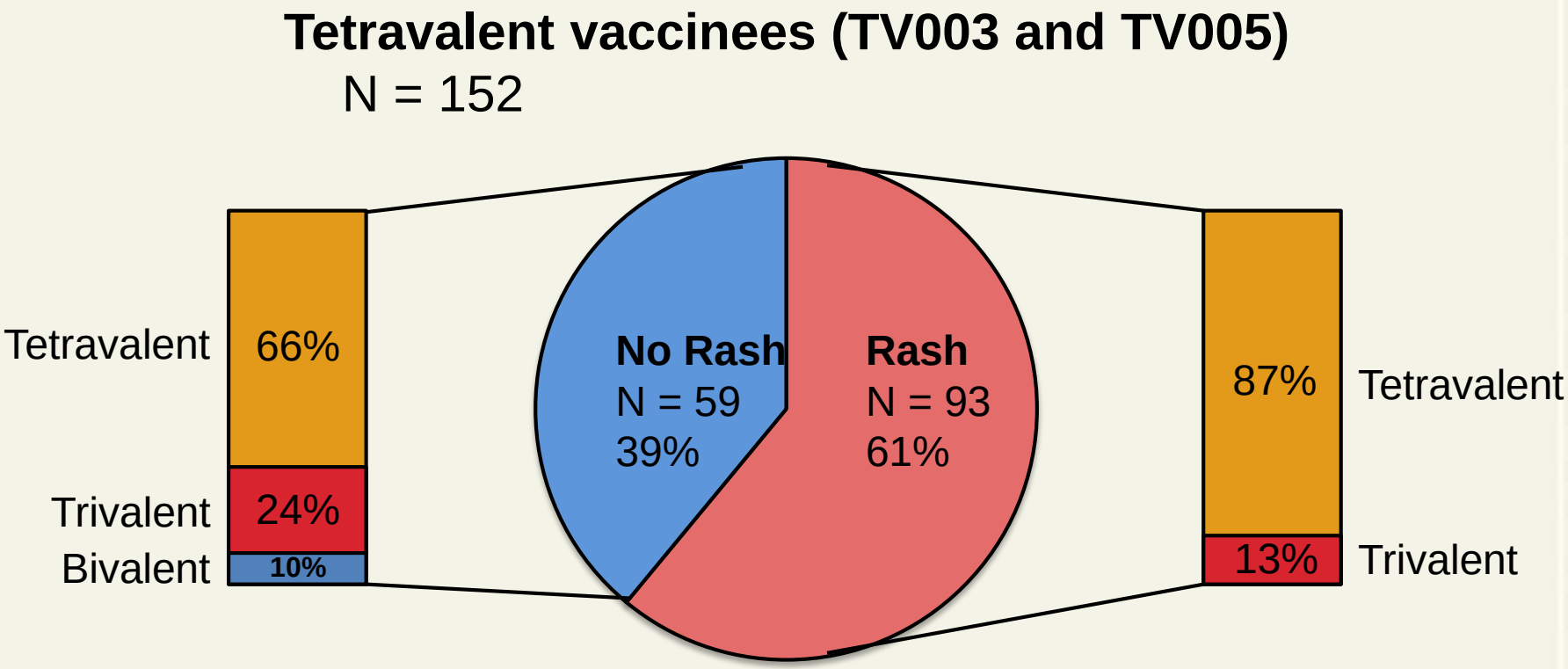


Wild-type dengue Rash



CID 2004: 38 (15 May)

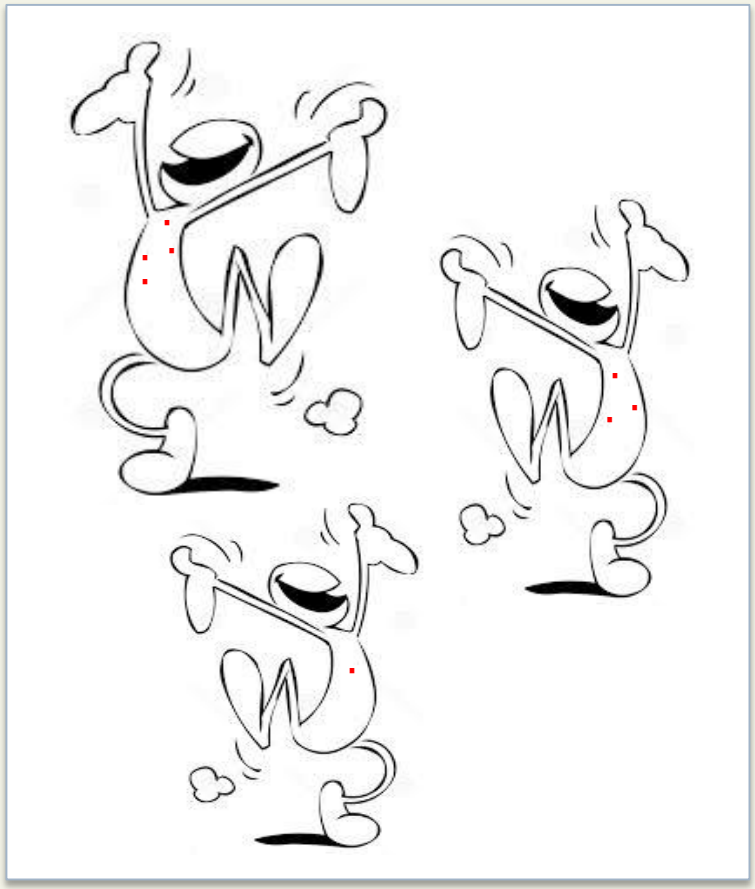
Vaccine rash is predictive of a tetravalent antibody response



A vaccinee is statistically more likely to have a tetravalent antibody response if they present with a vaccine-associated rash (*P* = 0.002, Chi-square)

(Source: *CIR268.03* N=20, *CIR268.05* N=19, *CIR279.03* N=38, *CIR279.05* N=39, *CIR283.03* N=36)

Vaccine rash is predictive of a tetravalent antibody response



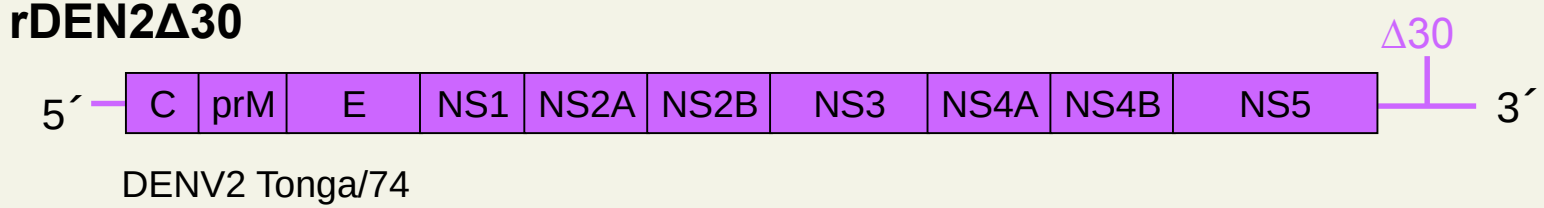
Maybe it's a "happy" rash

Other vaccines with rash side-effects:

- MMR
- Varicella
- Zoster
- Yellow fever
- Japanese encephalitis

DENV challenge of vaccinees

rDEN2Δ30 Challenge strain



- Derived from Tonga/74 strain isolated from DENV-2 outbreak that caused milder disease and lower levels of viremia
- Different genotype than DENV-2 in TV003/TV005
- Not attenuated in rhesus monkeys

DEN2Δ30 in healthy volunteers

Subjects received 10^3 pfu of rDEN2Δ30:

- 100% of subjects have viremia:
  - Mean peak titer = 300 pfu/ml serum (Vaccine yields 3 – 6 pfu/mL)
- 80% of subjects with diffuse rash
  - Half were moderate in intensity
- 40% of subjects with neutropenia
  - Half were Moderate: ANC nadir = 592/mm^3 and 695/mm^3
  - Half were Mild: ANC nadir = 806/mm^3 and 961/mm^3
- No subject developed fever, elevated LFTs, or signs of vascular leak

Evaluation of vaccine efficacy

Day 0
Vaccination

Day 180
Challenge

TV-003
N = 24

Placebo
N = 24

10^3 PFU
DEN2Δ30
N = 41

Efficacy endpoints:

Primary: Protection against viremia

Secondary: Protection against rash
Protection against neutropenia

DENV-2 Vaccine Challenge Study

Viremia post-challenge with DEN2Δ30						
Cohort	N	Frequency of viremia	Mean peak Viremia	Viremia range	Mean day of onset	Mean duration (days)
Placebo	20	**100%**	2.3 ± 0.1	1.5 – 2.9	4.7 ± 0.6	5.6 ± 0.5
TV-003	21	**0%**	n/a	n/a	n/a	n/a

Rash presentation post-challenge with DEN2Δ30					
Cohort	N	Frequency of rash	Mean day of onset	Mean duration (days)	Intensity
Placebo	20	**80%**	9.6	8.1	38% moderate 62% mild
TV-003	21	**0%**	n/a	n/a	n/a

- **TV-003 provides 100% efficacy against DENV-2 challenge viremia and rash**

DENV-2 Vaccine Challenge Study

		% seroconverted ($PRNT_{50} \geq 10$)				Mean peak titer (GMT)			
Vaccine	N	DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4
TV-003	24	92	100	100	100	47	84	152	270
		92% tetravalent response							
					Day 180:	22	50	43	82
Post-Chall.	21					35	124	51	79
					Fold rise:	1.6	2.5	1.2	0.9

- **Overall vaccine response to DENV-2 is not boosted following challenge**

Vaccine Challenge Study

Questions we may be able to answer:

- What is the immunological correlate of protection?
- What are the mediators of antibody dependent enhancement?
- What role does cross-reactive antibody play in protection/risk?

CIR 300: Trivalent vaccination followed by DEN2Δ30 challenge

Day	N	Treatment
0	18	Trivalent vaccine mixture – DEN1, DEN3, DEN4
0	6	Placebo
180	All	Challenge with DEN2Δ30

- IND for DENV-3 challenge strain DEN3Δ30 to be submitted
- Testing suitability of DENV-1 and DENV-4 strains

Age de-escalation study – Bangkok
WRAIR / AFRIMS / Phramongutkhlao (PMK) Hospital
WRAIR PI: Dr. Louis Macareo
PMK PI: Dr. Veerachai Watanaveeradej

Objectives:

a. Safety in healthy adults, adolescents, and children
b. Determine immunogenicity 4 - 26 weeks post vaccination
c. Access frequency, quantity, and duration of viremia
d. Determine the effect of pre-existing antibody

Study design: Placebo-controlled, double blind, healthy subjects
Begin with adults, proceed to adolescents, then children
One or two vaccine doses (6 month interval)
Clinical labs and virology every other day for first 16 days
Serology on days 28, 56, 72, and 180 after each dose.

Cohort size:

		Vacc. date
Adults (18 – 50 years)	84 (30 +30 + 24 placebo)	Dec. 6, 2014
Adolescents (13 – 17 years)	70 (50 + 20 placebo)	Mar 14, 2015
Older children (5 – 12 years)	70 (50 + 20 placebo)	Aug 1, 2015
Younger children (1 – 4 years)	70 (50 + 20 placebo)	Nov 7, 2015
	294 Total	

Age de-escalation studies – Bangkok
WRAIR / AFRIMS / Phramongutkhlao (PMK) Hospital

Adults (18 – 50 years old):

			Frequency of indicated AE (%)												
Treatment	N	% reporting AE	ALT	Arth-ralgia	Rash	Fatigue	Fever	Head-ache	IS erythema	IS pain	Leuko-cytosis	Myalgia	Neutro-penia	Photo-phobia	Retro-orbital
003	30	63	3	10	13	17	17	30	23	17	3	13	3	0	17
005	30	83	3	7	40	33	13	33	27	37	10	23	0	3	7
Placebo	24	63	0	4	8	0	0	25	29	13	8	13	4	8	13
P-value* for 003		1.000	1.000	0.620	0.682	0.059	0.059	0.766	0.862	0.720	0.579	1.000	1.000	0.192	0.720
P-value* for 005		0.120	1.000	1.000	0.020	0.003	0.120	0.561	1.000	0.062	1.000	0.483	0.444	0.579	0.646

* Fisher Exact test – Two tailed
Data only for vaccine-related AE's

Adolescents (13 – 17 years old):

			Frequency of indicated AE (%)												
Treatment	N	% reporting AE	ALT	Arth-ralgia	Rash	Fatigue	Fever	Head-ache	IS erythema	IS pain	Leuko-cytosis	Myalgia	Neutro-penia	Photo-phobia	Retro-orbital
005	50	74	2	14	18	30	28	42	20	28	2	24	0	4	21
Placebo	20	65	0	0	5	10	15	25	10	25	5	25	0	10	15
P-value* for 005		0.560	1.000	0.180	0.262	0.122	0.359	0.274	0.487	1.000	0.493	1.000	1.000	0.573	0.743

* Fisher Exact test – Two tailed
Data only for vaccine-related AE's

Age de-escalation study – Dhaka
icddr, b
PI: Dr. Rashidul Haque

Objectives:

a. Safety in healthy adults, adolescents, and children
b. Determine immunogenicity 4 - 8 weeks post vaccination
c. Determine durability of immune response through week 26
d. Access frequency, quantity, and duration of viremia
e. Determine the effect of pre-existing antibody

Study design: Placebo-controlled, double blind, healthy subjects
Begin with adults, proceed to adolescents, then children
One vaccine dose
Clinical labs and viremia determinations
Serology on days 28, 56, and 180 after each dose.

Cohort size:

Adults (18 – 50 years)	48 (36 + 12 placebo)
Adolescents (11 – 17 years)	48 (36 + 12 placebo)
Older children (5 – 10 years)	48 (36 + 12 placebo)
Younger children (1 – 4 years)	48 (36 + 12 placebo)
	192 Total

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