Safety of Dengue Vaccine: Concerns and Consequences

PIDSP 24TH ANNUAL CONVENTION, FEB 16-17 2016
CROWNE PLAZA GALLERIA , ORTIGAS

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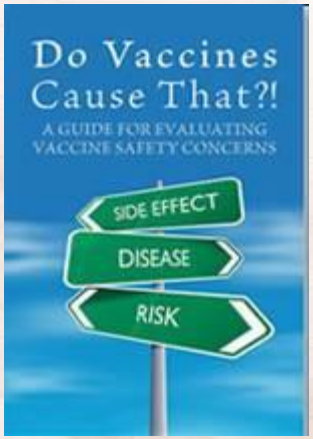
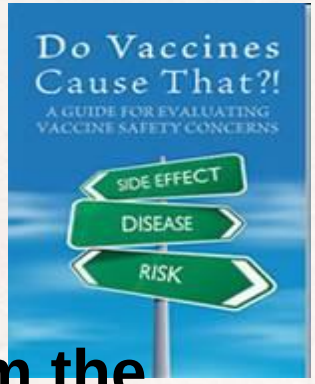




Disclosure of Interest

I have received research grants from the following for the last 3 years:

- Novartis

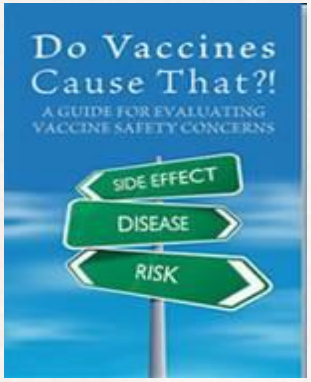
-Sequirus

-Sanofi Pasteur

Honoraria for speaking engagements:

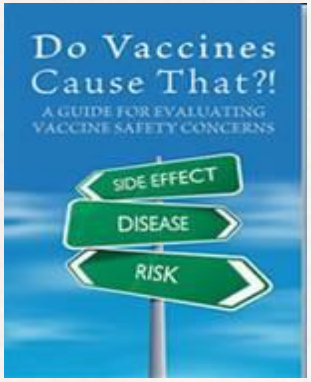
-GSK

-Sanofi Pasteur



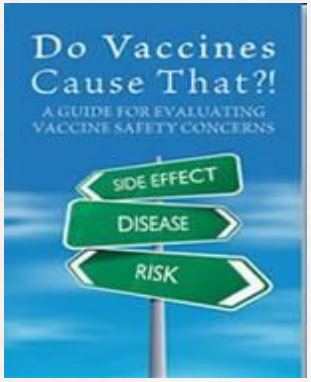
PERSPECTIVE

Childhood Immunization



- **Most successful preventive health measure**
- **“An ounce of prevention is worth more than a pound of cure”**

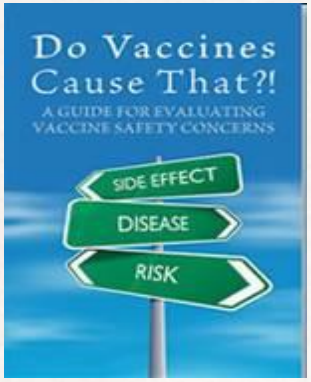
Immunization



Recommendations for Vaccination

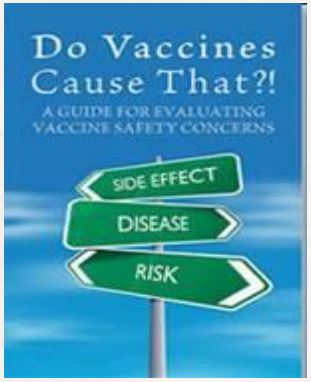
- Characteristics of immunobiologics
- Scientific knowledge on active & passive immunization
- Epidemiology of diseases
- Judgements of public health officials and specialist

Immunization



- No vaccine is completely safe nor completely effective
- Benefits
  - Partial to complete protection
  - Asymptomatic or mild infection
  - Severe consequences

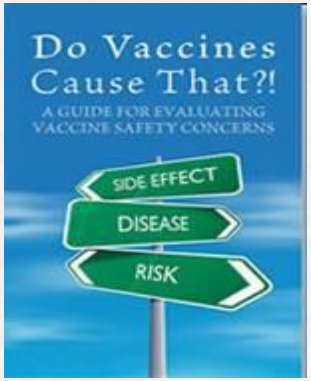
Risk of Vaccination



- **Common, minor, and inconvenient side effects**
- **Rare, severe, and life-threatening conditions**

Recommendations balance scientific evidence of benefits, cost, and risk to achieve optimal levels of protection

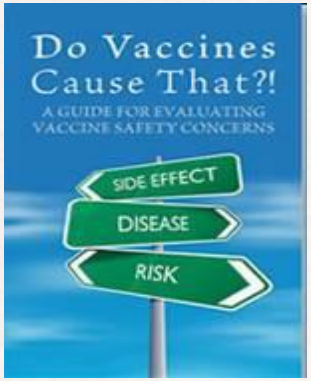
Quality and safety of vaccines from development to delivery



- High standard of safety
- Stringent measures to ensure quality and safety
  - Research and Development
  - Manufacturing
  - Licensing
  - Transport
  - Storage
  - Use of vaccines
  - Disposal of needles & other equipment

Ref: www.who.int/entity/mediacentre/factsheets/fs295/en/

Research and Development of Vaccines



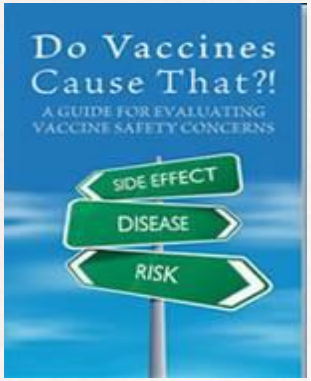
- **Vaccines carefully evaluated:**
  - **Effectiveness**
  - **Potential harmful effects**
- **Good safety results → phased trials with humans**

Safety Monitoring of Licensed Vaccines

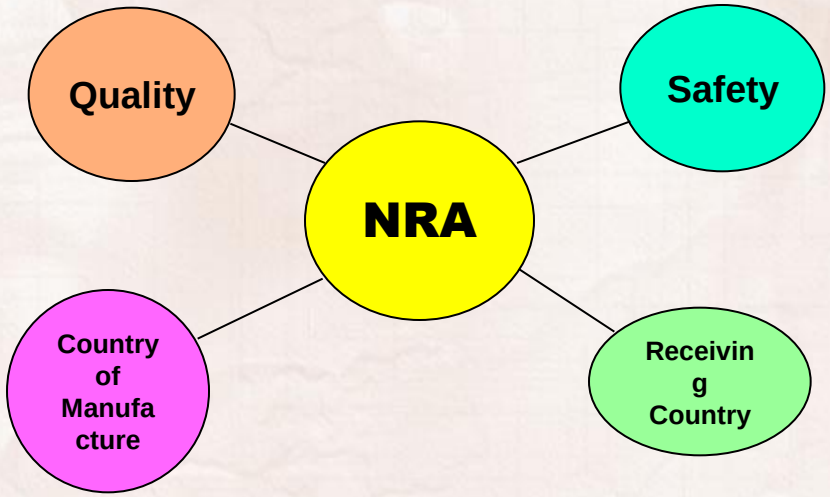
- **Vaccines licensed for general use and administered to large populations → monitoring continues**
  - **Identify less common adverse events**
  - **Events that occur after a long time**
  - **Events that occur in specific subgroups of target population**

Ref: www.who.int/entity/mediacentre/factsheets/fs295/en/

Manufacturing of Vaccines



- **Regulations ensure safety and quality of vaccines**
  - **Identification (characterization) of starting material**
  - **Compliance with GMP**
  - **Control procedures**
  - **Release of vaccines on a lot-by-lot basis by National Regulatory Authorities**

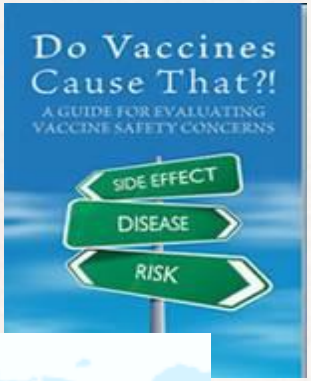


Ref : www.who.int/entity/mediacentre/factsheets/fs295/en/

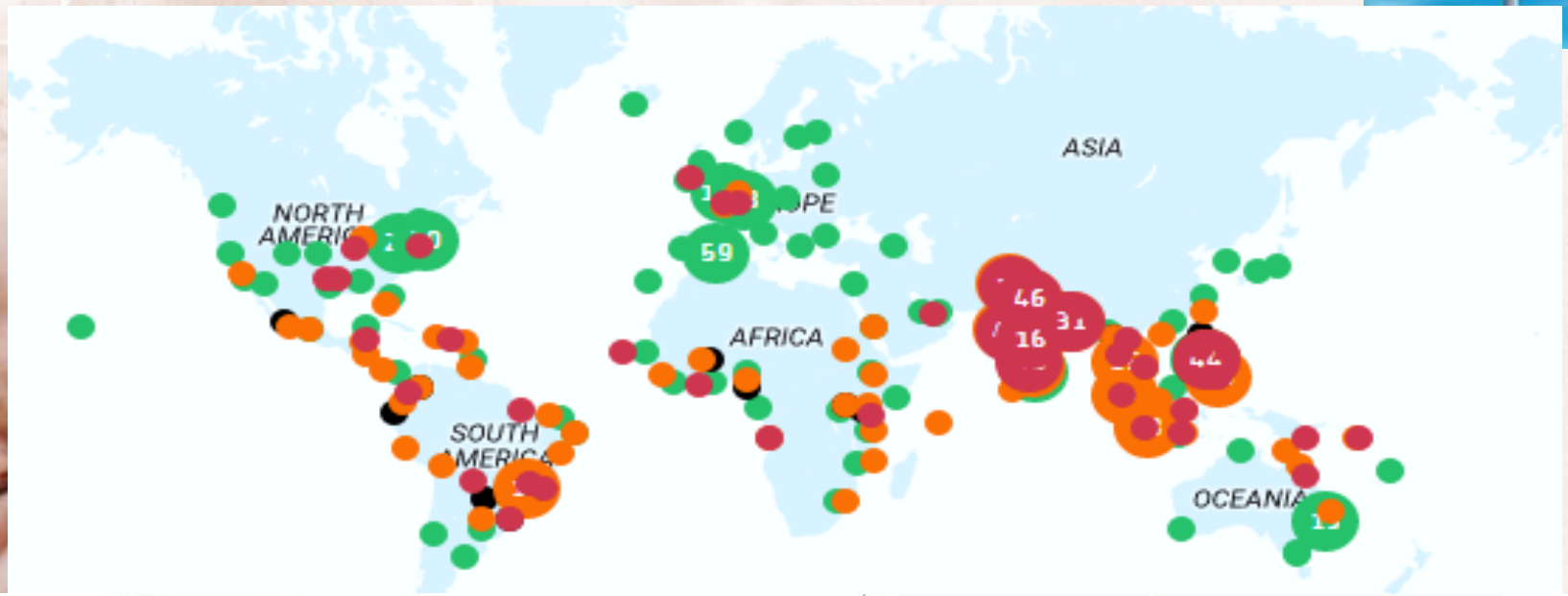

Where
we choose to
focus
makes all the
difference
in what we see
When Changing Nothing Changes Everything
Spring 2017


Do Vaccines Cause That?!
A GUIDE FOR EVALUATING VACCINE SAFETY CONCERNS
SIDE EFFECT
DISEASE
RISK
DENV
Safety First
Dengue Reality
Dengue Vaccine Development
Dengue Vaccination Safety

Dengue Reality



DENGUE TRACK BETA



35% No dengue around

39% Friends of Dengue Track users who have been diagnosed, or Dengue Track users with undiagnosed cases of dengue

20% Dengue Track users and their family members who have been diagnosed

5% Dengue cases experienced over 6 months ago

Latest Dengue Epidemiology

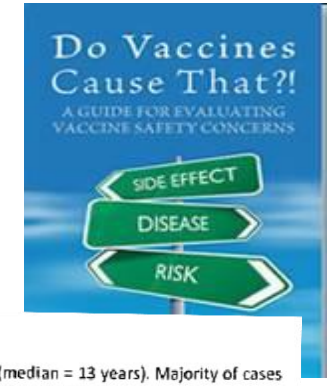
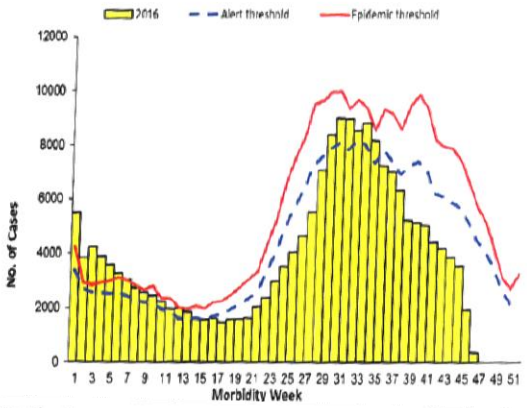


Fig. 1 Suspect Dengue Cases by Morbidity Week
Philippines, as of November 26, 2016 (N=192,253)



Geographic Distribution

Most of the cases were from the following regions: **Region VI** (12.6%), **Region VII** (12.2%), **Region IVA** (10.4%), **Region III** (9.4%) and **Region XII** (8.4%).

Profile of Cases

Ages of cases ranged from less than 1 month to 100 years old (median = 13 years). Majority of cases were male (52.3%). Most (39.5%) of the cases belonged to the 5 to 14 years age group.

Fig.4 Suspect Dengue Cases by Age Group and Sex
Philippines, as of November 26, 2016 (N= 192,253)

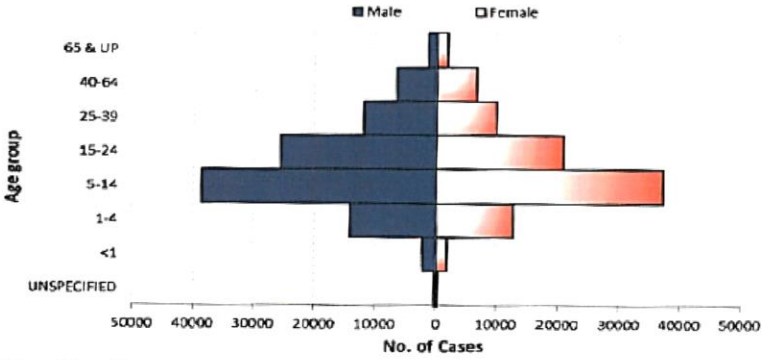


Fig. 3 Suspect Dengue Cases by Region
Philippines, 2016* vs 2015 (N=192,253)

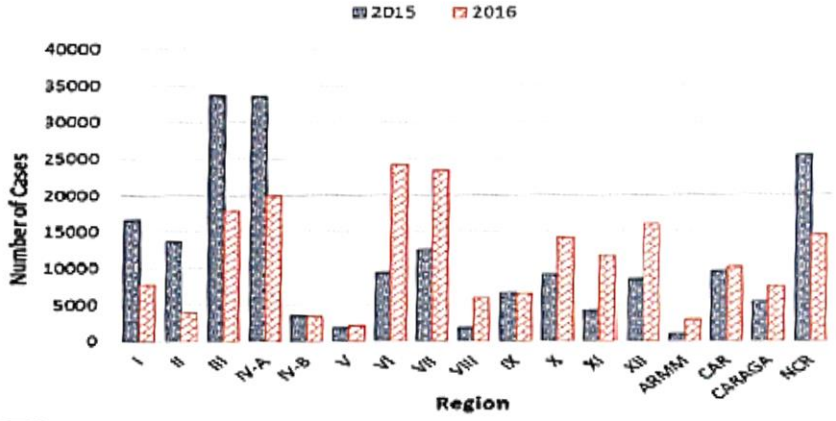
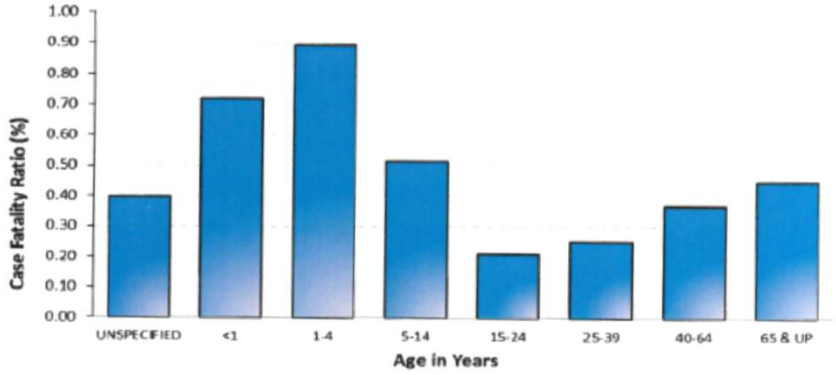
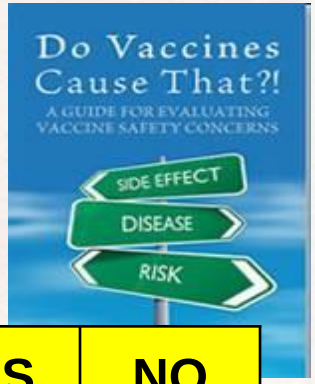


Fig. 5 Suspect Dengue Case Fatality Rate (CFR) by Age Group,
Philippines, as of November 26, 2016 (n=880)

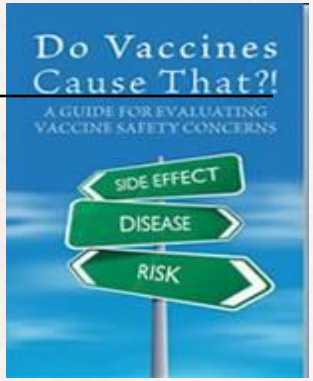


Dengue Burden is Real



	YES	NO
Vector Is Present In Philippines	✓	
All 4 Dengue Serotypes present in Philippines	✓	
Affects All Populations	✓	
Dengue can be a serious and fatal disease	✓	
Dengue is a costly disease.	✓	
There is treatment available .		✓
Epidemiology data shows increasing incidence.	✓	
Vector Control Programs able to control dengue cases.		✓

Components of the Dengue Vaccine Development Guidelines



Dengue case definitions and classifications	Safety
Defining the primary end point in dengue vaccine trials	Additional considerations for dengue vaccine trials
Proposed secondary efficacy end points	Ethical considerations
Choice of immunological assay	
Selection of sites for conducting clinical trials	

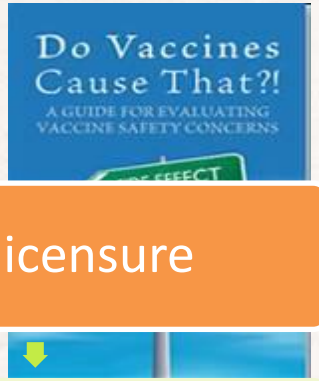
Hombach ,Joachim . Guidelines for clinical trials of dengue vaccine in endemic areas
Initiative for Vaccine Research, Immunization, Vaccines & Biologicals, Family & Community Health, WHO, Geneva, Switzerland

Clinical trials and assessment of vaccine safety

	Activity	Sample size (estimates)	Detection of Adverse events	
			Common	Rare
Clinical Trial Phase I	Test the safety and immunogenicity of a vaccine candidate in a few low-risk individuals (usually healthy adults) to determine tolerability.	10 – 100	+/-	–
Clinical Trial Phase II	Monitor safety, potential side effects, immune response, and determine optimum dosage and schedule.	100 – 1,000	+	–
Clinical Trial Phase III	Address clinical efficacy in disease prevention and provide further safety information from more heterogeneous populations and longer times of observation.	1,000 – 10,000	+	–
Submission	The vaccine application is submitted to regulatory authorities for approval to market.			
Introduction	Involves making the vaccine available for use.			

http://vaccine-safety-training.org/overview-and-outcomes-1.html

DENGUE VACCINE DEVELOPMENT GUIDELINE: SAFETY



Pre-licensure short-term

Phases I to III

Monitoring

Pre-licensure long-term

Phases II and III

Monitoring of serious adverse reactions (SAEs): 6months or more after the last vaccination,

relative risk compared with controls

A Phase III trial could be stopped after 1–2 years to assess efficacy and continue for 2–4 more years to assess long-term safety, even beyond licensure

Post-licensure

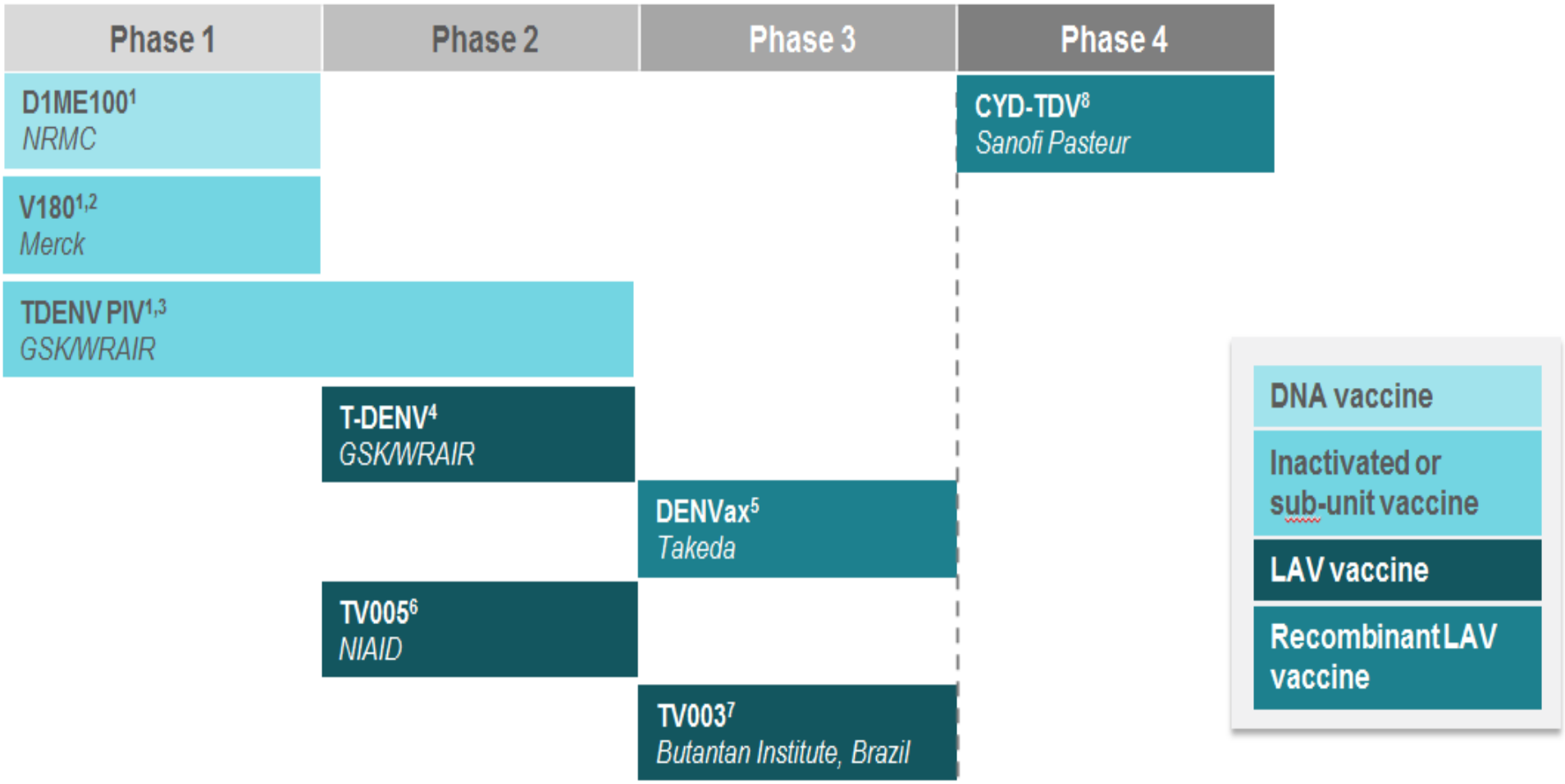
Phase IV

The safety schedule should be extended to follow-up of the participants enrolled in Phase III and IV trials, and include national/regional epidemiological dengue surveillance after licensure.

This approach is to identify safety signals related to rare events and extend the veracity of the conclusions drawn rom the original dataset

Hombach ,Joachim . Guidelines for clinical trials of dengue vaccine in endemic areas
Initiative for Vaccine Research, Immunization, Vaccines & Biologicals, Family & Community Health, WHO, Geneva, Switzerland

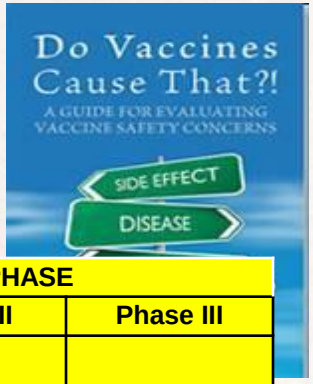
DENGUE VACCINES IN DEVELOPMENT



- CYD-TDV, recombinant YF17D; DNA, deoxyribonucleic acid; GSK, GlaxoSmithKline; LAV, live-attenuated vaccine; NIAID, National Institute of Allergy and Infectious Diseases, USA; NRMC, Naval Research Medical Center, USA; TDENV PIV, tetravalent dengue vaccine purified inactivated virus; WRAIR, Walter Reed Army Institute of Research, USA.

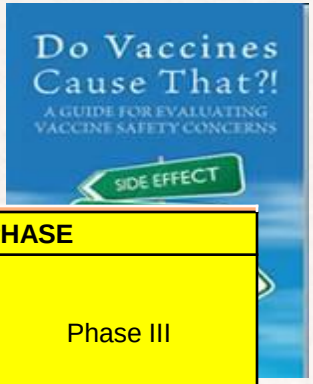
1. Schwartz LM *et al. Vaccine* 2015;33(29):3293–8; 2. ClinicalTrials.gov ID: NCT02450838; 3. ClinicalTrials.gov ID: NCT02421367; 4. Watanaveeradej V *et al. Am J Trop Med Hyg* 2014;91(1):119–28; 5. ClinicalTrials.gov ID: NCT02747927; 6. ClinicalTrials.gov ID: NCT02678455; 7. ClinicalTrials.gov ID: NCT02406729; 8. Gailhardou S *et al. PLoS Negl Trop Dis* 2016;10(7):e0004821.

Vaccines Candidates Against Dengue, July 2016



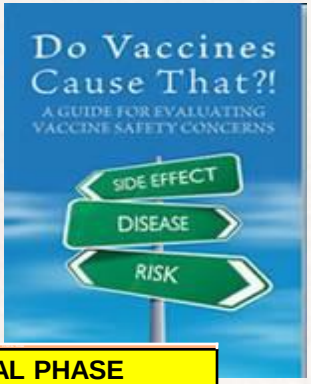
CANDIDATE VACCINE	MANUFACTURER	VACCINE TYPE	MECHANISM OF ATTENUATION OR INACTIVATION	VALENT	PRECLINICAL	CLINICAL PHASE		
						Phase I	Phase II	Phase III
CYD-TDV	Sanofi Pasteur	Live attenuated	Skeleton of the vaccine Yellow fever + Dengue premembrane proteins	Tetravalent	X	X	X	X
DENVax	Takeda	Live attenuated	DENV2 whole strand attenuated in Primary liver and dog liver cells Further attenuated by mutation in the NS3 + DENV1 / 3/4 gene in skeleton of DENV2	Tetravalent	X	X	X	
TV003/TV005	NIAID (NIH) Butantan Institute	Live attenuated	Wild strand with mutations (DENV1-3 + DENV2 recombined in skeleton of DENV4)	Tetravalent	X	X	X	
TDENV PIV	GSK WRAIR (US) Fiocruz	Purified Inactivated	Inactivated formalin	Tetravalent	X	X		

Vaccines Candidates Against Dengue, July 2016



CANDIDATE VACCINE	MANUFACTURER	VACCINE TYPE	MECHANISM OF ATTENUATION OR INACTIVATION	VALENT	PRECLINICAL	CLINICAL PHASE		
						Phase I	Phase II	Phase III
V180	Merck	Subunit Recombined	Wild premature and protein Wrapping truncated via its expression in Drosophila S2 cells	Tetravalent	X	X		
D1ME100	NMRC (US)	ADN	Protein prM / E of DENV1 expressed under Control of human cytomegalovirus Promoter of plasmid vector VR1012	Tetravalent	X	X		
TLAV-TPIV	WRAIR (US)	Live attenuated	Sensitization with heterologous reinforcement with Living attenuated tetravalent, and vaccine Purified inactivated with adjuvant Aluminum, tetravalent	Tetravalent	X	X		

Vaccines Candidates Against Dengue, July 2016



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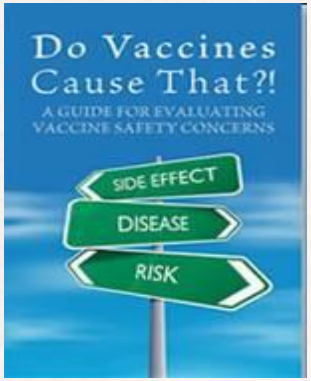
						Phase I	Phase II	Phase III
	IPK CIGB	Subunit Recombined	EDIII-p64k fusion proteins and proteins Of EDIII-capsid fusion expressed in E. Coli EDIII-p64k fusion proteins and proteins Of EDIII-capsid fusion expressed in E. Coli	Monovalent	X			
	Vaxinnate	Subunit Recombined	Bivalent Fusion Proteins 80E-STF2 Expressed in baculoviruses / cells of Insects	Tetravalent	X			
	NHRI	Subunit Recombined	Consensus EDIII proteins expressed in E. Coli	Tetravalent	X			
	CDC (US)	AND	Protein prM / E expressed in a vector	Tetravalent	X			

Vaccines Candidates Against Dengue, July 2016



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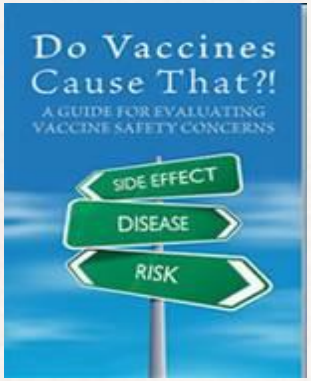
						Phase I	Phase II	Phase III
EDIII-HBsAg VLPs or ectoE-based VLPs expressed in P. pastoris	ICGEB	VLP	EDIII-HBsAg VLPs the ectoE-based VLPs Expressed in P. pastoris	Tetravalent	X			
	Themis Bioscience Institut Pasteur	Virus as a vector	EDIII and DENV-1 expressed ectoM By live attenuated measles virus vector	Tetravalent	X			
	Global Vaccines	Virus as a vector	E85 expressed by single cycle of VEE virus vector	Tetravalent	X			
Psoralen-inactivated DENV	NMRC (US)	Purified virus Inactivated	Psoralen-inactivated DENV	Monovalent	X			
Purified inactivated DENV	Fiocruz	Purified Inactivated	Purified inactivatedDENV		X			
Inactivated virus (+VEE-particle adjuvant)	Global Vaccines	Purified Inactivated	Inactivated virus (+ VEE-particle) Adjuvant)	Tetravalent	X			

Vaccines Candidates Against Dengue, July 2016



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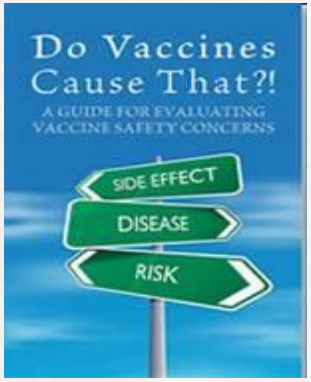
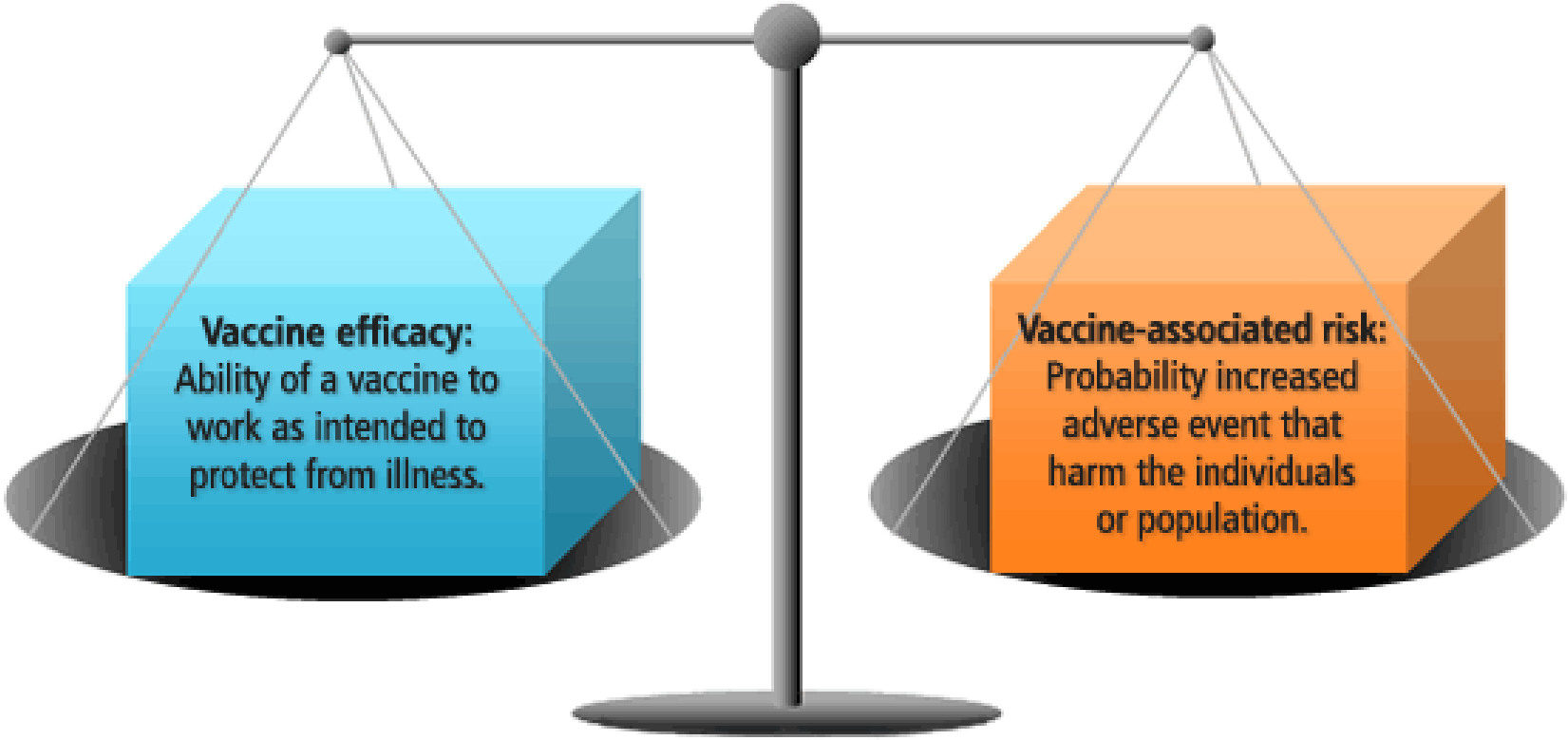
						Phase I	Phase II	Phase III
DEN/DEN chimeric viruses	Chiang Mai University Mahidol University NSTDA BioNet-Asia	Live attenuated	DEN / DEN live chimeric viruses Attenuated	Monovalent	X			
DEN host range mutations	Arbovax	Live attenuated	DEN host range mutations	Tetravalent	X			
DEN-SA 14 14 2	Beijing Institute	Live attenuated	DEN-SA 14 14 2	Monovalent	X			

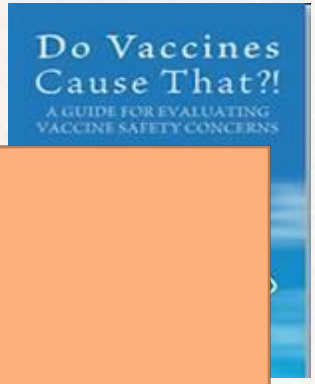

Do Vaccines Cause That?!
A GUIDE FOR EVALUATING VACCINE SAFETY CONCERNS
SIDE EFFECT
DISEASE
RISK
NO VACCINE GIVES YOU 100% PROTECTION

Striking a balance





Potential benefits of an effective vaccine must be weighed against potential risk of an AEFI.



PATHOGEN
POLIO

Benefits > Risk

http://polioeradication.org/polio-today/polio-prevention/the-vaccines/opv/

PATHOGEN	VACCINATION RISK	VACCINATION BENEFITS	REALITY
ROTAVIRUS			

Benefits > Risk

http://www.who.int/immunization/position_papers/PP_rotavirus_january_2013_presentation.pdf?ua=1

Risk of acquiring illnesses following infection versus risk following vaccination

	Measles infection [a]	Measles vaccine [b]
Otitis	7 – 9%	0
Pneumonia	1 – 6%	0
Diarrhoea	6%	0
Post-infectious encephalomyelitis	0.5/1 000	1/100 000 – million
SSPE	1/100 000	0
Anaphylaxis	0	1/100 000 – million
Thrombocytopenia	Not properly quantified [c]	1/30 000 [d]
Death	0.1 – 1/1 000 (up to 5 – 15%)	0

a Risks after natural measles are calculated in terms of events per number of cases.

b Risks after vaccination are calculated in terms of events per number of doses.

c Although there have been several reports of thrombocytopenia occuring after measles including bleeding, the risk has not been properly quantified.

d This risk has been reported after MMR vaccination and cannot be only attributed to the measles component.

MMR = measles, mumps and rubella; **SSPE** = subacute sclerosing panencephalitis.

P. Duclos, BJ Ward. Measles Vaccines, A Review of Adverse Events, Drug Safety 1998; Dec 19 (6): 435—454

The Impact of Vaccines on Infectious Disease Morbidity in the United States

	Pre-vaccine Era Estimated Annual Morbidity in the US*	Most Recent Reports of Cases in the US†	% Decrease
Diphtheria	21,053	0†	100%
H. Influenzae	20,000	243†	99%
Hepatitis A	117,333	11,049†	91%
Hepatitis B	66,232	11,269†	83%
Measles	530,217	61†	99%
Mumps	162,344	982†	99%
Pertussis	200,752	13,506†	93%
Pneumococcal Disease	16,069	4,167†	74%
Polio	16,316	0†	100%
Rubella	47,745	4†	99%
Congenital Rubella	152	1†	99%
Smallpox	29,005	0†	100%
Tetanus	580	14†	98%
Varicella	4,085,120	449,363†	89%

Adapted from; CDC. *JAMA*, November 14, 2007; 298(18):2155–63. † CDC. *MMWR*, January 8, 2010; 58(51,52):1458–68. ‡ 2008 estimates, *S. pneumoniae* estimates from Active Bacterial Core Surveillance.

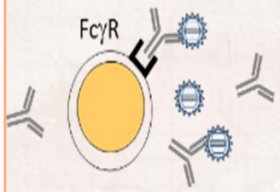
PATHOGEN	REALITY	VACCINATION BENEFITS	VACCINATION RISK
DENGUE VIRUS	Number of dengue cases increased from 0.4 to 1.3 million between 1996-2005, reaching 2.2 million in 2010 and 3.2 million in 2015 **WHO recommendation:** Consider introduction of deng… geog… (nati… where epidemiological data indicate a high burden of disease Dengue vaccine introduction should be part of a comprehensive dengue control strategy	Available vaccine: Efficacy demonstrated •symptomatic dengue cases were prevented •reduction in severe dengue •reduction in cases of… Efficacy demonstrated regardless of serotype or previous exposure to dengue	**Potential risks** • Safety signal of increased risk of hospitalization in vaccinated group ○ Antibody dependent enhancement (ADE) of infection ▪ Neurotropism/ Viscerotropism

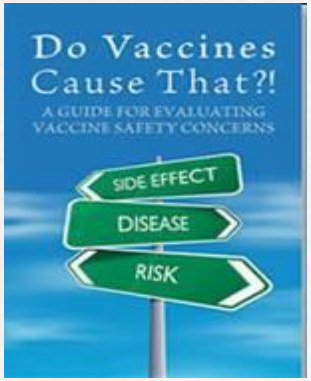
SAFE?

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/08/WC500095721.pdf

SAFETY CONCERNS : DENGUE VACCINE

Concern: The vaccine has the 4 dengue viruses . This can cause and transmit dengue.





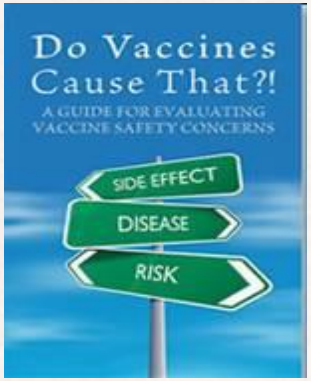
Fact:

1. **No.**
2. **The potential risk associated with live attenuated recombinant vaccine has been assessed form the preclinical vaccine development.**
3. **In the preclinical trial, mosquitos were artificially infected with the vaccine viruses . Virus replicated poorly in mosquitos to allow transmission.**

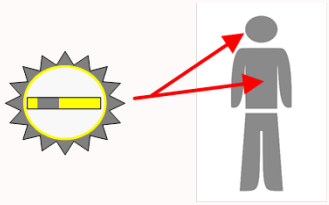
WHO. Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live attenuated); Peoposed replacement of Annex 1 of WHO Technical Report Series, N°932;2011

Guy B et al. Preclinical and clinical development of YFV 17D-based chimeric vaccines against dengue, West Nile and Japanese encephalitis viruses. Vaccine, 2010, 28(3):632-49

SAFETY CONCERNS : DENGUE VACCINE



Theoretical Risk:



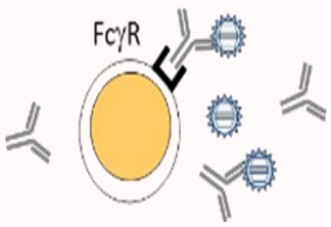
Viscerotropic and Neurotropic disease may take place after vaccination with the chimeric vaccines because of the YFV 17D component.

Fact:

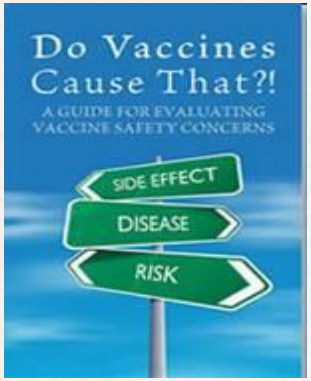
1. **CV-WN /JE-CV replicated prominently at skin site and lymphoid tissues, generally sparing vital organs.**
2. **Chimeric viruses display lower growth than YFV 17D in hepatic cells.**
3. **Chimeric viruses are not neuroinvasive.**
4. **Chimeric viruses are less neurovirulent than YFV 17D vaccine after direct inoculation.**

Cottin P, Niedrig M, Domingo C. Safety profile of the yellow fever vaccine Stamaril®: a 17-year review. Expert Rev Vaccines. 2013; 12(11):1351-68.
Guy B et al. Preclinical and clinical development of YFV 17D-based chimeric vaccines against dengue, West Nile and Japanese encephalitis viruses. Vaccine, 2010, 28(3):632-49

SAFETY CONCERNS : DENGUE VACCINE



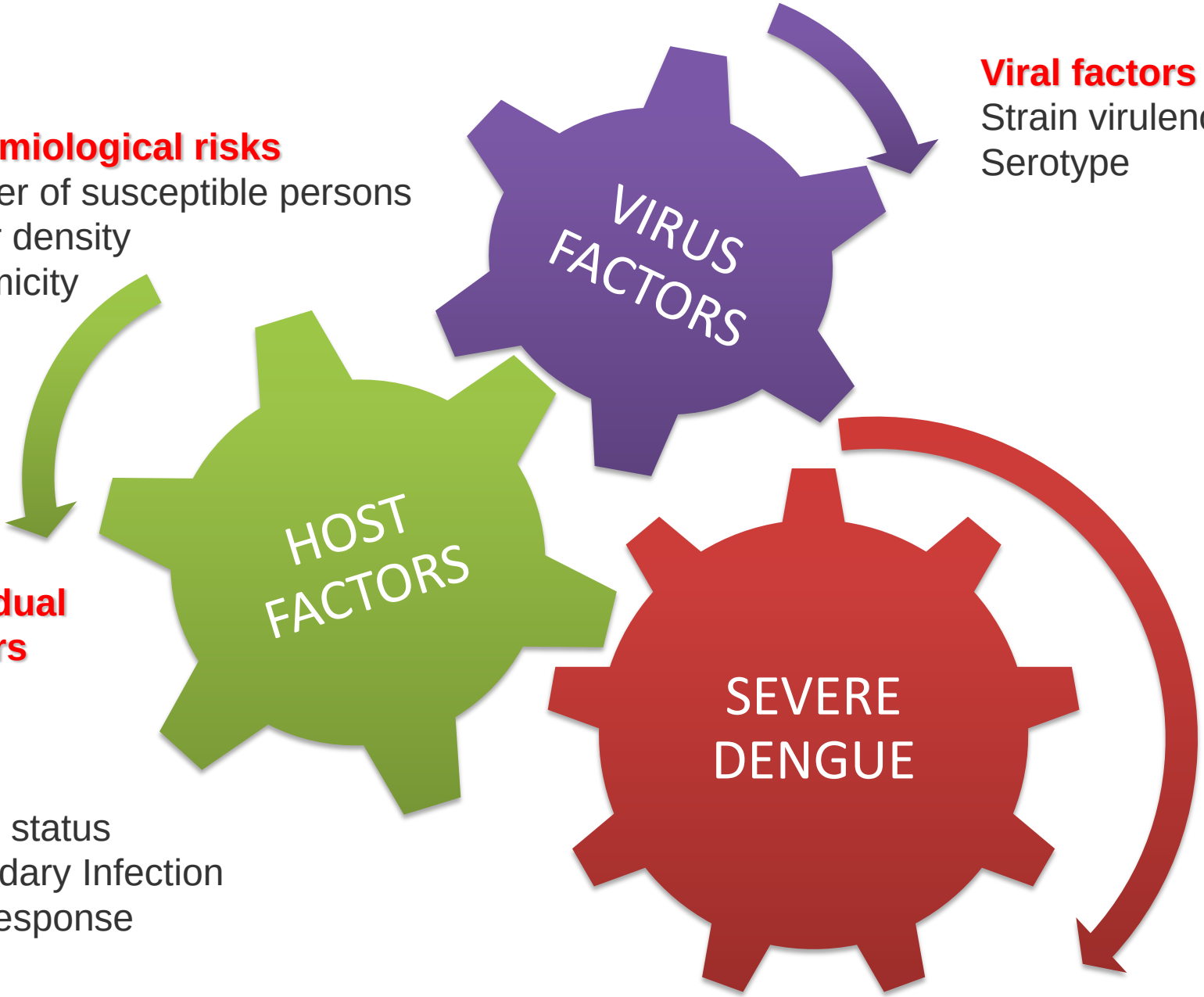
Risk: Severe dengue is higher in those vaccinated upon secondary infection.



Fact:

1. **Severe dengue is a multifactorial disease.**
2. **Severity can be linked to other factors - viral serotype/genotype/clade and host factors (genetic, co-morbidities, co-infections, age).**
3. **Severe disease can occur in primary infection.**

What causes SEVERE DENGUE disease?



Viral factors
Strain virulence
Serotype

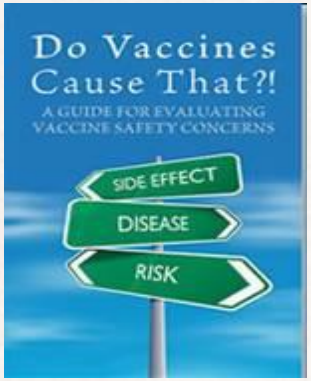
Epidemiological risks
Number of susceptible persons
Vector density
Endemicity

Individual factors

Age
Origin
Health status
Secondary Infection
Host response
HLA

SAFETY CONCERNS : DENGUE VACCINE

Concern : Increased risk of severe disease is caused by antibody dependent enhancement

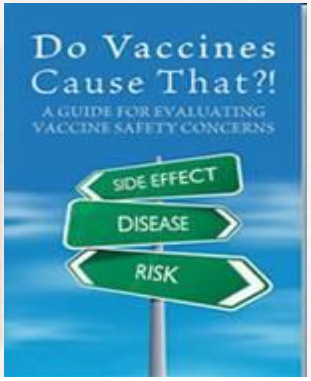


Fact:

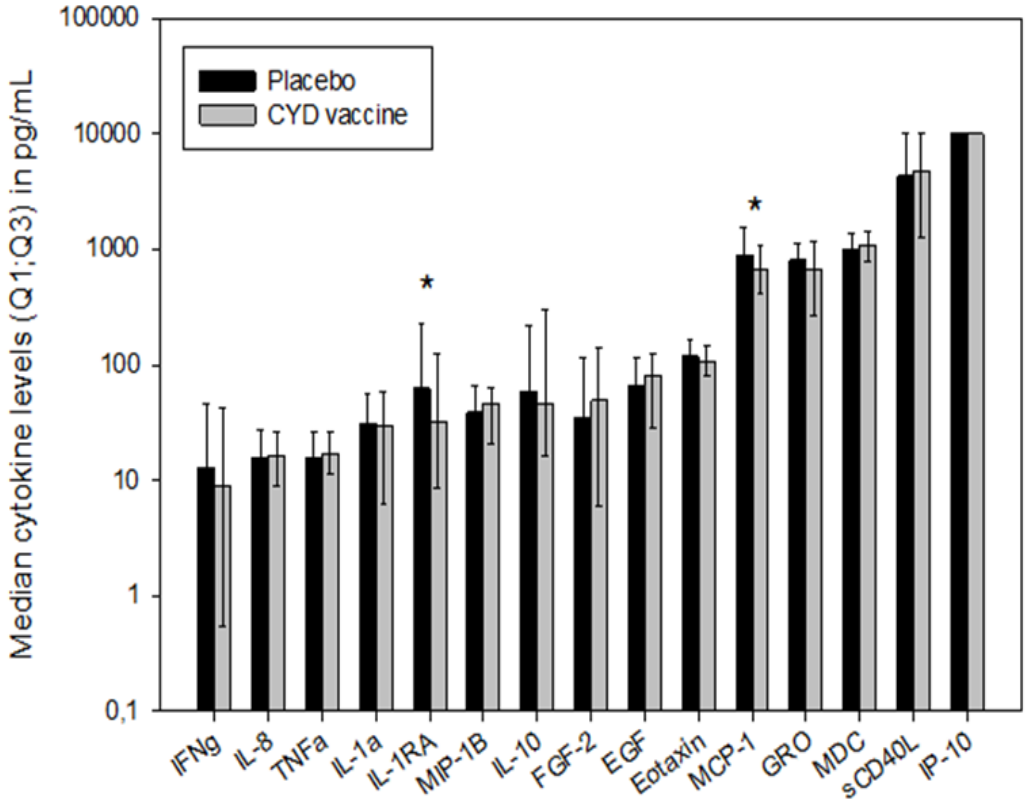
1. **ADE has been demonstrated in vitro with primary cells or cell lines.**
2. **Pre-existing in vitro ADE levels do not correlate with disease severity upon natural infection.**
3. **In vivo observations do not support a potential role for increased ADE in vaccines as compared to placebo**

- Laoprasopwattana K, et al. Dengue Virus (DV) enhancing antibody activity in preillness plasma does not predict subsequent disease severity or viremia in secondary DV infection. J Infect Dis. 2005 192(3): 510-9.
- Libraty DH, et al. A prospective nested case-control study of Dengue in infants: rethinking and refining the antibody-dependent enhancement dengue hemorrhagic fever model. PLoS Med. 2009 Oct;6(10):e1000171
- Meltzer E, Schwartz E. A travel medicine view of dengue and dengue hemorrhagic fever. Travel Med Infect Dis. 2009 Sep;7(5):278-83

Fact: **In vivo observations do not support a potential role for increased sensitization/ADE in vaccines as compared to placebos**

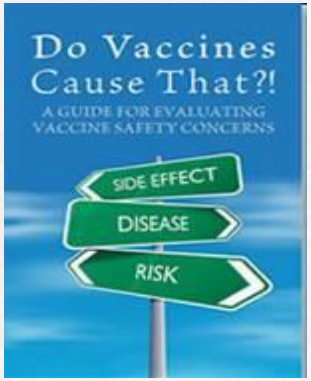


- **No differences in immune profiles between hospitalized vaccines and placebos**
- **No excess of deleterious cytokines, which would rule out excess ADE activity in vaccines versus placebos**

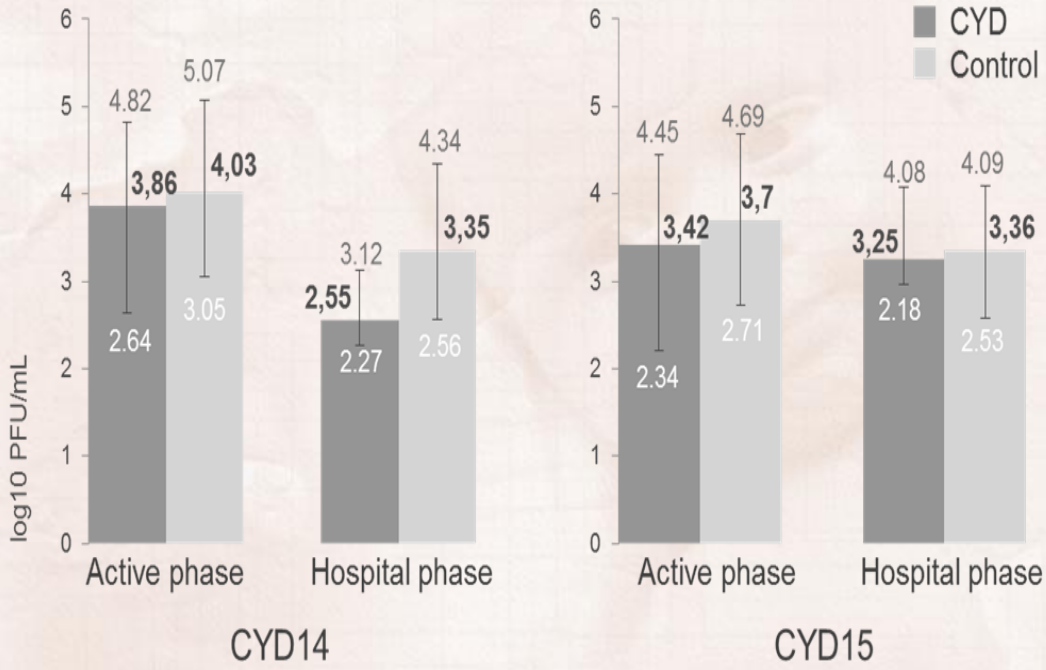


- Harenberg A, et al. Cytokine Profile of Children Hospitalized with Virologically-Confirmed Dengue during Two Phase III Vaccine Efficacy Trials. PLoS Negl Trop Dis. 2016;10(7):e0004830

Fact: **In vivo observations do not support a potential role for increased sensitization/ADE in vaccines as compared to placebos**



- **Pattern of hospitalized cases, including severe disease, remains similar to that observed in the control group during the active phase.**
- **No increased breakthrough viremia in vaccinees compared to placebos**

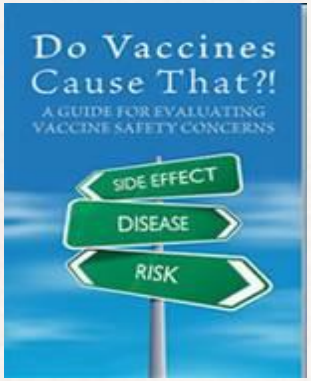


Quantified viremia ≥LLOQ (log_{10} PFU/mL) based on pan-Dengue qRT-PCR ; median (Q1, Q3)

Sampling between 0-5 days post onset of symptoms

Hadinegoro SR, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. N Engl J Med 2015;373:1195–206.

Dengue Vaccine Clinical Data Review

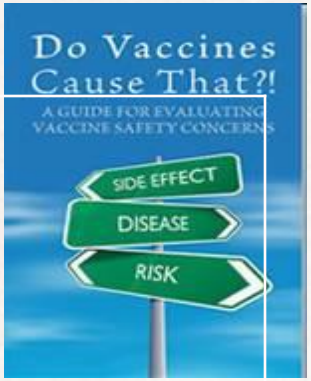


Fact: **Continued reduction of hospitalized dengue cases from 9 years and above**

- **Asian Efficacy trial in Year 3 and Year 4 in the 9 and above age group**
- **Latin America Efficacy trial in Year 3 and Year 4 in the 9 and above age group**
- **Thailand Proof of concept study in 9 years and above (dose 1 to year 6)**

Fact: **Clinical standpoint**

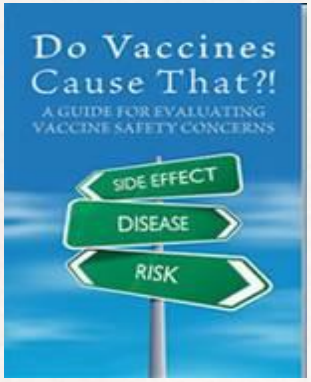
- **No significant differences in clinical picture**
- **No increased viremia**
- **No cytokine pattern associated with increased disease enhancement in vaccine *vs* placebo**



CYD14 LONG TERM FOLLOW-UP RESULTS BY STUDY YEAR – HOSPITALIZED VCD (ANY SEVERITY) IN SUBJECTS 2-14 YEARS OF AGE & BY AGE GROUP

Age Group	Relative Risk Year 3	Relative Risk Year 4
2-5 years	7.45 (1.15, 313.80)	1.42 (0.58,3.99)
<9 years	1.58 (0.61,4.83)	1.19 (0.65,2.28)
>9 years	0.57 (0.18, 1.86)	0.73 (0.34, 1.61)
All age groups	1.04 (0.52,2.19)	0.98 (0.62,1.59)

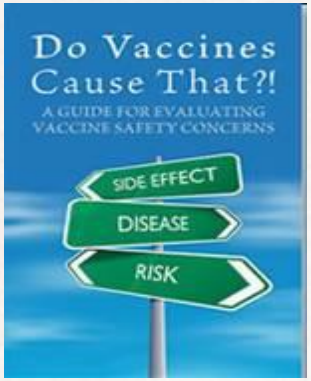
Dengue Vaccine Clinical Data Review



- **Elevated risk among vaccinated primarily seen in the 2-5 year old age group in Year 3**
  - **Risk diminishes in Years 4 and 5**
  - **Trend in the relative risk against dengue hospitalization with time suggest waning protection**

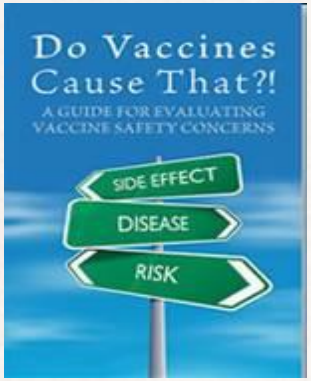
EXPLANATION?

Explanation of the excess risk of hospitalized cases in 2-5 year olds from YEAR 3 in CYD 14



- **Plausible hypothesis**
  - **Relationship of AGE, SEROSTATUS or both**
  - **Vaccination primes the immune system similar to a natural infection**
  - **After a period of cross protection: IMMUNITY wanes**
    - **SEROPOSITIVE: response to a first natural infection is as if it was the 3rd or later infection (less risk of serious disease)**
    - **SERONEGATIVE: response to the first natural infection is as if it was 2nd infection (associated with higher risk of serious disease)**
- **Actual data**
  - **Excess risk is greatest in YEAR 3 in the CYD 14 in the 2-5 year old DIMINISHES in YEAR 4 and YEAR 5.**

What does this imply?

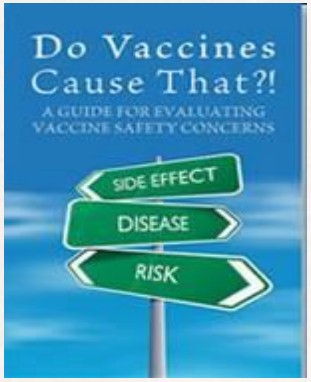


Age is a factor.

1. **Surrogate of prior exposure**
   - **Older the age, the higher chance of having been infected**
   - **Seroprevalence data shows that at 9 yrs of age 89% are seropositive**
2. **Qualitative differences in immune responses could also exist according to age**
3. **Immaturity at both physiological and immunological levels may exists**

Hanna-Wakim, R. et al. Age-related increase in the frequency of $CD4^+$ ... enterotoxin B during childhood. J. Infect. Dis. 200, 1921–1927 (**2009**)

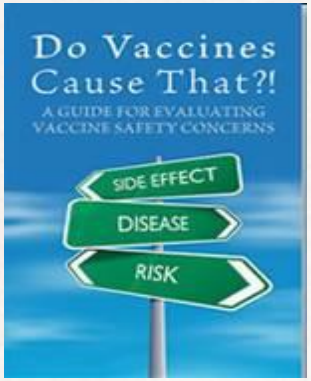
Serostatus is a factor.



1. **Seronegative status which is more likely to occur in younger children.**
2. **Vaccination may present itself as a attenuated subclinical primary infection**
   - **a subsequent first wild-type infection will be analogous to a secondary infection, presenting a higher risk of being severe**

Guy and Jackson, Nat Rev Microbiol, 2016; 14(1):45-54
Coudeville et al, Vaccine 2016

Serostatus and Vaccine data



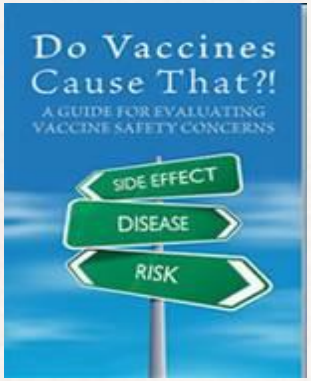
Vaccine Efficacy	Seropositive	Seronegative
Aged 9–16 years	81.9% (67.2–90.0)	52.5% (5.9–76.1)

Trend: Independent impact of AGE in SERONEGATIVES:

Vaccine Efficacy	Seronegative Relative Risk
≥ 9 years	0.937% (0.24, 4.37)
<9 years	1.707%(0.53, 7.19)

Wilder-Smith, A et al. Journal of Infectious Diseases. July 2016.

FACTORS INTERCONNECTED



AGE

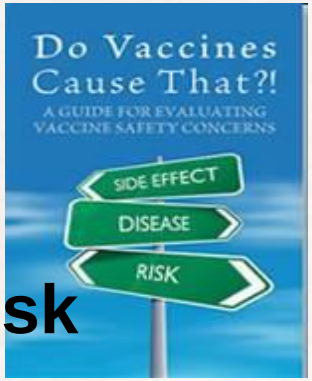
IMMUNE RESPONSE

DISEASE OUTCOME/ VACCINE OUTCOME

WANING

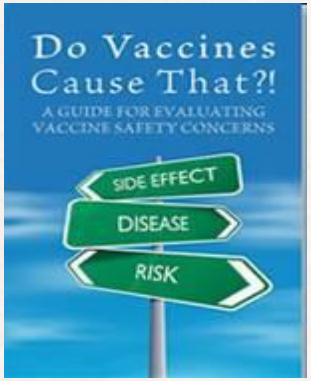
SEROSTATUS

GACVS Dengue Vaccine Assessment



- Acknowledge increased relative risk of hospitalized dengue in YEAR 3 in 2-5 yr old vaccinated population
- Highlight importance of understanding potential factors associated with increased risk
- Recommended monitoring the risk of severe dengue among individuals who are seronegative at baseline
- Recommend robust, surveillance(emphasis on estabishing disease and vaccination history)
- http://www.who.int/vaccine_safety/committee/reports/Jul_2016/en/

GAVCS SAFETY ASSESSMENT



- **Dengue vaccine is well tolerated**
- **SAEs similar across CYD/Placebo in phase 3 trials**
- **Hypothetical vaccine associated viscerotropic and neurotropic disease risk**
- **Understanding the potential factors associated with the increased relative risk of hospitalized and severe dengue among some trial participants is a priority**

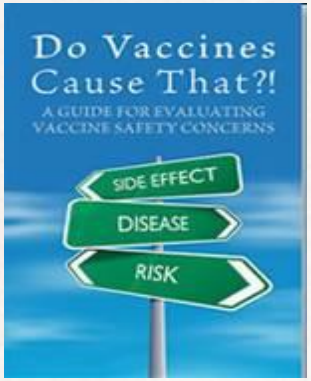
http://www.who.int/vaccine_safety/committee/reports/Jul_2016/en/

GAVCS SAFETY ASSESSMENT

- **With surveillance, requires allocating resources for registries and ensure cases of hospitalized dengue are confirmed in accordance w/established case definition**
- **Recommends that existing and planned clinical efficacy trials should be evaluated in depth and include careful assessment of pre-immunization seropositivity**
- **Data will contribute to greater understanding of potential risk factors and immunology of dengue infection and severe dengue post-vaccination**

http://www.who.int/vaccine_safety/committee/reports/Jul_2016/en/

SAFETY CONCERNS : DENGUE VACCINE

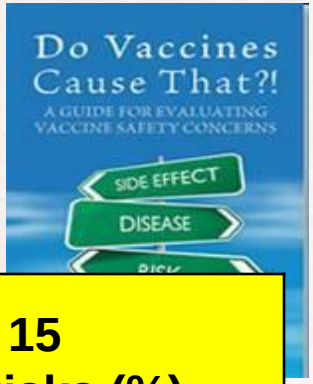


Theoretical Risk: Increased hospitalization in the < 9 yrs old can occur in the > 9 yrs old?

Fact:

1. **Data does not show increased hospitalization in > 9 years old.**
2. **In vaccinated children >=9 years of age -- continued and consistent reduction of hospitalized and severe VCD has persisted for 4 years from dose 1.**
3. **Imbalance in <9 was restricted only to 2-5 year old age group.**

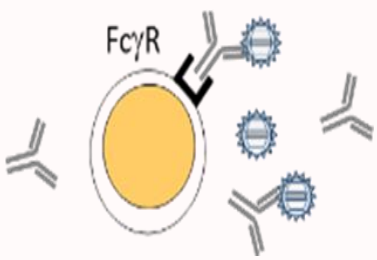
Hospitalized dengue (any severity) cases observed in 9–16 year olds in Year 4 of CYD14 and CYD15



	CYD 14 Relative Risks (%)	CYD 15 Relative Risks (%)
Efficacy Surveillance phase		
YEAR 1	0.39 (0.12, 1.17)	0.166 (0.05, 0.48)
YEAR 2	0.08 (0.01, 0.25)	0.214 (0.10, 0.43)
Long Term Follow Up phase		
YEAR 3	0.57 (0.18,1.88)	0.533 (0.25,1.16)
YEAR 4	0.73 (0.34, 1.61)	0.334 (0.10,1.05)
Entire study	0.39 (0.24, 0.60)	0.291 (0.19, 0.44)

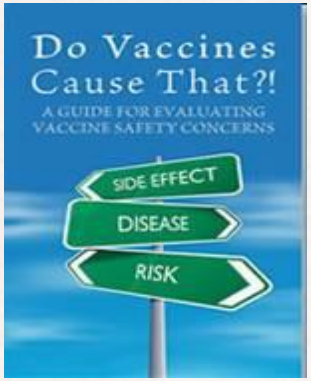
1. Hadinegoro SR, *et al.* Poster presented at the 5th Pan American Dengue Research Network Meeting, 20–23 April 2016, Panama City, Panama; 2. Cortez M. Poster presented at the 65th Annual Meeting of the ASTMH, 13–17 November 2016, Atlanta, Georgia, USA.

SAFETY CONCERNS : DENGUE VACCINE



Theoretical Risk:

Seronegative individuals are more prone to severe disease

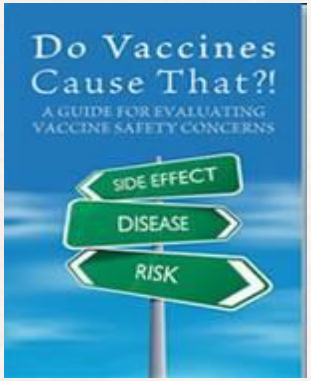


Fact

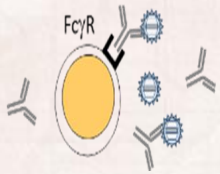
1.Results showed no effect of baseline flavivirus serostatus on dengue vaccine reactogenicity.

2. Overall, the safety profile after each dose was shown to be consistent regardless of the subjects' age, gender, country or dengue baseline status.

OTHER CONCERNS : DENGUE VACCINE



CONCEPT: The Long Term Follow Up is on-going because of the risk of severe disease seen in the trial.



Fact:

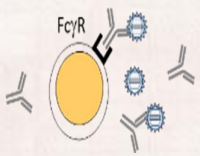
1.Assessment of dengue vaccine safety should extend over several dengue seasons.

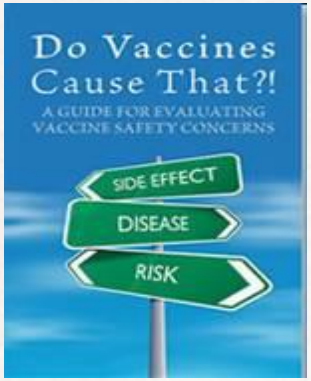
2.5 years is the duration of safety follow-up studies currently recommended by the WHO for the development of dengue vaccines

WHO. Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live attenuated); Poposed replacement of Annex 1 of WHO Technical Report Series, N°932;2011

OTHER CONCERNS : DENGUE VACCINE

CONCEPT: Serotesting is recommended prior to use.





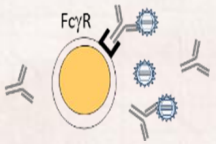
Fact:

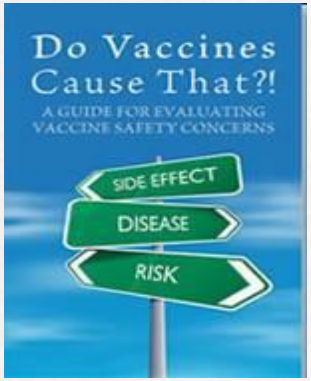
1. **Vaccine demonstrated efficacy regardless of serostatus.**
2. **WHO recommendation:**
   - **not stipulate the need for individual serotesting prior to vaccination nor an absolute need for seroprevalence data before introducing a dengue vaccination program**
   - **a combination of seroprevalence, surveillance data, and programmatic factors should define the target population**

1. Dengvaxia® Generic Labeling Document; 2. Hadinegoro SR, et al. N Engl J Med 2015;373(13):1195–1206; 3. Dengue.Info. Press releases. Available from: http://dengue.info/#overlay=content/all-press-releases. Accessed January 2017; 4. Dengvaxia product information [singapore]; 5. Andries AC, et al. BMC Infectious Diseases 2016; 16:201; 6. USE OF DENGVAXIA™ IN SINGAPORE. MoH Circular No. 68/2016; 7. Dengue Vaccine: WHO Position Paper. Weekly Epidemiological Record 2016; 8. Summary of the WHO position paper. Available from: http://www.who.int/immunization/policy/position_papers/WHO_Position_Paper_dengue_2016_summary.pdf. Accessed January 2017

OTHER CONCERNS : DENGUE VACCINE

CONCEPT: Serotesting is recommended prior to use.





Fact:

3. WHO recommendation: conclusion on individual testing prior to vaccination

- **Fact: limitations of available tests**
- **Fact: logistical challenges in implementing serotesting prior to vacciation**
- **Fact: lack of documented harm**

4. Rapid test available indicated for the purpose of diagnosing acute dengue infections. Tests neither validated nor designed to detect previous infections.

WHO. Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live attenuated); Poposed replacement of Annex 1 of WHO Technical Report Series, N°932;2011

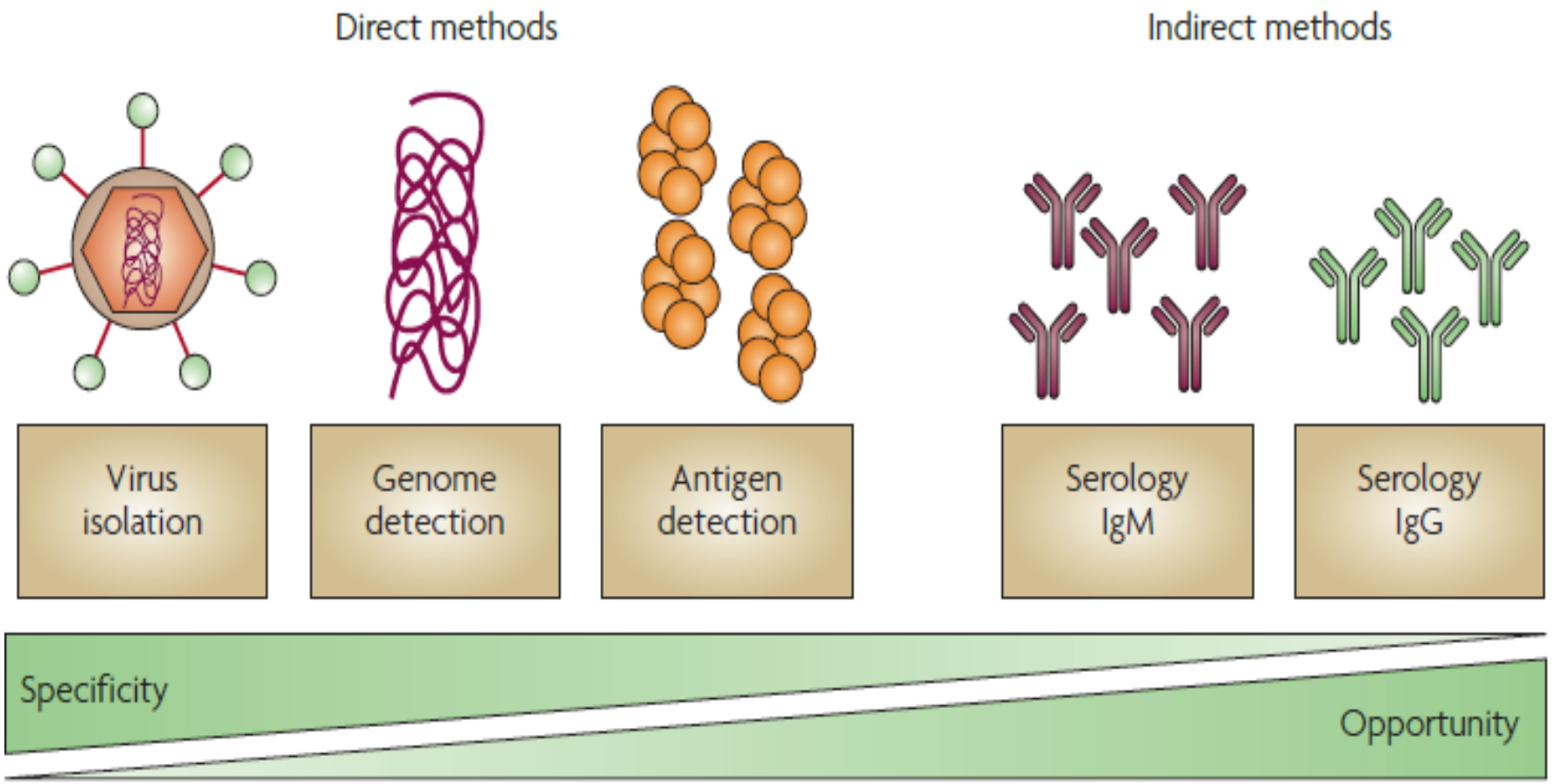
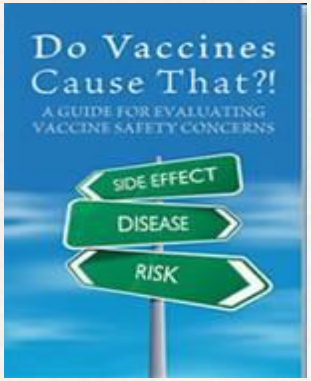


Figure 1 | **Comparative merits of direct and indirect laboratory methods for the diagnosis of dengue infections.** Opportunity refers to the fact that antibody testing is usually the most practical diagnostic option available.

Peeling RW et al. Nature Reviews. December 2010

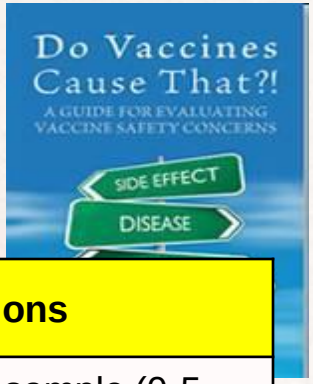
Laboratory Confirmation of DENV infection



Virus Detection	Serology	Molecular Method
Virus Isolation	• IgM antibody-capture ELISA (MAC-ELISA) • IgG ELISA • Plaque reduction neutralization test (PRNT)	• Reverse transcriptase-polymerase chain reaction (RT-PCR) • Detection of Dengue non-structural protein 1 (NS1)

Dengue vaccine: WHO position paper. July 2016. WER No. 30

Advantages and limitations of Different Dengue Diagnostic Tests



Diagnostic Tests	Advantages	Limitations
Viral Isolation and Identification	• Confirmed infection • Specific • Identifies serotype	• Requires acute sample (0-5 days post onset) • Requires expertise and appropriate facilities • Takes more than 1 week • Does not differentiate between primary and secondary infection • Less commonly used • Expensive
RNA detection (RT-PCR)	• Confirmed infection • Sensitive and specific • Identifies serotype and genotype • Results in 24-48 hours • Offer earlier and more specific diagnosis (80-90% sensitivity if assessed 1-3 days post-onset)	• Potential false-positives owing to contamination • Requires acute sample (0-5 days post onset) • Requires expertise and expensive laboratory equipment • Does not differentiate between primary and secondary infection

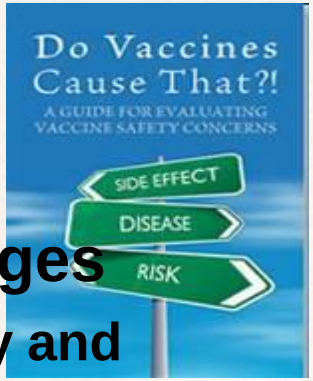
Peeling RW et al. Nature Reviews. December 2010
Dengue Vaccine: WHO position paper – July 2016. WER No. 30

Diagnostic Tests	Advantages	Limitations
Antigen detection		
Clinical Specimens (eg. Blood in an NS1 assay)	• Confirmed infection • Easy to perform • Less expensive than virus isolation or RNA detection • Offer earlier and more specific diagnosis (80-90% sensitivity if assessed 1-3 days post-onset)	• Not as sensitive as virus isolation or RNA detection
Tissues from fatal cases (eg. Immunohistochemistry)	• Confirmed infection	• Not as sensitive as virus isolation or RNA detection • Requires expertise in pathology
Serological tests		
IgM or IgG seroconversion	• Confirmed infection • Least expensive • Easy to perform	• IgM levels can be low in secondary infections • Need for multiple samples (IgG acute and convalescent samples) • Can differentiate between primary and secondary infection* • Does not allow serotyping • Susceptible to cross-reactivity with other flaviviruses • Variable sensitivity by timing of specimen collection
IgM detection (single sample)	• Identifies probable dengue cases • Useful for surveillance, tracking outbreaks and monitoring effectiveness of interventions	• IgM levels can be low in secondary infections

*Primary infection: IgM-positive and IgG-negative (if samples are taken before day 8-10); secondary infection: IgG should be higher than 1,280 haemaggltuination inhibition in convalescent serum

Peeling RW et al. Nature Reviews. December 2010
Dengue Vaccine: WHO position paper – July 2016. WER No. 30

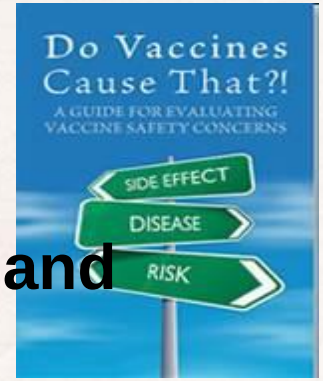
Global Consequences



- **Deployment of vaccine poses novel logistical and administrative challenges**
  - **Apparent association of vaccine efficacy and pre-vaccination serostatus will force schedules to be set on smaller geographical scales – complicate vaccine delivery and increase cost**
- **Authorities will need to explain to public why some communities are immunized while others are excluded**
  - **Provoke public concern, public and health worker confusion**
- **Availability of vaccine may discourage political and financial commitment to vector control, surveillance other preventive measures**

Bulletin WHO vol. 94, Number 11, November 2016 785-860

Global Consequences



- **Balance between expected benefits and identifiable hazards is complex**
  - **In naïve individuals, benefit may not be as clear as as in those with seropositive status**
  - **Communicating this dilemma to the public may discourage uptake**
  - **Concealing information could severely damage public trust**
- **WHO established the Pre-Qualification programme to assure safety and effectiveness of vaccines**
  - **As this evolved, reliance on national regulatory authorities became the cornerstone**
    - **WHO will strengthen the global regulatory framework of vaccines**

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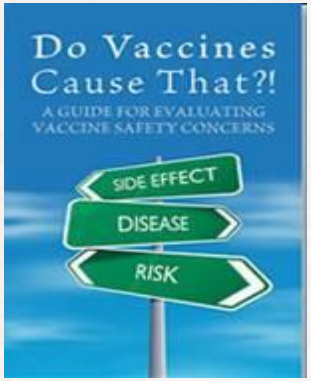
Vaccine Benefits
vs
Vaccine Risk

PATHOGEN	REALITY	VACCINATION BENEFITS	VACCINATION RISK
DENGUE VIRUS	Number of dengue cases increased from 0.4 to 1.3 million between 1996-2005, reaching 2.2 million in 2010 and 3.2 million in 2015 **WHO recommendation:** Consi[illegible] dengu[illegible] geogr[illegible] (natio[illegible]) where epidemiological data indicate a high burden of disease Dengue vaccine introduction should be part of a comprehensive dengue control strategy	Available vaccine: Efficacy demonstrated •symptomatic dengue cases were prevented •reduction in severe dengue Efficacy demonstrated regardless of serotype or previous exposure to dengue	**Potential risks** ○ Safety signal of increased risk of hospitalization in vaccinated group ▪ Antibody dependent enhancement (ADE) of infection ▪ Neurotropism/ Viscerotropism

Benefit > Risk

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/08/WC500095721.pdf

Vaccine Safety Misconceptions



"Vaccines cause many harmful side effects, illnesses and even death – not to mentions possible long term effects"

- **A child more likely to be seriously injured by one of the diseases than by vaccine**
- **Benefits of vaccination outweigh, slight risk and injuries, deaths occur without vaccines**
- **Not to use vaccines is unethical, unforgivable and inhuman**

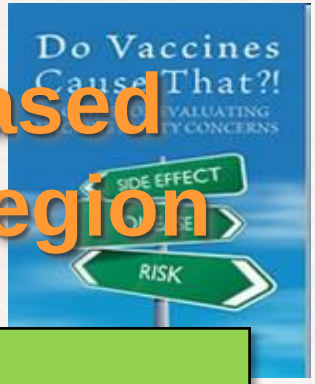
Ref : http://www.who.int/immunization_safety/aefi/immunization_misconceptions/en/

Risk from Disease vs Risk from Vaccines

DISEASE	VACCINES
Measles **Pneumonia = 1 in 20** **Encephalitis = 1 in 2,000** **Death = 1 in 3,000**	MMR **Encephalitis or severe allergic reaction = 1 in 1,000,000**
Mumps **Encephalitis = 1 in 300**	
Rubella **Congenital Rubella Syndrome = 1 in 4** **(If woman becomes infected early in pregnancy)**	
Diphtheria **Death = 1 in 20**	DTP **Continuous crying, then full recovery = 1 in 100.**
Tetanus **Death = 3 in 100**	**Convulsions or shock, then full recovery = 1 in 1,750**
Pertussis **Pneumonia = 1 in 8** **Encephalitis = 1 in 20** **Death = 1 in 200**	**Acute encephalopathy = 0 - 10.5 in 1,000,000** **Deaths = None proven**

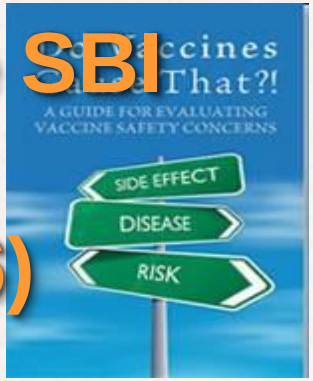
Ref : http://www.who.int/immunization_safety/aefi/immunization_misconceptions/en/

Round 1 Dengue Vaccine School-based Immunization Coverage Report by Region



Region	Total no. of Schools	Total no. of Grade 4 enrolled pupils (Masterlist)	Tot. no. of pupils w/ approved parental consent	Total no. of pupils vaccinated	Vaccination Coverage	
					Based on Masterlist	Based on approved parental consent
NCR	524	203,626	113,152	104,412	51%	92%
3	2,963	232,707	211,461	205,058	88%	97%
4A	2,680	292,772	209,690	182,520	62%	87%
Total	**6,167**	**729,105**	**534,303**	**491,990**	**67%**	**92%**

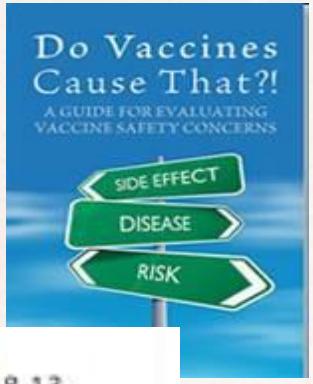
Cumulative AEFI Cases after Dengue SBI Round 1 (March 18, 2016 – August 20, 2016)

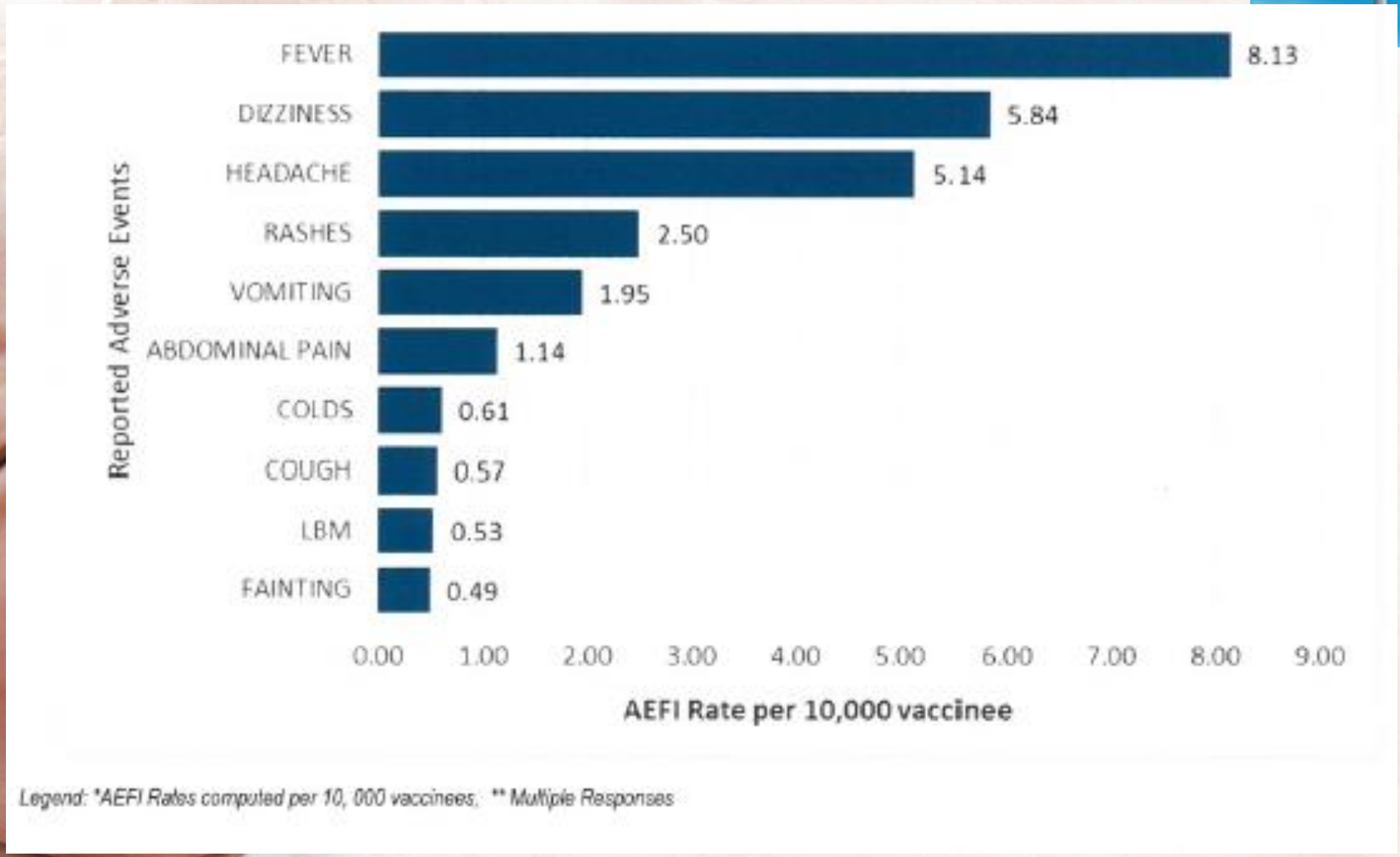


Region	Total Children Vaccinated	Minor AEFI Cases	Serious AEFI Cases	Total AEFI	% of Total AEFI among vaccinated	*Deaths*
III	205,058	382	20	402	0.19%	*2*
IV-A	182,341	516	4	520	0.28%	*0*
NCR	101,604	10	3	13	0.01%	*0*
Total	**489,003**	**908**	**27**	**935**	**0.19%**	***2***

- **935** reported AEFIs from March 18– August 20, 2016
- Age range: 9-17 years (**median 10 years**)
- Sex: **Female** (484, 52%), **Male** (451, 48%)
- Types of AEFI: **Minor** (908, 97%), **Serious /hospitalized** (27, 3%)

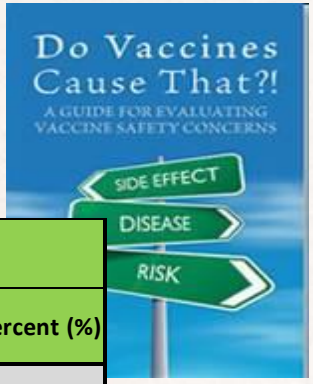
Top 10 AEFI** rates experienced among minor AEFI cases
Dengue SBI Round1





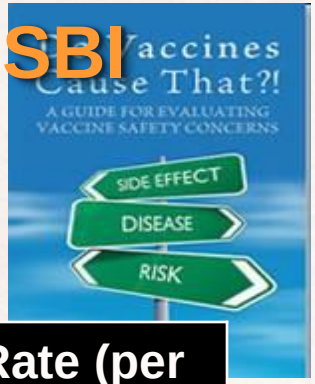
*Legend: *AEFI Rates computed per 10, 000 vaccinees, ** Multiple Responses*

Round 2 Summary Report



Item	Region NCR		Region 3		Region 4A		Total	
	Number	Percent (%)	Number	Percent (%)	Number	Percent (%)	Number	Percent (%)
Number of Schools:	524		2,962		2,680		6,166	
Number of Schools Started Vaccination (b/a)*100	249	48	2,916	98	948	35	4,113	67
Number of Schools Completed Vaccination (c/b)*100	266	107	569	20	580	61	1,415	34
Number of Grade 4 Pupils Vaccinated in 1st Dose	104,412		205,058		182,520		491,990	
Number of Pupils in Schools that Started Vaccination (e/d)*100	63,659	61	204,063	100	58,894	32	326,616	66
Number of Pupils Vaccinated in 2nd Dose (f/d)*100	55,027	53	167,363	82	74,457	41	296,847	60
Number of Pupils Deferred (for follow-up by the health worker)	2,334		31,459		6,219		40,012	
Total no. of pupils can't tract (trans-out, drop out)	184		4,696		884		5,764	
Number of Pupils Refused	6,114		545		2,175		8,834	

AEFI Rate of Reported AEFIs for Dengue SBI Round 2 as of February 2, 2017

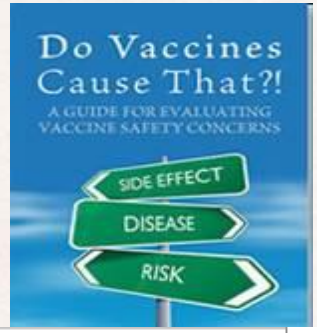


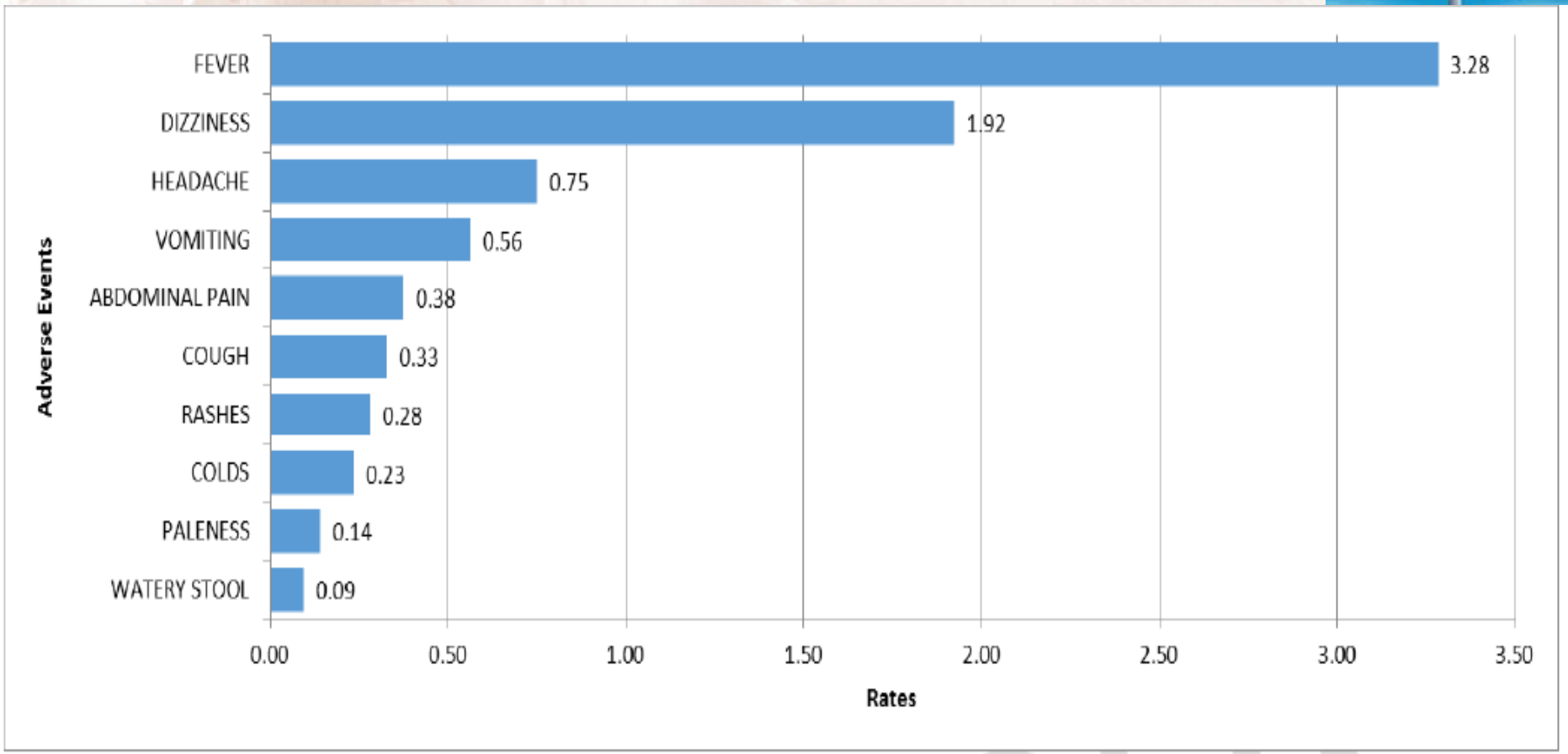
Region	Minor	Serious	Total	No. of pupils vaccinated w/ 2nd dose	AEFI Rate (per 10,000 vaccines)
III	133	6	139	143,370	9.70
IV-A	16	0	16	41,261	3.88
NCR	0	1	1	28,492	0.35
Total	**149**	**7**	**156**	**213,123**	**7.32**

AEFI Cases:

- **156 cases**
- AEFI Rate of **7.32 per 10,000 pupils vaccinated**
- Age range: 9 - 11yo (**median 10yrs**)
- 7 were serious AEFI cases: **4 were classified as coincidental, 3 were pending**

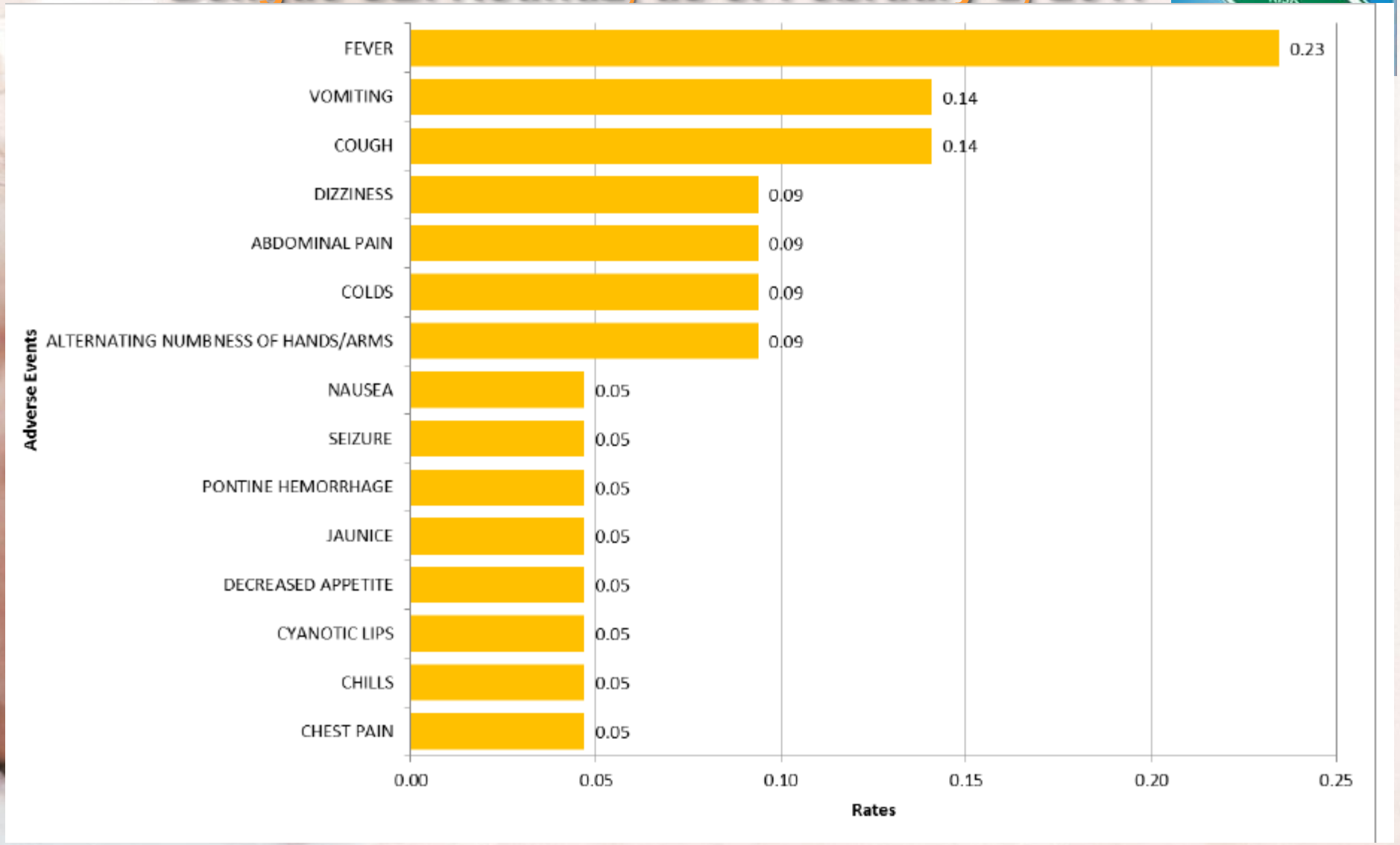
Top 10 AEFI** rates experienced among minor AEFI cases
Dengue SBI Round2, as of February 2, 2017





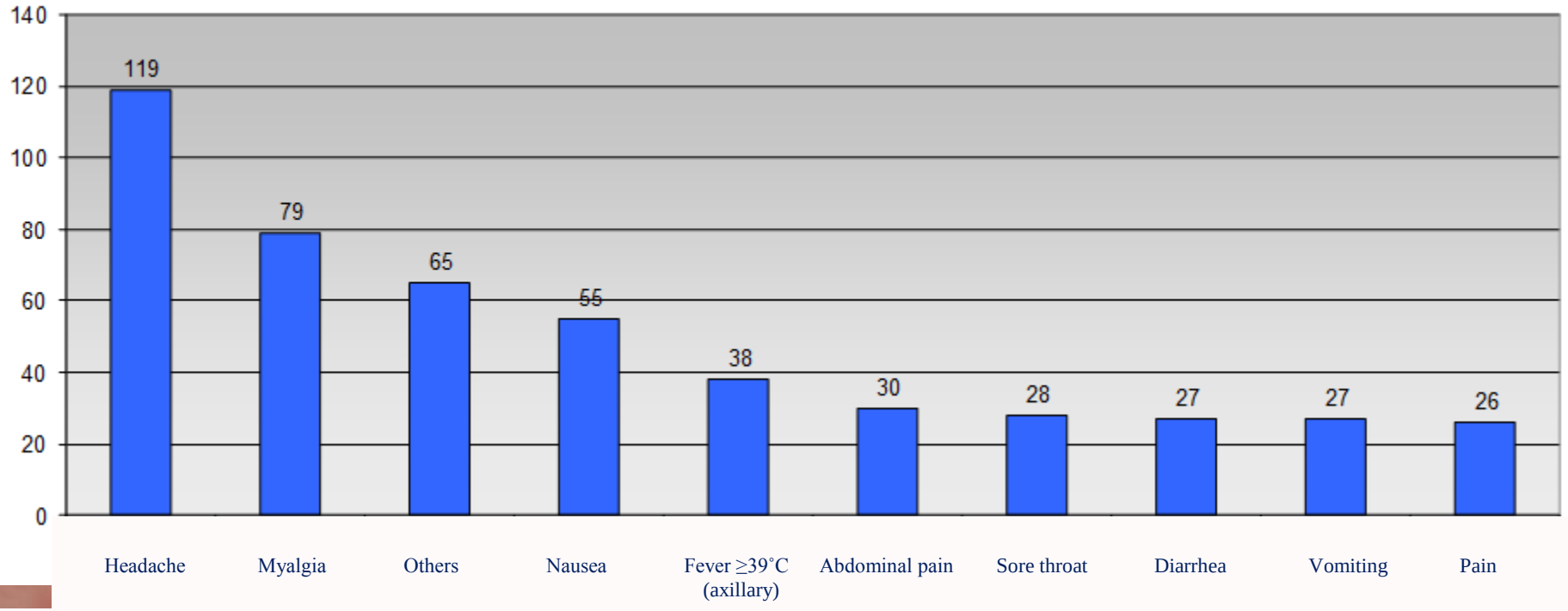
*Legend: ** Multiple Responses, per 10, 000 vaccinated pupils*

AEFI rates experienced among serious AEFI cases
Dengue SBI Round2, as of February 2, 2017



State Secretary of Health

(Dengue vaccine adverse events reported in the SI-EAPV PARANA, 2016)

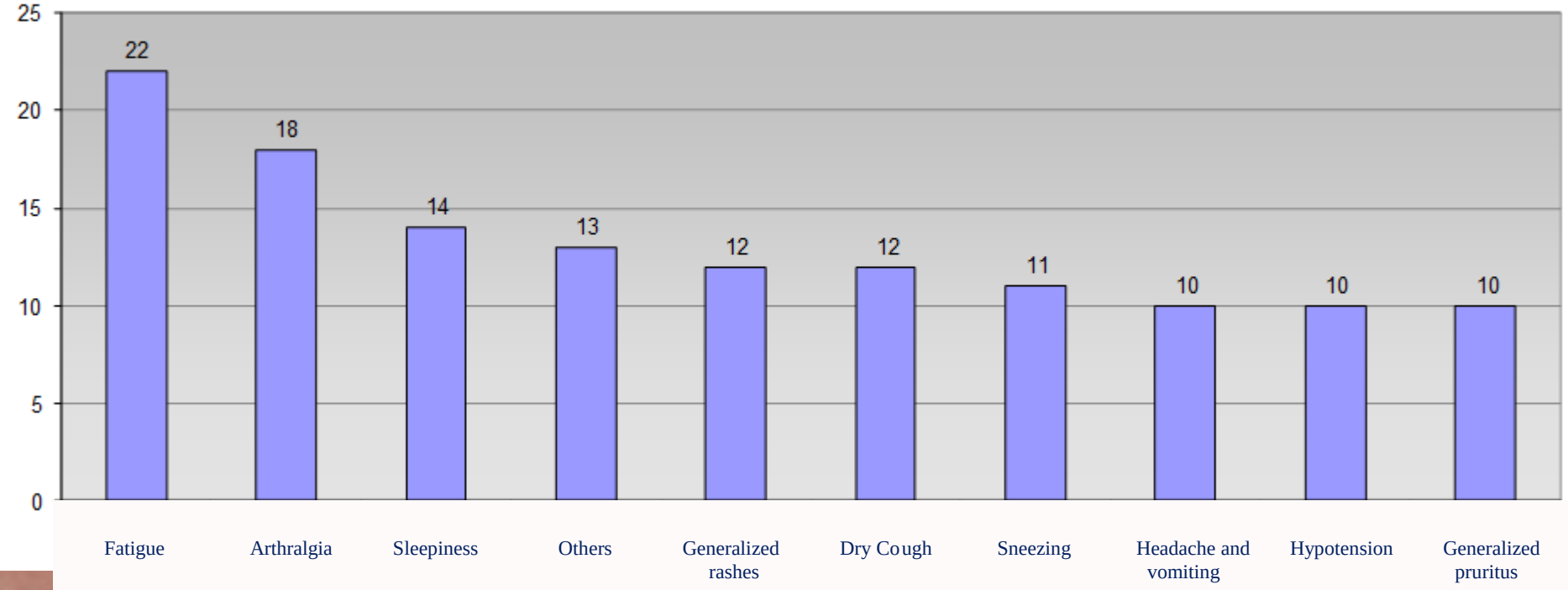


Download: SI-EAPV – 320 reported cases from 08/13 to 12/08/2016

Acknowledgment: Data from Parana Ministry of Health

State Secretary of Health

(Dengue vaccine adverse events reported in the SI-EAPV PARANA, 2016)

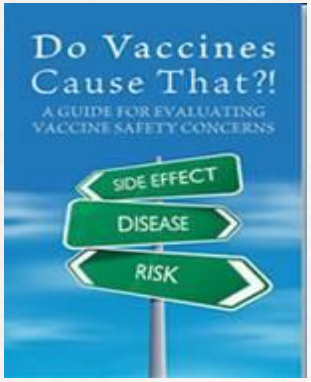


Fonte: SI-EAPV - 320 Casos notificados de 13/08 a 08/12/2016

Download: SI-EAPV – 320 reported cases from 08/13 to 12/08/2016

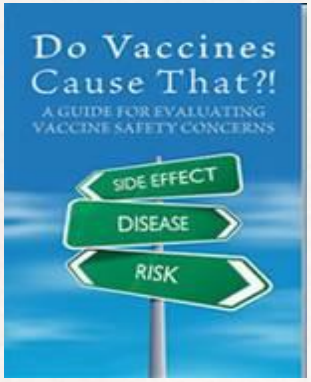
Acknowledgment: Data from Parana Ministry of Health

Immunization

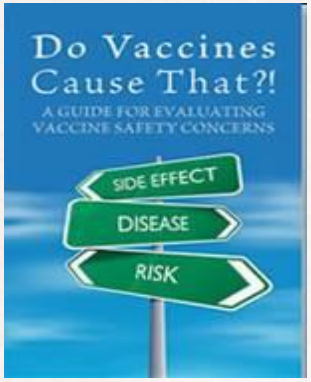


- **No vaccine is without risk**
- **Balance scientific evidence of benefits, costs, and risks when recommending vaccines**
- **Protect against infectious disease**

Vaccine Safety



- **Practitioner has responsibility to listen, understand patient concerns, fears, beliefs**
- **Strengthen bond of trust between patient and provider**
- **Decide arguments effective in persuading patients to accept vaccination**



The pessimist complains about the wind;
The optimist expects it to change;
The realist adjusts the sails


Thank you....
Hi hi hi.....