Getting more vaccines to more people
ASIAN VACCINE CONFERENCE
ASVAC 2019

Symposium 6

Neuro Vaccines

Vaccines to Prevent Brain Damage in Newborns/Fetuses

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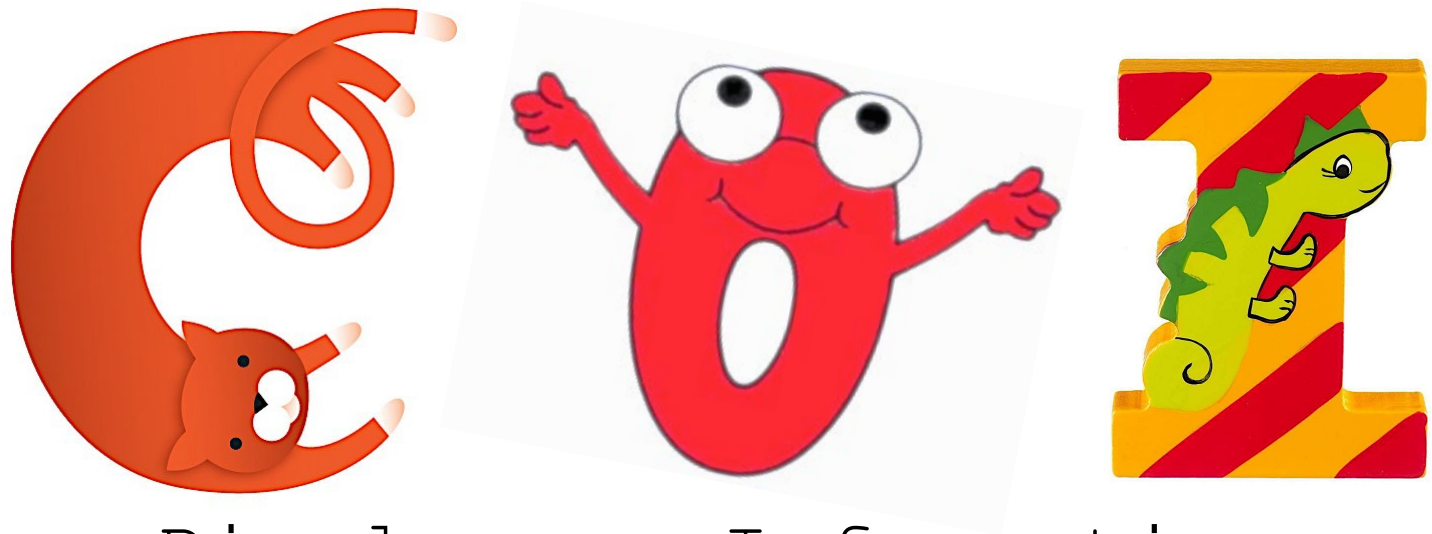
School of Tropical Medicine & Global Health
Nagasaki University, Japan



Disclosure Information

Hiroyuki Moriuchi

I have the following financial relationships to disclose:

✓ Honoraria (Lecture fee) from: Merck (MSD), GSK

I will mention a number of unapproved vaccines, including ones developed by the abovementioned companies.

T O R C H complex

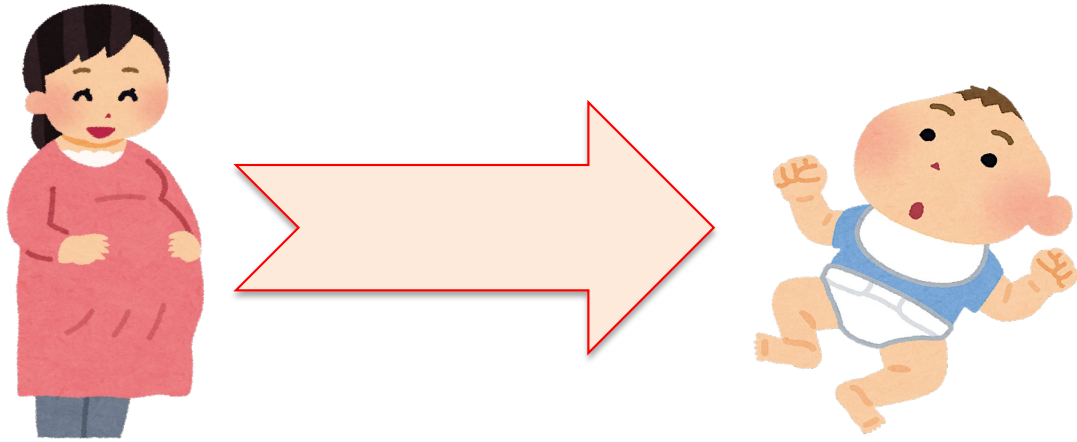
Toxoplasma

Others
(Syphilis, Zika virus)

Rubella

Cytomegalovirus

Herpes simplex virus



- Brain damage (microcephaly, hydrocephalus, calcification, cortical atrophy, etc.)
- Sensorineural hearing loss
- Chorioretinitis

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Herpes simplex virus

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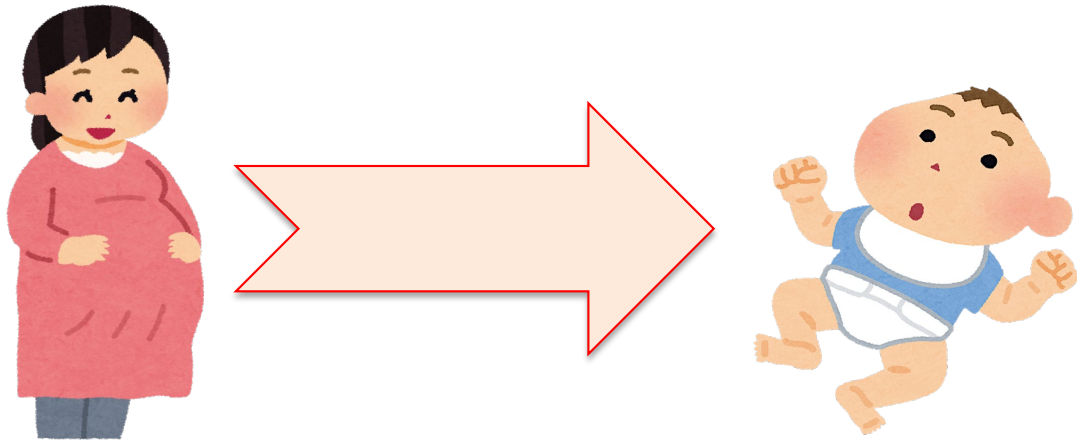
Cytomegalovirus

Rubella



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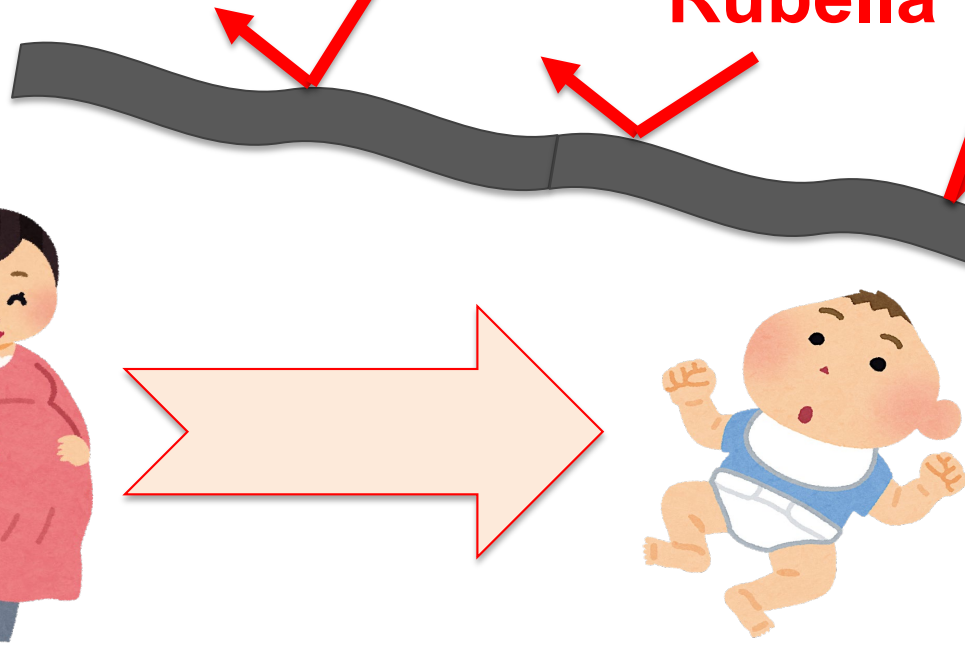

Vaccines

to prevent fetal/neonatal brain damage following maternal infection

T O R C H complex

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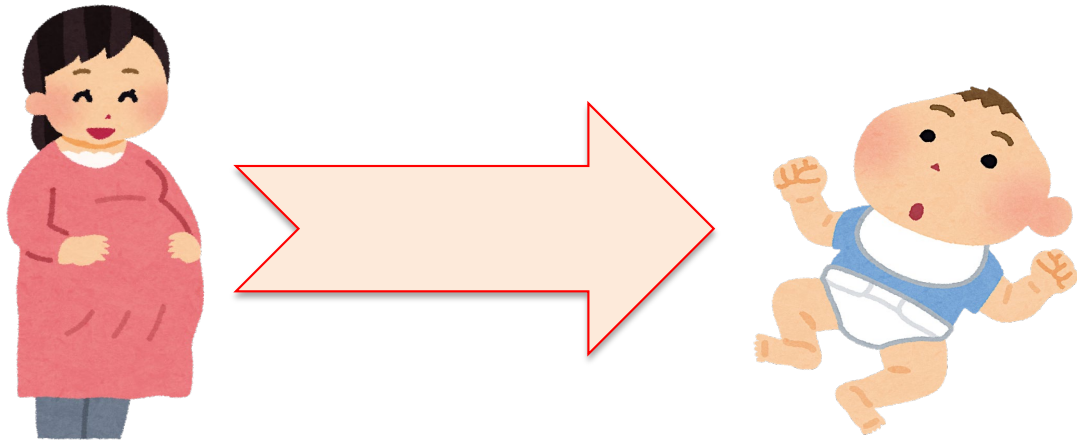


Burden of Congenital CMV Infection

Congenital CMV infection rates in live births

Japan*	0.32%
North America, Europe, & Australia	0.5 – 1%
Latin America, Africa & most Asian countries	1 – 2%

Estimated annual live births with congenital CMV

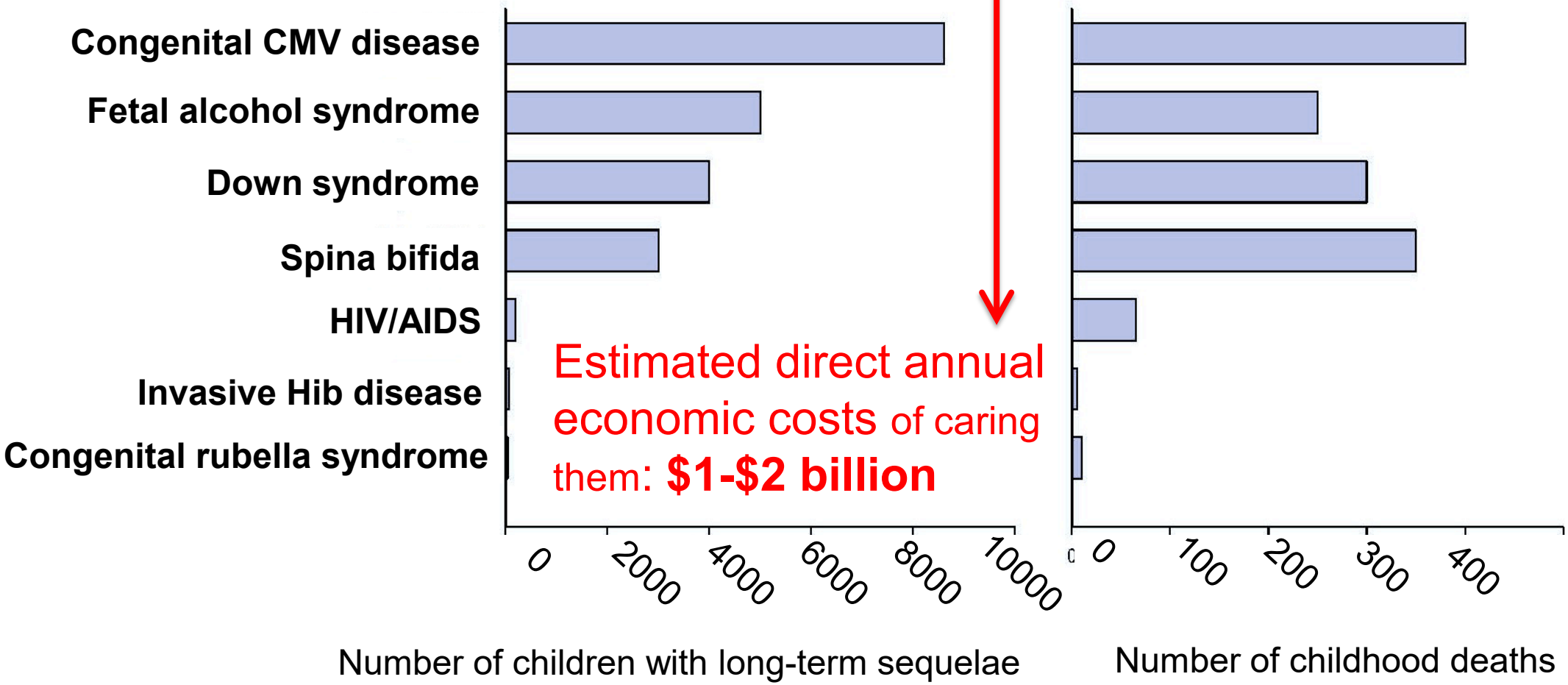
Brazil	~ 35,000
India	270,000 ~ 540,000
Japan*	3,000
Nigeria	65,000 ~ 130,000
USA	20,000 ~ 30,000

https://www.who.int/immunization/research/meetings_workshops/PDVAC_2017_CMV_Plotkin.pdf?ua=1

*Koyano S, Inoue N, Oka A, Moriuchi H, et al. BMJ Open 2011;1:000118

Estimates of the annual burden of the prominent childhood diseases/syndromes in the USA

An estimated 40,000 children are born with congenital CMV, causing an estimated 400 deaths and leaving approximately 8,000 children with permanent disabilities every year.



Vaccines for the 21st Century

Institute of Medicine, USA

http://www.nap.edu/catalog/550.html

Candidate vaccines according to a cost-effectiveness ratio of cost per QALY

Level I	Most favorable	Save money and QALYs
Level II	More favorable	Costs <$10,000 per QALY saved
Level III	Favorable	Costs >$10,000 and <$100,000 per QALY
Level IV	Less favorable	Costs >$100,000 per QALY saved

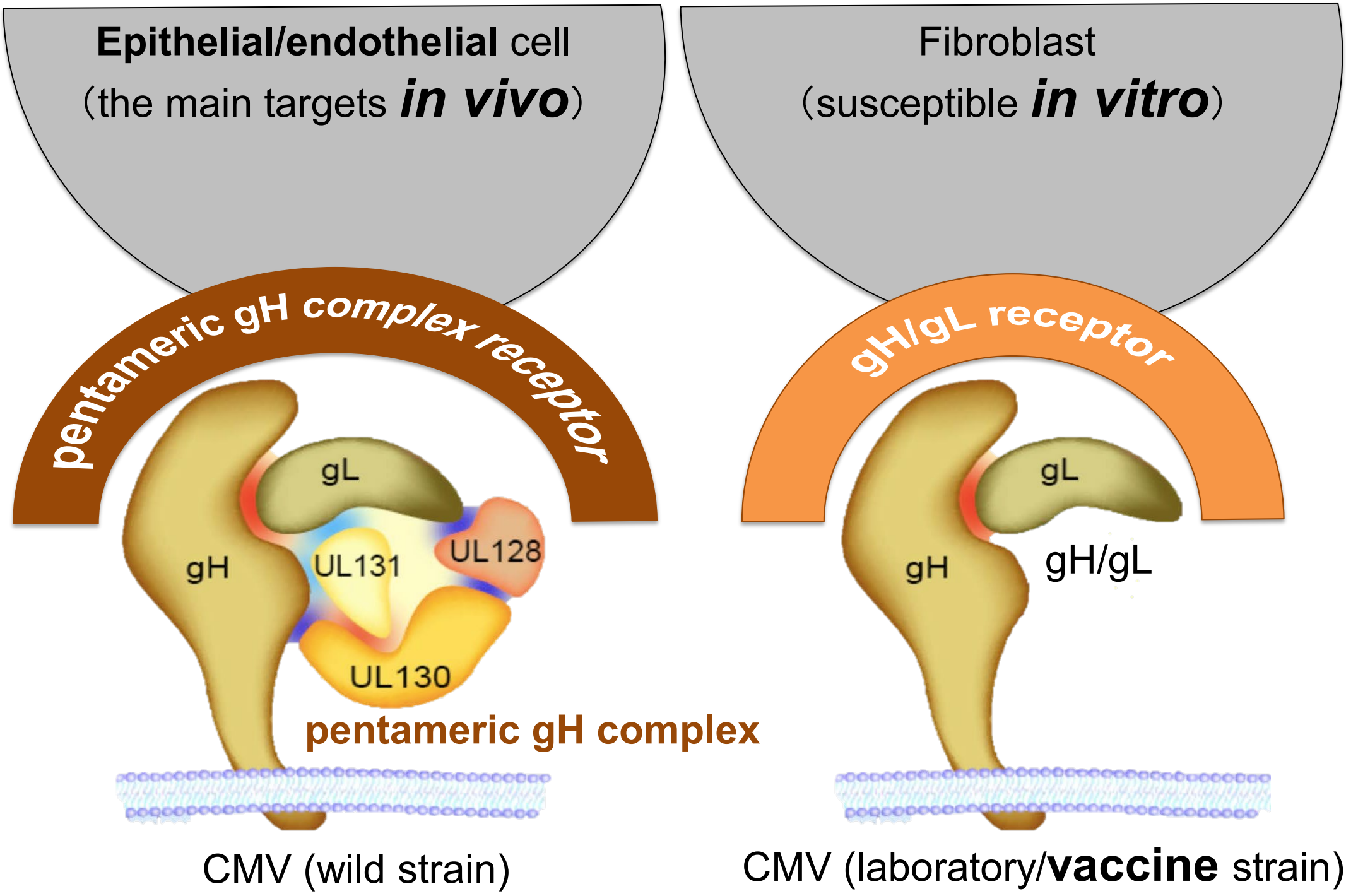
- **CMV vaccine** administered to 12-year-olds
- **Group B streptococcus vaccine** to be well-incorporated into routine prenatal care and administered to women during first pregnancy and to high-risk adults
- **Influenza virus vaccine** administered to the general population (once per person every 5 years, or one-fifth of the population
- **Insulin-dependent diabetes mellitus therapeutic vaccine**
- **Multiple sclerosis therapeutic vaccine**
- **Rheumatoid arthritis therapeutic vaccine**
- ***Streptococcus pneumoniae* vaccine** to be given to infants and to 65-year-olds

Live attenuated CMV vaccine

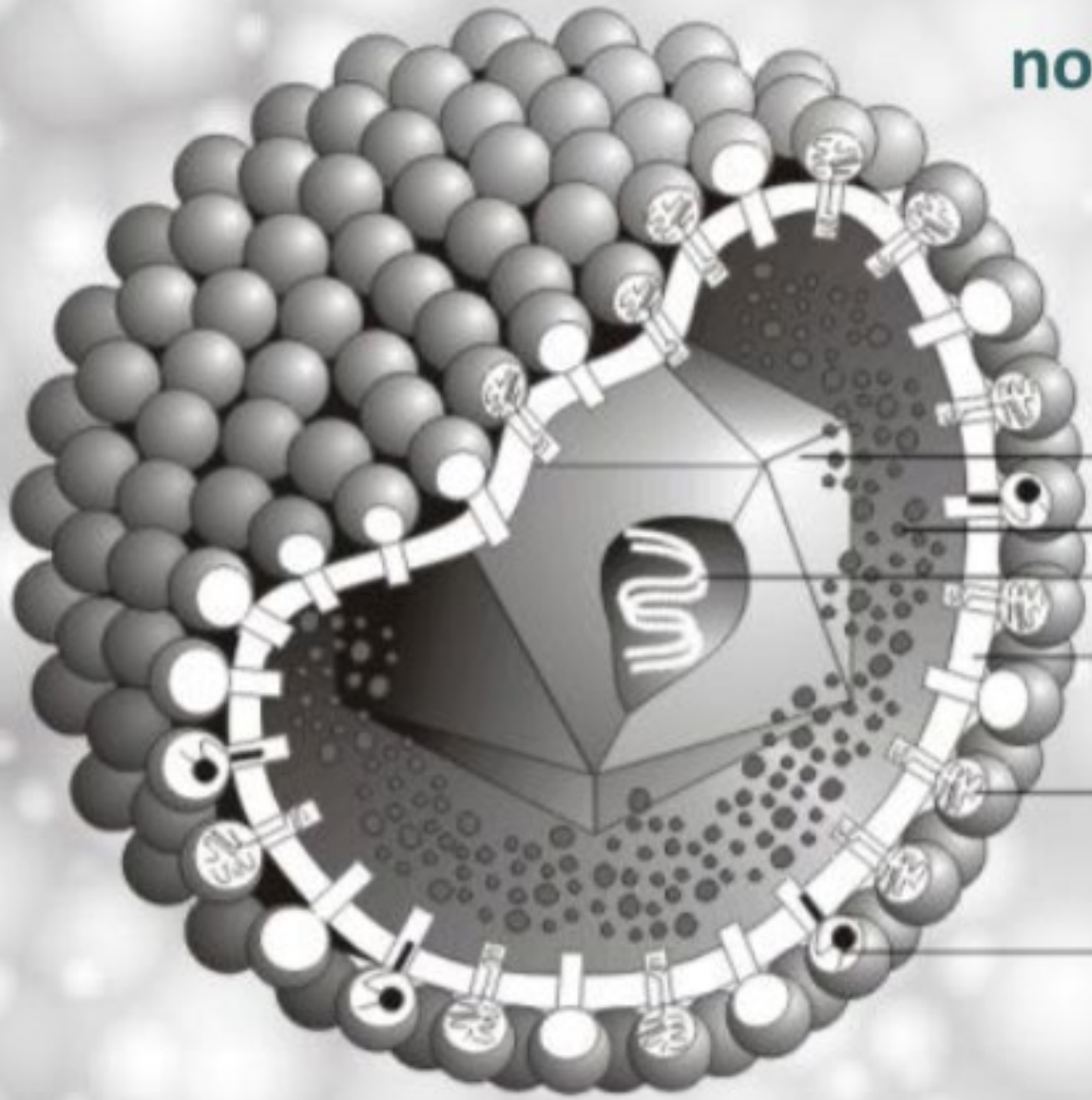
Recombinant CMV gB vaccine

failed

Several decades of extensive research have not met such urgent need


Epithelial/endothelial cell
(the main targets in vivo)
Fibroblast
(susceptible in vitro)
pentameric gH complex receptor
gH/gL receptor
gL
gH
UL131
UL128
UL130
pentameric gH complex
gL
gH
gH/gL
CMV (wild strain)
CMV (laboratory/vaccine strain)

Inducing Cell-mediated Immunity



non-structural protein: IE1

Major targets for cell-mediated immunity

pp65, pp150

Major targets for humoral immunity

gB

gH/gL/ UL128-131

Maternal humoral immunity did not prevent congenital CMV infection

The New England Journal of Medicine 2001; 344: 1366-71

INTRAUTERINE TRANSMISSION OF CYTOMEGALOVIRUS TO INFANTS OF WOMEN WITH PRECONCEPTIONAL IMMUNITY

SURESH B. BOPPANA, M.D., LISA B. RIVERA, M.P.H., M.B.A., KAREN B. FOWLER, DR.P.H., MICHAEL MACH, PH.D., AND WILLIAM J. BRITT, M.D.

Eleven of the 16 mothers with infected infants (69%) had antibodies against the gH epitopes present on two laboratory CMV strains, AD169 and Towne.
In a woman who is seropositive for CMV, reinfection with a different CMV strain can lead to intrauterine transmission and symptomatic congenital infection.

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Virology 2013; 58: 474-8

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

Short communication

Cytomegalovirus (CMV) glycoprotein H-based serological analysis in Japanese healthy pregnant women, and in neonates with congenital CMV infection and their mothers

Kazufumi Ikuta[a], Toshio Minematsu[b], Naoki Inoue[c], Takahiko Kubo[d], Kimisato Asano[e], Kei Ishibashi[f], Takashi Imamura[g], Hidetaka Nakai[h], Tetsushi Yoshikawa[h], Hiroyuki Moriuchi[i], Shigeyoshi Fujiwara[j], Shin Koyano[k], Tatsuo Suzutani[a,*]

Two (11%) of 18 cases of congenital CMV infection occurred via maternal CMV reinfection.
Maternal humoral immunity did not prevent congenital CMV infection with another gH subtype.

Likelihood of Transplacental Transmission of CMV from Mothers with Primary and Non-primary infection

From mothers	
with **primary** infection	**30 ~ 50%**
with **non-primary** infection	**0.2 ~ 2%**

Estimated Annual Number of Children with Congenital CMV in the USA from Mothers with Primary and Non-primary Infection during Pregnancy

Wang et al., Clin Infect Dis 2011

Children with congenital CMV	
born to sero**negative** mothers	**3,722** (4,419 ~ 16,049)
born to sero**positive** mothers	**29,918** (23,508 ~ 36,830)

Non-primary infection occurs more frequently than primary infection

Challenges for Developing CMV Vaccines

- Protective immune responses have not been defined.
- Preexisting seroimmunity does not provide complete protection.
- Most infants with congenital CMV in highly seropositive populations including low- and middle-income countries (LMIC) are born to mothers with preexisting seroimmunity.

↓

Vaccine strategies that have been focused on preventing primary maternal infection during pregnancy may not be appropriate.

- Precise estimates of disease burden in LMIC are limited.

↓

Insufficient interest by vaccine manufacturers and policymakers.

CMV Vaccine Candidates in Development or Clinical Trials

Live CMV Vaccines

Vaccine		Manufacturer	Clinical trials
Towne-Toledo chimera		MedImmune	
Replication-defective virus		Merck	Phase IIb
Alphavirus replicon		Novartis	Phase I
Vectored	MVA	City of Hope	Phase I
	Adeno	Queenland Inst	
	LCMV	Hookipa	Phase II
	ALVAC	Pasteur/Merieux	

Non-living CMV Vaccines

Vaccine (platform/Ag)		Manufacturer	Clinical trial
Subunit (recombinant)	gB	Sanofi Pasteur	Phase II
		GSK	
	Pentameric gH complex	Human Biomed	
Peptides		City of Hope	
DNA	gB + pp65	Astellas/Vical	Phase III
	gB + pp65 + IE1		Phase I
RNA (mRNA in LNP)		GSK/Moderna	
Dense bodies		Vaccine Project Management (Germany)	
eVLP*	gB	Variation Biotech	Phase I
	gB, pentameric gH, etc	RedVax GmbH	

*enveloped virus-like particle

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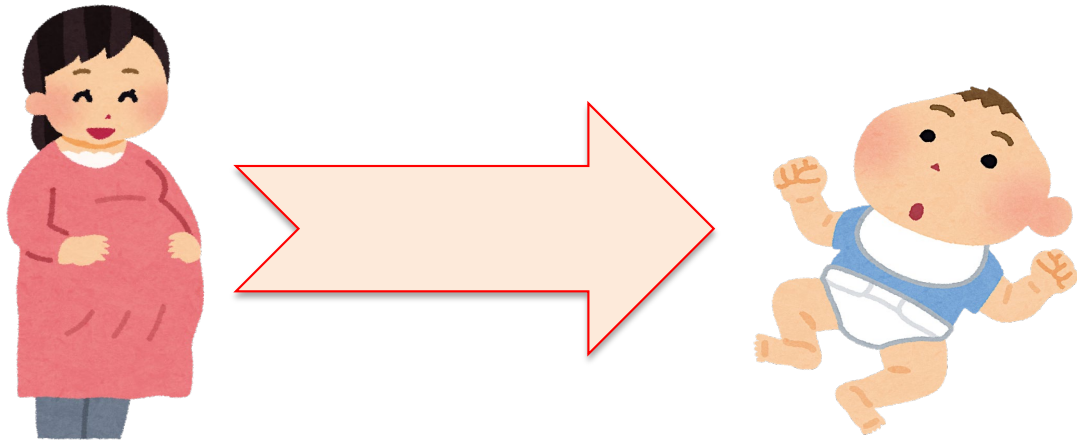
Cytomegalovirus

Rubella



FLAVIVIRUS

Enveloped ssRNA(+) virus

Yellow fever virus

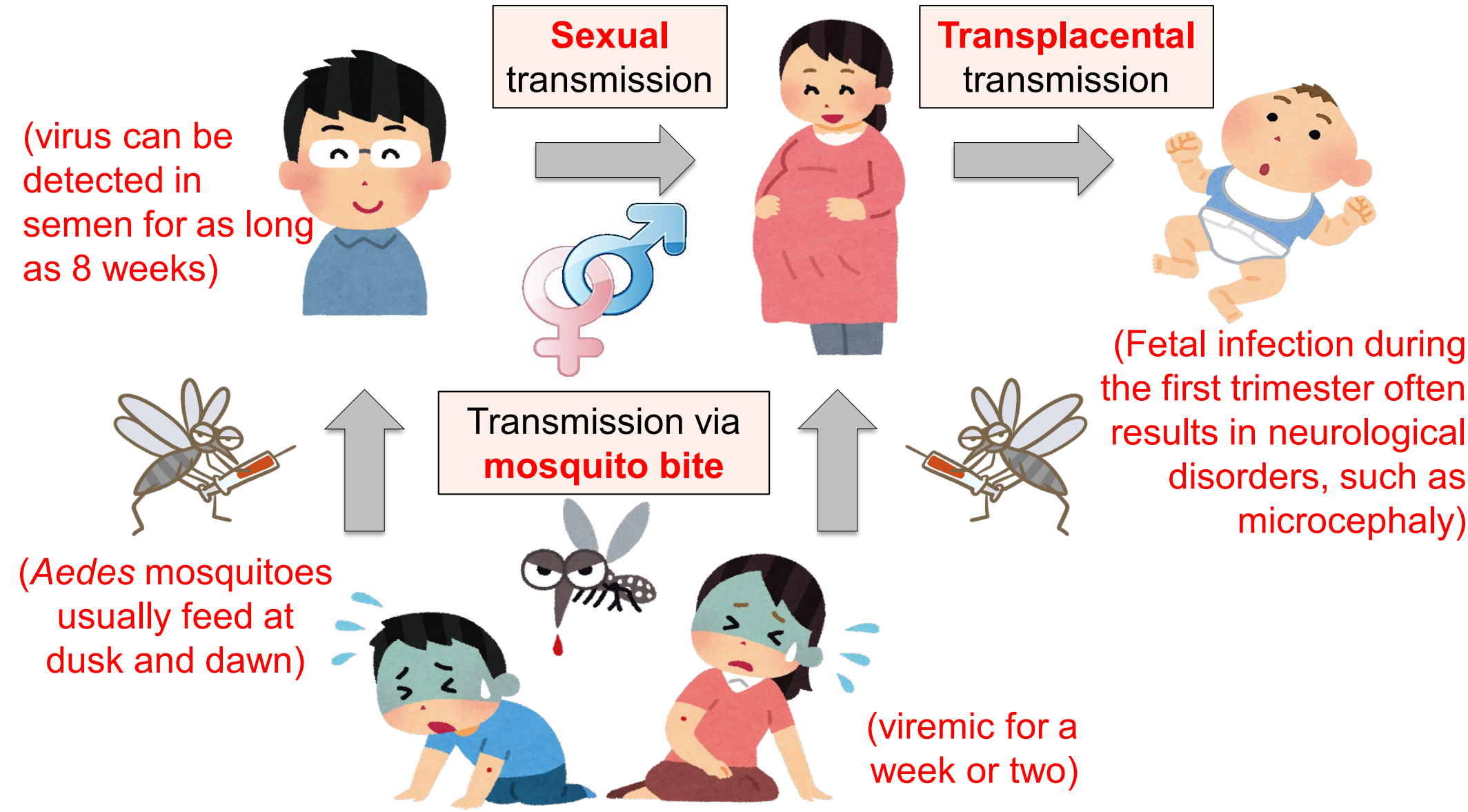
Dengue virus

Zika virus

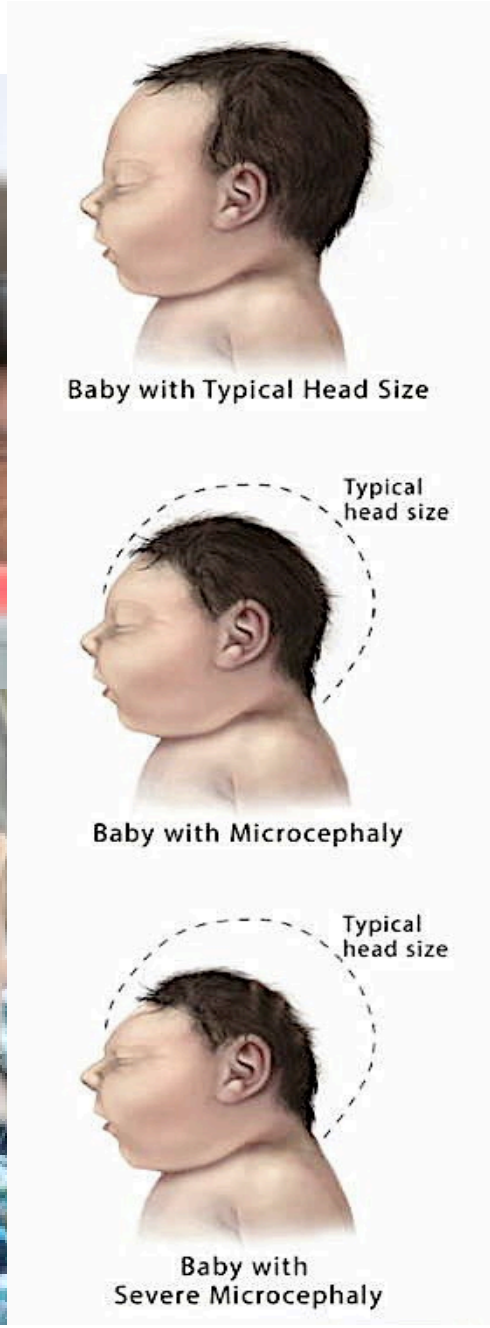
West Nile virus

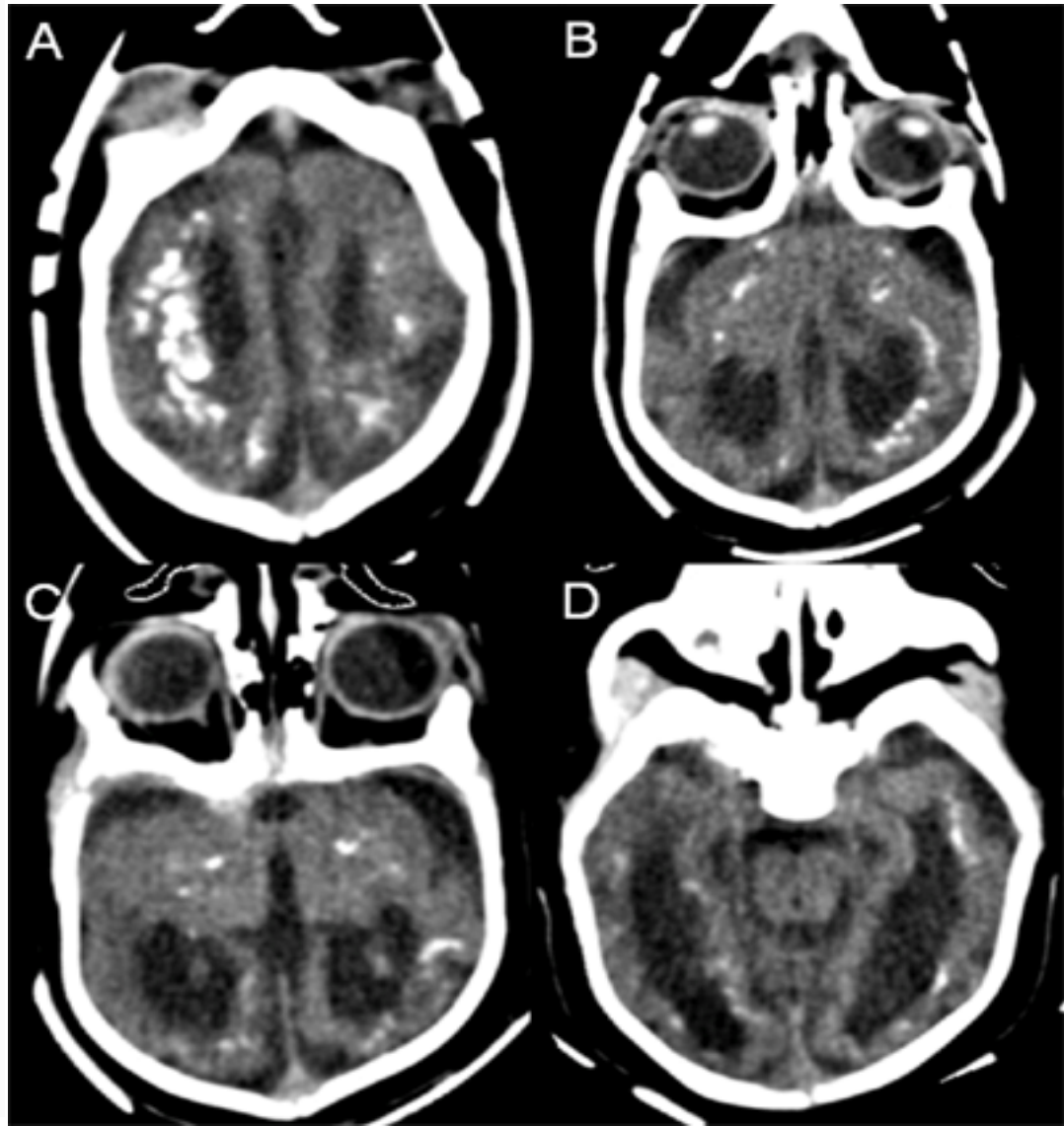
Japanese encephalitis virus

Zika Virus Transmission Cycle



Microcephaly

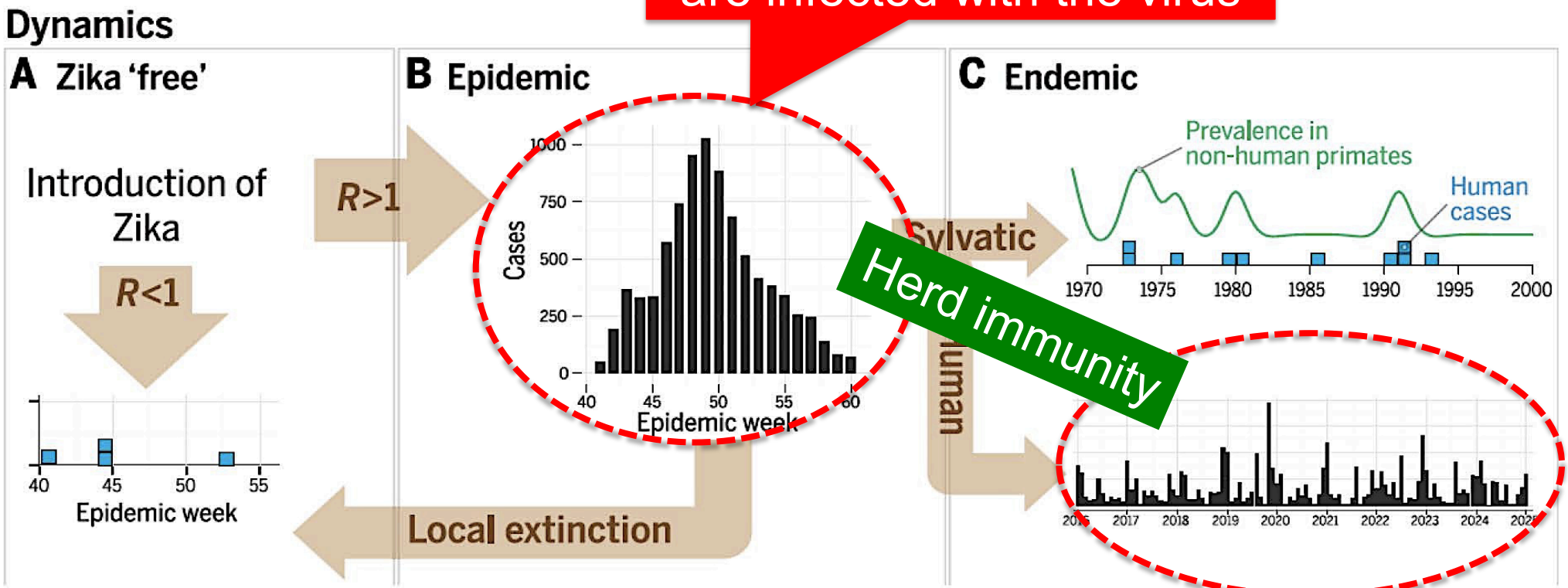




Scenarios from Introduction through Outbreak to Endemic of Zika Virus Infection

Everyone is susceptible

Both adults and children are infected with the virus

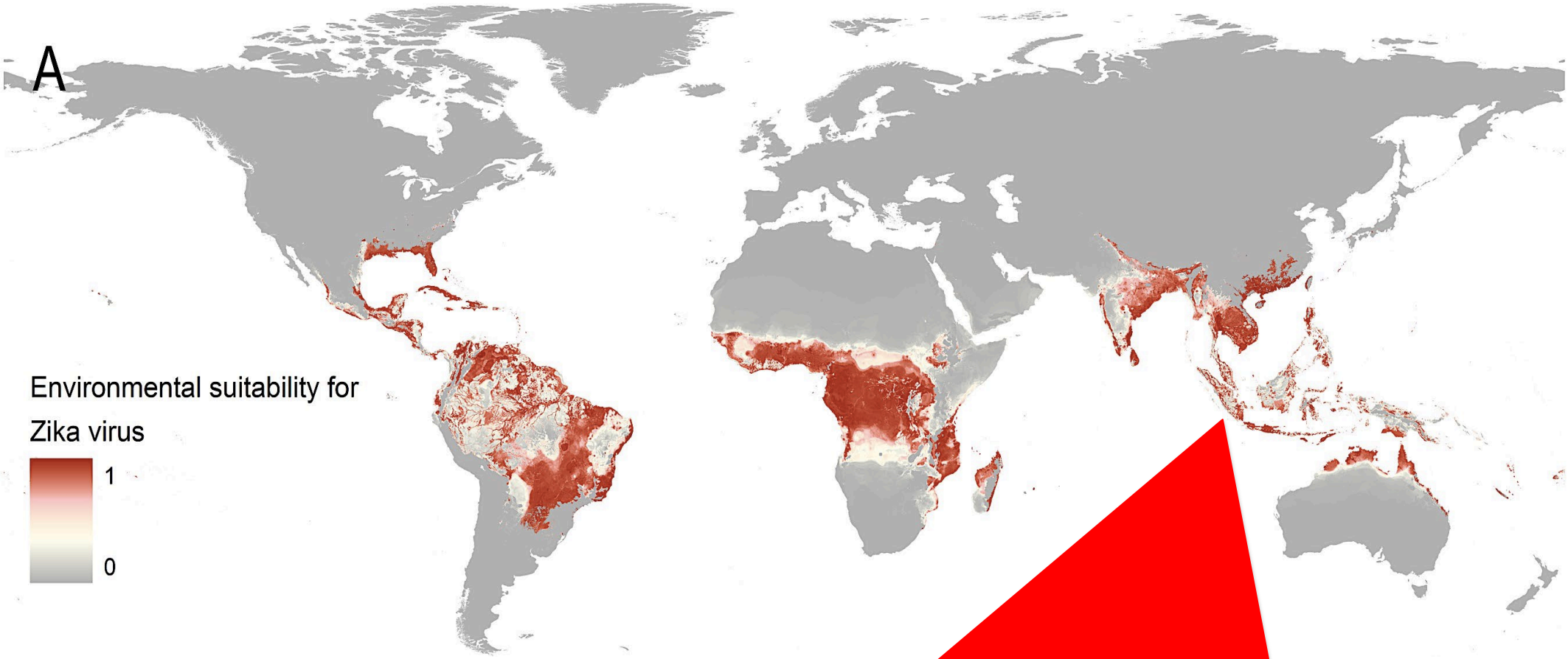


Children are susceptible

Children are almost exclusively infected with the virus

Mapping global environmental suitability for Zika virus

Messina JP et al. e-Life 2016



Asia should be regarded as a Zika virus-endemic area.

Mosquitoes in Vietnam Carry Zika virus!

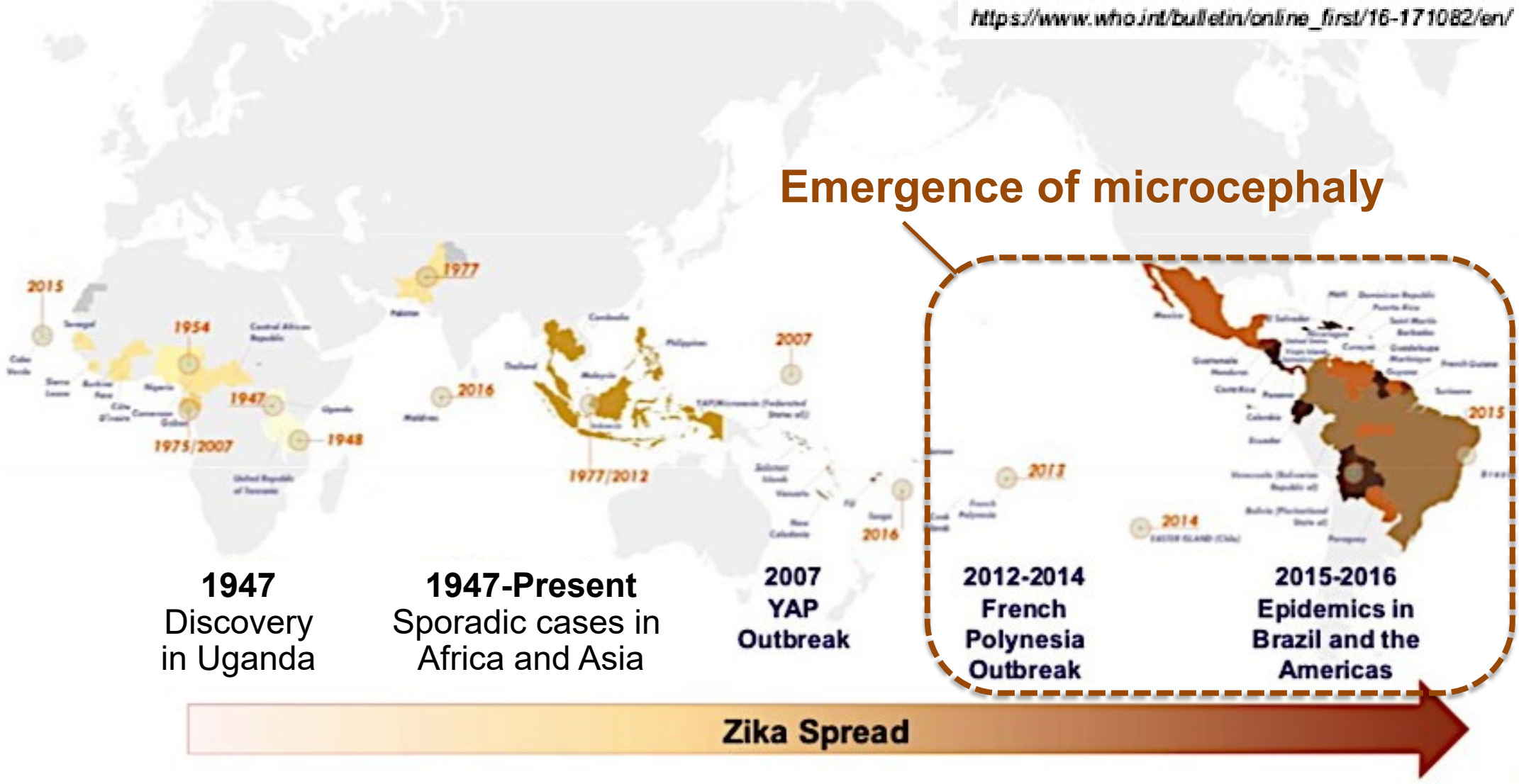
Date: Sun 16 Oct 2016 01:34 pm (GMT+7)
Source: VN Express International [edited]
http://e.vnexpress.net/news/news/zika-virus-mosquitoes-detected-in-central-vietnam-3484407.html>

Viet Nam's National Institute of Hygiene and Epidemiology has discovered a small population of the *Aedes aegypti* mosquitoes carrying the Zika virus in the tourist town of Nha Trang in the central province of Khanh Hoa.

Out of 23,682 mosquitoes, 56 or **0.24% of the total, tested positive for Zika virus** and 26 or **0.12% for Dengue virus**, according to a study conducted by the institute from March 2015-May 2016.

Zika virus history (1947 ~ 2016)

https://www.who.int/bulletin/online_first/16-171082/en/



Why are we recognizing ZIKV as such an awful virus NOW?

Asian strains may be less pathogenic than those in Latin America.

Science

REPORTS

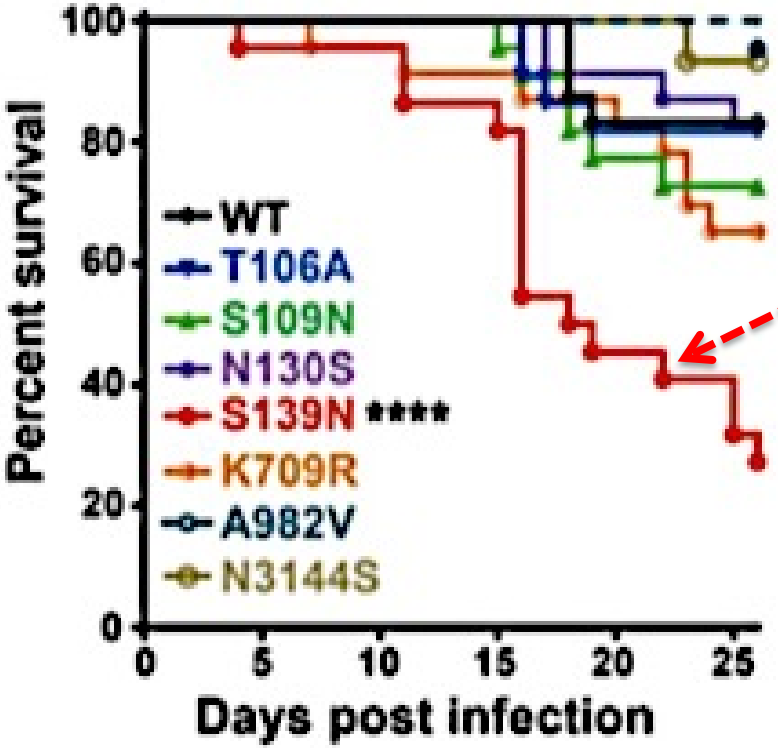
Cite as: L. Yuan *et al.*, *Science* 10.1126/science.aam7120 (2017).

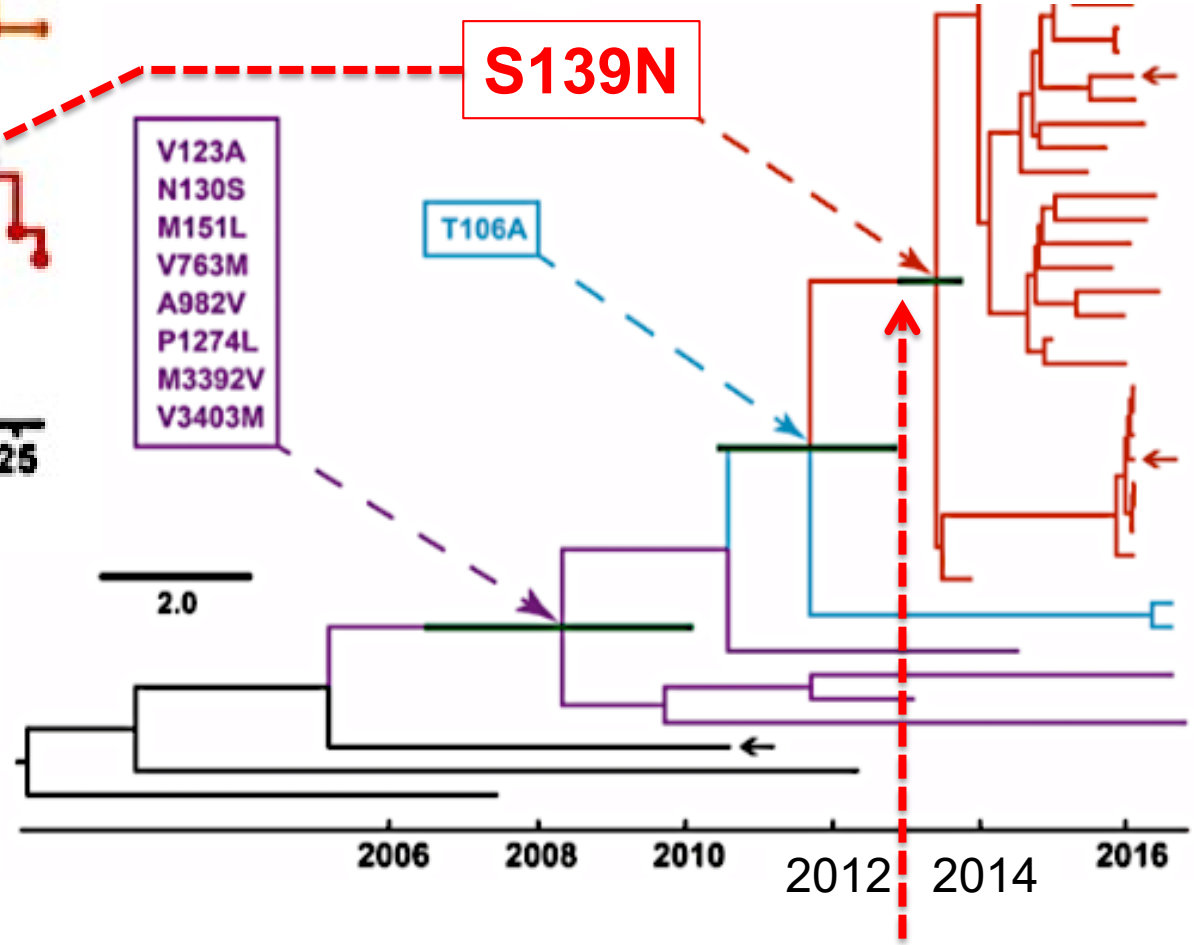
A single mutation in the prM protein of Zika virus contributes to fetal microcephaly

Ling Yuan,[1,2*] Xing-Yao Huang,[3*] Zhong-Yu Liu,[3*] Feng Zhang,[1,2*] Xing-Liang Zhu,[1,2*] Jiu-Yang Yu,[3*] Xue Ji,[3] Yan-Peng Xu,[3] Guanghui Li,[1,2] Cui Li,[1,2] Hong-Jiang Wang,[3] Yong-Qiang Deng,[3] Menghua Wu,[4] Meng-Li Cheng,[3,5] Qing Ye,[3] Dong-Yang Xie,[3,5] Xiao-Feng Li,[3] Xiangxi Wang,[6] Weifeng Shi,[7] Baoyang Hu,[4] Pei-Yong Shi,[8] Zhiheng Xu,[1,2,9†] Cheng-Feng Qin[3†]

Zika virus (ZIKV) has evolved into a global health threat due to its unexpected causal link to microcephaly. Phylogenetic analysis reveals that contemporary epidemic strains have accumulated multiple substitutions from their Asian ancestor. Here, we show that a single serine to asparagine substitution (S139N) in the viral polyprotein substantially increased ZIKV infectivity in both human and mouse neural progenitor cells (NPCs), led to more significant microcephaly in the mouse fetus, and higher mortality in neonatal mice. Evolutionary analysis indicates that the S139N substitution arose before the 2013 outbreak in French Polynesia and has been stably maintained during subsequent spread to the Americas. This functional adaption makes ZIKV more virulent to human NPCs, thus contributing to the increased incidence of microcephaly in recent ZIKV epidemics.

The S139N mutant virus shows enhanced neurovirulence in neonatal mice





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https://www.who.int/bulletin/online_first/16-171082/en/

1947
Discovery in Uganda

1947-Present
Sporadic cases in Africa and Asia

2007
YAP Outbreak

Emergence of microcephaly

2012-2014
French Polynesia Outbreak

2015-2016
Epidemics in Brazil and the Americas

Zika Spread

Introduction of the S139N mutation

THE LANCET
Infectious Diseases
Vol. 17 p. 805 August 2017

Zika virus infection and microcephaly in Vietnam

Even if less pathogenic, ZIKV in Asia should never be non-pathogenic.

*Meng Ling Moi, Thi Thu Thuy Nguyen, Co Thach Nguyen, Thi Bich Hau Vu, Mya Myat Ngwe Tun, Tho Duoc Pham, Ngoc Thanh Pham, Thuan Tran, Kouichi Morita, Thi Quynh Mai Le, Duc Anh Dang, *Futoshi Hasebe*

Nagasaki University, Japan; NIHE, Vietnam

Figure: Facial features of a child aged 4 months exposed to Zika virus in Vietnam
The infant was born by spontaneous vaginal delivery (bodyweight 2·6 kg; length 50 cm; head circumference 22 cm at birth).

Successful Flavivirus Vaccines

Vaccine type		Disease
Live attenuated	By serial passaging in mouse and chicken tissue (→YFV 17D)	Yellow fever (YF)
	SA14-14-2 strain	Japanese encephalitis (JEV)
	Chimeric virus containing the prM and E proteins of JEV and attenuated YFV 17D	
Inactivated	Inactivate the attenuated SA14-14-2 strain grown in Vero cells	
	Highly purified inactivated whole virus grown in primary chicken embryo cells	Tick-borne encephalitis

How about dengue virus (DENV) vaccines?

Challenges for Developing DENV Vaccines

- DENV consists of 4 serotypes that are substantially different from each other in the amino acid sequence of their E proteins.
- Previous infection with one serotype can predispose the severe forms of dengue (DHF/DSS) upon re-infection by another serotype.
- Endemic regions with co-circulating different serotypes have enormously expanded, followed by dramatic increase in the incidence of DHF/DSS.

✓ Cross-reactive non-neutralizing antibodies (such as those present after infection with a heterologous serotype in sequential infections) and neutralizing antibodies at suboptimal concentrations can lead to antibody-dependent enhancement (ADE) of FcR-bearing cells.

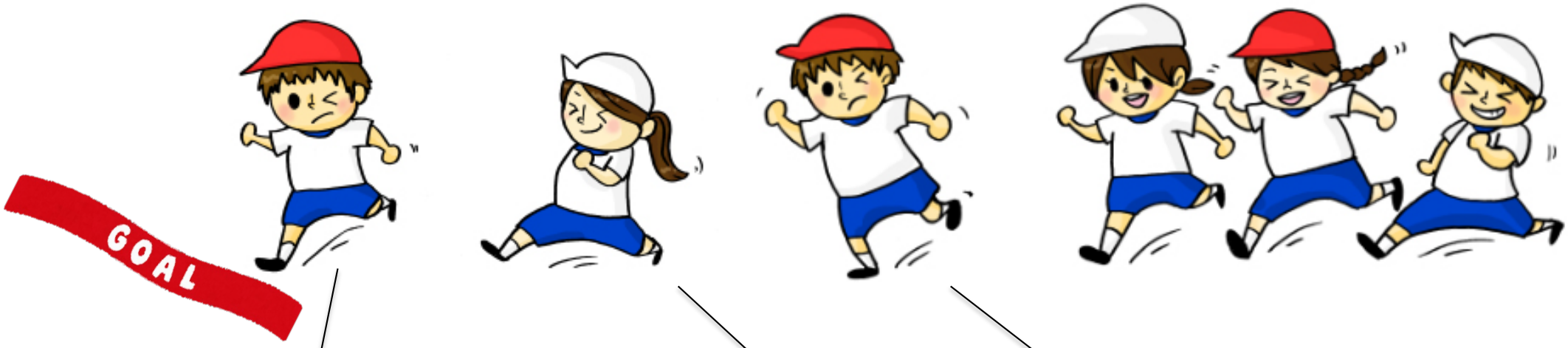
✓ Pre-existing cross-reactive T cells are also less efficient in viral clearance but can cause "cytokine storm".

↓

"Capillary leakage" ---- Development of DHF/DSS

Dengue Vaccine Race

Approved **Phase III** In Development



Sanofi-Pasteur

CYD-TDV (Dengvaxia®)

A live attenuated tetravalent chimeric vaccine made by replacing the prM and E genes of YFV attenuated 17D strain vaccine with those from the four DENV serotypes

NIH/Butantan

TetraVax-DV

A tetravalent admixture of live attenuated monovalent vaccines

Takeda

DENVax (TAK-003)

A recombinant chimeric vaccine with DENV1, DENV3, and DENV4 components on a DENV2 backbone

The New York Times

F.D.A. Approves the First Vaccine for Dengue Fever, but Limits Its Use

By Katie Thomas May 3, 2019

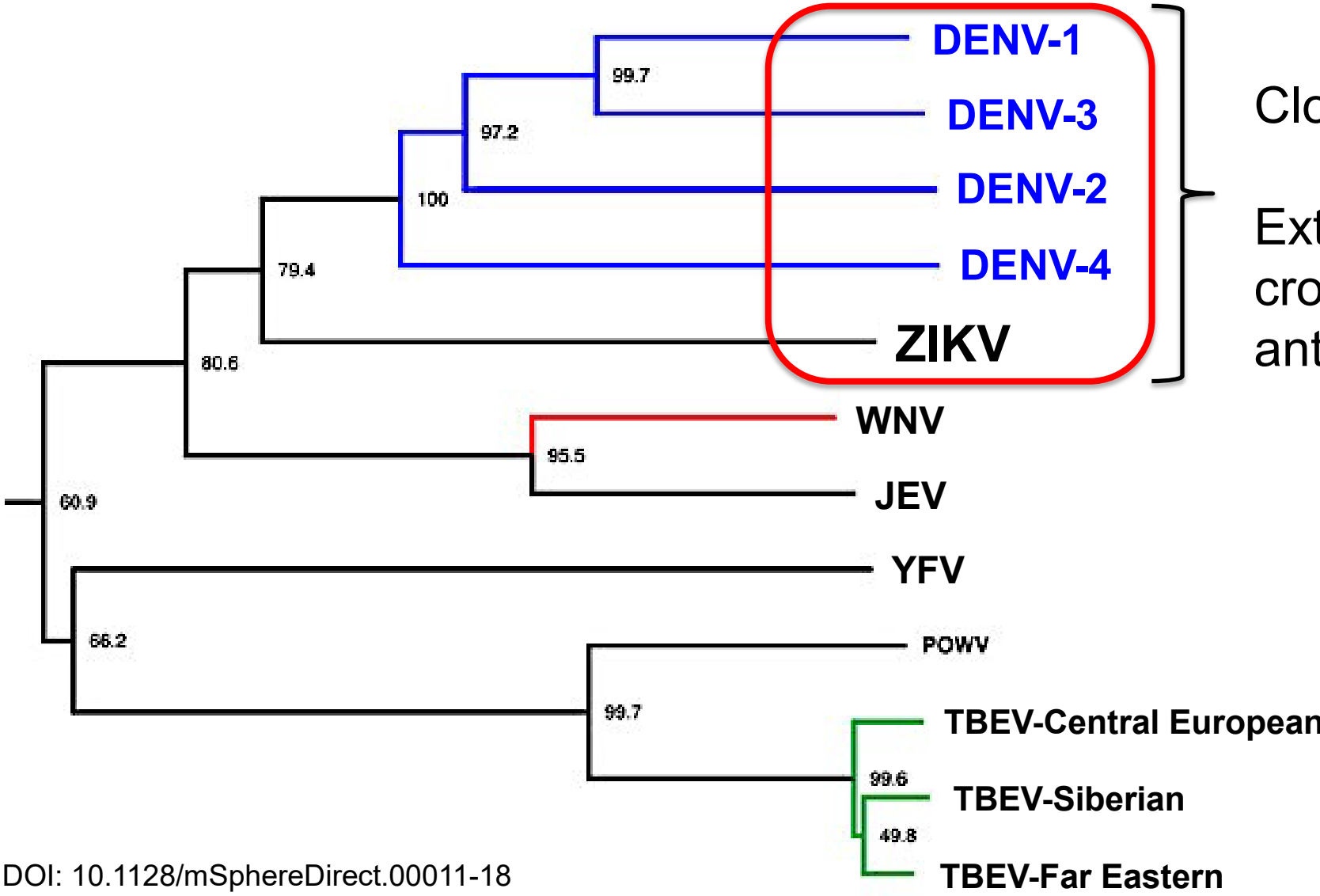
The Food and Drug Administration has approved the first vaccine for dengue, Dengvaxia, but placed significant restrictions on its use because the vaccine has been shown to put some people at heightened risk for a severe form of the disease.

That decision came after Sanofi announced that in rare cases, if people who never had dengue were vaccinated and later became infected, the vaccine might provoke a much more severe form of the illness.

On May 1, the F.D.A. limited its approval to people aged 9 to 16 who live in areas where dengue is endemic and who are shown by lab testing already to have been infected with the disease.

In Manila, relatives of children who had died after receiving the Dengvaxia vaccine attended a hearing in 2018. Philippine officials halted use of Sanofi's vaccine amid concerns about the health risks.Noel Celis/Agence France-Presse — Getty Images

Phylogenetic tree of medically important flaviviruses based on E protein amino acid diversity



Closely related

↓

Extensive cross-reaction of anti-E protein Ab

DOI: 10.1128/mSphereDirect.00011-18

Challenges for Developing Zika Virus Vaccines

- Four serotypes of DENV and Zika virus are closely related.
- Neutralizing antibody to any one of them is cross-reactive with other viruses.

↓

Pre-existing immunity against DENV may predispose serious Zika disease (CZS), and vice versa (DHF/DSS).

SCIENCE ADVANCES | RESEARCH ARTICLE

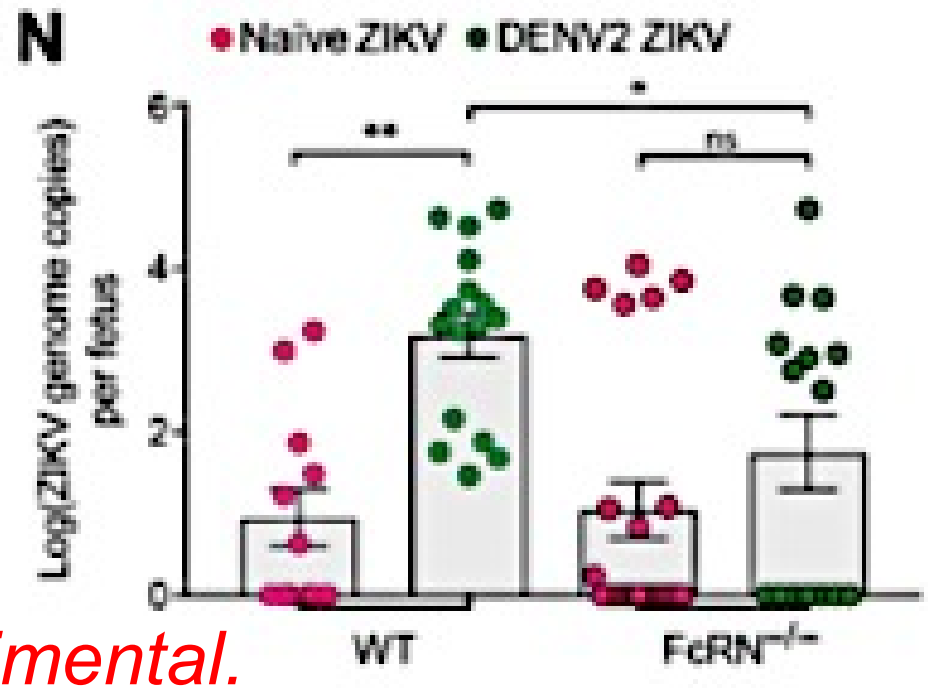
Sci. Adv. 2019; 5 : eaav3208 27 February 2019

IMMUNOLOGY

Maternal immunity and antibodies to dengue virus promote infection and Zika virus–induced microcephaly in fetuses

Abhay P. S. Rathore[1,2*], Wilfried A. A. Saron[1*], Ting Lim[1], Nusrat Jahan[1], Ashley L. St. John[1,2,3†]

Maternal DENV immunity leads to FcRn-dependent enhancement of fetal Zika virus infection.



Suboptimal immunity can be detrimental.

Challenges for Developing Zika Virus Vaccines

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- Neutralizing antibody to any one of them is cross-reactive with other viruses.

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Pre-existing immunity against DENV may predispose serious Zika disease (CZS), and vice versa (DHF/DSS).

- A rapid emergence of ZIKV-associated Guillain-Barre syndrome (GBS) has been observed during its outbreak.

↓

ZIKV vaccination may also induce the emergence of GBS.

Challenges for Developing Zika Virus Vaccines

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- A rapid emergence of ZIKV-associated Guillain-Barre syndrome (GBS) has been observed during its outbreak.

↓

ZIKV vaccination may induce the emergence of GBS.

- Precise estimates of disease burden in Asia are limited.

↓

Insufficient interest by policymakers in Asian countries.

KHANH HOA BIRTH COHORT STUDY

National Institute of Hygiene and Epidemiology (NIHE), Hanoi, Vietnam
Khanh Hoa Provincial Public Health Service
Khanh Hoa General Hospital (KHGH), Nha Trang, Vietnam
Nagasaki University, Nagasaki, Japan

Approximately 2,000 pairs of mothers and babies were enrolled.

↓

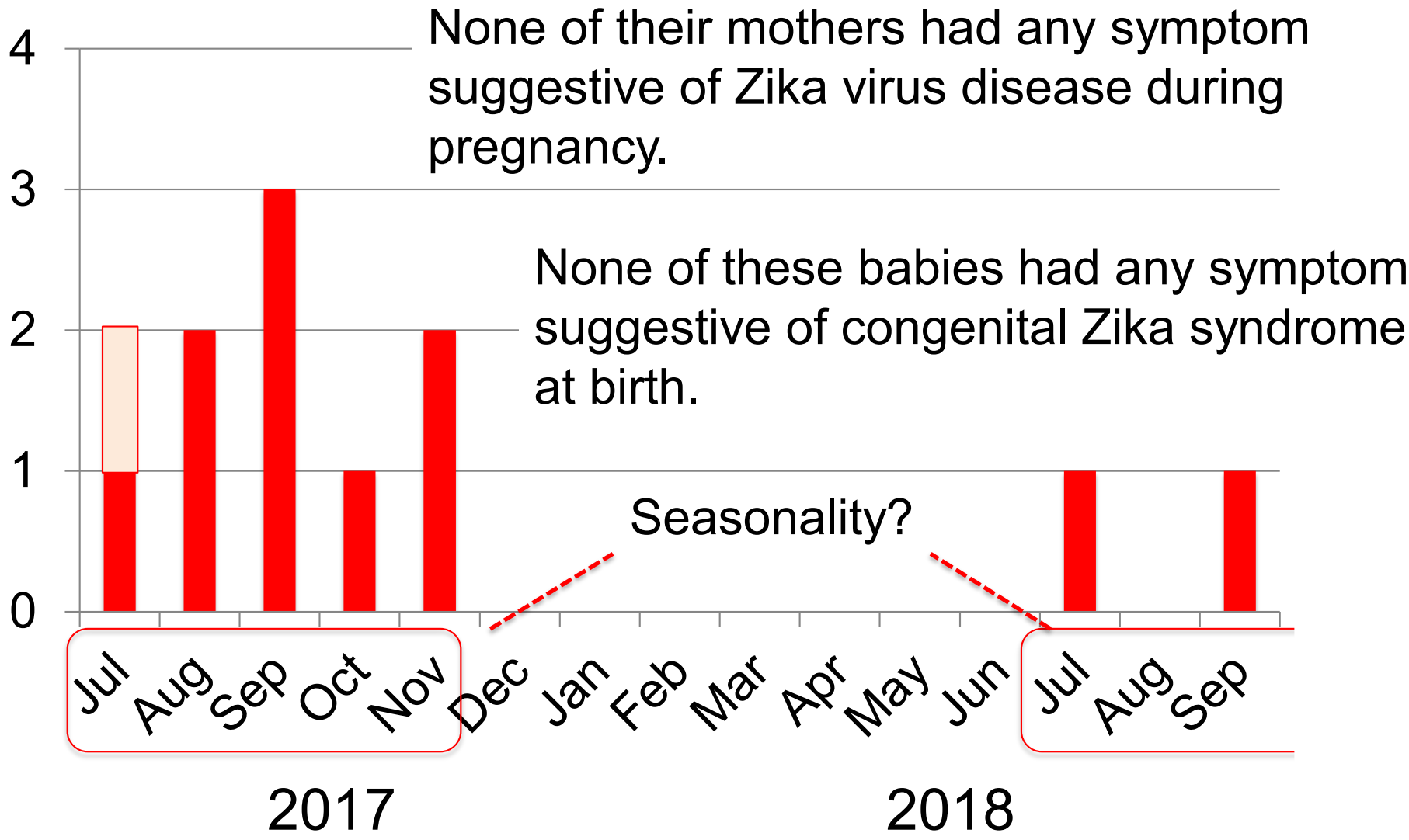
- ✓ Cord blood sera were tested for flavivirus serology.
- ✓ Saliva and cord blood specimens were tested for Zika virus RNA.

Summary of Infants with Congenital Zika Virus Infection

	Sample ID	Age (Y)	Sample collection date	IgM P/N ration (>2.0)			Flavi IgG (x1000)	ZIKV NT	PCR	
				ZIKV	DENV	JEV			PL	Saliva
Part 2	P-10	42	Jul/15	12.3	0.8	5.5	59.3	640	ND	+
Part 1 (Birth Cohort)	BC-54	34	Jul/27	2.0	0.7	0.6	41.7	1280	+	+
	BC-114	34	Aug/21	3.3	0.7	0.1	8.5	640	+	-
	BC-126	38	Aug/24	3.7	0.8	0.3	29.5	640	+	-
	BC-162	29	Sep/6	3.7	2.5	2.3	72.2	1280	+	-
	BC-171	29	Sep/8	2.0	0.6	0.5	17.3	640	-	-
	BC-292	23	Oct/25	2.0	0.8	0.5	31.7	2560	-	+
	BC-315	28	Nov/2	17.9	14.9	13.1	72.9	20480	-	-
	BC-321	42	Nov/6	7.9	6.0	5.8	57.4	2560	+	-
	BC-3112	21	Sep/22	8.6	2.0	0.6	10.3	1280	+	+
	BC-3786	28	Jul/18	2.0	1.4	0.5	33.4	320	ND	-
	BC-4013	25	Sep/19	2.3	0.6	1.2	24.0	640	ND	-

Incidence of congenital Zika infection: 0.54% in BC

Cases of Congenital Zika Virus Infection



Summary of Infants with Congenital Zika Virus Infection

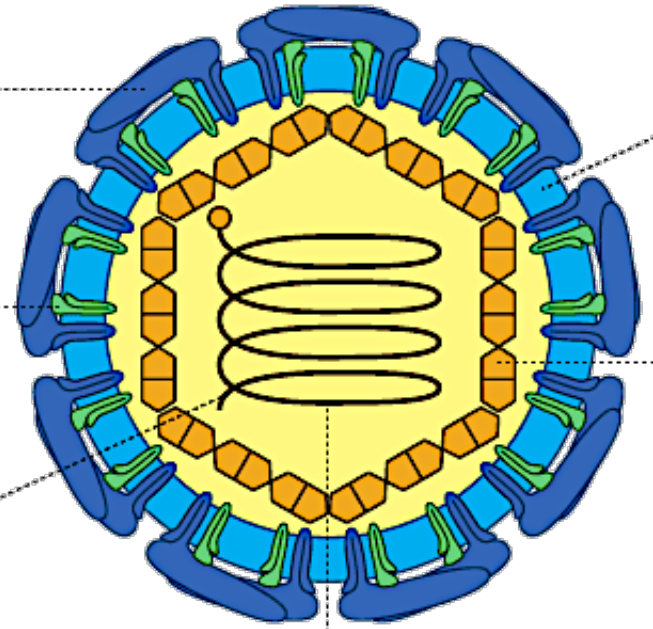
Sample ID	Neutralization titer (FRNT50)					
	ZIKV	JEV	DENV-1	DENV-2	DENV-3	DENV-4
P-10	**640**	80	160	160	160	160
BC-54	**1280**	160	80	160	160	320
BC-114	**640**	<80	<80	80	<80	<80
BC-126	**640**	80	160	160	160	<80
BC-162	**1280**	80	320	320	320	320
BC-171	**640**	<80	80	160	<80	80
BC-292	**2560**	80	640	640	160	320
BC-315	**20480**	160	5120	5120	5120	1280
BC-321	**2560**	320	160	320	<80	640
BC-3112	**1280**	160	320	160	160	320

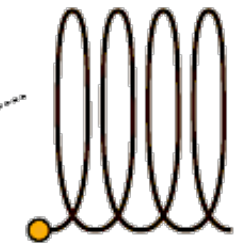
All of them had anti-DENV antibody

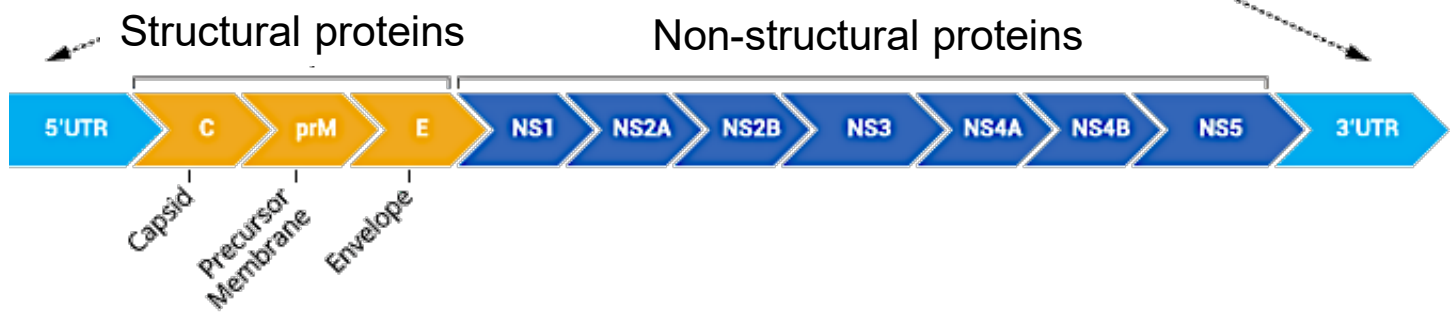
→ Pre-existing immunity against DENV predisposed CZI?

Envelope protein

The main Zika virus immunogen







Zika virus structure

https://www.promega.jp/resources/pubhub/inspiration/zika-perspectives-responses/

ZIKV Vaccine Candidates in Clinical Trials

Platform		Immunogen	Name	Main sponsor	Phase
DNA		prM-E	VRC5283	NIAID	II
			VRC5288	NIAID	I
			GLS-5700	GeneOne Life Science	I
mRNA		prM-E	mRNA-1325	Moderna Therapeutics	I
Inactivated virions		Whole virion	ZPIV	NIAID	I
			BBV121	Bharat Biotech	I
			PIZV	Takeda	I
			VLA1601	Valneva	I
Viral vector	Measles virus	prM-E	MV-ZIKV	Themis Bioscience	I
	Adenovirus	M-E	Ad26.ZIKV.001	Janssen	I
Live attenuated		Whole virion	rZIKV/D4Δ30-713	NIAID	I

T O R C H complex

Toxoplasma

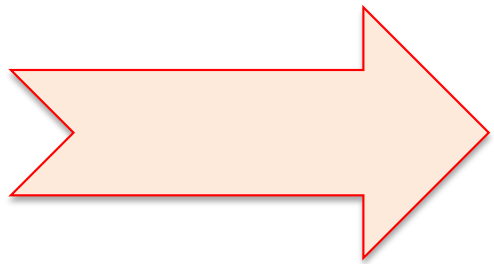
Herpes simplex virus

Others

(Syphilis, Zika virus)

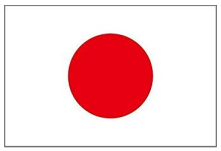
Cytomegalovirus

Rubella



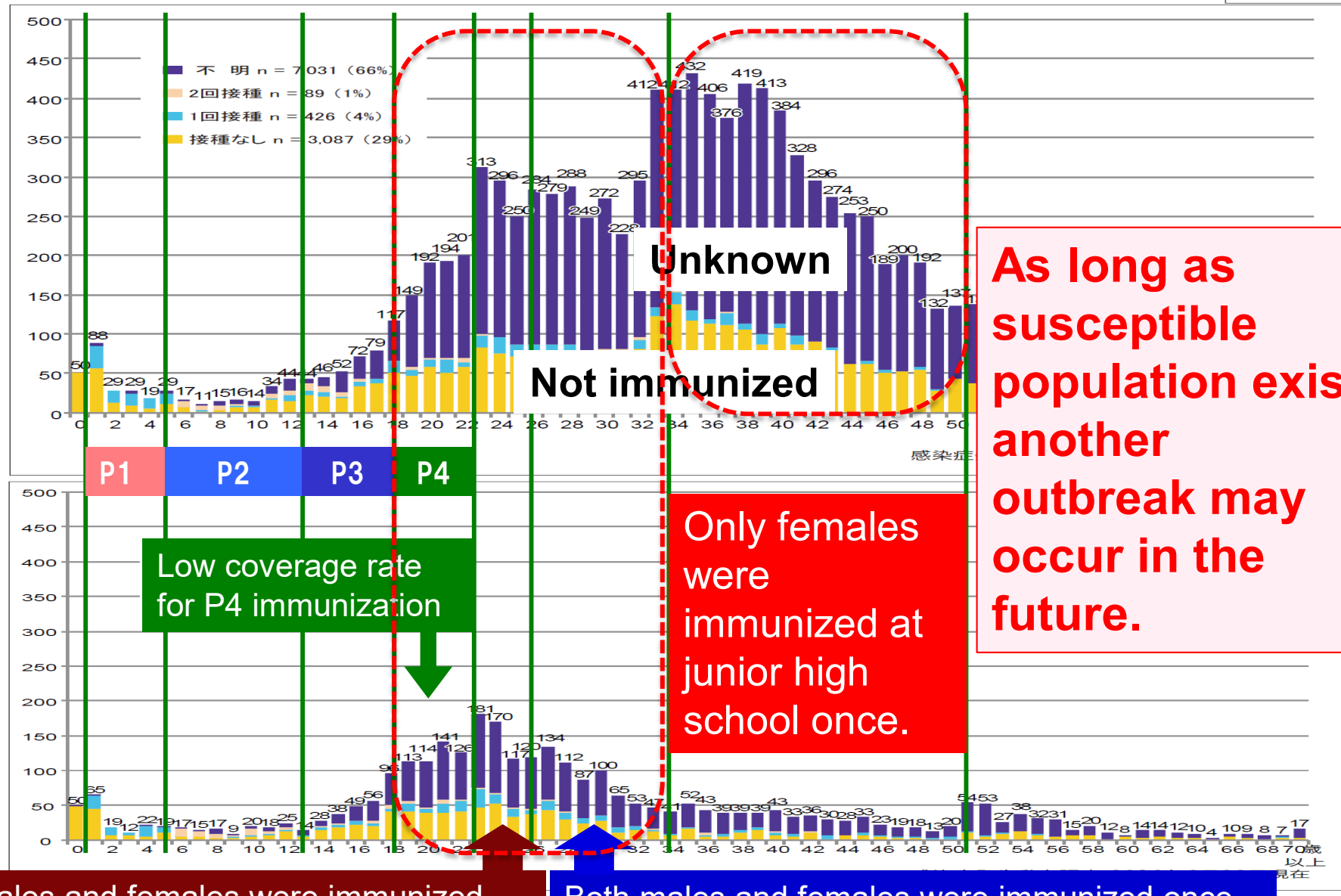
The only TORCH pathogen that we have useful vaccines against all over the world

Rubella outbreak in 2012-13 and subsequent emergence of CRS cases

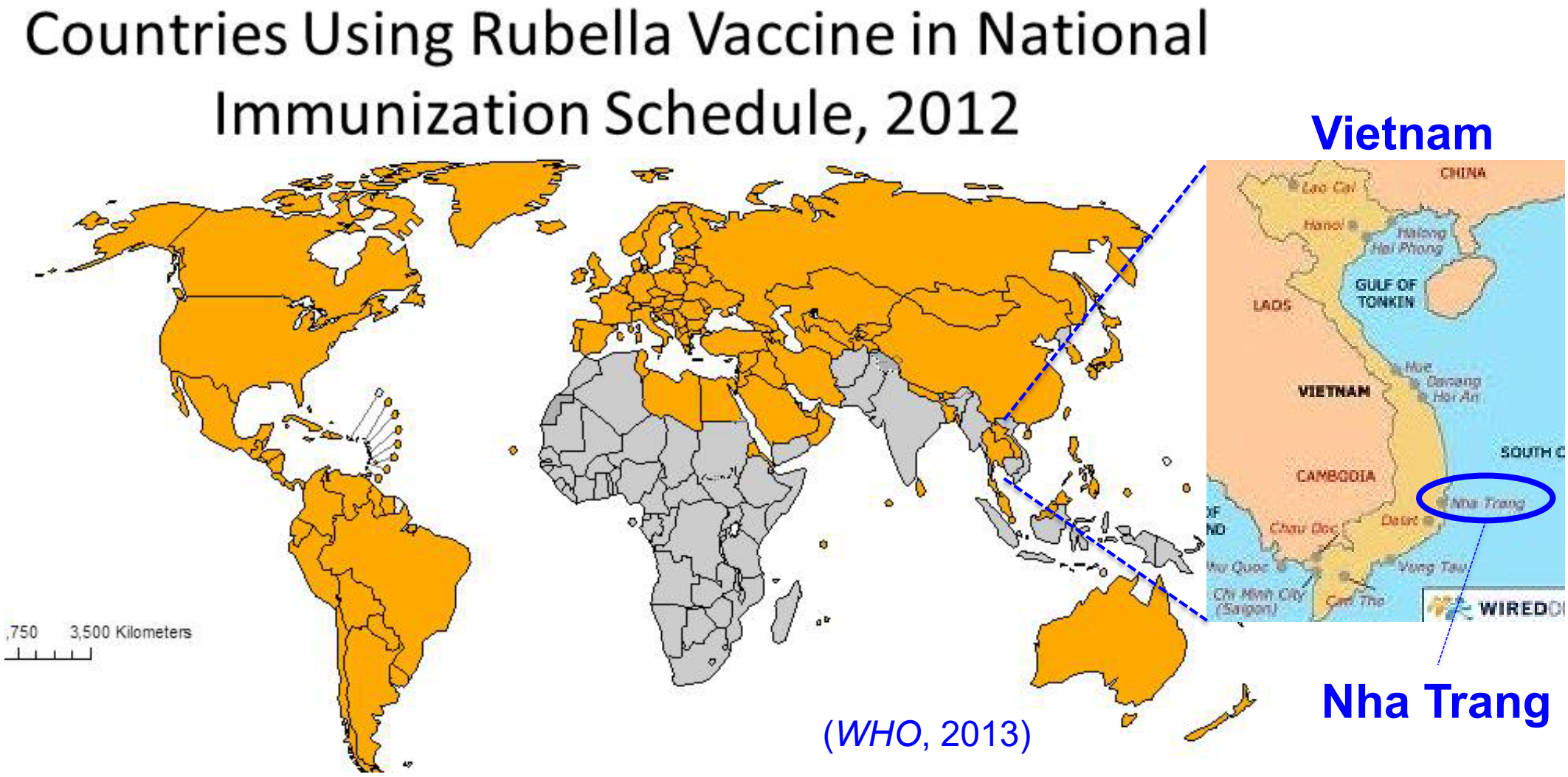


(Ministry of Health, Labor and Welfare, Japan)

Rubella cases by gender, age and vaccination status (2013)



Rubella-containing vaccine had not been introduced into national immunization program until 2015 in Vietnam.



Vaccine 32 (2014) 1192–1198

Contents lists available at ScienceDirect

Vaccine

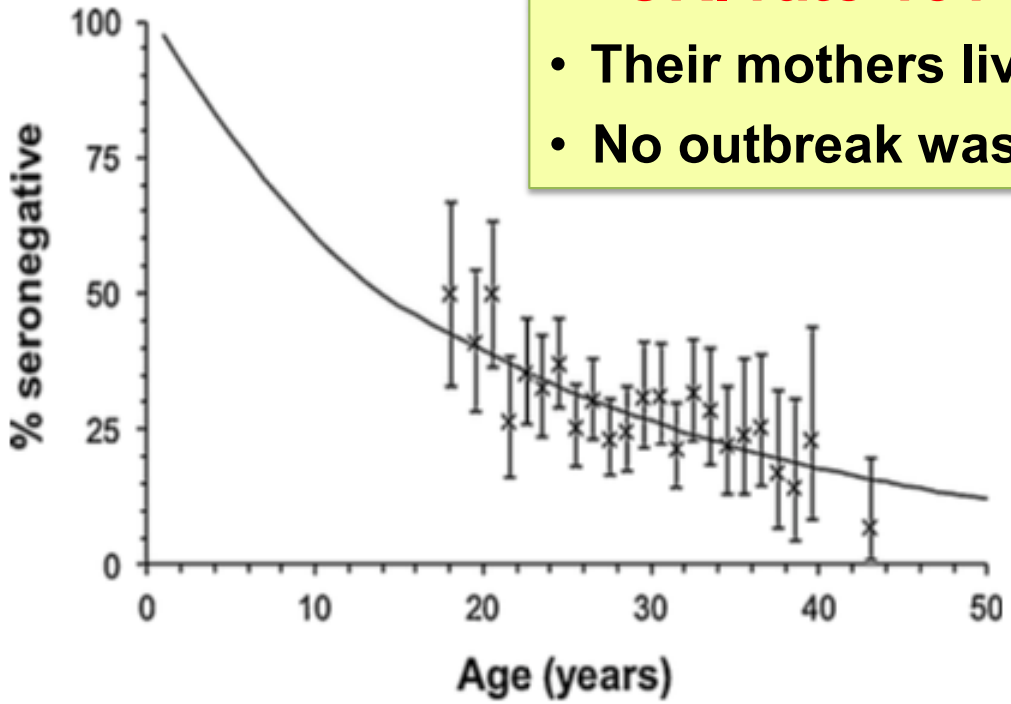
journal homepage: www.elsevier.com/locate/vaccine

Rubella-IgG positive in 71%
⇒ 28.9% (95%CI: 26.9-30.9) pregnant women were susceptible to rubella.

Seroprevalence of rubella in the cord blood of pregnant women and congenital rubella incidence in Nha Trang, Vietnam

Masami Miyakawa[a,1], Hiroshi Yoshino[b], Lay Myint Yoshida[b], Emilia Vynnycky[c,f], Hideki Motomura[a], Le Huu Tho[d], Vu Dinh Thiem[e], Koya Ariyoshi[b], Dang Duc Anh[e], Hiroyuki Moriuchi[a,*]

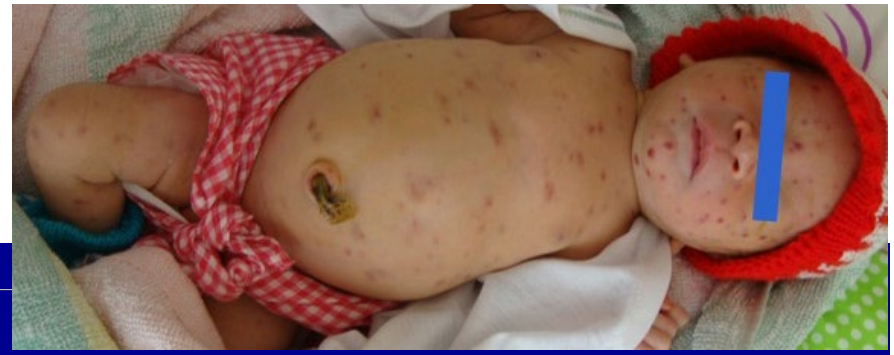
Rubella-IgM positive in 3 infants
⇒ CRI rate 151 (95%CI: 0-322) per 100,000 live births
- **Their mothers lived in different residential areas.**
- **No outbreak was reported in the area during study period.**

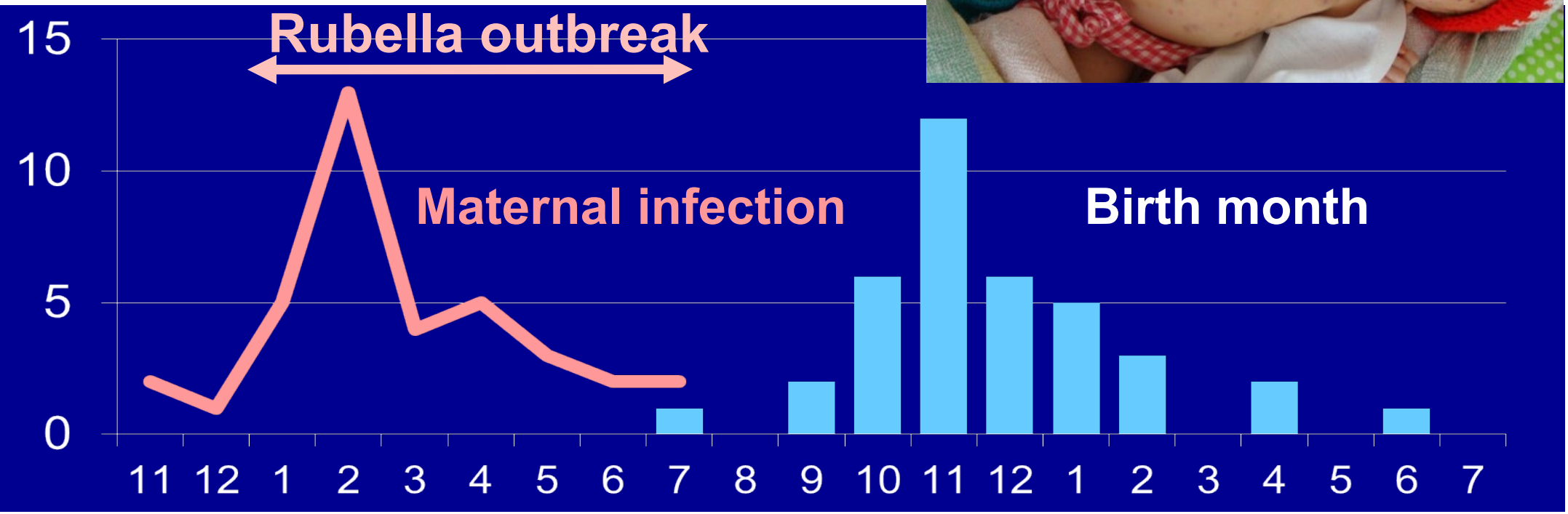


Mathematical modeling estimated that 3788 (95%CI: 3283-4143) infants with CRS would be born annually in Vietnam with 234 (95%CI: 207-262) cases per 100,000 live births

Rubella outbreak in Nha Trang, followed by the emergence of CRS between 2011 and 2012

- A total of 38 babies were enrolled (**2.1 cases per 1000 live births**).
- M : F = 17 (45%) : 21 (55%)
- 14 (**37%**) **died**.





Viet Nam Launches Largest Measles-Rubella Immunization Campaign with United Nations Support

Ha Noi, 11 October 2014 -

The current campaign aims to reach 23 million children ages 1-14 with the MR vaccine over the next six months.

UNICEF Viet Nam\2014\Truong Viet Hung

Earlier this year, Viet Nam witnessed an unprecedented rise in measles infections which affected more than 5000 children including the loss of more than 140 young lives.

→ followed by the routine immunization for children aged 18 months

The MR immunization campaign, which lasts through to February 2015, is part of Viet Nam's commitment to the Measles & Rubella Initiative, a global partnership to ensure that no child dies from measles or is born with congenital rubella syndrome. The Measles & Rubella Initiative is led by the American Red Cross, the United Nations Foundation, the U.S. Centers for Disease Control and Prevention, UNICEF and the World Health Organization.

World Health Organization
Western Pacific Region

Rubella in Vietnam

Start surveillance & Awareness-raising activities

Catch-up campaign for children aged 9 months -14 years

Routine immunization for children aged 18 months

Year	Rubella cases	Rubella outbreak
2004~2005	*Estimated*: a couple of millions cases annually	Outbreak*
|		
2010~2011		Outbreak*
2012	7,259	No outbreak
|		
2014	193	
2015	765	
2016	301	
2017	83	
2018	20	

*Confirmed***

Every 6 yrs?

*Vaccine 2014; 32: 7065
**WHO WPRO

Pregnant women

2009-2010 Birth Cohort

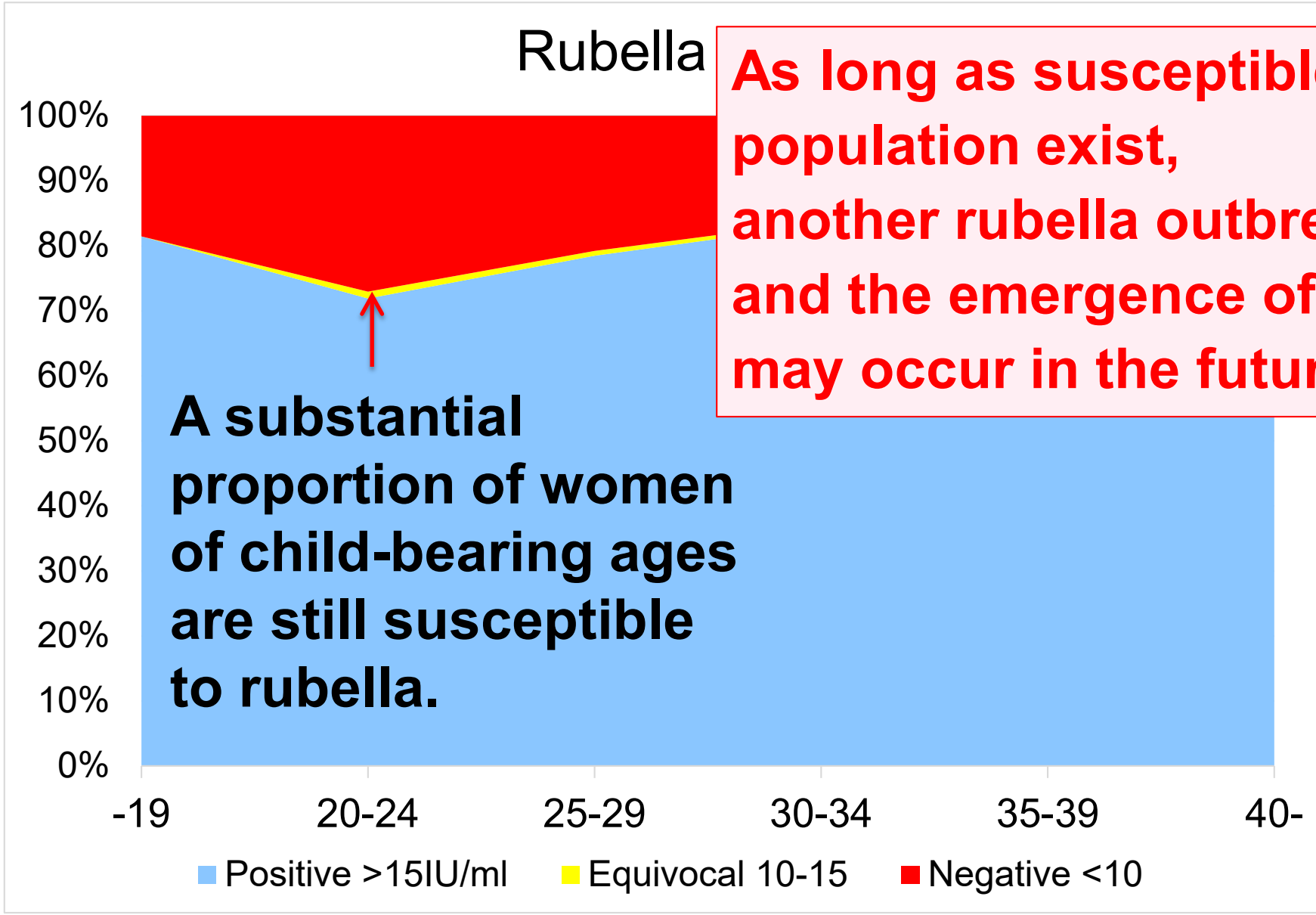
Rubella	Tested, N	Positive, N (%)
RT-PCR (saliva)	-	-
IgM	1,988	3 (0.15%)
IgG	1,988	1414 (71.1%)

2017-2018 Birth Cohort

Rubella	Tested, N	Positive, N (%)
RT-PCR (saliva)	2,038	0 (0%)
IgM	2,038	0 (0%)
IgG	1,977	1,564 (79.1%)

More than 20% of pregnant women are still susceptible to rubella.

Seroprevalence of Rubella among Pregnant Women in Nha Trang, Vietnam (2017-2018)



Vaccine is a Diamond

Development & Distributi

Not only Development but also Distribution of Vaccines to those who need is critical.