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Infectious Diseases in Pregnant Women, Fetuses and Newborns

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Zika virus infection in pregnancy: clinical cases

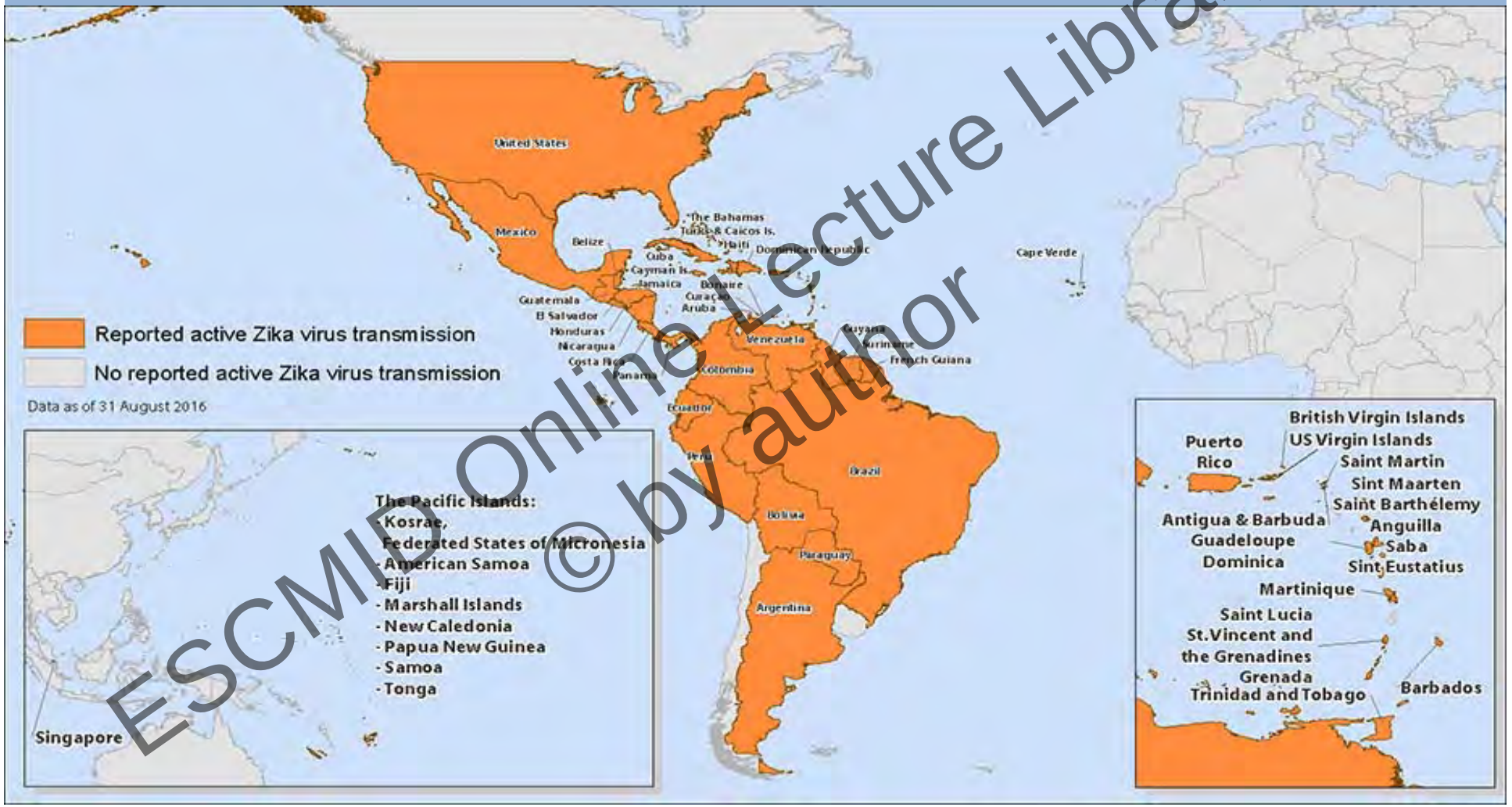
Maurizio Zavattoni, MD

SS Virologia Molecolare, SC Microbiologia e Virologia,
IRCCS Policlinico San Matteo, Pavia (Italy)

History of Zika

Zika virus was first discovered in 1947 and is named after the Zika Forest in Uganda. In 1952, the first human cases of Zika were detected and since then, outbreaks of Zika have been reported in tropical Africa, Southeast Asia, and the Pacific Islands. Zika outbreaks have probably occurred in many locations. Before 2007, at least 14 cases of Zika had been documented, although other cases were likely to have occurred and were not reported. Because the symptoms of Zika are similar to those of many other diseases, many cases may not have been recognized.

All Countries & Territories with Active Zika Virus Transmission



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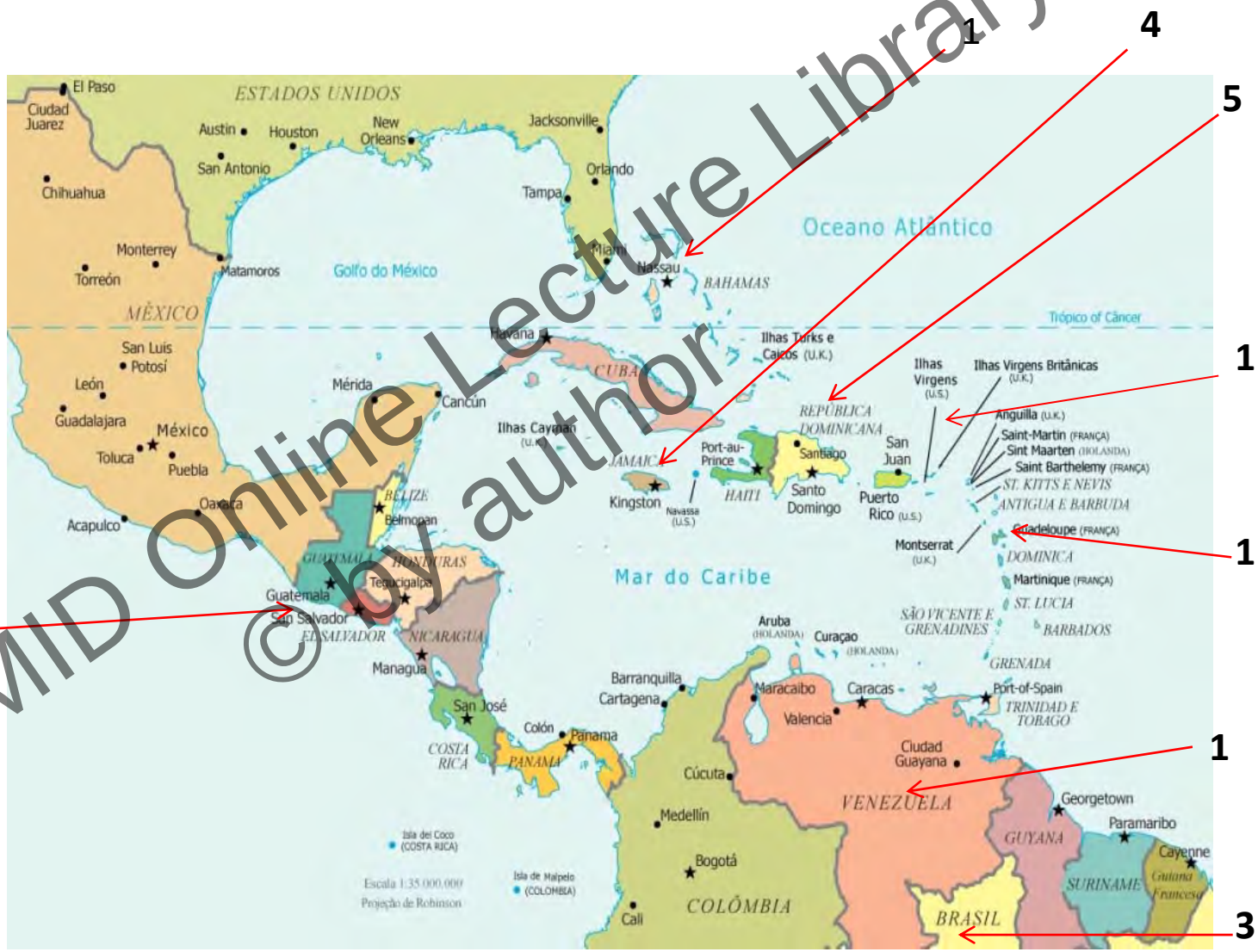
Content source:

Centers for Disease Control and Prevention
National Center for Emerging and Zoonotic Infectious Diseases (NCEZID)
Division of Vector-Borne Diseases (DVBD)

Countries visited by italian Zika virus infected patients

70% (12/17) of patients with Zika virus infection visited Caribbean islands.



Transmission & Risks

From mother to child

A pregnant woman can pass Zika virus to her fetus during pregnancy. Zika is a cause of microcephaly and other severe fetal brain defects. We are studying the full range of other potential health problems that Zika virus infection during pregnancy may cause.

A pregnant woman already infected with Zika virus can pass the virus to her fetus during the pregnancy or around the time of birth.

To date, there are no reports of infants getting Zika virus through breastfeeding. Because of the benefits of breastfeeding, mothers are encouraged to breastfeed even in areas where Zika virus is found.

Transmission & Risks

Through sex

Zika can be passed through sex from a person who has Zika to his or her partners. Zika can be passed through sex, even if the infected person does not have symptoms at the time. It can be passed from a person with Zika before their symptoms start, while they have symptoms, and after their symptoms end. Though not well documented, the virus may also be passed by a person who carries the virus but never develops symptoms.

Studies are underway to find out how long Zika stays in the semen and vaginal fluids of people who have Zika, and how long it can be passed to sex partners. We know that Zika can remain in semen longer than in other body fluids, including vaginal fluids, urine, and blood.

Material	Method	Minimum (days)	Maximum (days)
Whole blood	RT-PCR	5	58
Plasma	RT-PCR	First day of symptoms	14-16
Urine	RT-PCR	First day of symptoms	15-29
Saliva	RT-PCR	First day of symptoms	29
Semen	RT-PCR	10	58-62 up to 92
Milk	RT-PCR	3 post-partum	8 post-partum
Serum	EIA IgG		
Serum	EIA IgM		

Zika virus symptomatic cases

In 13/18 (72%) cases of Zika virus infection were symptomatic.

In samples collected from symptomatic patients between 1-8 days (median 5 days) after onset, Zika virus RNA was detected in:

- 13/13 (100%) urine
- 9/11 (82%) saliva
- 4/7 (57%) semen
- 5/13 (38,5%) plasma

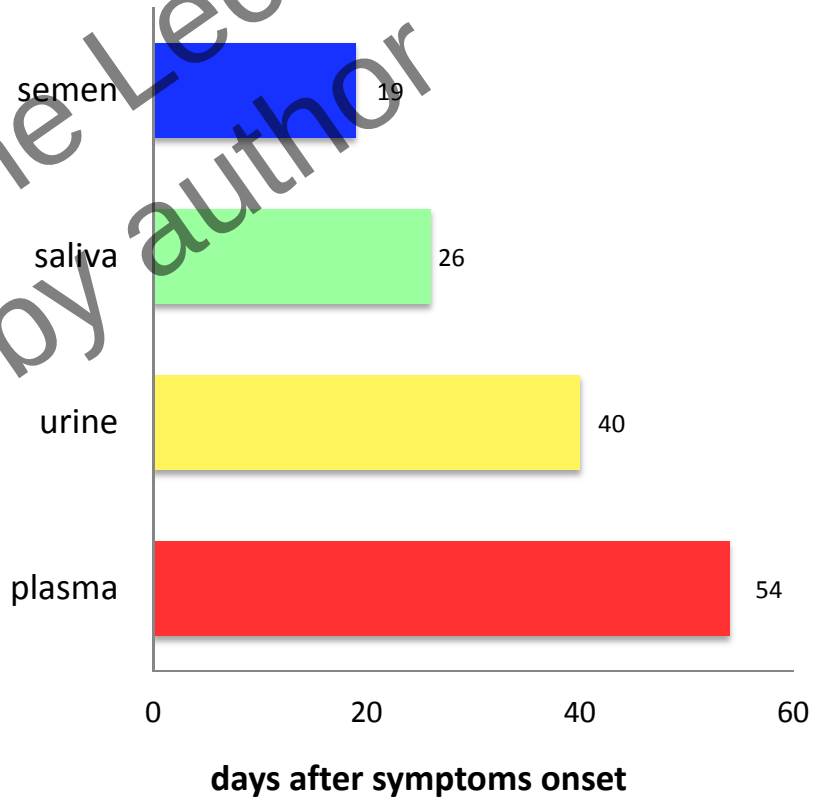
In the symptomatic phase of the infection were detected:

- Zika virus IgM in 7/13 (54%) patients
- Zika virus IgG in 0/13 (0%) patients

Persistence of Zika virus RNA in different biological samples

Zika virus RNA has been detected after onset of symptoms up to:

- 54 days in plasma
- 40 days in urine
- 26 days in saliva
- 19 days in semen



Q:What should pregnant women who have recently traveled to an area with Zika do?
A: Pregnant women who have recently traveled to an area with Zika should talk to their doctor about their travel, even if they don't feel sick. Pregnant women should see a doctor if they have any Zika symptoms during their trip or within 2 weeks after traveling. All pregnant women can protect themselves by avoiding travel to an area with Zika, preventing mosquito bites, and following recommended precautions against getting Zika through sex.

For Pregnant Women Who Travelled to an Area with Zika

► Any symptoms of Zika during your trip or within 2 weeks of returning?

- YES
- Symptomatic treatment (if necessary) and counselling
- Test for Zika

Within 8 days from the onset of symptoms

→ RT-PCR in whole blood, plasma, saliva, urine
→ IgM and neutralizing antibodies (confirm)

From 9 to 28 days after the onset of symptoms

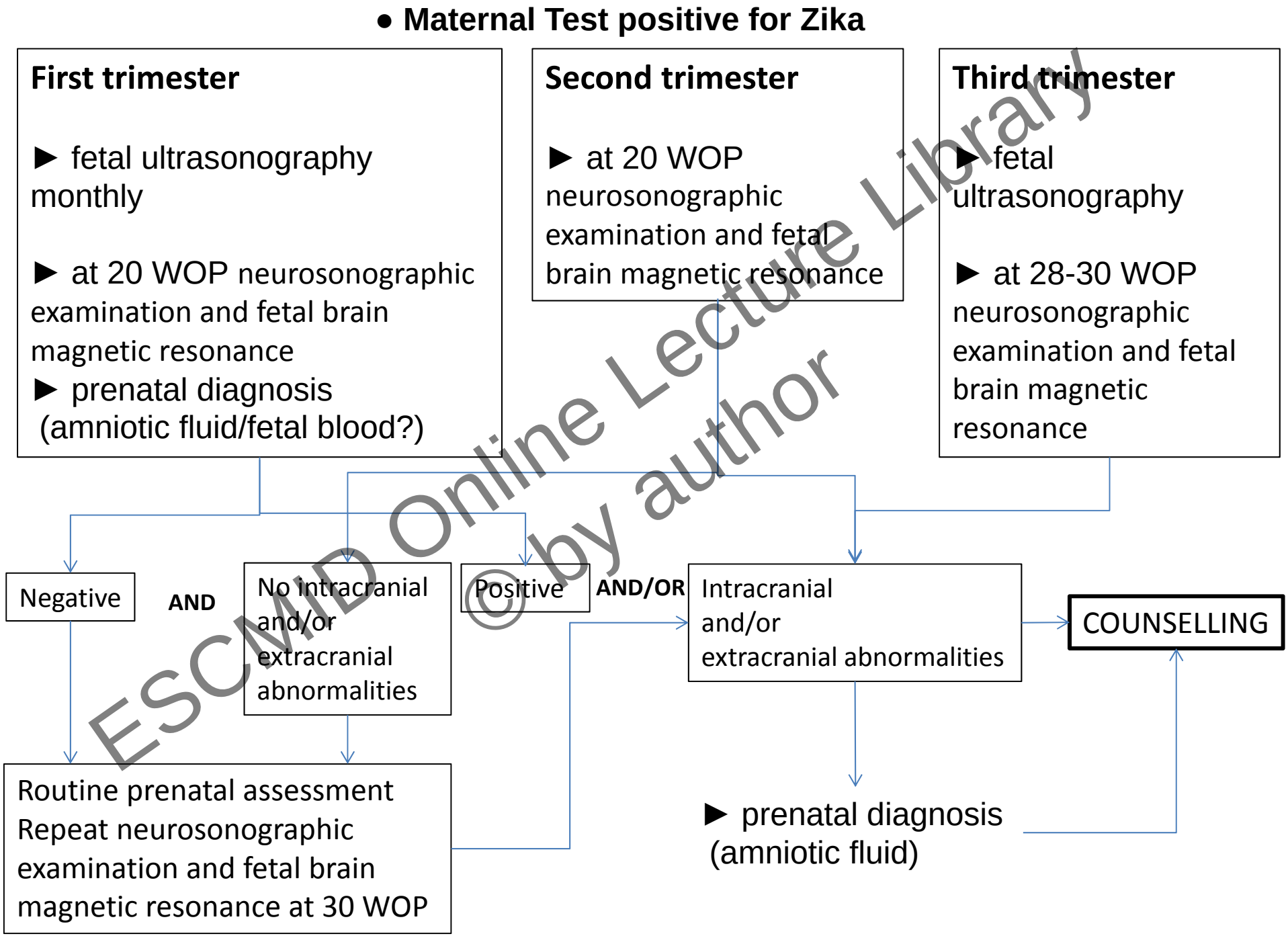
→ RT-PCR in urine
→ IgG/IgM and neutralizing antibodies (confirm)

More than 28 days after the onset of symptoms

→ IgG/IgM and neutralizing antibodies (confirm)

- NO

→ RT-PCR in whole blood, plasma, saliva, urine
→ IgG/IgM and neutralizing antibodies (confirm)



The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

Modeling Zika Virus Infection in Pregnancy

Indira U. Mysorekar, Ph.D., and Michael S. Diamond, M.D., Ph.D.

Four recently published mouse-model studies have addressed the causal relationship between ZIKV infection in pregnancy and pathologic changes in fetuses.
Three of the studies introduced different ZIKV strains into pregnant mice through peripheral inoculation routes (intravenous, intraperitoneal, or subcutaneous), and two studies inoculated ZIKV directly into the fetal brain.

Although the time scale differs substantially, neuronal developmental processes in rodents and humans are remarkably parallel.

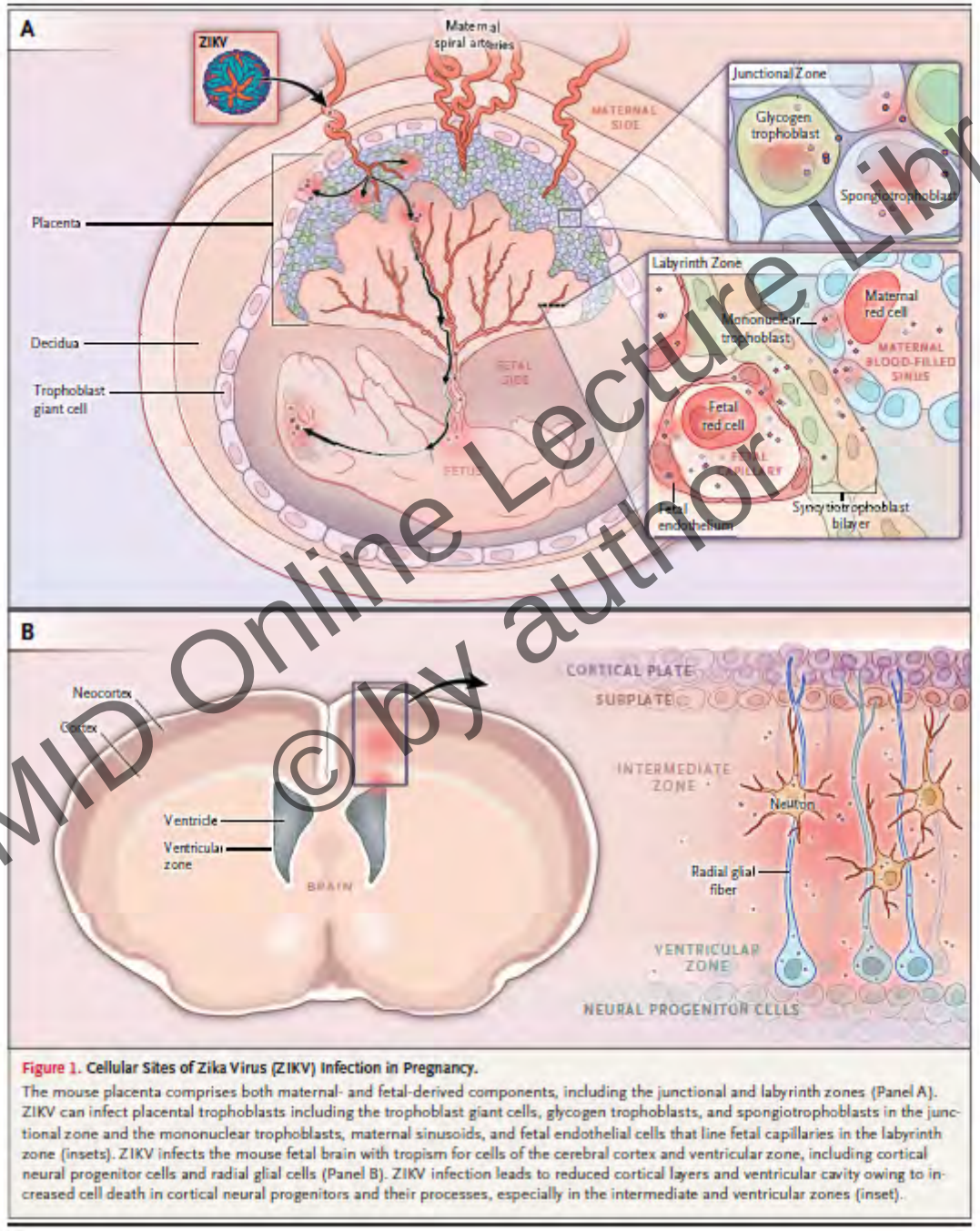


Figure 1. Cellular Sites of Zika Virus (ZIKV) Infection in Pregnancy.

The mouse placenta comprises both maternal- and fetal-derived components, including the junctional and labyrinth zones (Panel A). ZIKV can infect placental trophoblasts including the trophoblast giant cells, glycogen trophoblasts, and spongiotrophoblasts in the junctional zone and the mononuclear trophoblasts, maternal sinusoids, and fetal endothelial cells that line fetal capillaries in the labyrinth zone (insets). ZIKV infects the mouse fetal brain with tropism for cells of the cerebral cortex and ventricular zone, including cortical neural progenitor cells and radial glial cells (Panel B). ZIKV infection leads to reduced cortical layers and ventricular cavity owing to increased cell death in cortical neural progenitors and their processes, especially in the intermediate and ventricular zones (inset).

ZIKV gains access to the fetus during pregnancy after crossing the placental barrier, which is composed of different types of trophoblasts and ancillary cells (Fig. 1)

Early in pregnancy, ZIKV infection may lead to severe placental vascular damage and a reduction in fetal blood vessels and blood flow. Alternatively, ZIKV could cross the placental barrier without excessive damage and spread to the fetal brain, where it preferentially infects and injures neuronal progenitor cells.

Infection and death of neuroprogenitor cells could inhibit neuronal-cell differentiation, which would explain the cortical thinning, malformation of brain structures, and microcephaly that are observed during pregnancy in humans.

A 41-year-old Salvadoran woman living in Italy since 2005 was on holiday in El Salvador with her husband from January 11, to February 12, 2016 . She had her last menstrual period on December, 05 and she discovered to be pregnant when arrived in El Salvador. On February 13 (9 WOP), one day after her arrival in the Italian residency, she became ill with maculopapular facial rash, generalized hitching, cough and diffuse arthromyalgias, which lasted 3-4 days

patient	Days after onset	ZIKV			DENV			Flavivirus		
		Real-time RT-PCR (copie/ml)			Real-time RT-PCR (copie/ml)			Heminested Pan-Flavivirus RT-PCR		
		plasma	urine	saliva	plasma	urine	saliva	plasma	urine	saliva
Mother	+5 (10 WOP)	1496	11879	113	negative	negative	negative	positive	positive	positive
	+16 (12 WOP)	32	116	negative	ND	ND	ND	positive	positive	positive
	+31 (14 WOP)	13	1	negative	ND	ND	ND	positive	negative	negative
	+45 (16 WOP)	7	negative	ND	ND	ND	ND	positive	positive	ND
	+59 (18 WOP)	1	negative	ND	ND	ND	ND	positive	negative	ND
	+74 (20 WOP)	negative	negative	negative	ND	ND	ND	positive	negative	negative
	+90 (22 WOP)	negative	ND	ND	ND	ND	ND	positive	ND	ND
	+108 (24 WOP)	negative	ND	ND	ND	ND	ND	positive	ND	ND
	+129 (28 WOP)	negative	ND	ND	ND	ND	ND	positive	ND	ND
	+150 (31 WOP)	negative	ND	ND	ND	ND	ND	positive	ND	ND
	+165 (33 WOP)	negative	negative	negative	ND	ND	ND	positive	negative	negative
	+198 (38 WOP)									
Fetus	20 WOP	negative						negative		
Neonate	39 WOP	negative	negative	negative				negative	negative	negative

Patient	Days after onset	ZIKV					DENV					
		IgM (EIA)	IgM (IFA)	IgG (EIA)	IgG (IFA)	Nt-Ab	IgM (EIA)	IgG (EIA)	Nt-Ab			
									D1	D2	D3	D4
mother	+5 (10 WOP)	negative	<1:10	positive	1:1280	1:640	negative	positive	1:2.560	1:160.000	1:640.000	1:640
	+16 (12 WOP)	negative	<1:10	positive	1:2560	1:1280	negative	positive	1:40.000	>640.000	>640.000	1:2.560
	+31 (14 WOP)	negative	1:10	positive	1:2560	1:2560	ND	ND	1:640.000	1:640.000	1:640.000	1:40.000
	+45 (16 WOP)	negative	<1:10	positive	1:2560	1:1280	ND	ND	ND	ND	ND	ND
	+75 (20 WOP)								1:380	1:5000	1:160.000	1:320
father	asymptomatic	negative	<1:10	negative	>1:10	1:10	negative	positive				
fetus	asymptomatic (20 WOP)	negative	<1:10	ND	ND	ND	negative	ND	ND	ND	ND	ND
neonate	asymptomatic (39 WOP)	negative	< 1:10									

Structural basis of potent Zika–dengue virus antibody cross-neutralization

Giovanna Barba-Spaeth[1,2*], Wanwisa Dejnirattisai[3*], Alexander Rouvinski[1,2*], Marie-Christine Vaney[1,2*], Iris Medits[4], Arvind Sharma[1,2], Etienne Simon-Lorière[5,6], Anavaj Sakuntabhai[5,6], Van-Mai Cao-Lormeau[7], Ahmed Haouz[8,9], Patrick England[9,10], Karin Stiasny[4], Juthathip Mongkolsapaya[3,11], Franz X. Heinz[4], Gavin R. Screaton[3] & Félix A. Rey[1,2]

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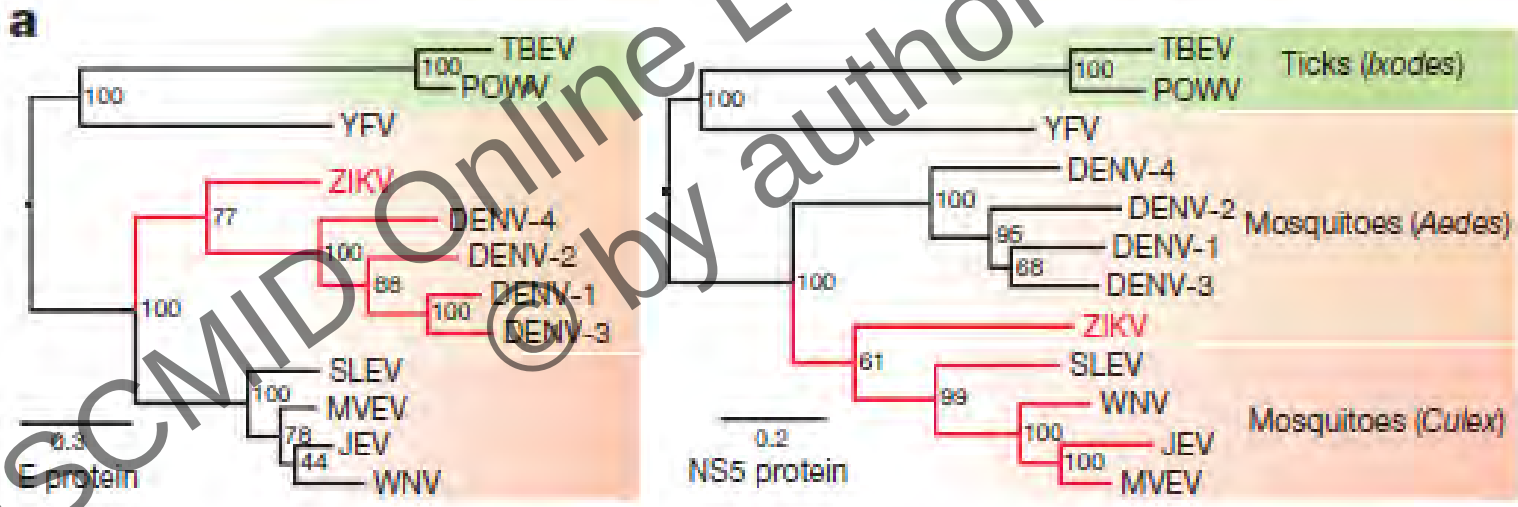

Flaviviruses have two structural glycoproteins, **prM and E** (for precursor membrane and envelope proteins, respectively), which form a heterodimer in the endoplasmic reticulum (ER) of the infected cell and drive the budding of spiky immature virions into the ER lumen. These particles transit through the cellular secretory pathway, during which the trans-Golgi-resident protease furin cleaves prM. This processing is required for infectivity, and results in the loss of a large fragment of prM and reorganization of E on the virion surface.

Flaviviruses have been grouped into serocomplexes based on cross-neutralization studies with polyclonal immune sera. The E protein is the main target of neutralizing antibodies.

Cleavage of prM allows E protein fluctuate from its tight packing at the surface of the virion, transiently exposing otherwise buried surfaces. One surface exposed by this 'breathing' is the **fusion-loop epitope (FLE),** which is a dominant cross-reactive antigenic site.
Although antibodies to this site can protect by complement-mediated mechanisms, as shown in a mouse model for West Nile virus, they are poorly neutralizing and lead to antibody-dependent enhancement, thereby aggravating Flavivirus pathogenesis

In a panel of antibodies isolated from patients with dengue disease, broadly neutralizing antibodies (bnAbs), termed EDE for E-dimer epitope, potently neutralize all four DENV serotypes.

The **EDE bnAbs** neutralize ZIKV as potently as they neutralize DENV. Furthermore, the FLE antibodies, which neutralize DENV although not as potently as the EDE bnAbs, do not neutralize ZIKV

Reduced Risk of Disease During Postsecondary Dengue Virus Infections

Sandra Olkowski,[1] Brett M. Forshey,[2,4] Amy C. Morrison,[1,4] Claudio Rocha,[4] Stalin Vilcarromero,[4] Eric S. Halsey,[4] Tadeusz J. Kochel,[4,a] Thomas W. Scott,[1,3] and Steven T. Stoddard[1,3]

Table 3. Parameter Estimates for Dengue Virus Serotype 3 (DENV-3) and DENV-4 Maximum Likelihood Models

Serotype, Parameter	OR (95% CI)	*P*
DENV-3[a]		
Naive	1.00 (reference)	
Monotypic	0.55 (.26–1.11)	.098
Multitypic[b]	0.048 (.018–.11)	<.001
Age	0.99 (.97–1.01)	.35
DENV-4[c]		
Naive	1.00 (reference)	
Prior exposure to DENV-1	0.45 (.21–.91)	.031
Prior exposure to DENV-2 or -3	0.97 (.57–1.63)	.90
Multitypic[b]	0.22 (.13–.38)	<.001
Age	1.07 (1.02–1.12)	.0039
Age squared	0.9989 (.998–.9996)	.0014

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Approximate R^2, 22.41%.

[b] Defined as having neutralizing antibody to ≥2 serotypes, as measured by a plaque reduction neutralization test.

[c] Approximate R^2, 6.94%

Conclusions

The risk of developing febrile dengue illness was significantly reduced in individuals with a history of ≥ 2 prior DENV exposures, despite the absence of preexisting antibodies specific to the infecting serotype.

STEP 5 Protect your partner

- Pregnant couples in which one or both partners have traveled to or live in an area with Zika should use a condom correctly, from start to finish, every time they have sex or should not have sex during the pregnancy.
- Not sharing sex toys can also reduce the risk of spreading Zika to sex partners.

STEP 5 Protect your partner

- People without a pregnant partner who recently traveled to or lived in an area with Zika
  - If you've been diagnosed with Zika or have (or had) symptoms, you can use condoms or not have sex for **6 months** after symptoms begin.
  - If you never developed symptoms, you can use condoms or not have sex for **8 weeks** after returning from travel, or while there is Zika in the area.

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