

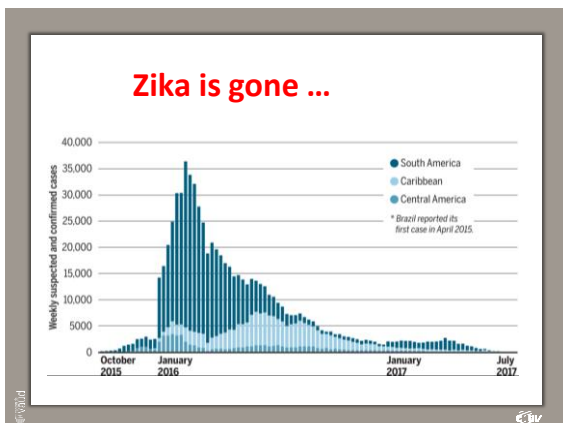
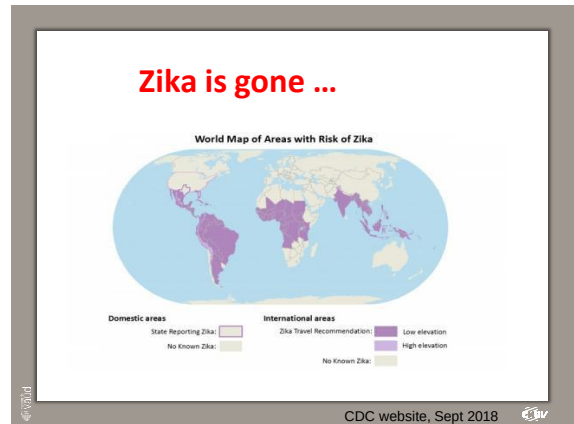
Prof David Baud
MD PhD
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Département de gynécologie-obstétrique
et génétique médicale

**CONGENITAL
ZIKA
SYNDROME**





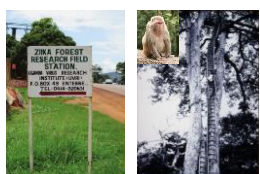


The question is not **if**,
but **when** and **where**
Zika will come back?



Discovery 1947, Uganda, Africa

Yellow fever research institute, Uganda
Rockefeller Foundation



Sentinel Rhesus monkeys in cages
in the canopy forest

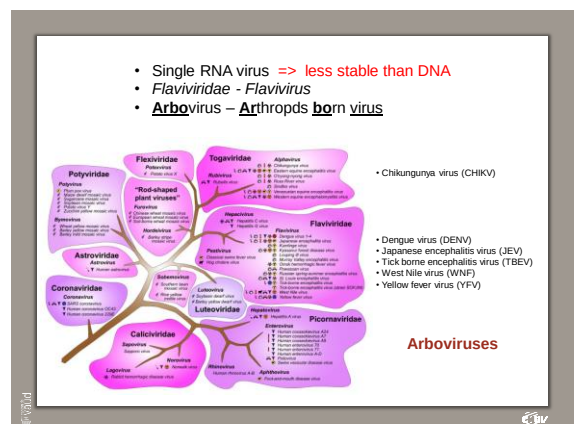
*Transmission of the Borna Disease virus to
"Yunnan Monkeys" and Humans
Vol. 46, No. 1, September, 1952.*

COMMUNICATIONS

ZIKA VIRUS

(I). ISOLATIONS AND BIOLOGICAL SPECIFICITY
BY
G. W. A. DICK,
The National Institute for Medical Research, London
S. F. KITCHEL,
Formerly staff member of the Division of Bacteria and Public Health, The Rockefeller
Foundation, New York, U.S.A.
and
A. J. HADDOW,
Formerly staff member of International Health Division, The Rockefeller Foundation, New
York, U.S.A.
(From the Virus Research Institute, London, U.K.)





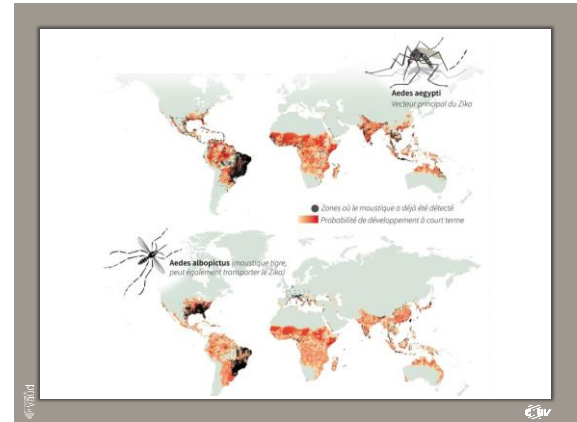
ZIKV Vectors

A. aegypti



A. albopictus

- Day-time biters
- Alive for 30 days
- Female infects eggs
- Eggs infectious >1 year



ZIKA positive sperm / vagina

ZIKA RNA

>1 year



13 days

Replicative ZIKA

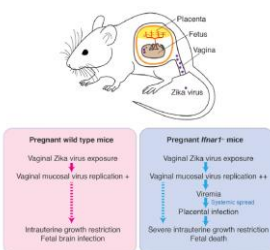
69 days

2 days

Venturi G, Euro Surveill. 2016
Frank C, Euro Surveill. 2016
D'Ortenzio E, NEJM. 2016
Musso D, Clin Microb Infect. 2017

Cell

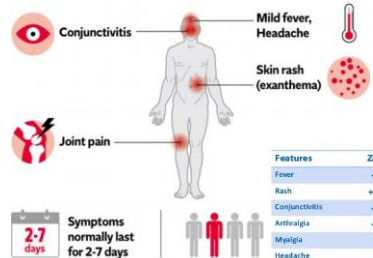
Vaginal Exposure to Zika Virus during Pregnancy Leads to Fetal Brain Infection



Vaginal infection
More efficient
s.cut. infection

Similar results in
Rhesus macaques

Yocke, Cell, 2016 Aug



Features	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	-	-
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Hemorrhage	-	++	-
Shock	-	+	-

Clinical course do not differ during pregnancy

Direct association Zika & microcephaly

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Zika Virus Infection in Pregnant Women in Rio de Janeiro — Preliminary Report

Patricia Brasil, M.D., Jose P. Pereira, Jr., M.D., Claudia Raja Gabaglia, M.D.,

Table 3. Infant Outcomes According to ZIKV Exposure.

Variable	ZIKV-Exposed Live-Born Infants (N = 117)*	ZIKV-Unexposed Live-Born Infants (N = 57)	P Value
Total number of adverse infant outcomes — no. (%)	49 (41.9)	3 (5.3)	<0.001

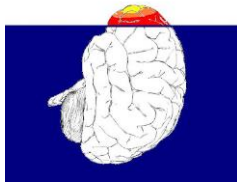
Congenital Zika Syndrome: definition



1. Severe microcephaly with partial collapse of the skull
 2. Thin cerebral cortices with subcortical calcifications
 3. Macular scars with pigmented retinal findings
 4. Congenital contractures
 5. Early hypertonia with evidence of extrapyramidal involvement
- Cerebral atrophy, ventriculomegaly, cerebellar hypoplasia, arthrogryposis

Moore CA, JAMA Pediatr. 2017.

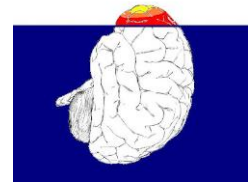
Congenital Zika Syndrome: SPECTRUM



Moore CA, JAMA Pediatr. 2017.

Congenital Zika Syndrome: SPECTRUM

Abnormal ophthalmologic findings in 33% of infants without CNS findings who were born to women with confirmed ZIKV infections during pregnancy



Zin AA, JAMA Pediatr. 2017.

Congenital Zika Syndrome: SPECTRUM

Maternal rash	Infant Zika virus IgM antibody by ELISA	Birth HC (cm) and (SD) [†]	Age (mos) at last follow-up	Follow-up HC (cm) and (SD) [‡]
3 mo.	CSF, serum +	29.5 (1.72)	11	39 (3.86)
2 mo.	CSF +	33.0 (-0.40)	10	41 (-3.33)
none	CSF, serum +	32.0 (-1.63)	11	43 (-2.11)
2 mo.	CSF +	31.0 (-1.65)	10	43 (-1.98)
5 mo.	CSF +	31.0 (-1.39)	12	36 (-6.18)
4 mo.	CSF +	33.0 (-0.78)	11	42 (-2.89)
none	CSF +	33.0 (-0.78)	12	40 (-4.68)
none	CSF +	32.0 (-1.95)	9	39.5 (-3.17)
3 mo.	CSF +	33.5 (-0.35)	11	42.5 (-2.50)
none	CSF +	32.0 (-2.00)	10	40 (-4.27)
none	CSF +	33.5 (0.02)	7	40 (-2.98)
none	serum +	32.5 (0.30)	7	40.5 (-1.33)
none	serum +	33.0 (-1.16)	5	40 (-2.12)

Normal at birth => post-natal development of anomalies

van des Linden, MMWR, 2017



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CORRESPONDENCE

Requests for Abortion in Latin America Related to Concern about Zika Virus Exposure




Aiken, NEJM, 2016

Zika world panic !!!




- No (unprotected) sex for 6 months
- Amniocentesis at 15 weeks for all exposed pregnant patients

Zika

Are we going to far?



Vouga & Baud, *Lancet*, 2017
 Vouga & Baud, *Lancet*, 2018
 Baud & Musso, *Lancet*, 2018

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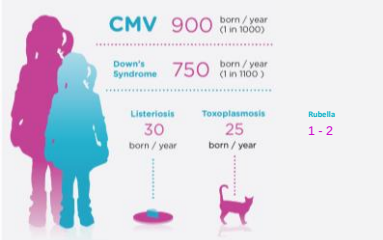
Département de gynécologie-obstétrique et génétique médicale

Cytomegalovirus

CMV

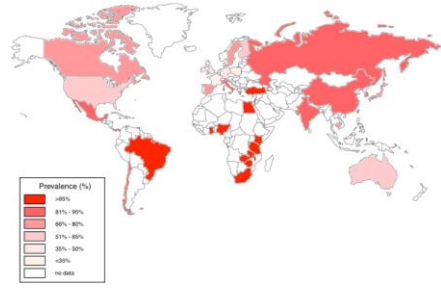


CMV – most common cause of birth defect



Condition	Number born / year	Prevalence (1 in ...)
CMV	900	1 in 1000
Down's Syndrome	750	1 in 1000
Listeriosis	30	-
Toxoplasmosis	25	-
Rubella	1-2	-

CMV – most common cause of birth defect



Prevalence (%)

- >85%
- 81%–85%
- 60%–80%
- 51%–60%
- 35%–50%
- <35%
- no data

CMV – most common cause of birth defect



The main way women catch CMV is from the **saliva** and **urine** of small children

DON'T SHARE



Avoid sharing food, drinks, cutlery or dummies with anyone

WASH WITH CARE



Wash hands and any items that have come into contact with bodily fluids with soap and water e.g. after feeding, wiping nose, changing nappy



CMV positive sperm



- **14 months** after infection
- Infect spermatozoae



No recommendation

Zika



- Only **4%** of male have replicative viruses
- Exceptional >30 days
- Decline of Zika

Postpone pregnancy attempts to **2 months** after exposure for both men and women

Vouga & Baud, *Lancet*, 2018

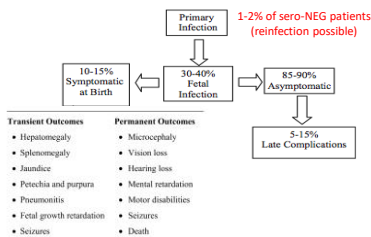
Zika ?

Similar to other teratogenic infections

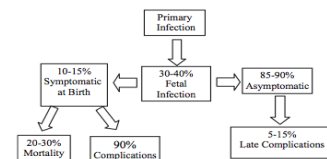


Vouga & Baud, *Lancet*, 2016
Panchaud & Baud, *CMR*, 2016
Schaub, Baud, *Lancet Child*, 2017

CMV – most common cause of birth defect

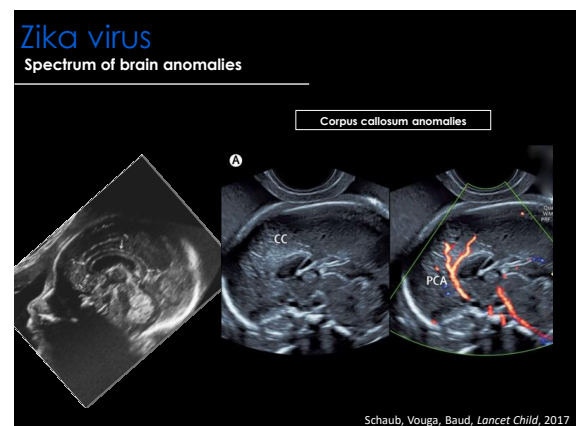
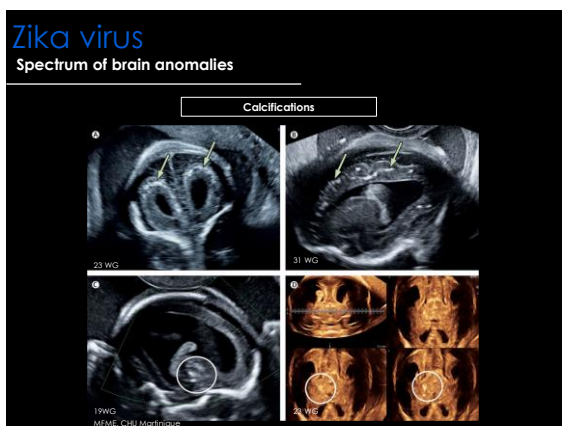
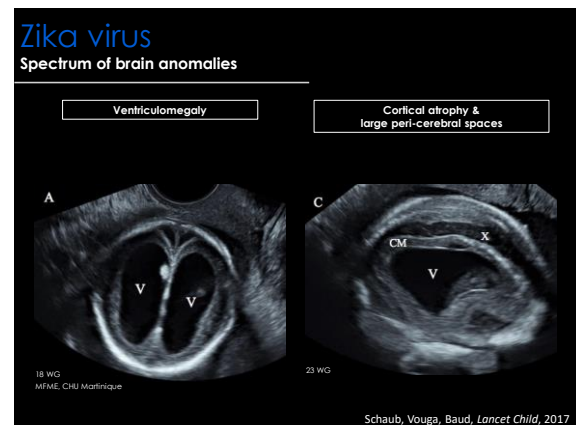
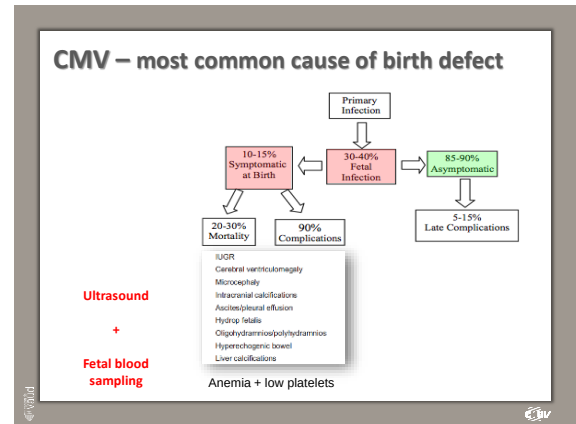
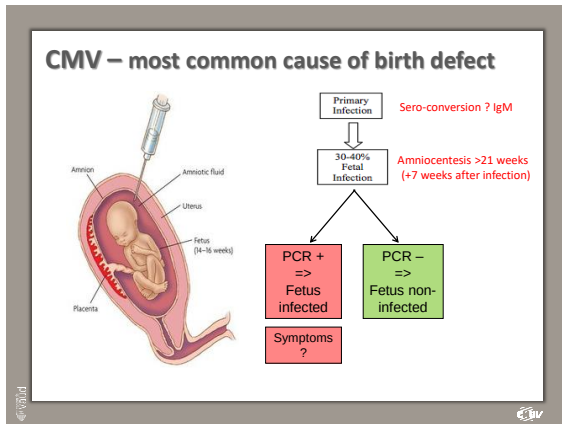


CMV – most common cause of birth defect



3%

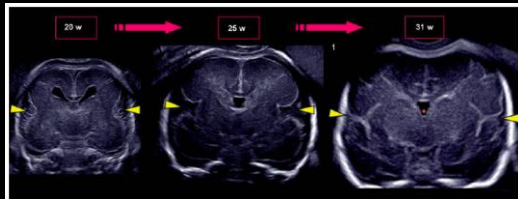
Severe anomalies in infected pregnant patients



Zika virus

Spectrum of brain anomalies

Gyration anomalies

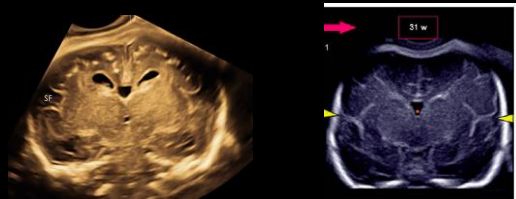


Recent Advances in 3D Assessment of Various Fetal Anomalies

Zika virus

Spectrum of brain anomalies

Gyration anomalies



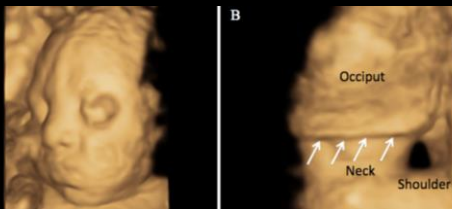
32WG
MFME, CHU Martinique

Schaub, Vouga, Baud, *Lancet Child*, 2017

Zika virus

Spectrum of brain anomalies

Cephalic dysmorphism



26WG
MFME, CHU Martinique

26WG

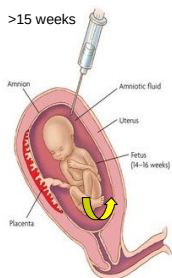
Schaub, Vouga, Baud, *Lancet Child*, 2017

Zika world panic !!!



- No (unprotected) sex for 6 months
- Amniocentesis at 15 weeks for all exposed pregnant patients

Vouga, Van Mieghem, Baud, *The Lancet*, 2016



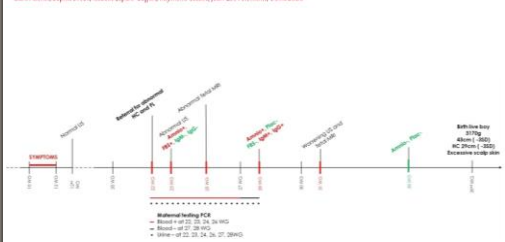
By analogy with CMV or TOXO infections:

- 1) ZIKV is only shed in the amniotic fluid once the fetal kidneys produce sufficient urine (>18–21 weeks' gestation)
- 2) Once sufficient time has elapsed for the virus to breach the placental barrier (at the earliest 6–8 weeks after infection)

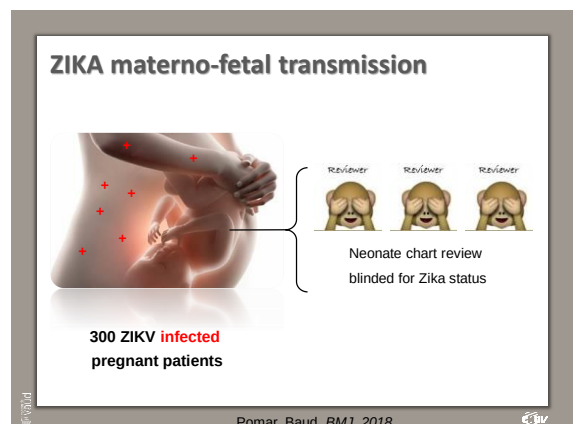
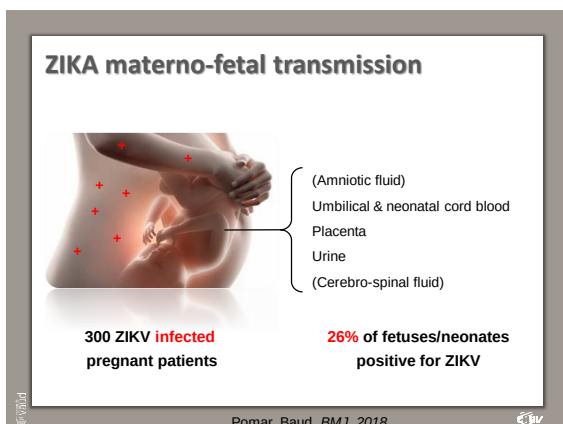
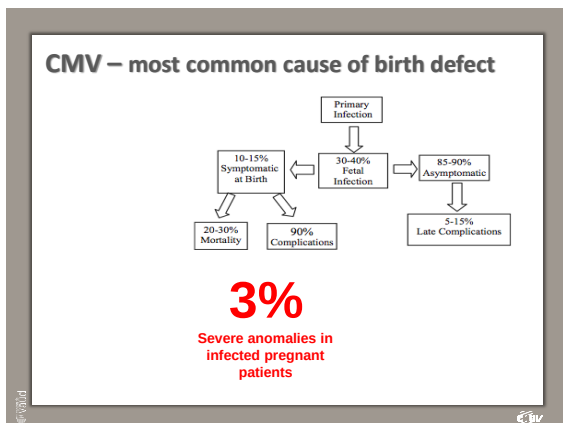
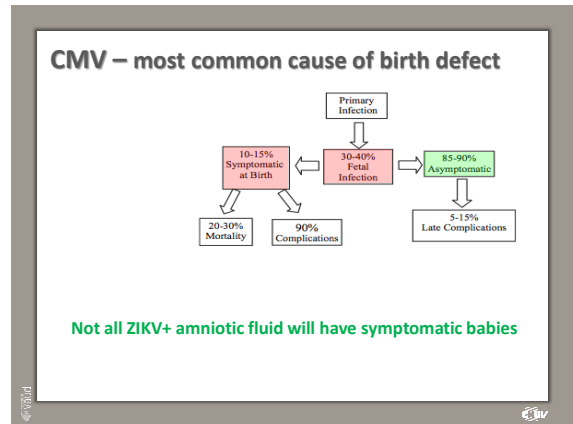
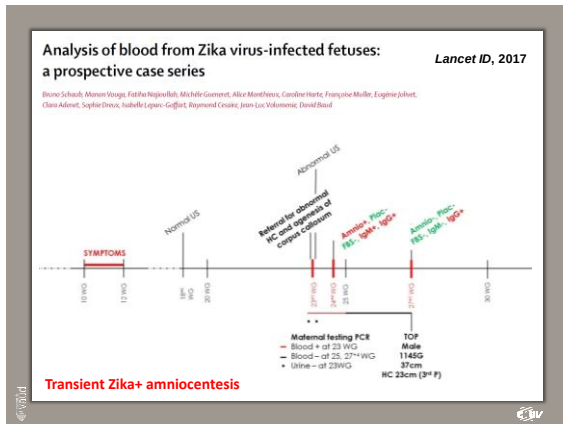
Analysis of blood from Zika virus-infected fetuses: a prospective case series

Lancet ID, 2017

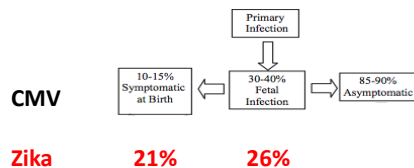
Bruno Schaub, Marion Vouga, Fatima Haghighat, Michelle Gervais, Fabrice Mouton, Caroline Hertz, Françoise Müller, Eugénie Jérent, Clara Adenis, Sophie Druce, Isabelle Epner-Goffard, Raymond Couvreur, Jean-Luc Vanhamme, David Baud



Transient Zika+ amniocentesis



ZIKA materno-fetal transmission



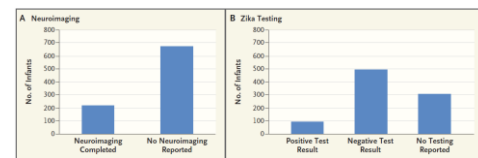
Pomar, Baud, *BMJ*, 2018

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Perspective
OCTOBER 19, 2017

A Devastating Delay — Zika and the Implementation Gap

Stephanie R. Morain, Ph.D., M.P.H., Susan H. Wootton, M.D., and Catherine Eppes, M.D., M.P.H.



Postnatal Neuroimaging and Zika Virus Testing Results for Infants in the U.S. Zika Pregnancy Registry, December 2015–December 2016.

For all exposed pregnant patient...

ZIKA IN PREGNANCY



Baud *et al*, *BMJ*, 2016

Panchaud, Vouga, Baud *et al*, *Lancet ID*, 2016

TAKE HOME MESSAGE

Zika similar to other teratogenic infections (CMV)

When you do not know,
No panic
look what is known in your field

Materno-fetal & Obstetrics Research Unit



MERCI

TEAM:

Manon Vouga
Milos Stojanov
Yndia Buffe
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COLLABORATORS:

Didier Musso - Polynesia
Marco Alves - Bern, CH
Bruno Schaub - Martiniques
Patrick Gerardin - Réunion
Duane Gubler - Singapore
Blaise Genton - CHUV

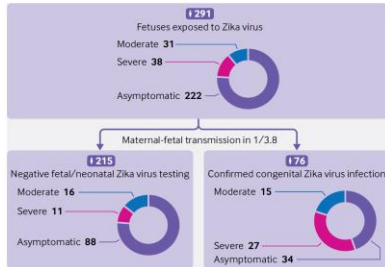
ZIKA materno-fetal transmission

Table 3 | Secondary fetal/neonatal outcomes. Values are numbers (percentages) unless stated otherwise

Details of clinical outcomes	Lab-confirmed ZIKV infection (n=74)	Negative fetal/neonatal ZIKV testing (n=210)
Median (IQR) gestational age at delivery, weeks	38.1 (35.5–39.4)	37.4 (35.0–39.5)
Maternal age <17 weeks at delivery*	6/62 (10%)	26/111 (23%)
Birthweight (SD), kg	2850 (2430–3120)	3015 (2740–3432)
Birthweight <1 kg	1/10 (10%)	5/106 (5%)
Birthweight <100 g	2/10 (20%)	1/106 (1%)
Head circumference <2 SD*	6/61 (10%)	19/212 (9%)
Head circumference <3 SD*	2/61 (3%)	2/212 (1%)
Clinical examination		
Jaundice	13 (20%)	20 (10%)
Hypotonia	2/10 (20%)	1/106 (1%)
Hypertonia	7/10 (70%)	11 (5%)
Seizures	1/10 (10%)	0/106 (0%)
Feeding dysfunction	8/10 (80%)	1/106 (1%)
Biological parameters – No/No tested (%)		
C-reactive protein >10 mg/L	6/11 (55%)	1/101 (1%)
Ammonia >140 µmol/L	1/10 (10%)	0/106 (0%)
Transaminases >150 U/L	7/10 (70%)	0/106 (0%)
Transaminases >100 U/L	0/10 (0%)	0/106 (0%)
Median (IQR) total bilirubin, mg/dL	186 (174–230)	172 (145–246)
Severe hyperbilirubinemia†	4/42 (10%)	0/161 (0%)
Anomalous amniocentesis >50 U/L	2/10 (20%)	0/101 (0%)
Anomalous amniocentesis >100 U/L	6/12 (50%)	0/101 (0%)
Anomalous amniocentesis >400 U/L	1/12 (8%)	0/101 (0%)

Pomar, Vouga, Baud, *BMJ*, 2018

ZIKA materno-fetal transmission



RR for severe outcomes = 7 [4-13]

Pomar, Vouga, Baud, *BMJ*, 2018

Analysis of blood from Zika virus-infected fetuses: a prospective case series

Lancet ID, 2017

Bruno Schaub, Marion Vouga, Fathe Nigam, Maïté Guimard, Alice Montheux, Caroline Hertz, Françoise Müller, Eugénie Joubert, Clara Adenot, Sylvie Drouot, Isabelle Leguen-Goffart, Raymond Crouzet, Jean-Luc Vialarmey, David Baud

All fetuses had **Fetal Blood Sampling**:

- liver cholestasis
- mild anemia

