JNI 19e Journées Nationales d'Infectiologie
du mercredi 13 au vendredi 15 juin 2018
Cité des Congrès de Nantes
Nantes et la région Pays de la Loire

Issues de grossesse et anomalies congénitales dans une cohorte de 546 femmes ayant présenté une infection symptomatique à virus Zika (ZIKV) au cours de l'épidémie de Zika dans les TFA

B. Hoen, A. Cabié, A. Funk, C. Herrmann-Storck,
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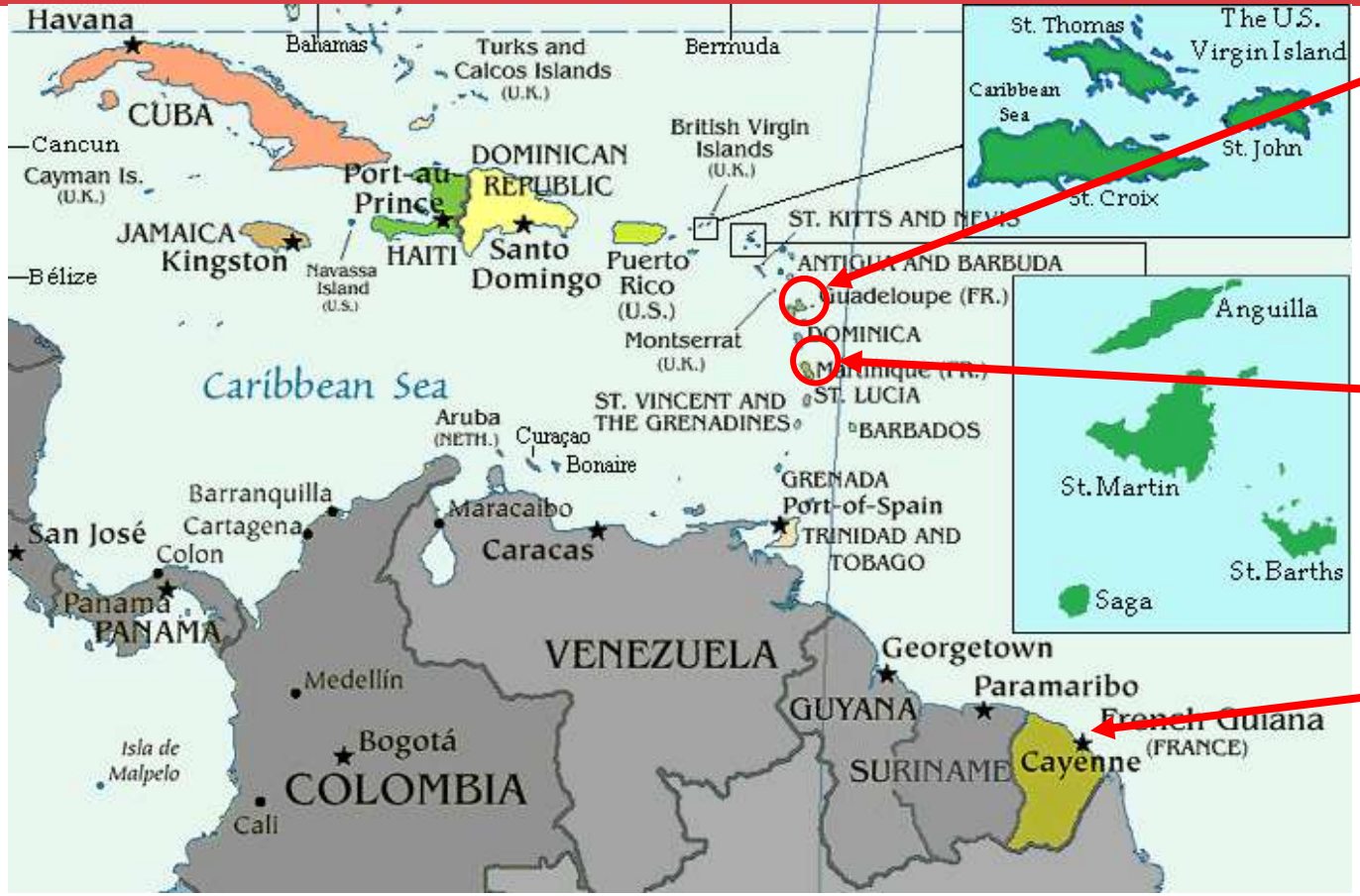
FTA: FWI and FG, an outlook

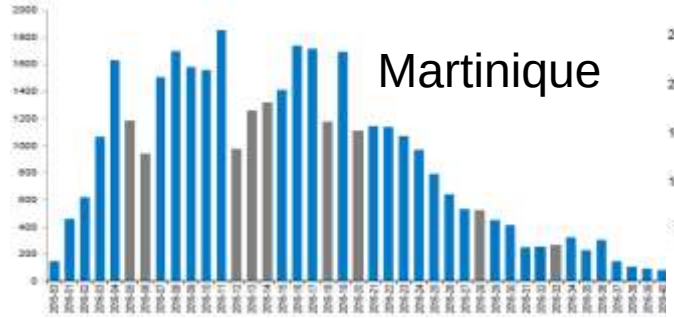


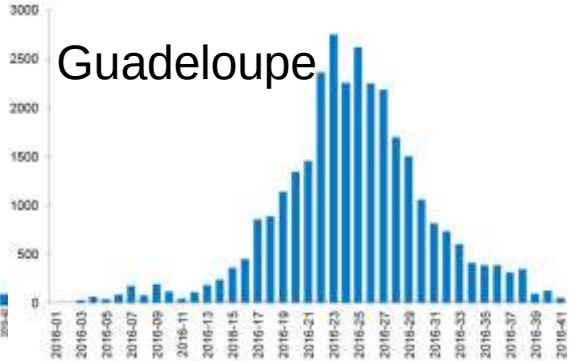
Guadeloupe
Pop: 405,000

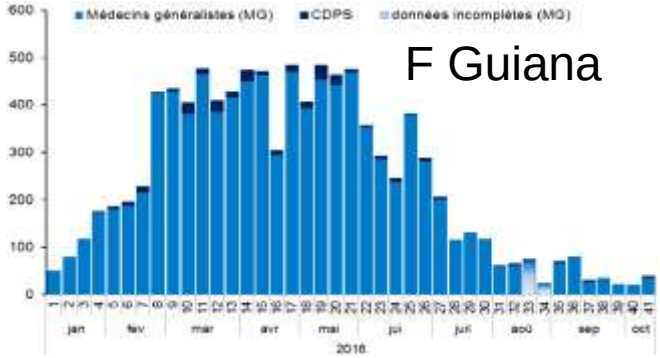
Martinique
Pop: 395,000

French Guiana
Pop: 255,000

Zika outbreaks in the FTA by the end of 2016







- Single-wave outbreak
- Attack rate 60%
- Rate of asymptomatic forms 80%

WHO declares Zika a Public Health Emergency

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 15, 2018 VOL. 378 NO. 11

Pregnancy Outcomes after ZIKV Infection in French Territories in the Americas

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Objectives of the ZIKA-DFA-FE cohort study

- Estimate the proportion of pregnancies with ZIKV infection
- Describe clinical manifestations of the disease during pregnancy
- Estimate the prevalence of microcephaly in utero and at birth
- Identify other complications not yet identified as complications of ZIKV
- Estimate the risk of birth defects /other complications according to
  - Gestational age at the time of ZIKV infection
  - Symptomatic ZIKV infection

Enrolment criteria

- Pregnant women with suspected ZIKV infection were referred to the prenatal diagnosis center in each territory, where they were tested for ZIKV infection and invited to consent to participate in ZIKA-DFA-FE
- They were included in this analysis if they met all the following criteria
  - ongoing pregnancy at any gestational age
  - clinical symptoms consistent with acute ZIKV infection, with at least one amongst pruritic skin rash, fever, conjunctival hyperemia, arthralgia, and myalgia
  - laboratory confirmation of recent ZIKV infection, based on a positive ZIKV RT-PCR test on serum or urine
- The date of ZIKV infection was considered to be the date of onset of the first ZIKV-related symptom

Pregnancy outcome definitions

- Live births (with or without abnormalities)
- Pregnancy losses
  - Miscarriage (intrauterine fetal death earlier than 20 weeks of gestational age)
  - Stillbirth (intrauterine fetal death at or after 20 weeks gestational age or intrapartum death during delivery)
  - Voluntary TOP
  - Medical TOP

Definitions for birth defects potentially associated with ZIKV infection

- 2 mutually exclusive categories*
  - brain abnormalities with or without microcephaly regardless of the presence of additional birth defects
  - neural tube defects and other early brain malformations, eye abnormalities, and other consequences of central nervous system dysfunction (arthrogryposis, clubfoot, congenital hip dysplasia, and congenital deafness) among those who had neither evident brain abnormalities nor microcephaly

** : Honein et al. Birth defects among fetuses and infants of US women with evidence of possible Zika virus infection during pregnancy. JAMA 2017;317(1):59-68*

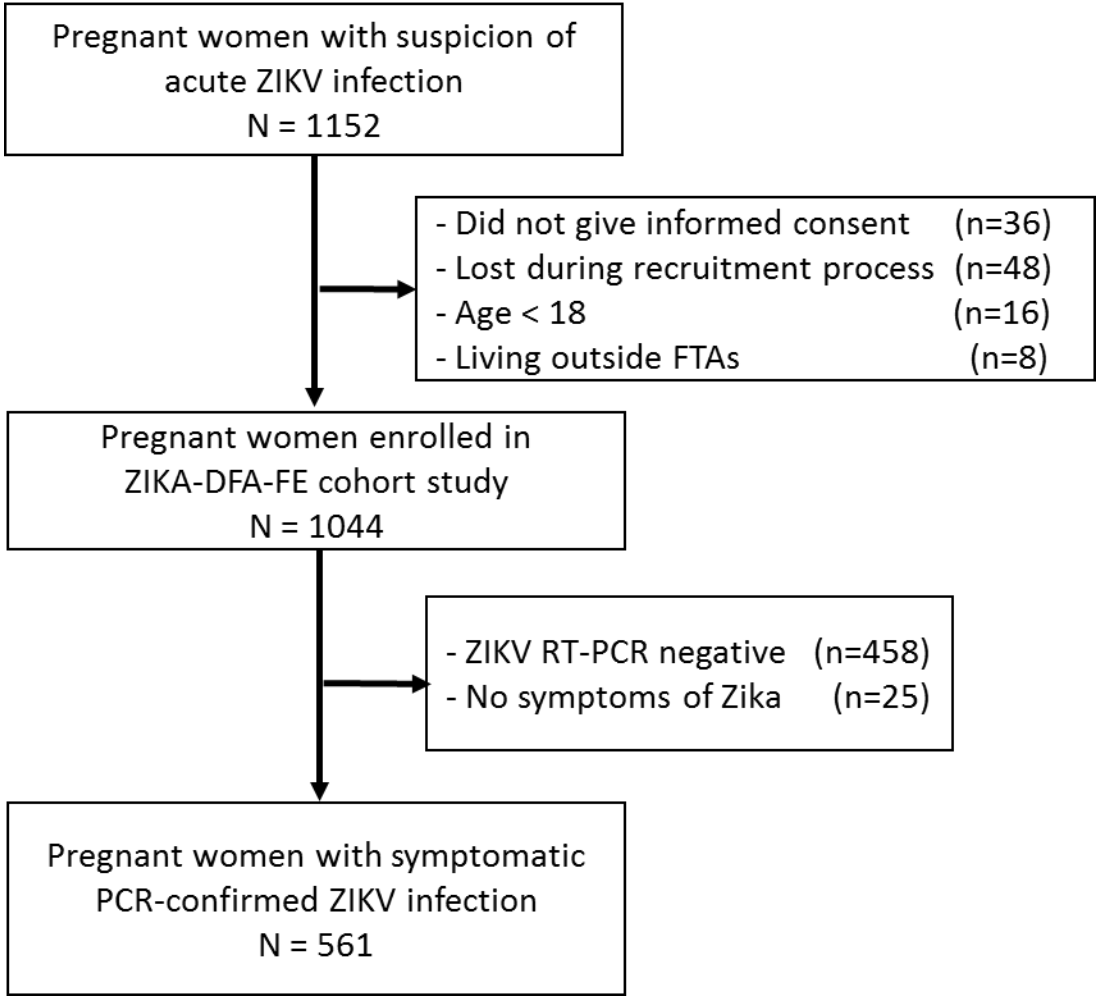
Definitions for Zika Congenital Syndrome (ZCS)*

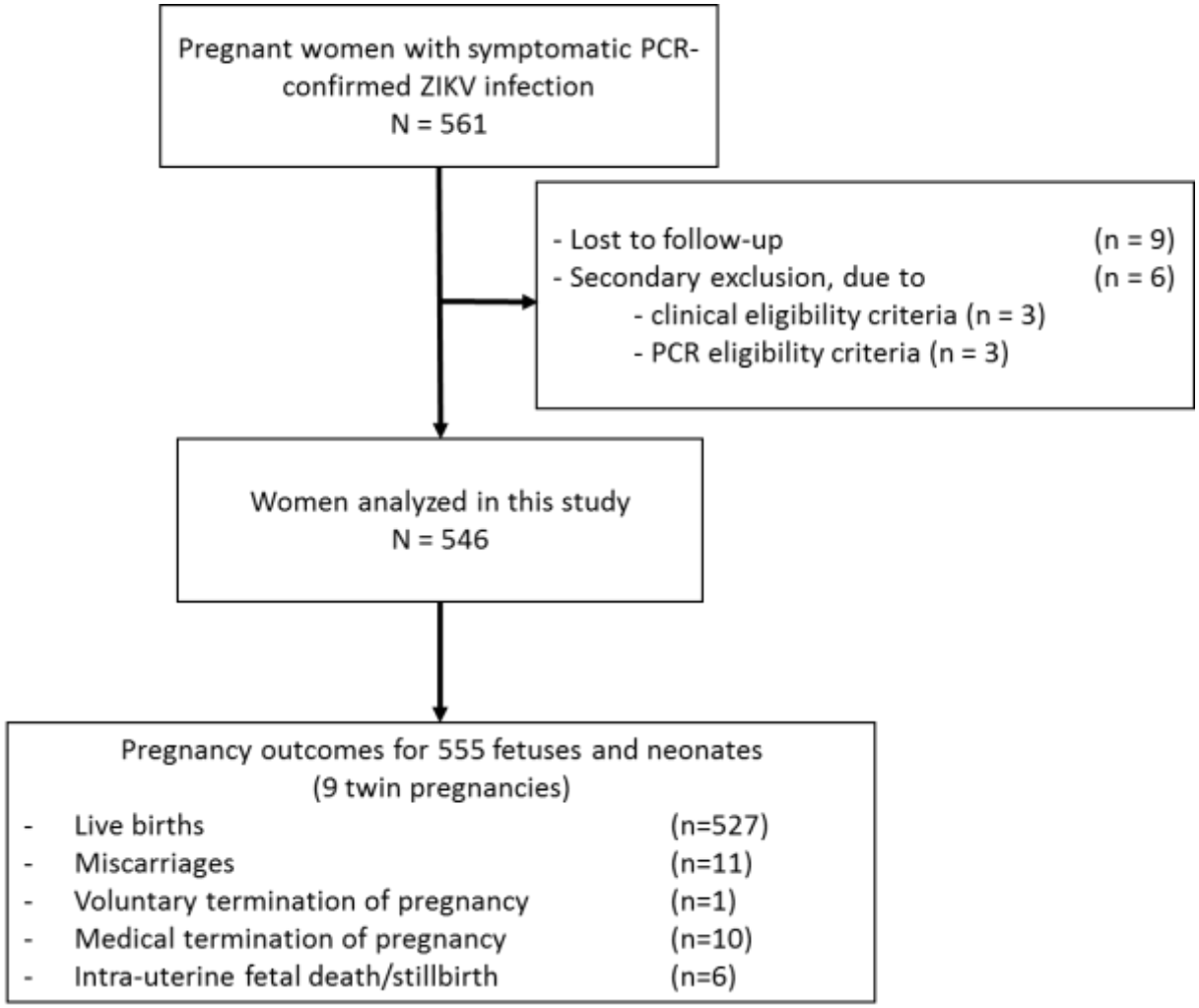
- one or more among
  - severe microcephaly (<-3SD)
  - brain abnormalities with a specific pattern of damage (e.g. calcifications, ventriculomegaly, cortical malformations)
  - damage to the back of the eye
  - joints with limited range of motion (e.g. clubfoot)
  - hypertonia that restricts body movement (e.g. arthrogryposis)

** : Moore et al. Characterizing the pattern of anomalies in Congenital Zika Syndrome for pediatric clinicians. JAMA Pediatr 2017;171(3):288-295*

Definitions for microcephaly

- Live birth: INTERGROWTH-21st (http://intergrowth21.ndog.ox.ac.uk/)
  - Severe: head circumference < –3 SD
  - Moderate: head circumference between –3 SD and –2 SD
    - Proportionate if neonate small for gestational age (weight < –1.28 SD according to the INTERGROWTH-21st standards for gestational age and sex)
    - Disproportionate otherwise
- Pregnancy loss
  - head circumference <-3 SD based on last ultrasound exam available


Pregnant women with suspicion of acute ZIKV infection
N = 1152
- Did not give informed consent (n=36)
- Lost during recruitment process (n=48)
- Age < 18 (n=16)
- Living outside FTAs (n=8)
Pregnant women enrolled in ZIKA-DFA-FE cohort study
N = 1044
- ZIKV RT-PCR negative (n=458)
- No symptoms of Zika (n=25)
Pregnant women with symptomatic PCR-confirmed ZIKV infection
N = 561


Pregnant women with symptomatic PCR-confirmed ZIKV infection
N = 561
- Lost to follow-up (n = 9)
- Secondary exclusion, due to (n = 6)
- clinical eligibility criteria (n = 3)
- PCR eligibility criteria (n = 3)
Women analyzed in this study
N = 546
Pregnancy outcomes for 555 fetuses and neonates
(9 twin pregnancies)
- Live births (n=527)
- Miscarriages (n=11)
- Voluntary termination of pregnancy (n=1)
- Medical termination of pregnancy (n=10)
- Intra-uterine fetal death/stillbirth (n=6)

Characteristics of ZIKV infection in the 546 women (1)

		N	%
Trimester of symptomatic ZIKV infection			
	1	185	33.9
	2	249	45.6
	3	112	20.5
Number of symptoms at Zika diagnosis			
	1	66	12.1
	2	111	20.3
	3	121	22.2
	4	95	17.4
	5+	153	28.0

Characteristics of ZIKV infection in the 546 women (2)

		N	%
Zika symptoms			
	Rash	519	95.1
	Arthralgia	300	54.9
	Itching	263	48.2
	Conjunctival hyperhemia	199	36.4
	Headache	161	29.5
	Myalgia	128	23.4
	Fever	123	22.5
	Limb swelling	104	19.0
	Pain behind eyes	102	18.7

Results of ZIKV testing in the 546 women

	Time of Zika infection					
	1st Trimester		2nd Trimester		3rd Trimester	
ZIKV RT-PCR Positive	185	100.0	249	100.0	112	100.0
ZIKV RT-PCR						
Blood and urine positive	121	65.4	159	63.9	66	58.9
Blood only positive	40	21.6	63	25.3	23	20.5
Urine only positive	24	13.0	27	10.8	23	20.5

Pregnancy outcomes, by trimester of ZIKV infection, in the 546 pregnant women and 555 fetuses and neonates (9 twin pregnancies)

	Trimester of Zika infection		
	1st trimester	2nd trimester	3rd trimester
NUMBER OF FETUSES AND NEONATES	189	252	114
PREGNANCY OUTCOMES			
Pregnancy losses	24 (12.7)	4 (1.6)	0
Miscarriage	11 (5.8)	0	
Voluntary termination of pregnancy	1 (0.5)	0	
Medical Termination of pregnancy (TOP)	9 (4.8)	1 (0.4)	
Stillbirth	3 (1.6)	3 (1.2)	
Live births	165 (87.3)	248 (98.4)	114 (100)

Pregnancy outcomes, by trimester of ZIKV infection, in the 546 pregnant women and 555 fetuses and neonates (9 twin pregnancies)

	1st trimester	2nd trimester	3rd trimester	Total
NUMBER FETUSES AND NEONATES	189	252	114	555
SUMMARY OF ABNORMALITIES POTENTIALLY RELATED TO ZIKV INFECTION				
Birth defects potentially associated with Zika infection	24 (12.7)	9 (3.6)	6 (5.3)	39 (7.0)
Brain abnormalities and/or microcephaly	22 (11.6)	9 (3.6)	5 (4.4)	
Neural tube defects, eye abnormalities, and consequences of CNS dysfunction	2 (1.1)	0	1 (0.9)	
Severe microcephaly	7 (3.7)	2 (0.8)	0	9 (1.6)
Moderate microcephaly	12 (6.3)	6 (2.4)	5 (4.4)	
Zika congenital syndrome	13 (6.9)	3 (1.2)	1 (0.9)	17 (3.1)

Additional results

- There was no statistical association between any potentially toxic pre-natal exposures (i.e., larvicides, repellants, alcohol, tobacco, illicit drugs) and birth defects
- No fetus abnormality or birth defect was observed in any of the cases of co-exposure to ZIKV and syphilis (n=4), toxoplasmosis (n=3), HIV (n=2), or cytomegalovirus (n=1)
- 31 women had an amniocentesis performed during the course of their pregnancy, with 27 karyotypings and 20 ZIKV RT-PCR assays
  - All karyotypes were normal except for a pericentric inversion of chromosome 2
  - ZIKV-RT PCR was positive in 7 cases

Summary of results

- In the offspring of women who developed acute symptomatic PCR-confirmed ZIKV infection during pregnancy
  - Overall risk of CNS/eye defects possibly associated with ZIKV infection 7.0 %
  - Overall risk of birth defects included in the current definition of ZCS 3.1 %
  - Overall risk of severe microcephaly (< - 3DS) 1.6 %
- Birth defects could be observed as a consequence of ZIKV infection at ANY pregnancy trimester BUT the risk of birth defects, ZCS, and severe microcephaly was higher when ZIKV infection occurred early in pregnancy
  - BD T1 12.7 % T2 3.6 % T3 5.3 % P = 0.001
  - ZCS T1 6.9 % T2 1.2 % T3 0.9 % P = 0.02
  - SMC T1 3.7 % T2 0.8 % T3 0 P = 0.002

Acknowledgments

- **ZIKA-DFA-FE Study Group**
  - Manon Boulard, André Cabié, Caroline Callier, Maylis Douine, Bruno Hoen, Mathieu Nacher, Kinda Schepers, and Benoit Tressières, Centre d'investigation Clinique Inserm 1424 Antilles-Guyane; Raymond Césaire, Centre de Ressources Biologiques de la Martinique; Jacqueline Deloumeaux and Stanie Gaete, Centre de Ressources Biologiques de la Guadeloupe; Philippe Kadhel, Eustase Janky, Catherine Ryan, and Teddy Toto, Service de Gynécologie-Obstétrique du CHU de Pointe-à-Pitre, Bruno Schaub and Alice Monthieux, Service de Gynécologie-Obstétrique du CHU de Fort-de-France, Gabriel Carles Service de Gynécologie-Obstétrique du CH de l'Ouest Guyanais; Arnaud Fontanet, Anna Louise Funk, and Yoann Madec, Institut Pasteur, Paris; Dominique Rousset, Institut Pasteur de Guyane; Minerva Cervantès, Cédric Laouénan, and France Mentré, INSERM, IAME, Paris Diderot University, Paris, France.
- **ZIKA-DFA-FE Scientific Committee**
  - Annie Lannuzel (CHUPPA) ; Jacqueline Deloumeaux (CHUPPA) ; Pierre Gressens (Inserm) ; Philippe Guerin ; Marc Lecuit (Institut Pasteur) ; Anna Funk (Institut Pasteur) ; Cédric Laouénan (REACTing) ; Minerva Cervantès (REACTing) ; Mathieu Nacher (CIC Cayenne) ; Olivier Fléchelles (CHUM) ; Fatiha Najioullah (CHUM) ; Gabriel Carles (CHOG) ; Claire Levy-Marchal (DRC, Inserm), Jean-Marc Rosenthal (CHU PPA), Caroline Callier, Bruno Hoen, Xavier de Lamballerie ; Fabrice Chretien (Institut Pasteur) ; Pierre Buekens ; Arnaud Fontanet (Institut Pasteur) ; Jean-Christophe Hébert (CHBT) ; Alexandre Léger (CHBT) ; Narcisse Elenga (CHAR) ; Alain Verloes (APHP) ; Christelle Delmas (Inserm) ; Anne Favre (CHAR) ; Kinda Schepers (CHUPPA) ; Laurent Mandelbrot (APHP) ; Sylvie Abel (CHUM) ; Yazdan Yazdanpanah (inserm) ; France Mentre (Inserm) ; Cedric Contaret (CHUM) ; Bruno Schaub (CHUM) ; Aissatou Signate (CHUM) ; Cécile Herrmann-Storck (CHUPPA) ; Philipe Kadhel (CHUPPA)
- **Women who altruistically participated in this study**
- **All health workers (physicians, midwives, clinical research assistants, health officers and epidemiologists) who joined their efforts to help conduct this study in each FTA**

Acknowledgments

- **Health workers (physicians, midwives, clinical research assistants, health officers and epidemiologists) who joined their efforts to help conduct this study in each FTA**
- *Guadeloupe*:
  - Myriam Atine, Lyderic Aubert, Marie Barrau, Kebe Beavogui, Christelle Celeste, Joelle Colat-Peyron, Elvire Couchy, Véronique Davidas, Lucetta Delver, Jacqueline Dubois, Stanie Gaete, Dorothée Harrois, Marie-Laure Lalanne-Mistrih, Mathilde Melin, Marie-France Mirane, Francelise Nadessein, Véronique Plantier, Marie-Josée Pelczar, Céline Rocquet, Magdalena Saint-Marc, Patrick Saint-Martin, Valérie Soter, Ingrid Soubdhan, Jennifer Taillefond, Lambo Velonasy, Véronique Walter
- *Martinique*:
  - Nicole Ambroisine, Gilda Belrose, Alain Blateau, Patricia Blondel, Isabelle Calmont, Valérie Decatrelle, Michèle Gueneret, Eugénie Jolivet, Isabelle Komla-Soukha, Corinne Plavonil, Marie-andrée Pyram, Jean-Luc Voluménie
- *Guyane*:
  - Antoine Adenis, Audrey Andrieu, Luisiane Carvalho, Sandy Dabrowski, Céline Delorme, Maryvonne Dueymes, Aniza Fahrasmane, Arthur Felix, Hélène Hilderal, Anne Jolivet, Justine Krajewsky, Véronique Lambert, Thomas Lemaitre, Myriam Livain, Jérémie Pasquier, Marion Petit-Sinturel, Céline Pomar, Léo Pomar, Stéphanie Rogier


Thank you for your attention

Back-up slides for discussion

Live births abnormalities
ZIKV non-infected vs infected in Guadeloupe (2016)

	ZIKV non-infected (n=490)	ZIKV infected *(Hoen et al, NEJM)* (n=241)
Severe or moderate microcephaly *& other neurological abnormalities*	0	0
Structural brain abnormalities	0	1 (0.4)
Severe microcephaly alone	11 (2.2)	1 (0.4)
Moderate-disproportionate microcephaly alone	10 (2.0)	6 (2.5)
Moderate-proportionate microcephaly alone	19 (3.9)	4 (1.7)
Ocular abnormalities	0	0
Consequences of CNS dysfunction	1 (0.2)	2 (0.8)*
Neural tube defects	0	1 (0.4)
Skeleton abnormalities	2 (0.4)	2 (0.8)*
Severe or moderate microcephaly & *genetic or chromosomal abnormalities*	1 (0.2)	1 (0.4)
Other	1 (0.2)	0
Neonates small for gestational age (weight<-1.28 SD)	66 (13.5)	33 (13.7)

*One infant in each category with both club foot and polydactyly

(Funk, in preparation)

ZIKA – DFA – FE : 5 work packages

- **WP1 :** identification and follow-up of pregnant women presenting with clinical symptoms of acute ZIKV infection, at any time of pregnancy
- **WP2 :** follow-up of pregnant women in whom embryofetopathy is suspected during pregnancy ultrasound monitoring
- **WP3 :** build up a serum collection from blood samples drawn once per trimester in any pregnant woman throughout the Zika outbreak
- **WP4 :** build up a collection of mother and cord blood sampled the day of delivery in any delivering woman throughout the Zika outbreak
- **WP5 :** build up a collection of maternal blood and fetal tissues in women in whom pregnancy, started during the Zika outbreak, would terminate with abortion, fetal death, or medical pregnancy termination

Results of TORCH testing in the 546 women

		Time of Zika infection					
		1st Trimester		2nd Trimester		3rd Trimester	
Syphilis	**Nb women tested**	150	81.1	206	82.7	87	77.7
	Positive	4	2.7	0	0	0	0
HIV	**Nb women tested**	161	87.0	210	84.3	97	86.6
	Positive	1	0.6	1	0.4	0	0
Toxoplasmosis (IgM)	**Nb women tested**	165	89.2	235	94.4	105	93.8
	Positive	1	0.6	0	0	2	1.9
Rubella (IgM)	**Nb women tested**	152	82.2	222	89.2	97	86.6
	Positive	0	0	0	0	0	0
CMV (IgM)	**Nb women tested**	20	10.8	30	12.0	14	12.5
	Positive	0	0	1	3.3	0	0
Any TORCH positive		**6**	**3.2**	**2**	**0.8**	**2**	**1.8**

Pregnancy outcomes, by trimester of ZIKV infection, in the 546 pregnant women and 555 fetuses and neonates (9 twin pregnancies)

	1st trimester	2nd trimester	3rd trimester
NUMBER OF FETUSES AND NEONATES	189	252	114
ALL ABNORMALITIES OBSERVED (fetus/infant)			
Neurological or ocular birth defects++	24 (12.7)	9 (3.6)	6 (5.3)
Severe microcephaly	7 (3.7)	2 (0.8)	0
Moderate microcephaly (disproportionate)	4 (2.1)	2 (0.8)	3 (2.6)
Moderate microcephaly (proportionate)	8 (4.2)	4 (1.6)	2 (1.8)
Intracranial calcifications	8 (4.2)	0	0
Ventriculomegaly	7 (3.7)	1 (0.4)	0
Lissencephaly	2 (1.1)	0	0
Other brain abnormalities	8 (4.2)	1 (0.4)	0
Neural tube defects	1 (0.5)	0	0
Eye abnormalities	0	0	0
Consequences of CNS dysfunction	1 (0.5)	0	1 (0.9)

Pregnancy outcomes, by trimester of ZIKV infection, in the 546 pregnant women and 555 fetuses and neonates (9 twin pregnancies)

	1st trimester	2nd trimester	3rd trimester
NUMBER OF FETUSES AND NEONATES	189	252	114
Other birth defects	2 (1.1)	3 (1.2)	1 (0.9)
Chromosomal	0	1 (0.4)+	0
Skeleton abnormalities	2 (1.1)	1 (0.4)	1 (0.9)
Other	0	1 (0.4)	0
Zika congenital syndrome	13 (6.9)	3 (1.2)	1 (0.9)

Number (%) abnormalities in fetuses/babies born from women with symptomatic Zika infection during pregnancy, Brazil, 2015-6

	First trimester (n=20)	Second trimester (n=71)*	Third trimester (n=34)
Fetal loss	5 (25.0)	2 (2.8)	2 (5.9)
Microcephaly	2 (10.0)	1 (1.4)	1 (2.9)
Other abnormalities	4 (20.0)	34 (47.2)	7 (20.6)
Total abnormalities	11 (55.0)	37 (51.4)	10 (29.4)

*percentages based on 72 births (1 twin pregnancy)

(Brasil, NEJM, 2016)

Birth defects in US women, 2015-6

- Births defects (%) for women infected during:
  - First trimesters only: 9/85 (10.6)
  - Second trimester only: 0/76 (0)
  - Third trimester only: 0/31 (0)
  - First, second, or third: 15/211 (7.1)
- Birth defects for women with:
  - Asymptomatic infection: 16/271 (5.9)
  - Symptomatic infection: 10/167 (6.0)
- Microcephalies:
  - 18/442 (4.1)

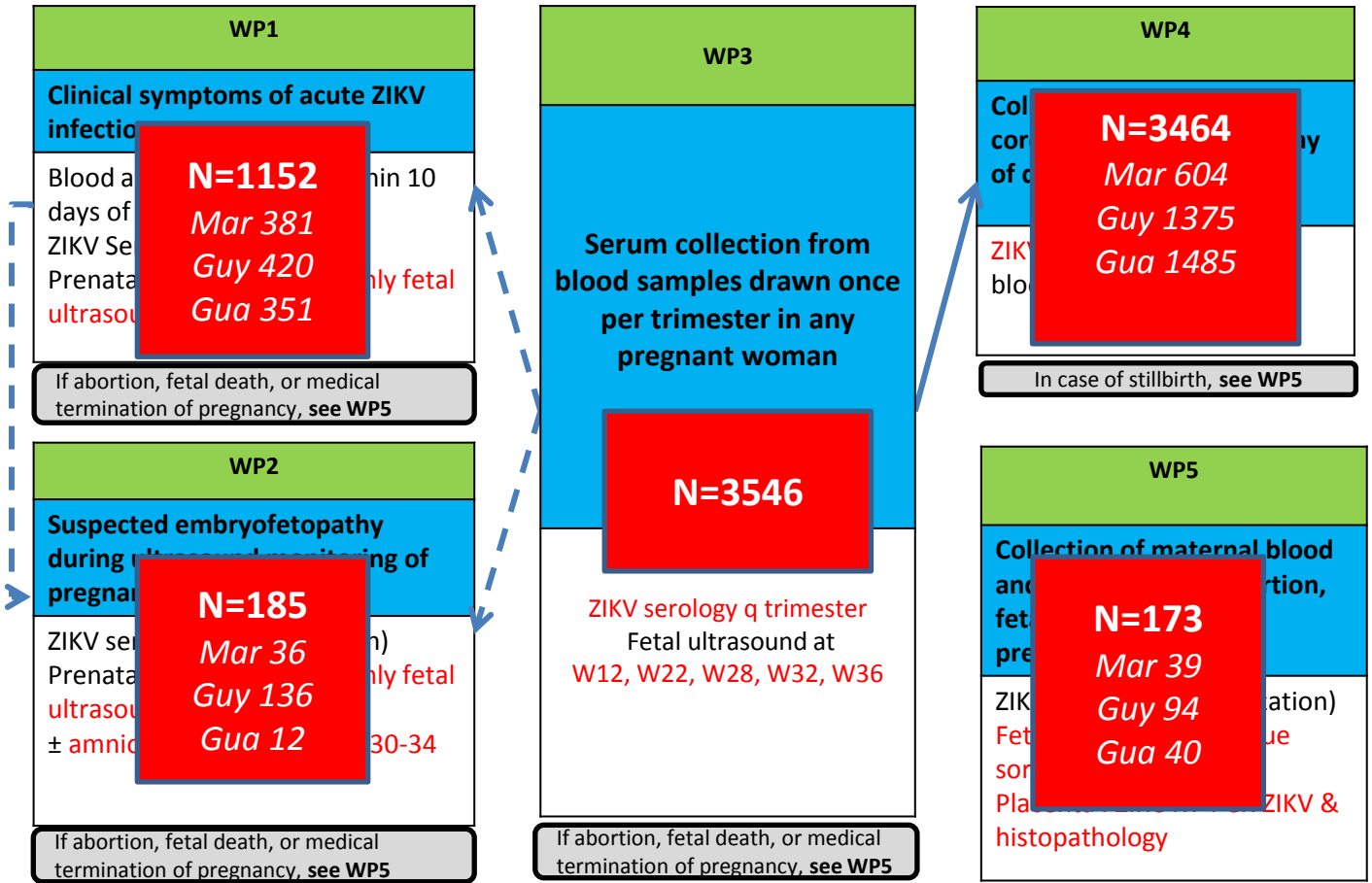
(Honein, JAMA, 2016)

Association and birth prevalence of microcephaly attributable to ZIKV infection among infants in Paraíba, Brazil, in 2015–16: a case-control study

- 2–5 infants per 1000 livebirths had microcephaly attributable to ZIKV
- Only 2 factors were significantly and independently associated with microcephaly
  - recent Zika virus infection (OR 21·9, 7·0–109·3)
  - mother with Zika-like symptoms in the first trimester (OR 6·2, 2·8–15·4).
- No evidence that the large number of cases of microcephaly in Brazil following the initial ZIKV outbreak was partly due to alternative risk factors, such as contaminated water, fish consumption, or toxin exposures
- Only 50% of the infants originally reported as having microcephaly had a head circumference < 3rd percentile for their sex and gestational age and when infants were measured again 1–7 months after birth, only 26% had microcephaly
- The most likely reason for the high rates of microcephaly initially reported in northeastern Brazil, was that the original case definitions were too sensitive and insufficiently specific

Krow-Lucal, Lancet Child Adolesc Health 2018

Observed numbers (3 FTA), end of enrollement



ZIKA-DFA: Regulatory and ethics issues

- ZIKA-DFA-FE
  - Jan 4 : project writing starts
  - Feb 5: regulatory frame for research defined (noninterventional research, sponsor Inserm)
    - Authorizations to be obtained from national IRB, CCTIRS (Advisory committee on personal information management in the field of health research), and CNIL (Committee for information technology and freedom)
  - Feb 16: all application files completed and dispatched, along with a request by the Director General of Health (MoH) to expedite evaluation
  - Mar 4: all authorizations granted
- ZIKA-DFA-BB
  - Feb 29 : project writing starts
  - April 10: regulatory frame for research defined (biomedical research, sponsor Inserm)
    - Authorizations to be obtained from national IRB and ANSM (French Medicines Agency)
  - April 20: all application files completed and dispatched
  - April 27: all authorizations granted