

Comparaison de la prévalence des anomalies congénitales observées chez les nouveau-nés de femmes enceintes infectées ou non infectées par le virus Zika au cours de la grossesse

Bruno Hoen, Anna L Funk, Benoit Tressières, Ingrid Vingadassalom, Eustase Janky, Philippe Kadhel, Catherine Ryan, Kinda Schepers, Stanie Gaete, Arnaud Fontanet

Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : Hoen Bruno

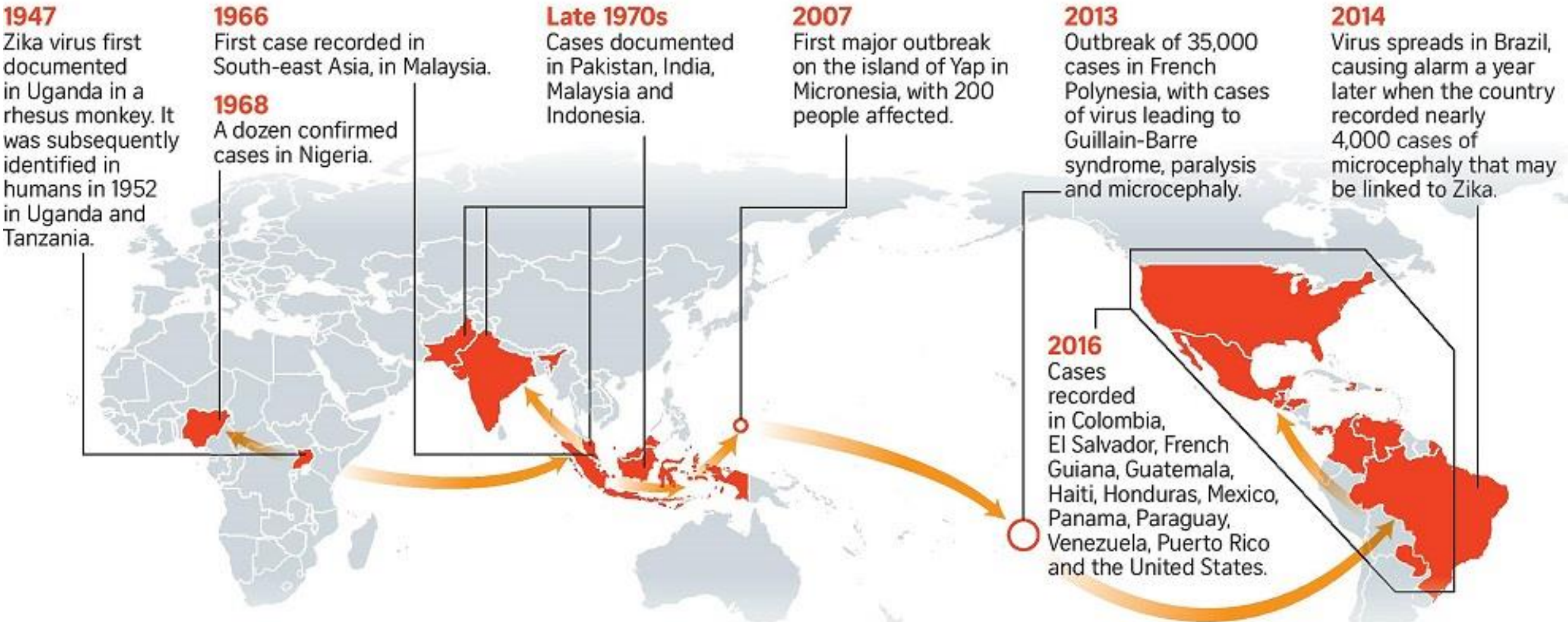
Titre : Zika au cours de la grossesse

L'orateur ne souhaite pas répondre

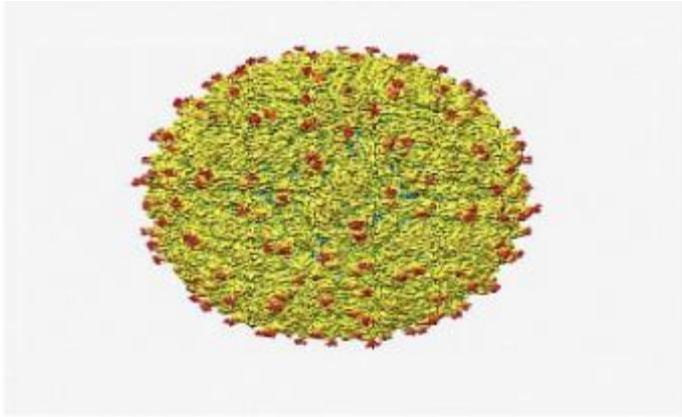
- Consultant ou membre d'un conseil scientifique OUI NON
- Conférencier ou auteur/rédacteur rémunéré d'articles ou documents OUI NON
- Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations OUI NON
- Investigateur principal d'une recherche ou d'une étude clinique OUI NON

How Zika virus spread

The mosquito-borne virus was first found in a monkey in Uganda in 1947, and very few cases of human infection were reported before 2007.



Zika Virus (ZIKV) Outbreak in the Americas



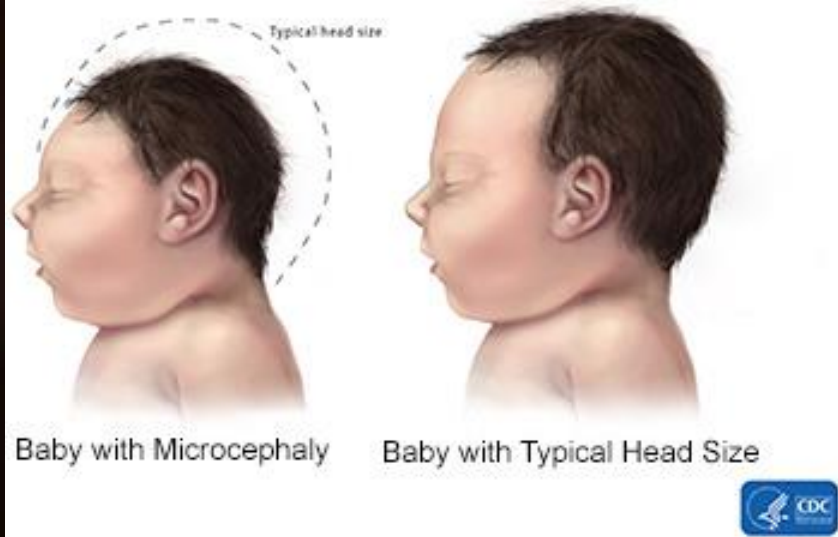
Zika Virus Structure – Sirohi et al.,
Science, 2016

- **2015:** ‘Rash causing’ illness, Brazil
- **Early 2016:** 48 countries with autochthonous transmission

- Severe neurological manifestations
 - Guillain-Barré Syndrome: 2014
 - Birth defects: November 2015



Ellison Wesley and his 2 month old brother, José, in Poco Fundo, Brazil © Felipe Dana, New York Times



November 2015
Cases of microcephaly reported in Brazil

Photograph: Felipe Dana/AP

Prenatal Zika Virus Infection – Cranial Morphology

Fetal Brain Disruption Sequence



Courtesy of Dr. Bill Dobyns & Dr. André Pessoa

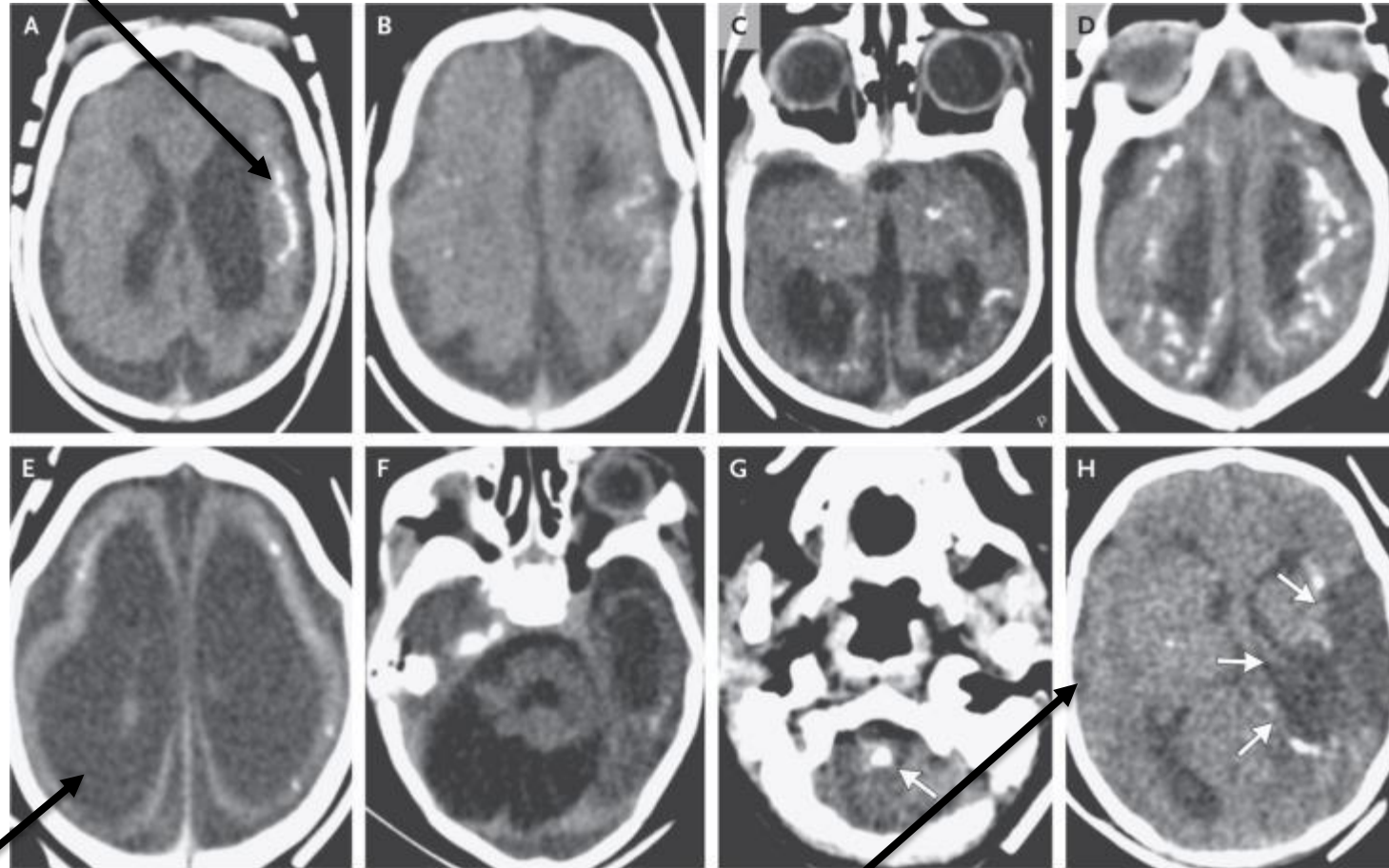
Prenatal Zika Virus Infection – Congenital Contractures





Computed tomography in infants with congenital microcephaly

Subcortical calcifications



Ventriculomegaly

Hypogyration

Hazin AN *et al.* N Engl J Med 2016

WHO declares Zika a Public Health Emergency



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“New
from
– Dr.
Fortu

**LE ZIKA
CIRCULE**

**FEMMES ENCEINTES
PROTEGEZ-VOUS!**

QU'EST-CE QUE LE ZIKA ?
C'est un virus qui, comme la dengue et le chikungunya, se transmet d'un individu à l'autre par l'intermédiaire d'un moustique appelé « *Aedes* ».

Une infection par le virus ZIKA peut être particulièrement dangereuse chez la femme enceinte et avoir de graves répercussions chez son enfant !

**PROTEGEZ-VOUS DES PIQÛRES
DE MOUSTIQUES**

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Le Zika circule

**FEMMES ENCEINTES
PROTEGEZ
-VOUS**

**TOUS RESPONSABLES
STOP AUX MOUSTIQUES !**

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: ANSM and IRB approval granted

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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Sylvie Cassadou, M.D., Raymond Césaire, M.D., Ph.D., Maylis Douine, M.D., Ph.D., Cécile Herrmann-Storck, M.D.,
Philippe Kadhel, M.D., Ph.D., Cédric Laouénan, M.D., Ph.D., Yoann Madec, Ph.D., Alice Monthieux, M.D.,
Mathieu Nacher, M.D., Ph.D., Fatiha Najioullah, Ph.D., Dominique Rousset, M.D., Ph.D., Catherine Ryan, M.D.,
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Jean-Luc Voluménie, M.D., Samson Yassinguez, M.D., Eustase Janky, M.D., Ph.D.,
and Arnaud Fontanet, M.D., Dr.P.H.

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

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

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

Pregnancy outcomes and Zika-related congenital abnormalities

Comparison of three international studies

	Brasil (n=126)	Honein (n=442)	Hoehn (n=555)
Pregnancy outcomes			
Pregnancy losses	9 (7.1)	47 (10.6)	28 (5.0)
Live births	117 (92.9)	395 (89.6)	527 (95.0)
Congenital abnormalities			
Microcephaly	4 (3.2)	18 (4.1)	32 (5.8)
Other brain abnormalities	30 (23.8)	18 (4.1)	12 (2.2)
Neural tube defects, eye abnormalities and consequences of CNS dysfunction	17 (13.5)	4 (0.9)	3 (0.5)
Total	58*(46.4)	26 (6.0)	39 (7.0)

*Includes the 9 pregnancy losses, 12 with isolated MRI findings, and 2 isolated SGA



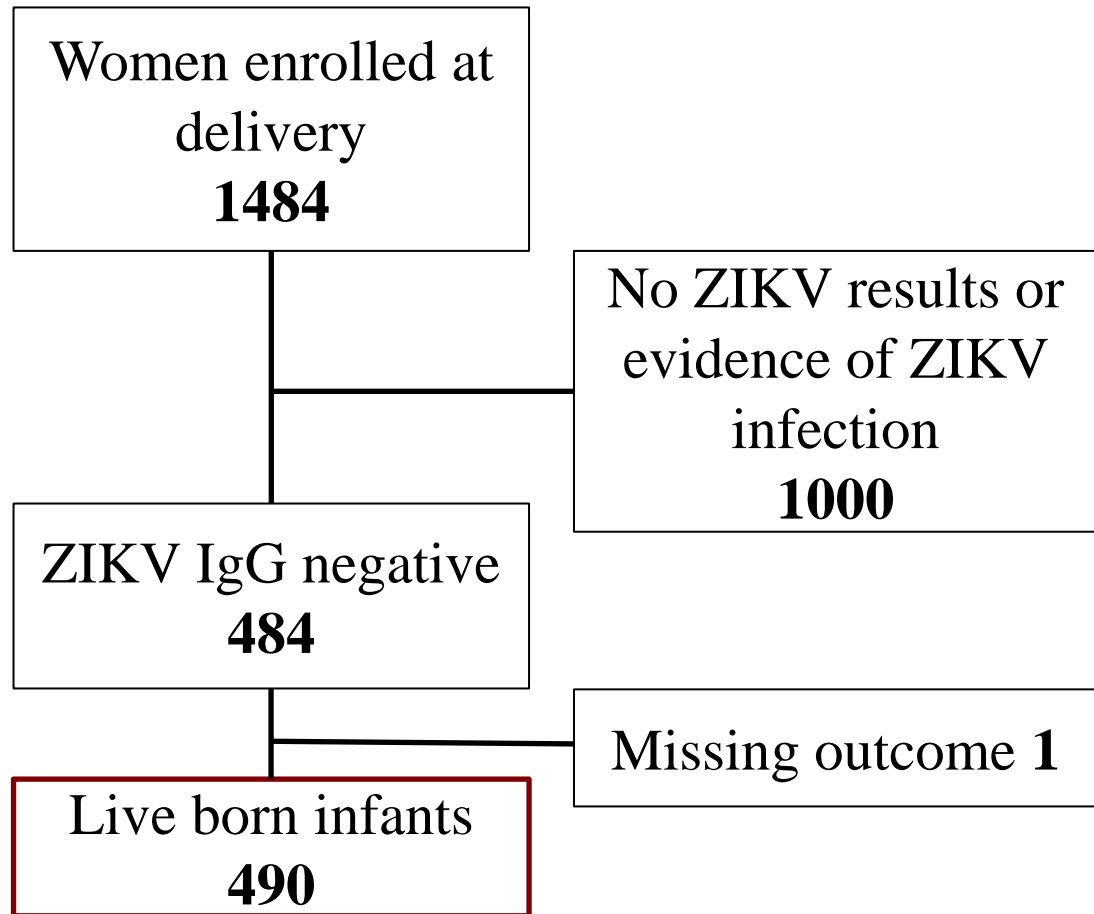
Comparison with a control group

- In Guadeloupe, Zika unexposed pregnancies/infants
- negative ZIKV IgG antibodies at delivery
 - Validation - Carpentier et al., *Submitted* 2019
 - 65 women, confirmed ZIKV during pregnancy
 - IgG detected at delivery in all women
 - Specificity confirmed by Plaque Reduction Neutralization Test (PRNT)

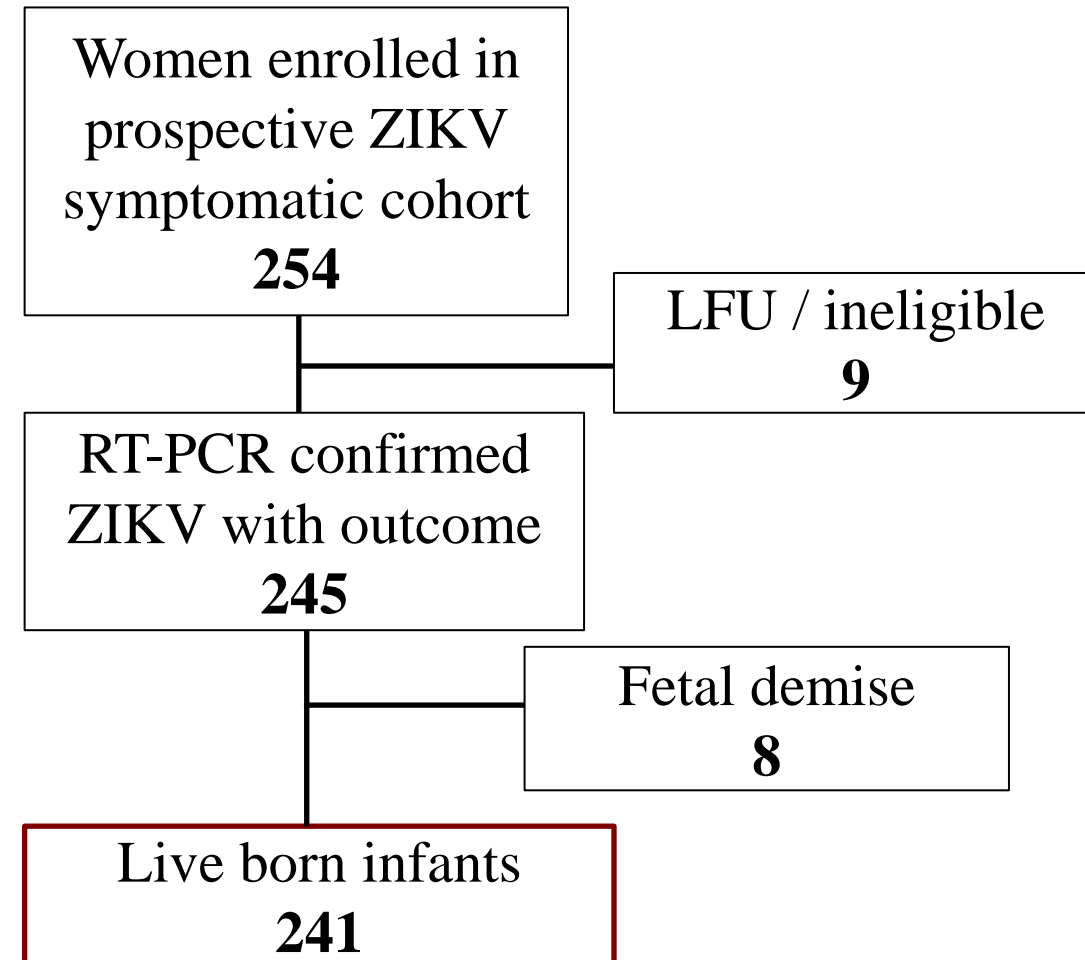


Live born infants in Guadeloupe

ZIKV-unexposed



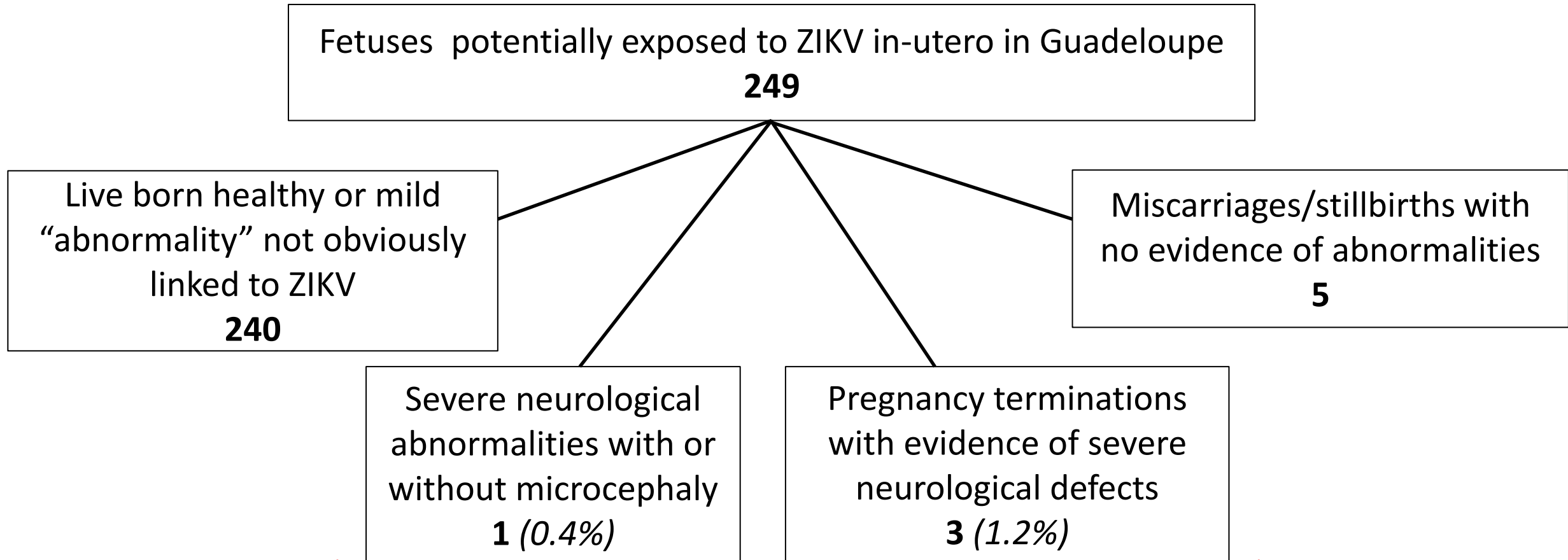
ZIKV-exposed [*Hoehn et al, 2018*]



Abnormalities: ZIKV unexposed vs exposed

Abnormality	ZIKV unexposed (N=490)	ZIKV exposed (N=241)
Small for gestational age	66 (13.5%)	33 (13.7%)
Microcephaly	40 (8.2%)	11 (4.6%)
Moderate-proportionate	19 (3.9%)	4 (1.7%)
Moderate-disproportionate	10 (2.0%)	6 (2.5%)
Severe	11 (2.2%)	1 (0.4%)
Microcephaly + other brain abnormalities	0	0
Other neurological/ocular	0	1 (0.4%)
Neural tube defects	0	1 (0.4%)
Club foot	1 (0.2%)	2 (0.8%)
Other (e.g. skeletal, genetic)	4 (0.8%)	3 (1.2%)

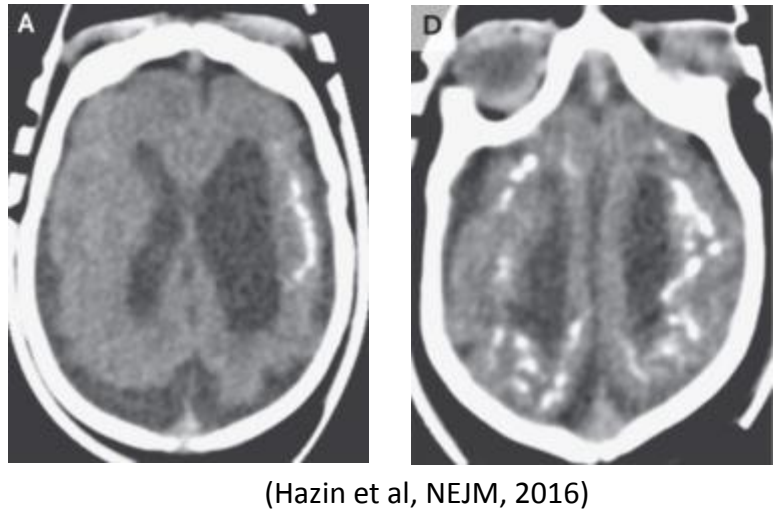
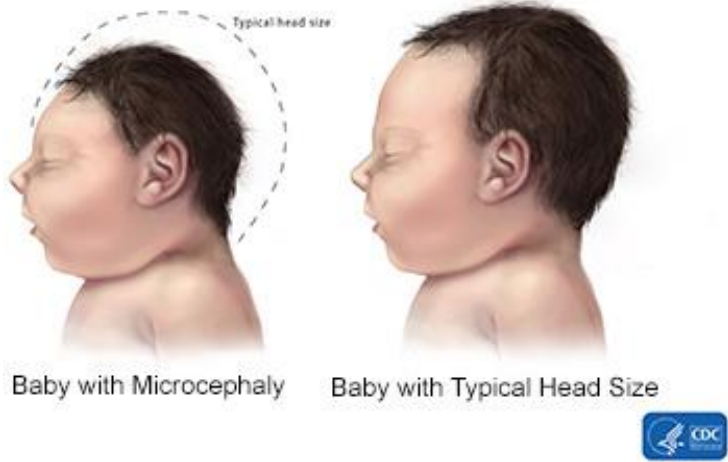
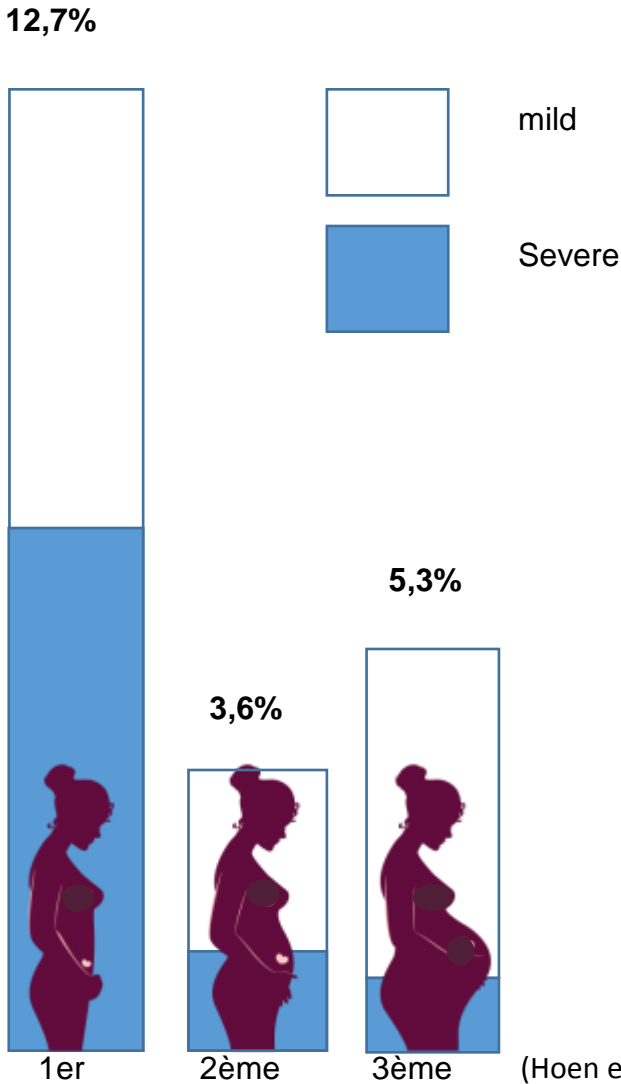
“Corrected” risk of ZIKV-related birth defects



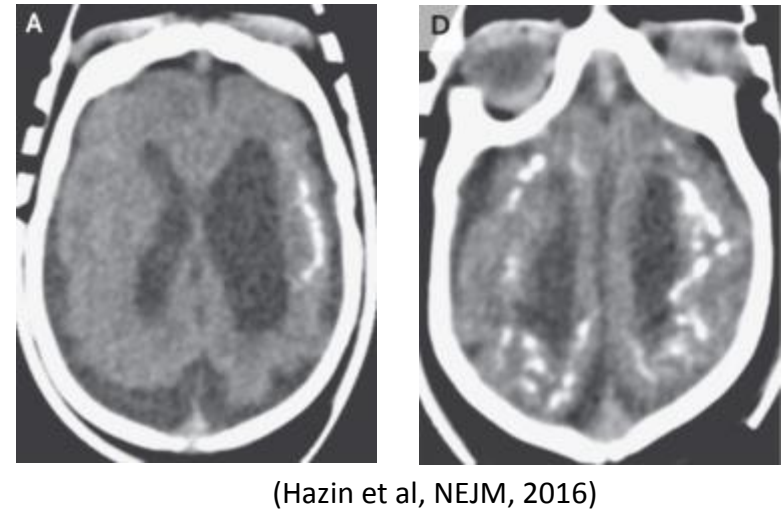
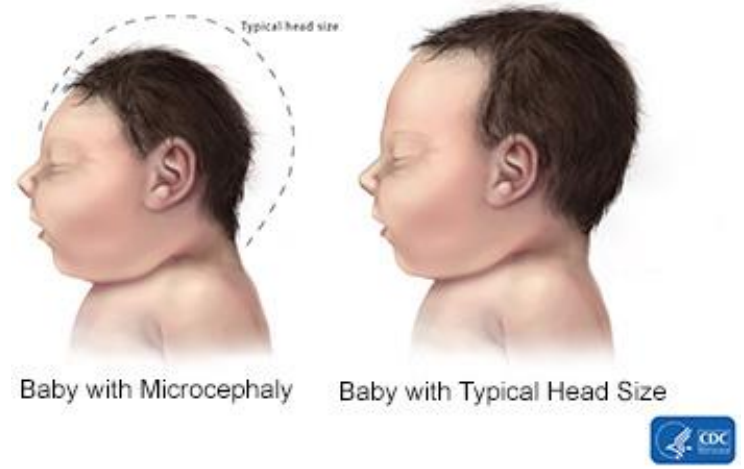
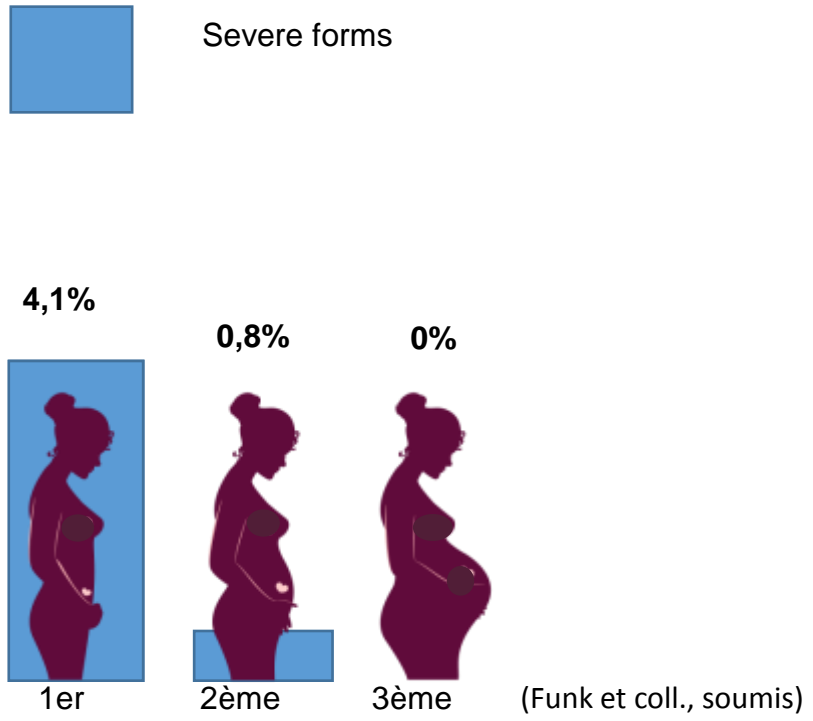
1.6% risk of severe birth defects
4.1% in 1st, 0.8% in 2nd, 0% in 3rd trimesters, respectively



ZIKV-related congenital neurological abnormalities, FTA 2016-2017 (n=555 fetuses et neonates)



ZIKV-related congenital neurological abnormalities, FTA 2016-2017 (n=555 fetuses et neonates)



Congenital abnormalities attributable to ZIKV

Preliminary conclusions

- Proportion of anomalies **attributable** to ZIKV may be less than 5%
- Importance of control groups
- **Meaning of isolated microcephaly questionable**
- **Universal standards for anthropometric measurements questionable**
- Ongoing follow-up of children born to ZIKV-exposed, and unexposed, women will tell us about more subtle abnormalities

Acknowledgements: Funding

- The project presented has received funding from French Ministry of Health (Soutien Exceptionnel à la Recherche et à l'Innovation), Laboratoire d'Excellence Integrative Biology of Emerging Infectious Diseases project (ANR-10-LABEX-62-IBEID), the European Union's Horizon 2020 Research and Innovation Program through the ZikAlliance consortium (Grant Agreement no. 73458), and by INSERM.
- Additional funding from the Institut Carnot-Pasteur Maladies Infectieuses (ANR 11-CARN 017-01) for Anna Funk PhD thesis grant



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 Laouéan, 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 Laouéan (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 Mentré (Inserm) ; Cedric Contaret (CHUM) ; Bruno Schaub (CHUM) ; Aissatou Signate (CHUM) ; Cécile Herrmann-Storck (CHUPPA) ; Philippe Kadhel (CHUPPA)

- **Women who participated in this study and demonstrated their altruism**

- **All actors (physicians, midwives, clinical research assistants, health officers and epidemiologists) who joined their efforts to help conduct this study in each FTA**

- **Staff of Clinical Research Departments in each FTA**

Acknowledgments

- **All actors (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, Dorothee 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 Bateau, 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

Specificity of Microcephaly Definitions

- **Review by Ashwal et al., *Neurology* 2009**
 - -3SD = 80% with imaging and developmental abnormalities
 - -2SD to -3SD = 40% with imaging and developmental abnormalities
- **Isolated fetal microcephaly**
 - Stoler-Poria et al., *Ultrasound Obstet Gynecol* 2010
 - Normocephalic similar outcomes with infants with HC between -2SD and -3SD