RICAI 2018

Infections materno-fœtales les nouveaux paradigmes

ZIKA

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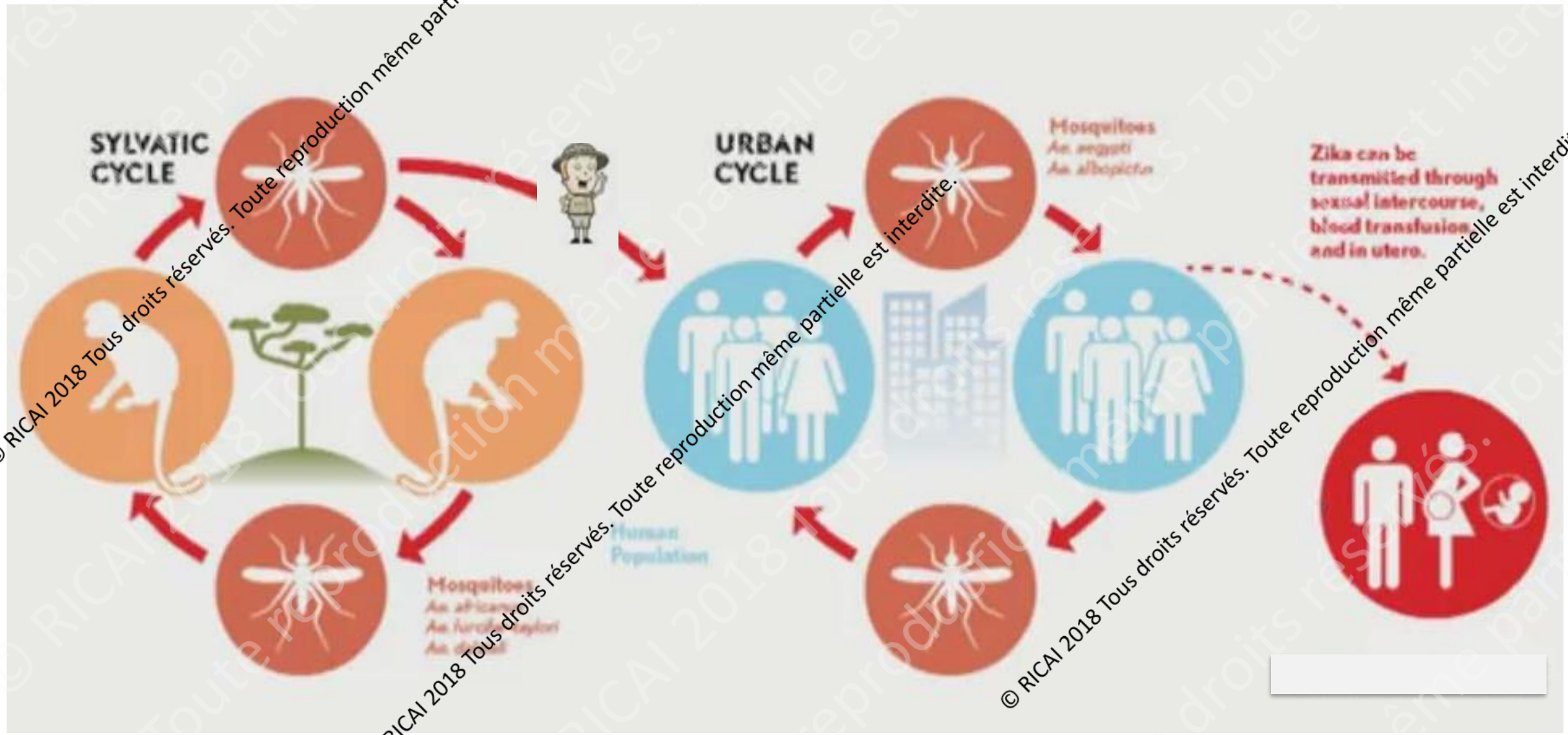
Haut Conseil de la Santé Publique

Zika : etymology – history

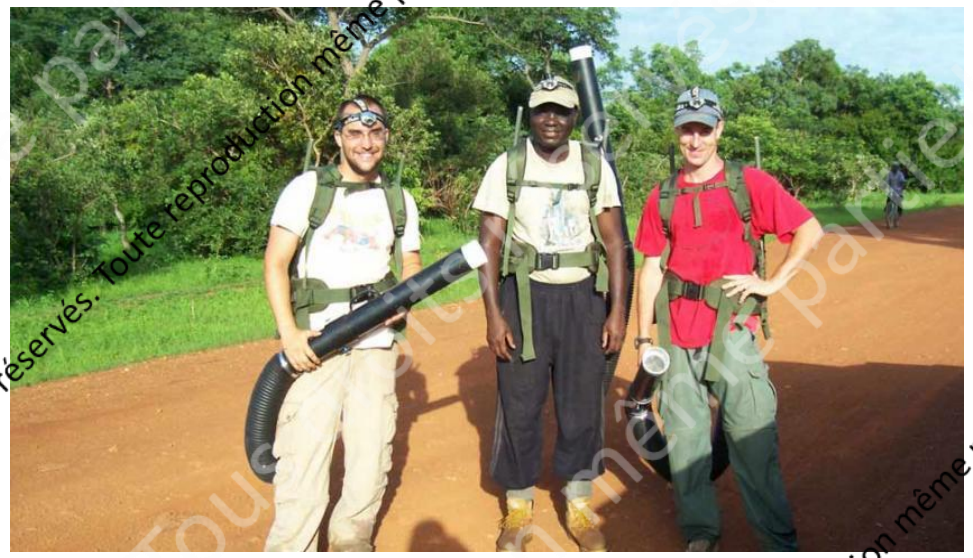
- 1947: Zika Forest, near Entebbe, Uganda
  - zika means “overgrown” in the Luganda language
  - East African Virus RI: fever in a rhesus macaque
  - virus isolated from its blood and described as Zika virus in 1952
- 1954: first isolation of the virus from a human in Nigeria
- 2007: dissemination of the virus worldwide
  - confirmed cases of Zika virus infection in Africa and Southeast Asia
  - major epidemic of Zika virus infection in Yap Island, Micronesia
- 2012 – 2015: new outbreaks in new areas
  - Polynesia, Easter Island, Cook Islands, and New Caledonia
  - Caribbean and Brazil

How ZIKV penetrates the human population



Sexual Transmission

Senegal → USA, 2008



Patients 1 and 2. Kobylinski (*left*), Foy (*right*), collecting mosquitoes in Senegal with medical entomologist Massamba Sylla, 2008.

Patient 3. Brian Foy *(left)* sexually transmitted the virus to his wife Joy Foy (*right*) upon return to the United States.

Venezuela → USA (Texas), 2016

- Recent traveller to Venezuela transmits to non-traveller in Texas

Has been documented in several instances since, always from man-to-sexual partner except for one case (woman-to-man)

ZIKV has been identified by PCR in the semen of men up to 6 months after acute symptomatic infection

Foy BD, et al. Emerg Infect Dis. 2011 May;17(5):880-2. www.sciencemag.org/news/2011/04/sex-after-field-trip-yields-scientific-first; http://edition.cnn.com/2016/01/26/health/zika-what-you-need-to-know/

Original Article

Persistence of Zika Virus in Body Fluids — Final Report

Detection of ZIKV RNA in Body Fluids and Anti–ZIKV IgM Antibody in Serum, According to the Number of Days after Symptom Onset

Table 3. Detection of ZIKV RNA in Body Fluids and Anti–ZIKV IgM Antibody in Serum, According to the Number of Days after Symptom Onset.*

Positivity and Days after Symptom Onset	ZIKV RNA					Anti–ZIKV IgM Antibody
	Serum	Urine†	Saliva	Vaginal Secretions	Semen	Serum
	number/total number (percent)					
Participant analyses						
Any interval after symptom onset	241/268 (89.9)	129/218 (59.2)	11/276 (4.0)	2/114 (1.8)	45/88 (51.1)	271/278 (97.5)
0–7 days	211/235 (89.8)	103/180 (57.2)	4/8 (50)	1/2 (50)	1/1 (100)	22/98 (22.4)
8–15 days	26/51 (51)	19/35 (54.3)	1/26 (3.9)	0/12	5/7 (71.4)	121/129 (93.8)
16–30 days	45/221 (20.4)	27/174 (15.5)	4/218 (1.8)	0/76	33/63 (50.8)	212/219 (96.8)
31–45 days	19/245 (7.8)	7/201 (3.5)	3/249 (1.2)	0/98	32/81 (39.5)	237/245 (96.7)
46–60 days	5/215 (2.3)	2/172 (1.2)	1/215 (0.5)	0/94	15/62 (24.2)	192/208 (92.3)
>60 days	3/259 (1.2)	1/212 (0.5)	0/268	1/112 (0.9)	15/82 (18.3)	195/263 (74.1)
Specimen analyses						
Any interval after symptom onset	327/2384 (13.7)	169/1894 (8.9)	15/2089 (0.7)	2/860 (0.2)	174/640 (27.2)	1590/2103 (75.6)
0–7 days	212/236 (89.8)	104/181 (57.5)	5/9 (55.6)	1/2 (50)	1/2 (50)	22/99 (22.2)
8–15 days	27/54 (50)	20/37 (54.1)	1/27 (3.7)	0/12	5/7 (71.4)	125/134 (93.3)
16–30 days	55/348 (15.8)	33/272 (12.1)	4/335 (1.2)	0/117	48/94 (51.1)	331/342 (96.8)
31–45 days	22/464 (4.7)	9/390 (2.3)	4/460 (0.9)	0/187	51/141 (36.2)	427/444 (96.2)
46–60 days	6/267 (2.2)	2/214 (0.9)	1/260 (0.4)	0/125	15/75 (20)	237/255 (92.9)
>60 days	5/1015 (0.5)	1/800 (0.1)	0/998	1/417 (0.2)	54/321 (16.8)	448/829 (54.0)

* The number of participants and specimens that were evaluated at each interval after the onset of symptoms varies because participants were enrolled as they presented for surveillance or tested positive as household contacts. Data for the 15 household contacts who were asymptomatic at the time of enrollment were excluded from this analysis, since there was no known date of symptom onset.

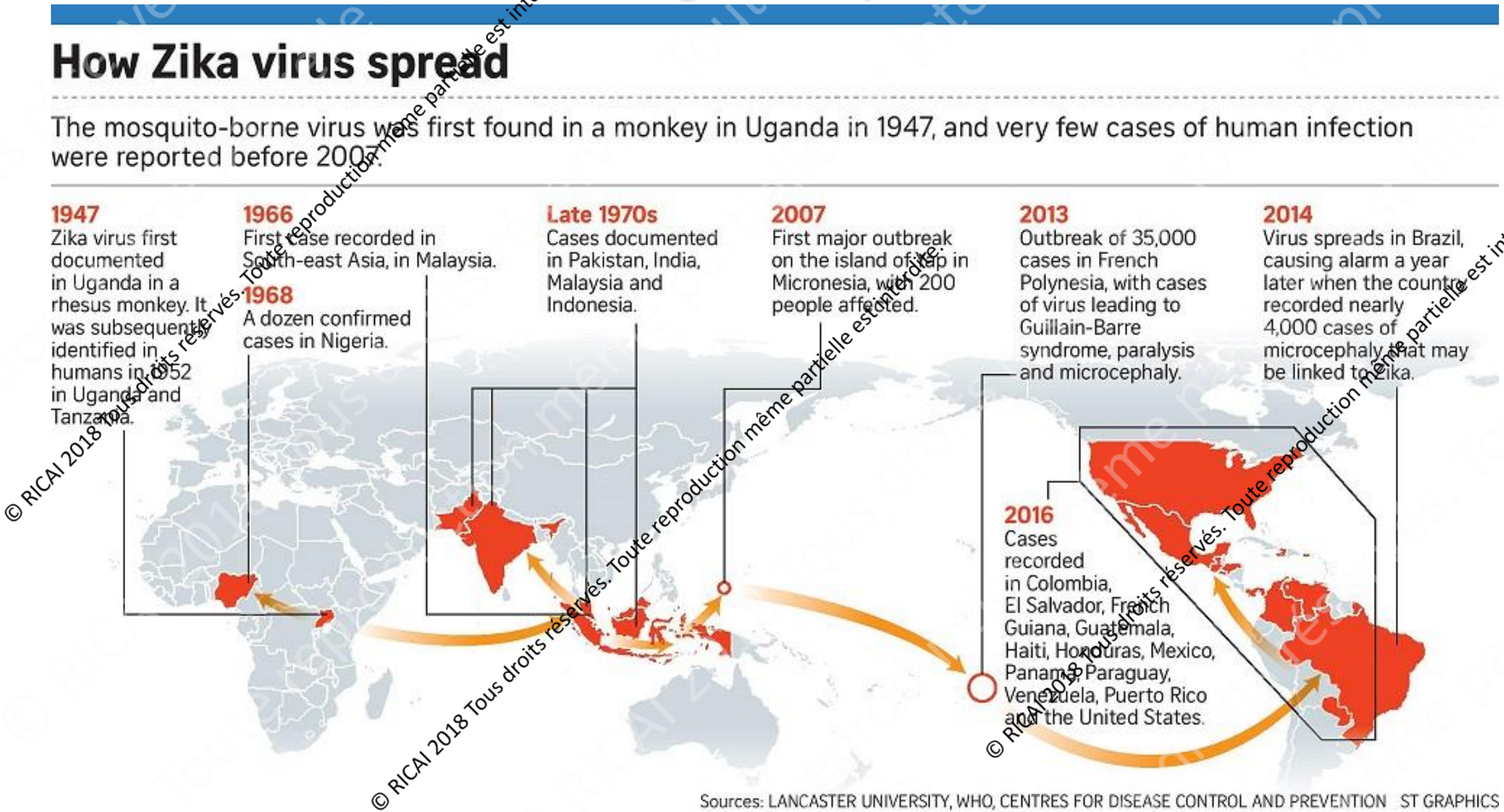
† Analyses of urine specimens were limited to the 75% of participants recruited from the SEDSS, since urine was not obtained at the screening visit in the other two sites.

In 95% of the men in this study, ZIKV RNA was cleared from semen after 4 months

N Engl J Med
Volume 379(13):1234-1243
September 27, 2018

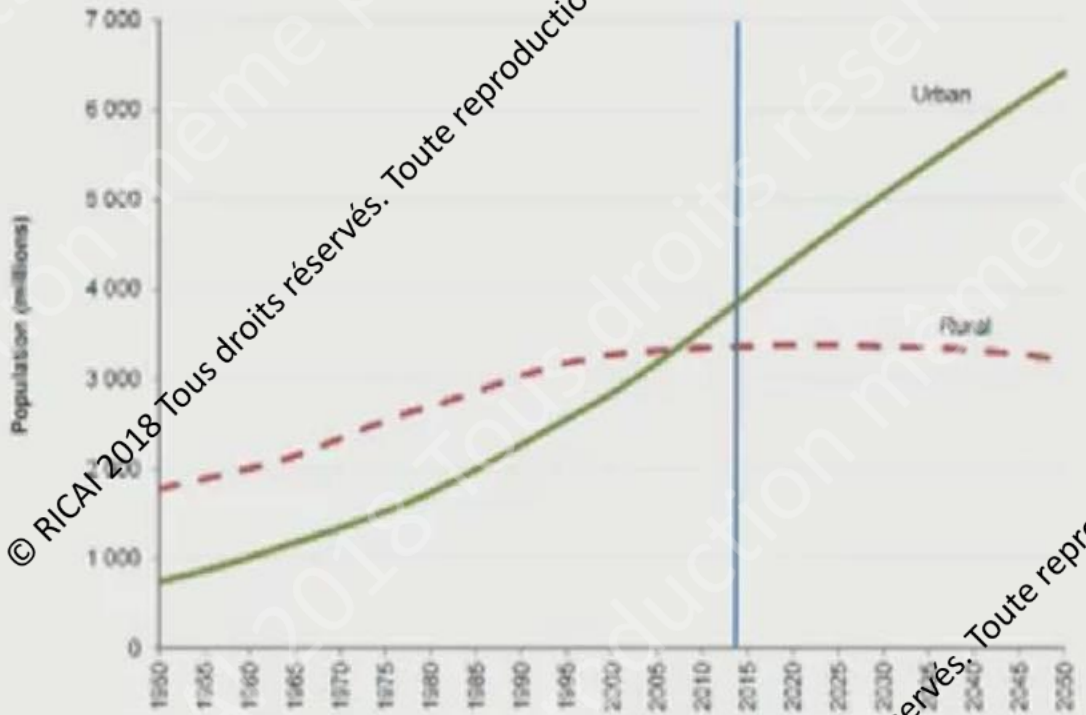
The NEW ENGLAND JOURNAL of MEDICINE

ZIKV global spread



Why is Zika spreading now?

World's Urban and Rural Populations



Source: UN Dept. of Economic and Social Affairs

International Arrivals

Source: World Tourism Organization

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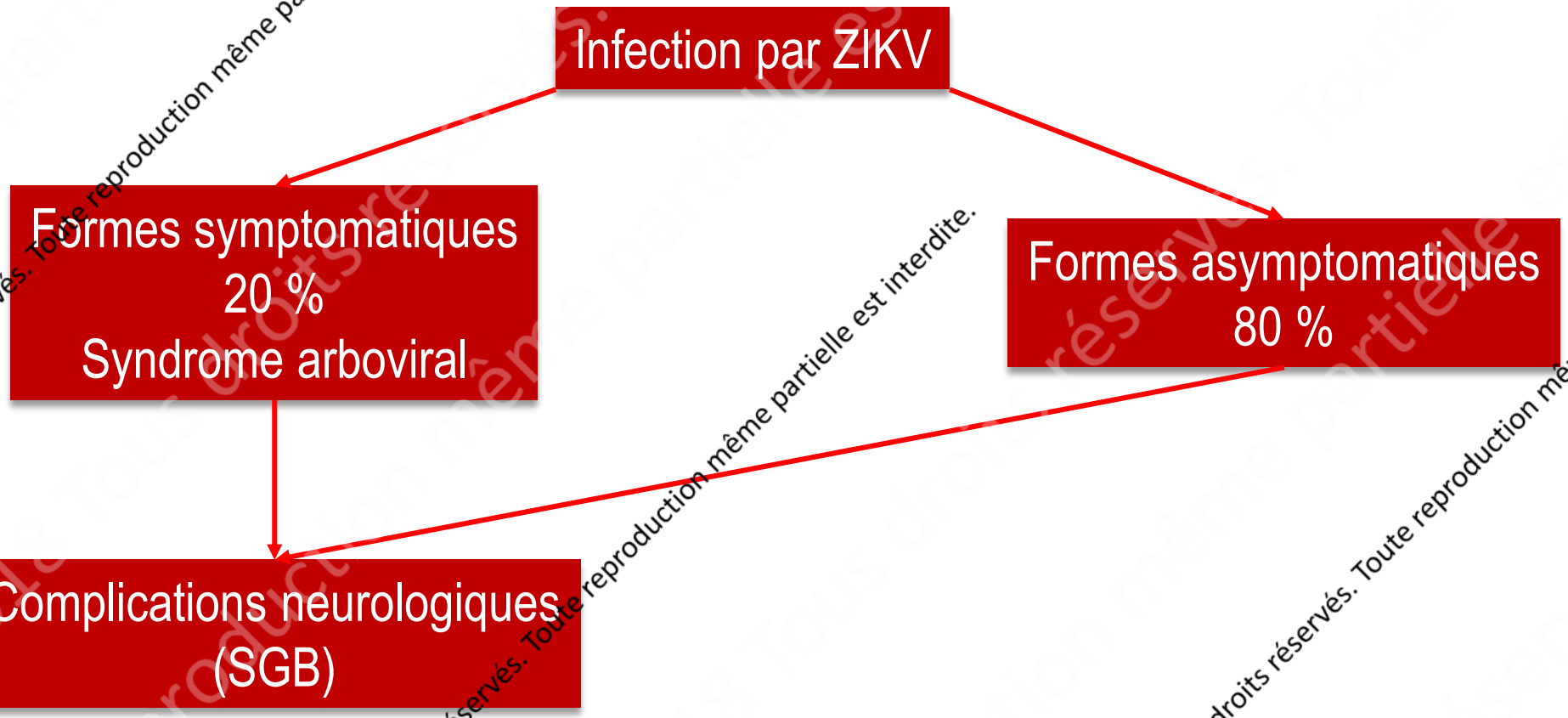
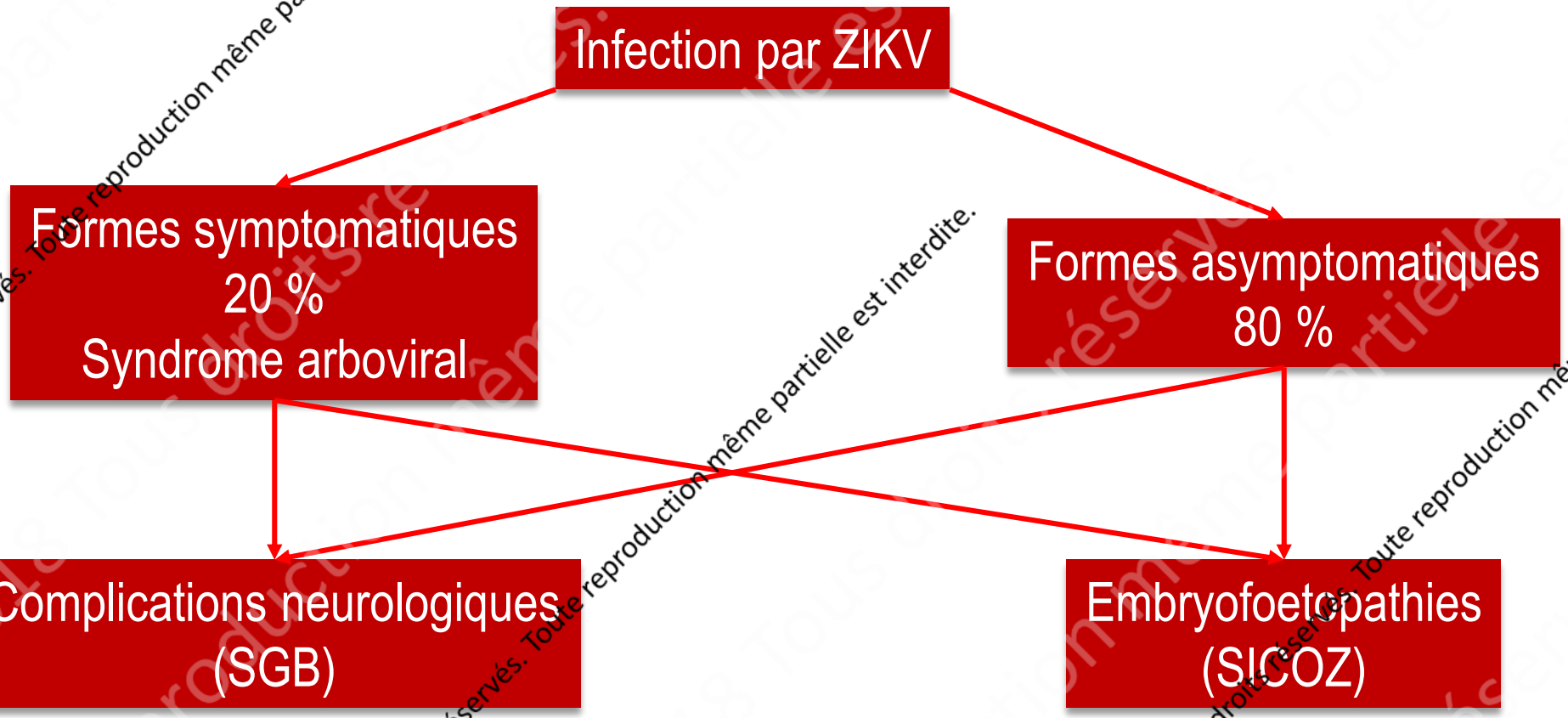
Manifestations cliniques de l'infection à virus Zika



Manifestations cliniques de l'infection à virus Zika



Microcephaly: association with Zika virus?

November 2015

-Notifications in Brazil

-Virus found in amniotic fluid

February 2016

WHO: Public Health Emergency of International Concern

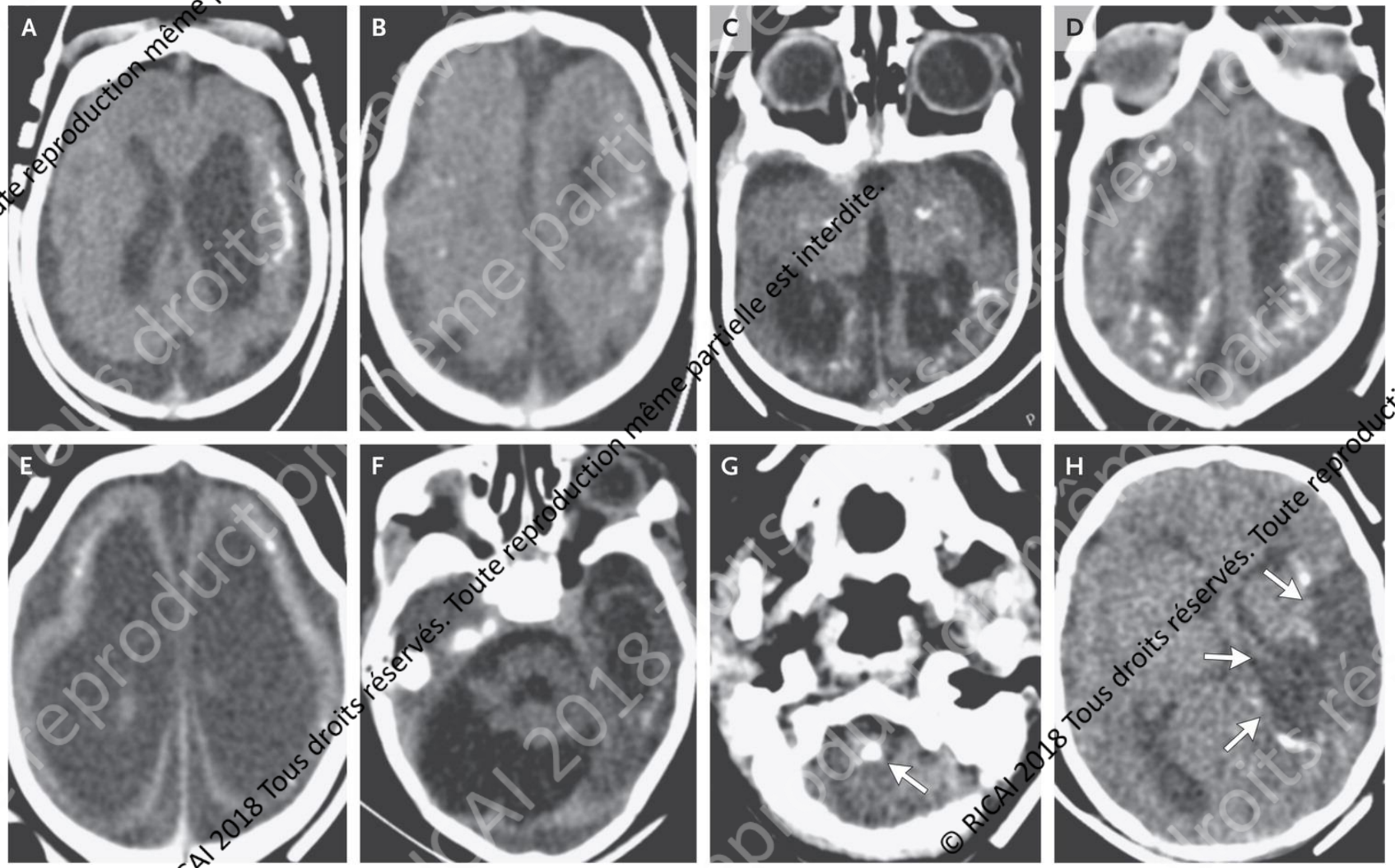
Photograph: Felipe Dana/AP; *http://www.theguardian.com/global-development/2016/jan/25/zika-virus-mosquitoes-countries-affected-pregnant-women-children-microcephaly; http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=33296&lang=en*

Computed tomography in infants with congenital microcephaly

Subcortical calcifications

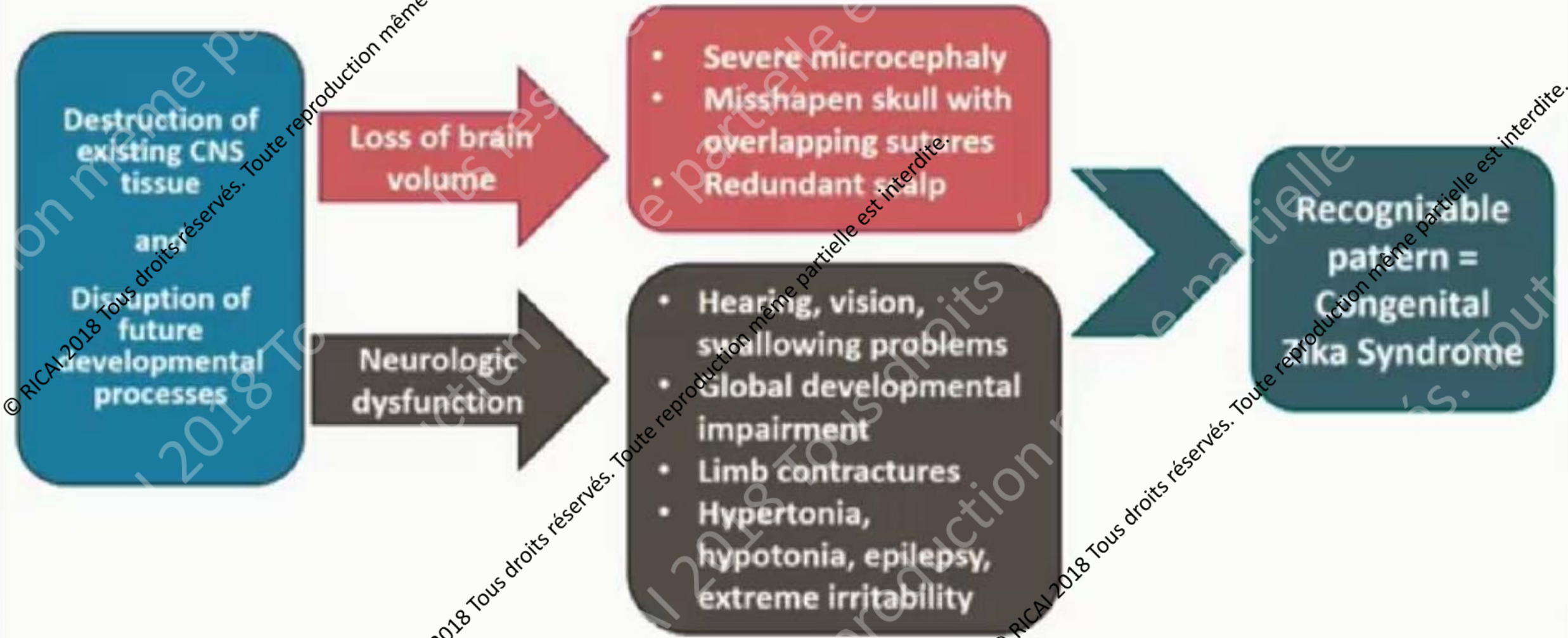
Ventriculomegaly

Hypogyration



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

Prenatal Zika Virus Infection – Congenital Zika Syndrome



Prenatal Zika Virus Infection – Cranial Morphology

Fetal Brain Disruption Sequence

Courtesy of Dr. Bl[illegible] Dobyns & Dr. André Pessoa

Prenatal Zika Virus Infection – Congenital Contractures

WHO declares Zika a Public Health Emergency o

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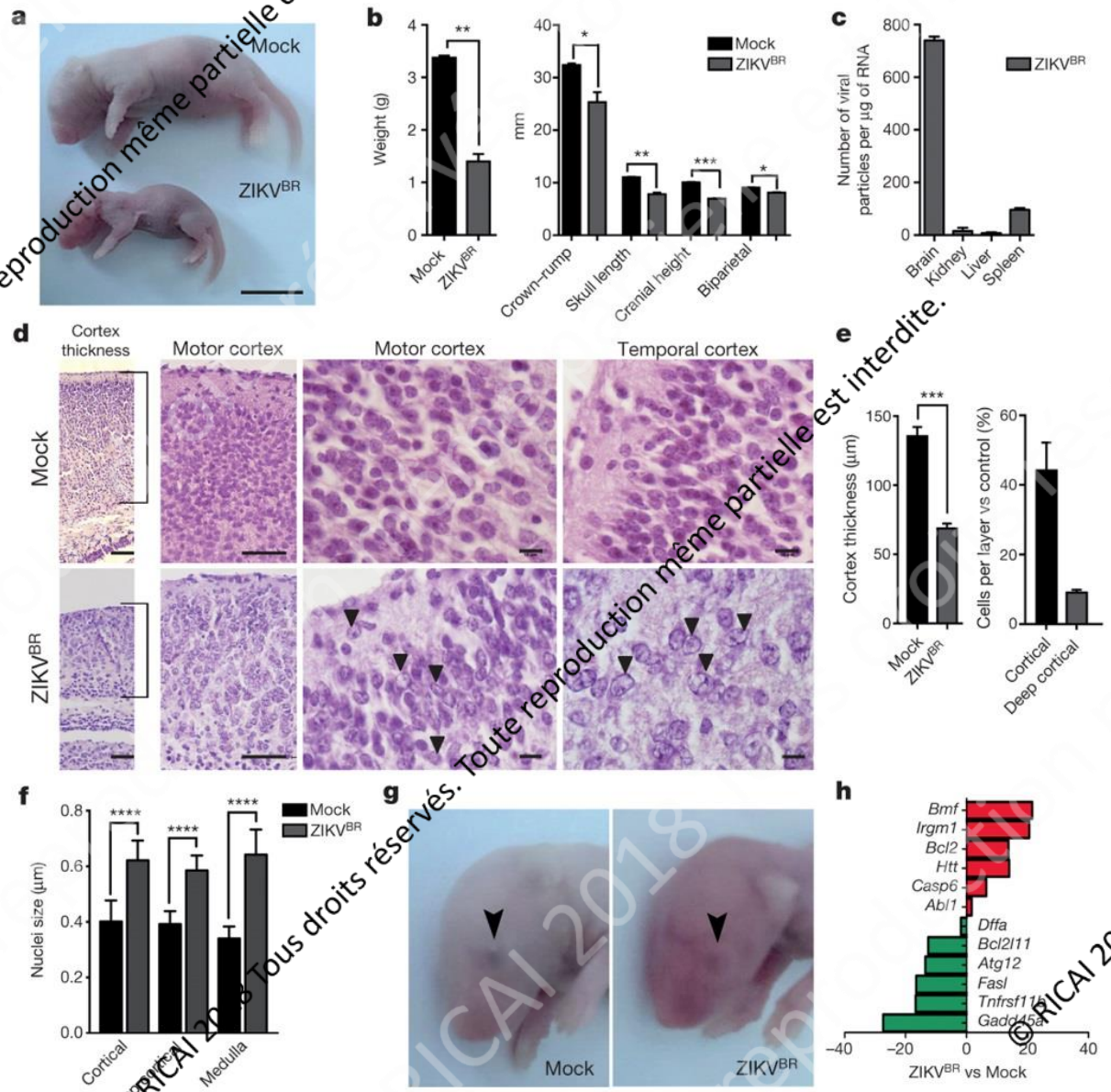
The Brazilian Zika virus strain causes birth defects in experimental models

- $ZIKV^{BR}$ infects mice fetuses, causing intrauterine growth restriction, including signs of microcephaly
- Moreover, the virus infects human cortical progenitor cells, leading to an increase in cell death
- The infection of human brain organoids results in a reduction of proliferative zones and disrupted cortical layers
- These results indicate that $ZIKV^{BR}$ crosses the placenta and causes microcephaly by targeting cortical progenitor cells, inducing cell death by apoptosis and autophagy, and impairing neurodevelopment

Cugola, Nature 2016

ZIKV^{BR} infection in SJL mice

IUGR



Neurotropic nature of the virus

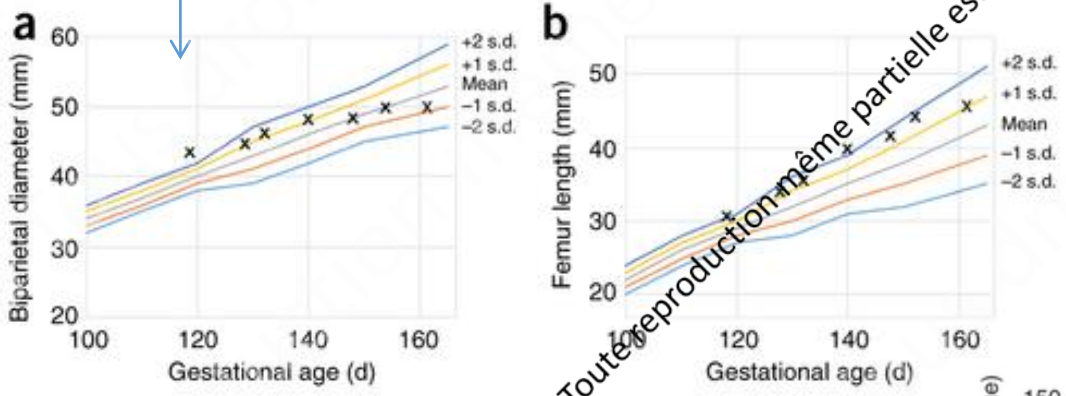
Cugola, Nature, 2016

Fetal brain lesions after SC inoculation of ZIKV Cambodia 2010 in a pregnant non human primate

Fetal biparietal diameter and femur length over time

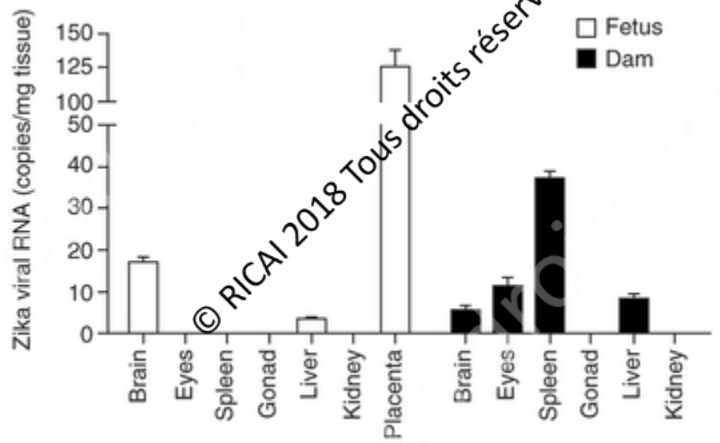
ZIKV SC injection (~28 weeks human pregnancy)

Caesarian section (~38 weeks human pregnancy)

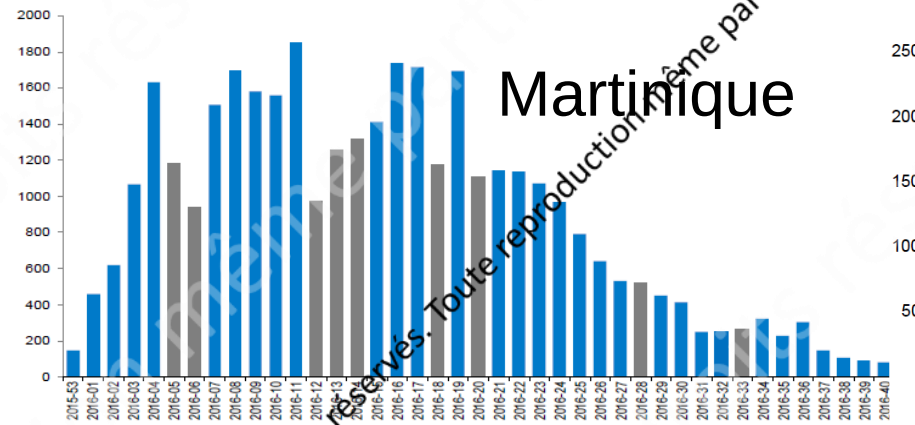


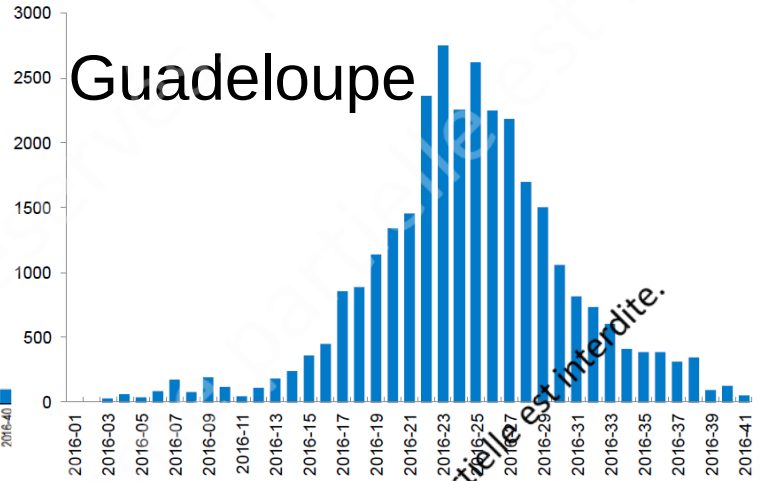
(Adams Waldorf, Nature Medicine, 2016)

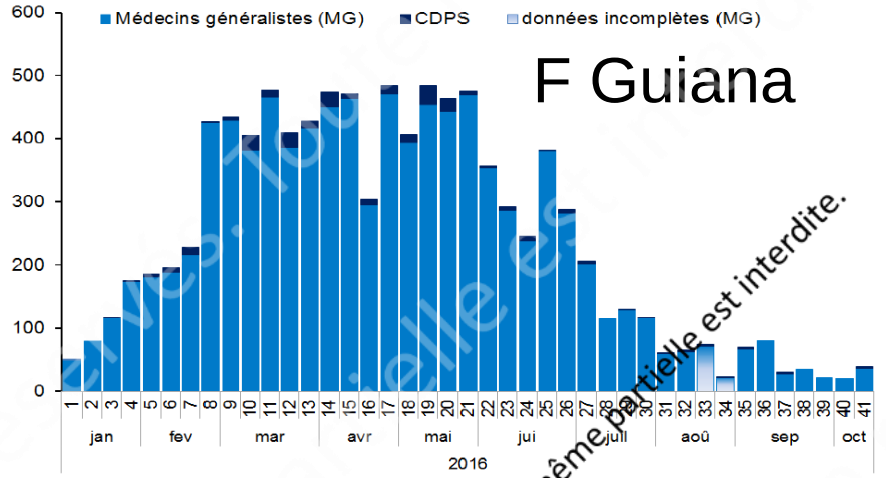
Zika viral load in fetus and dam



Zika outbreaks in the FTA by the end of 2016







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

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Pregnancy Outcomes after ZIKV Infection in French Territories in the Americas

Bruno Hoen, M.D., Ph.D., Bruno Schaub, M.D., Anna L. Funk, M.Sc., Vanessa Ardillon, M.D., Manon Boullard, M.Sc., André Cabié, M.D., Ph.D., Caroline Callier, M.Sc., Gabriel Carles, M.D., 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., Kinda Schepers, M.D., Ph.D., Sofia Stegmann-Planchard, M.D., M.P.H., Benoît Tressières, M.Sc., Jean-Luc Voluménie, M.D., Samson Yassinguezo, M.D., Ecstase 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

Pregnancy outcome definitions

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

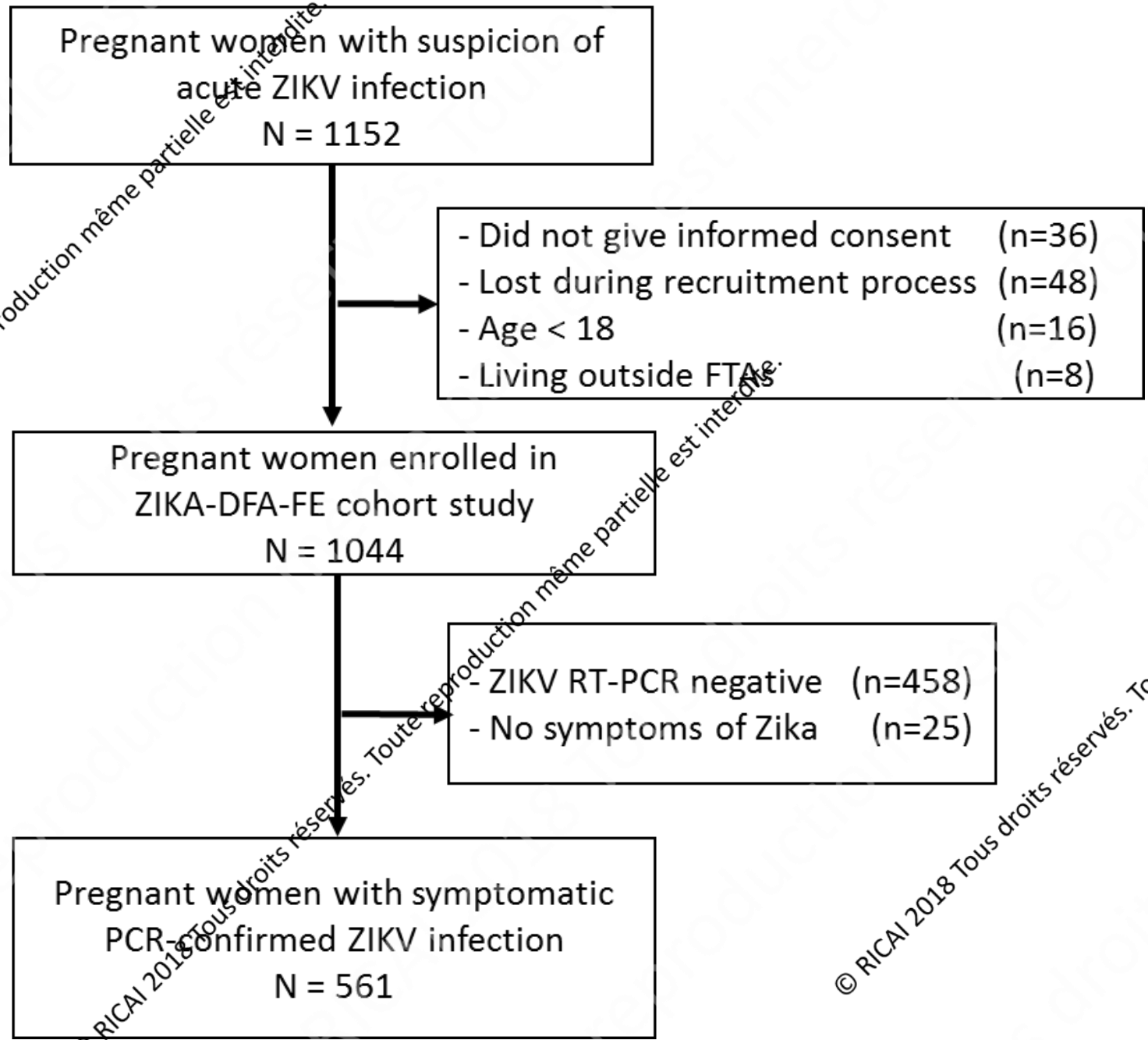
Definitions for microcephaly

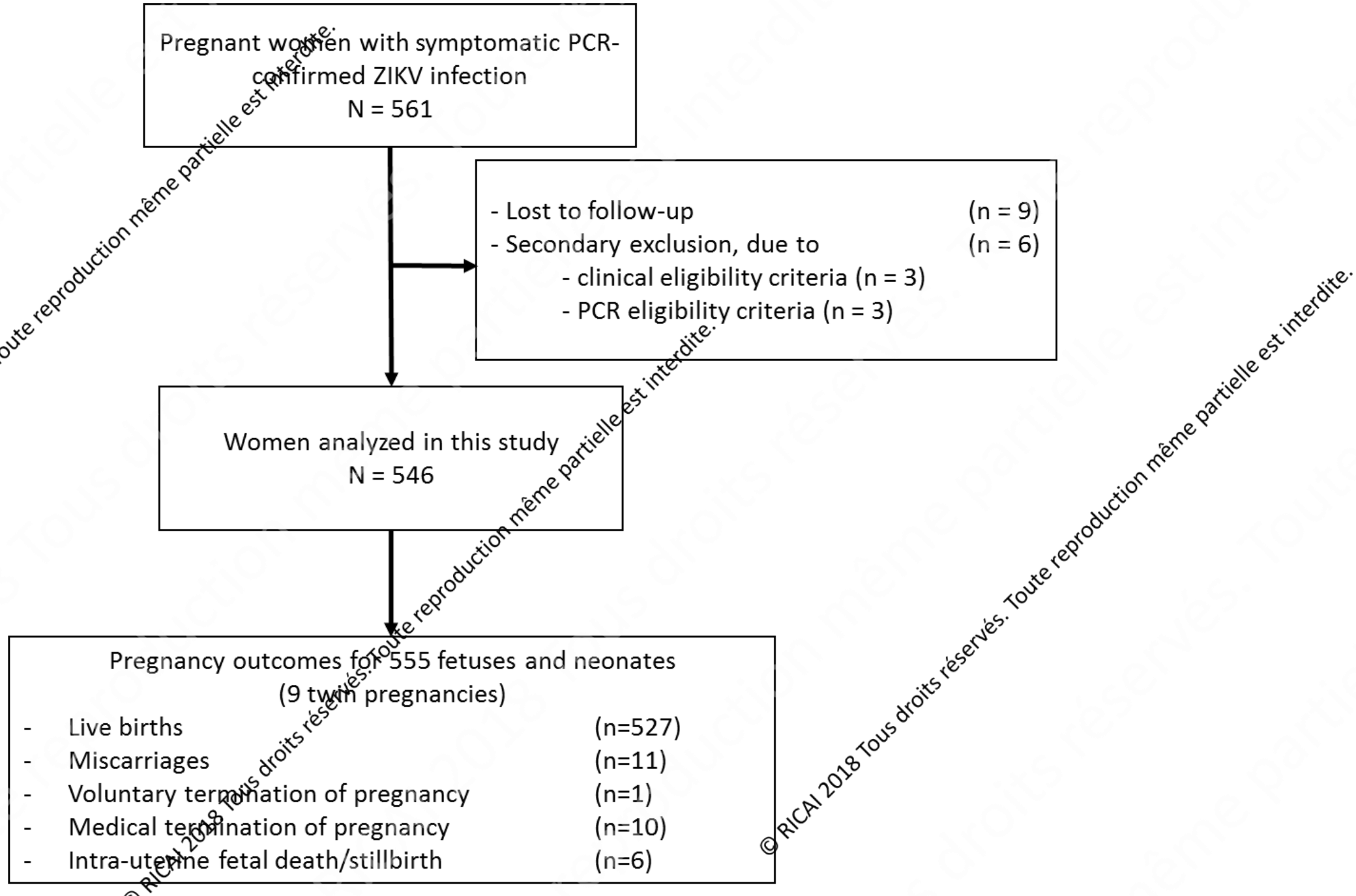
- Live birth: INTERGROWTH-21st (http://intergrowth21.ndog.ox.ac.uk/)
  - Severe: head circumference < –3 SD
  - Moderate: head circumference between –3 SD and –2 SD
    - Proportionate if neonate small for gestational age (weight < –1.28 SD according to the INTERGROWTH-21st standards for gestational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

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*





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

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**

Summary of results

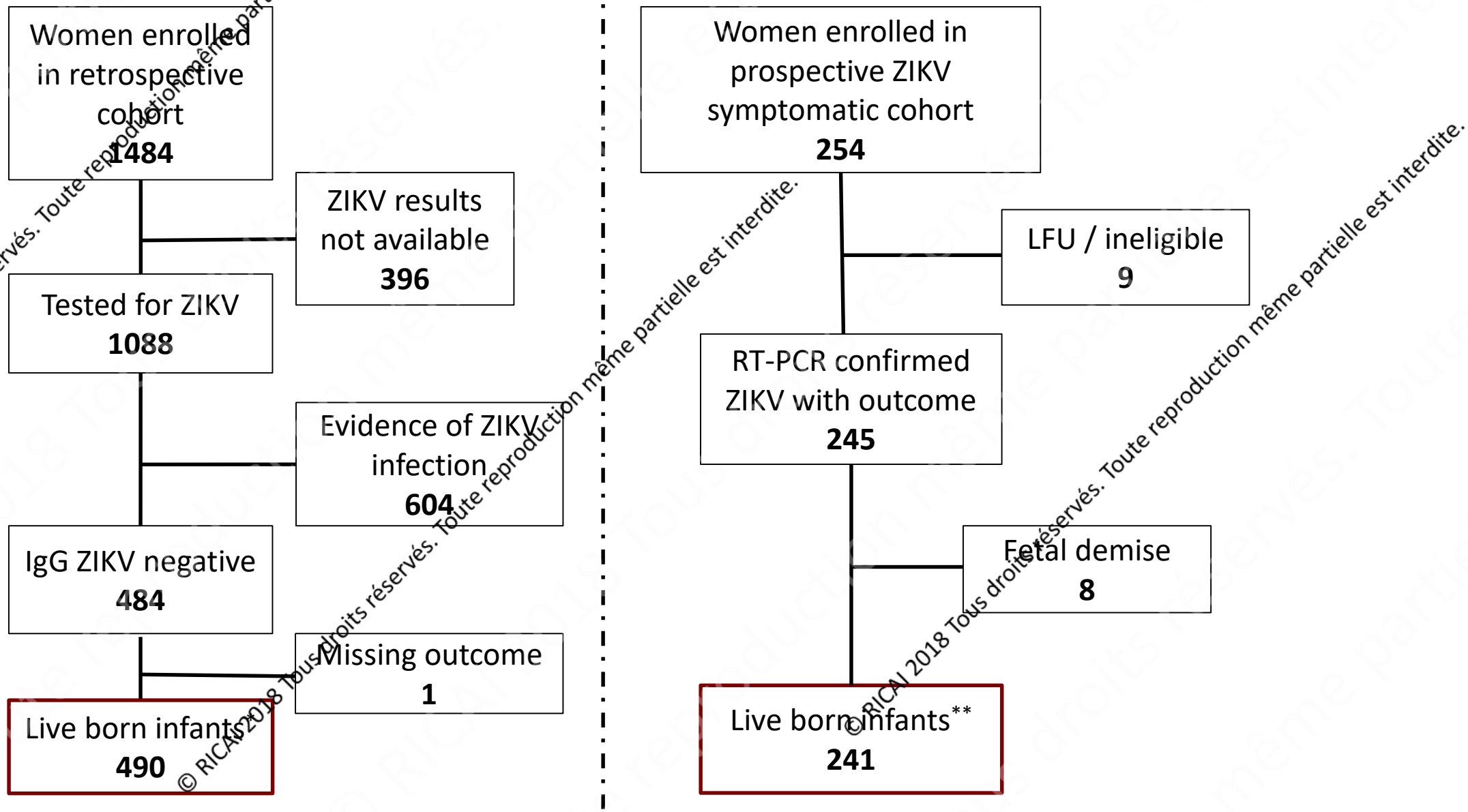
- In the offspring of women who developed acute symptomatic PCR-confirmed ZIKV infection during pregnancy
  - Overall risk of CNS/eye defects possibly associated with ZIKV infection 7.0 %
  - Overall risk of birth defects included in the current definition of ZCS 3.1 %
  - Overall risk of severe microcephaly (< - 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)	Hoen (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

Considering women in Guadeloupe only



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

	ZIKV non-infected	ZIKV infected *(Hoen et al, NEJM)*
Live births	**(n=490)**	**(n=241)**
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 & consequences of CNS dysfunction	1 (0.2)	2 (0.8)
Neural tube defect	0	1 (0.4)
Neonates small for gestational age (weight<-1.28 SD)	66 (13.5)	33 (13.7)

(Funk, submitted)

Congenital abnormalities
ZIKV non-infected vs infected in Guadeloupe (2016)

	ZIKV non-infected	ZIKV infected *(Hoen et al, NEJM)*
Pregnancy losses		**(n=249)**
Miscarriage	NA	2 (0.8)*
Voluntary termination of pregnancy	NA	**3 (1.2)**
Medical termination of pregnancy	NA	0
Stillbirth	NA	3 (1.2)*
Live births	**(n=490)**	
Structural brain abnormalities	0	**1 (0.4)**
Severe microcephaly alone	11 (2.2)	1 (0.4)
Moderate-disproportionate microcephaly alone	10 (2.0)	6 (2.4)
Moderate-proportionate microcephaly alone	19 (3.9)	4 (1.6)
Ocular abnormalities & consequences of CNS dysfunction	1 (0.2)	2 (0.8)
Neural tube defect	0	1 (0.4)
Neonates small for gestational age (weight<-1.28 SD)	66 (13.5)	33 (13.3)

*No evidence of neurological abnormality at autopsy

(Funk, submitted)

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

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 65
November 22, 2016

Description of 13 Infants Born During October 2015–January 2016 With Congenital Zika Virus Infection Without Microcephaly at Birth — Brazil

- 13 infants with normal head size at birth and laboratory evidence of congenital Zika virus infection
  - All infants had brain abnormalities on neuroimaging consistent with CZS, including decreased brain volume, ventriculomegaly, subcortical calcifications, and cortical malformations
  - 11/13 infants developed microcephaly after birth
- These findings provide evidence that among infants with prenatal exposure to Zika virus, the absence of microcephaly at birth does not exclude congenital Zika virus infection or the presence of Zika-related brain and other abnormalities

Maternal-fetal transmission and adverse perinatal outcomes in pregnant women infected with Zika virus: prospective cohort study in French Guiana

Léo Pomar,[1,2] Manon Vouga,[1] Véronique Lambert,[2] Céline Pomar,[1,2] Najeh Hcini,[2] Anne Jolivet,[3,4] Guillaume Benoist,[5] Dominique Rousset,[6] Séverine Matheus,[6] Gustavo Malinger,[7,8] Alice Panchaud,[9,10,11] Gabriel Carles,[2] David Baud[1]

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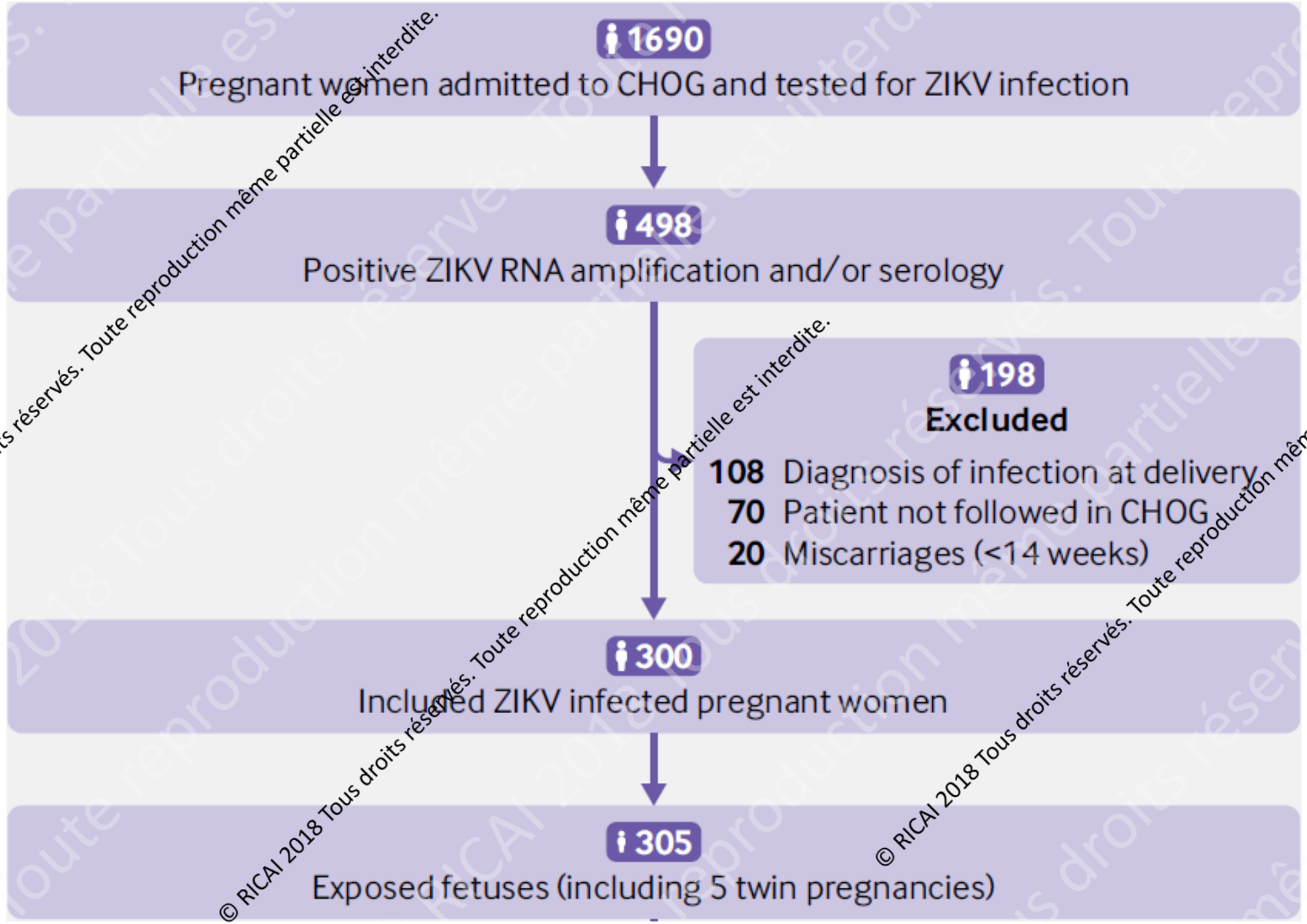
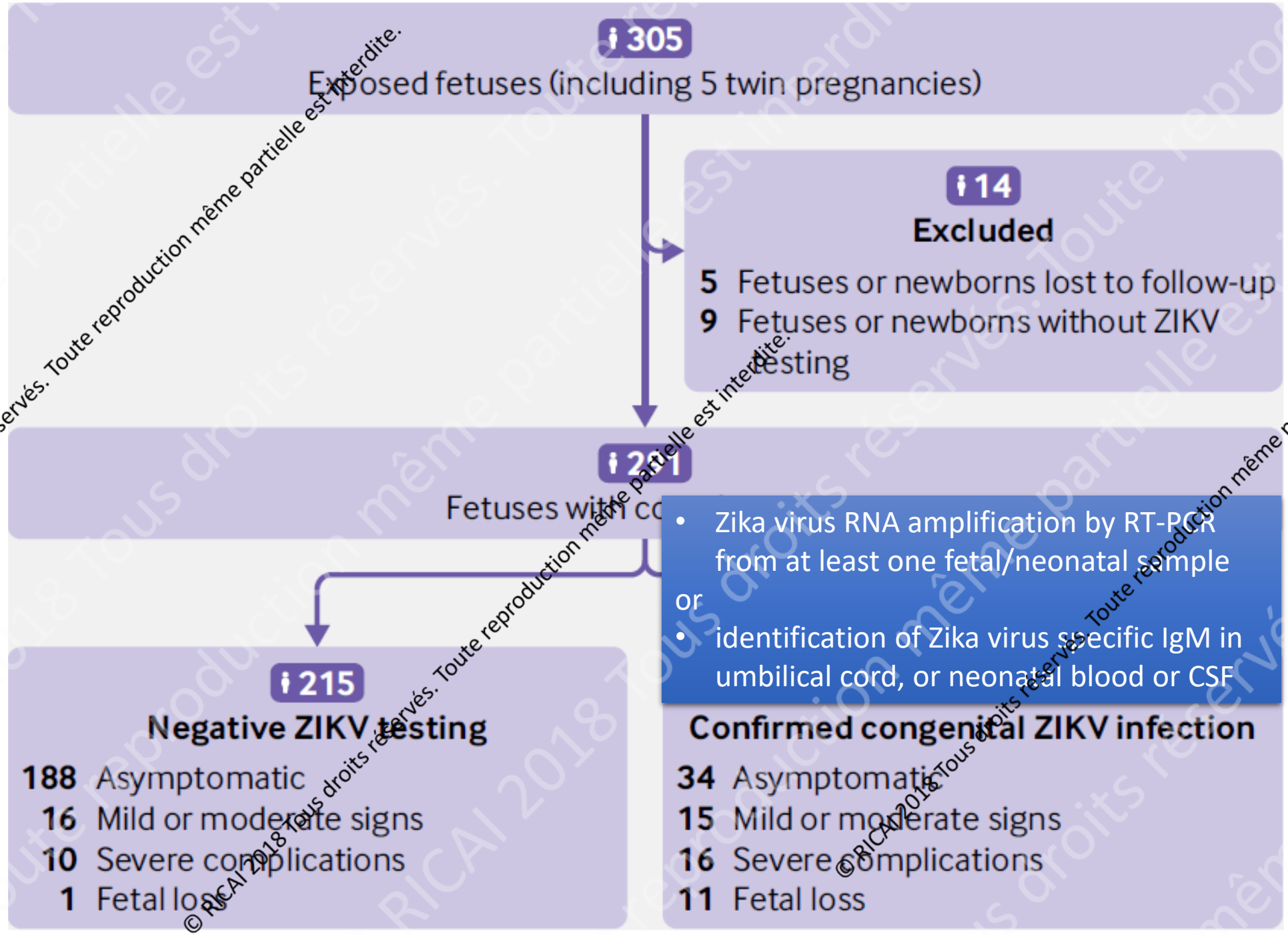
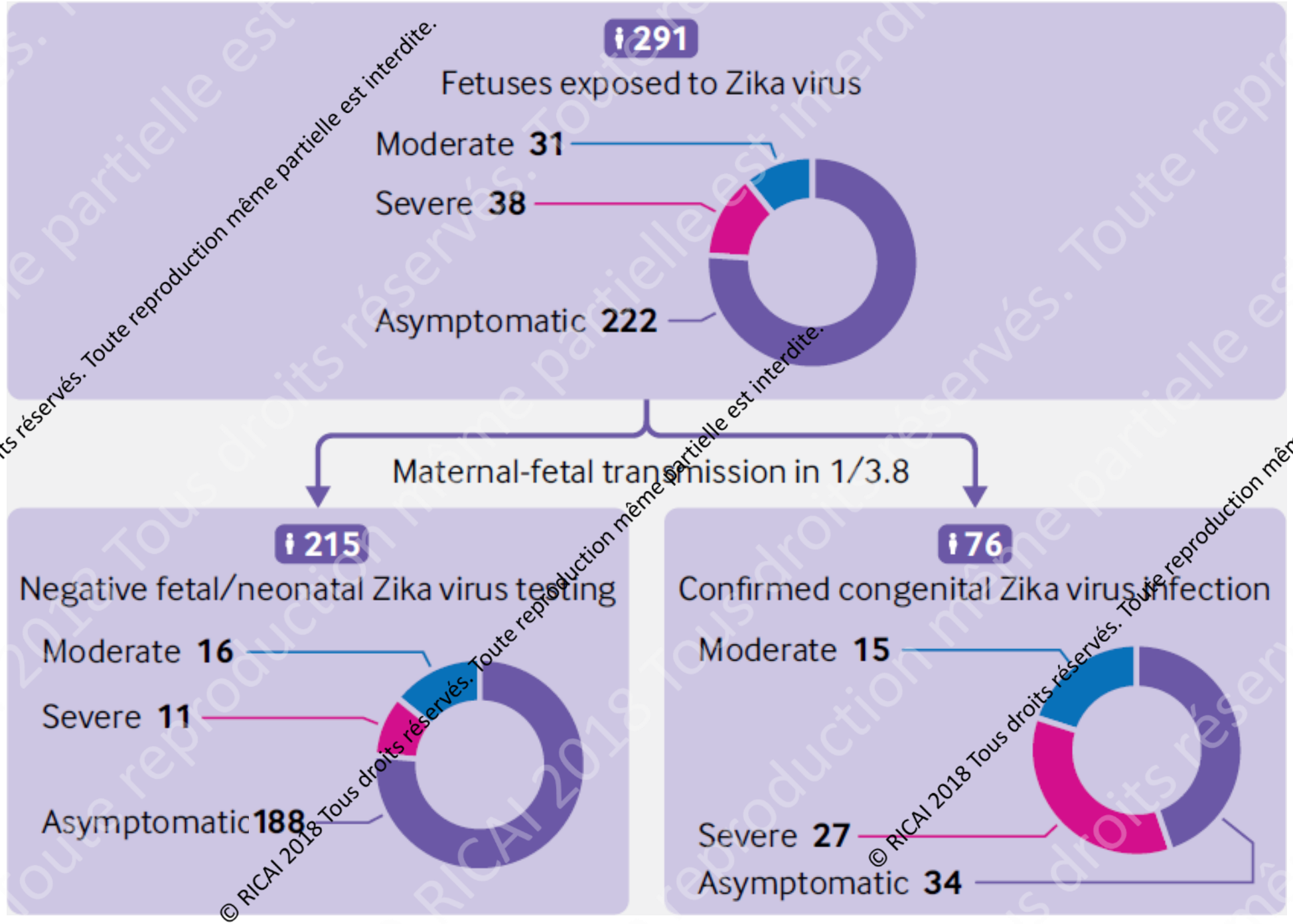
http://dx.doi.org/10.1136/bmj.k4431
Published on line, October 31, 2018







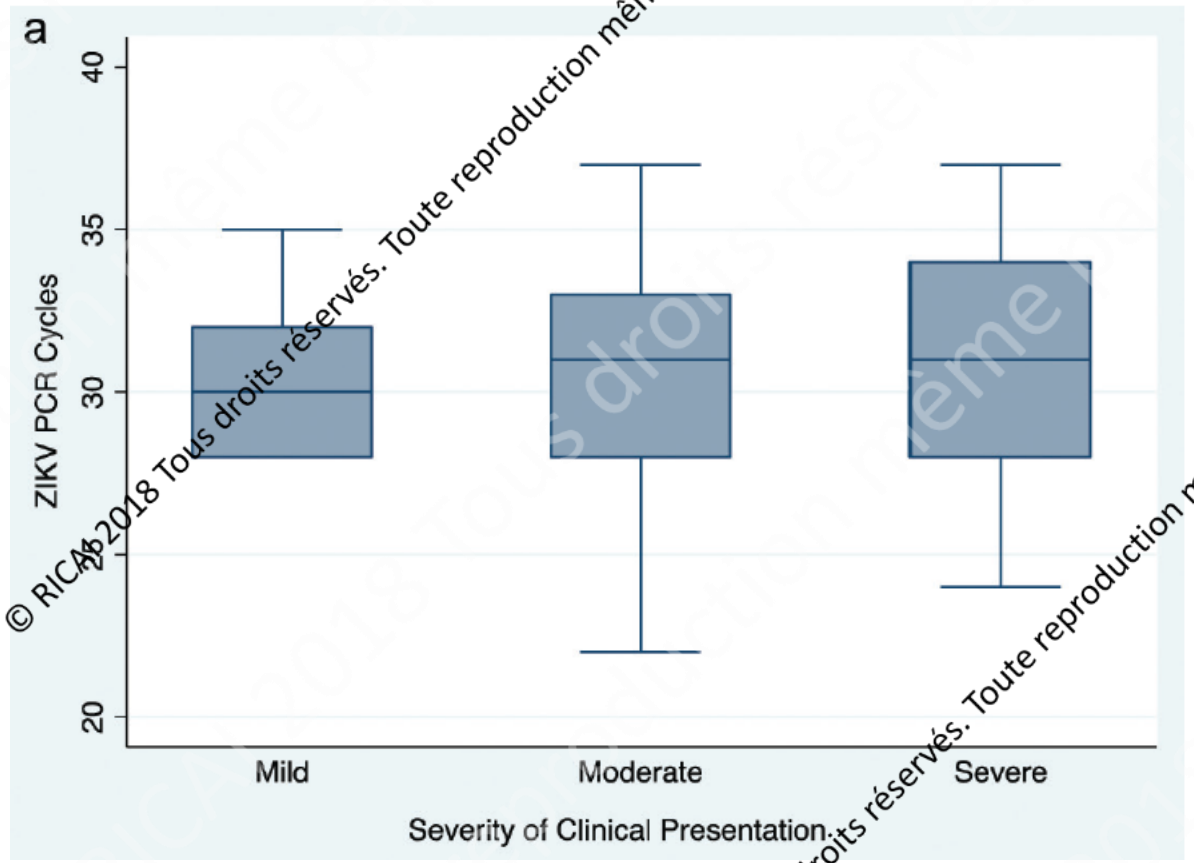
Maternal ZIKV disease severity, virus load, and their relationship to birth outcomes (1)

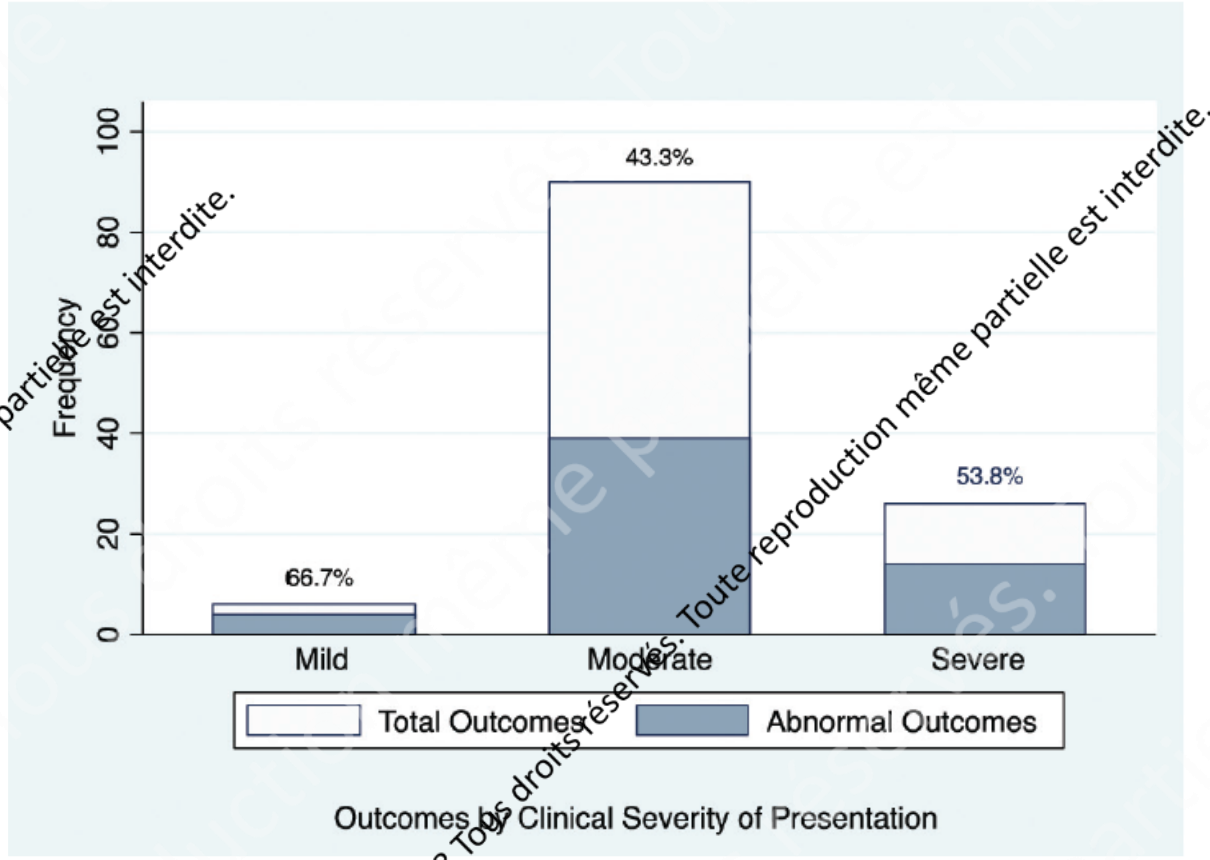
Category	Grade	Score
Severity of rash	Mild: 1+	1
	Moderate: 2+	2
	Severe: 3+	3
Duration of fever	Mild: No fever	1
	Moderate: Fever lasting 1–2 days	2
	Severe: Fever lasting ≥ 3 days	3
Multisystem involvement	Mild: ≤ 2	1
	Moderate: 3–4	2
	Severe: ≥ 5	3
Duration of illness	Mild: ≤ 5 days	1
	Moderate: 6–9 days	2
	Severe: ≥ 10 days	3

- The severity of presentation was calculated as a sum of the 4 individual categories (min = 4 and max = 12)
- The overall clinical severity score was divided into 3 severity grades
  - Mild 3-4
  - Moderate 5-8
  - Severe 9-12

Halai UA, CID 2017;65:877–83

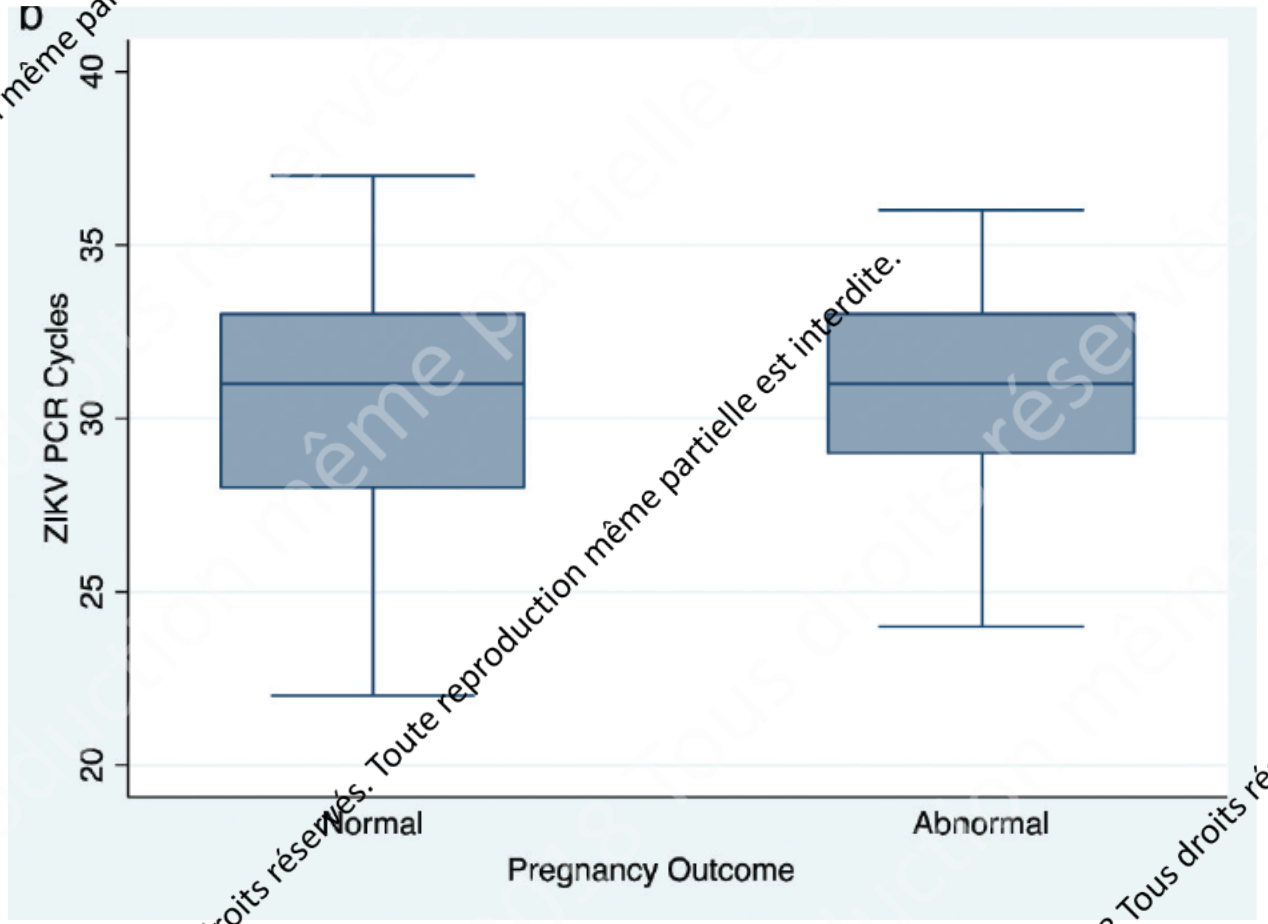
Maternal ZIKV disease severity, virus load, and their relationship to birth outcomes (2)





Halai UA, CID 2017;65:877–83

Maternal ZIKV disease severity, virus load, and their relationship to birth outcomes (3)



Congenital ZIKV syndrome was associated neither with maternal disease severity nor ZIKV-RNA load at time of infection

Halai UA, CID 2017;65:877–83

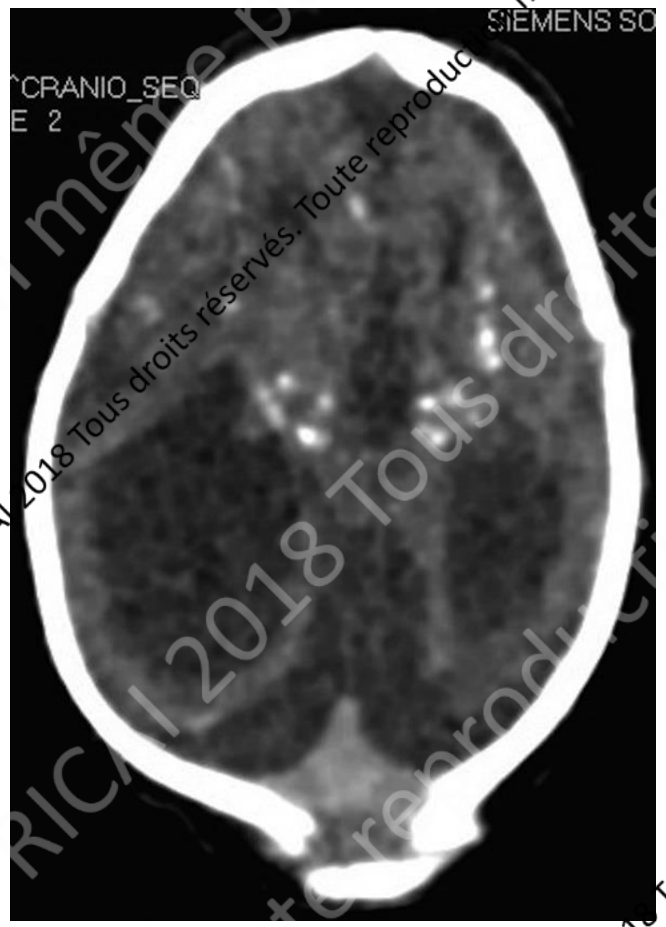
Atteintes auditives et infection aiguë à ZIKV

Sensorineural hearing loss in a case of congenital Zika virus – First case ever reported (1)

- A newborn from a twin pregnancy delivered by CS during the 37th WOG
  - Microcephaly (HC at birth = 28 cm) and bilateral clubfoot
  - The other twin was normal
  - His mother reported a rash and fever on about the 28th day of pregnancy
- Hearing evaluation
  - Transient otoacoustic emissions were absent
  - Auditory brainstem response (ABR) to clicks
    - No response from the left ear
    - In the right ear, response to clicks at 99 dB
    - Frequency-specific ABR with tone bursts confirmed bilateral profound hearing loss
- Etiologic evaluation
  - Capture ELISA was positive for ZIKV IgM on the CSF)
  - TORCH serologies negative

Leal MC, Braz J Otorhinolaryngol 2016

Sensorineural hearing loss in a case of congenital Zika virus – First case ever reported (2)



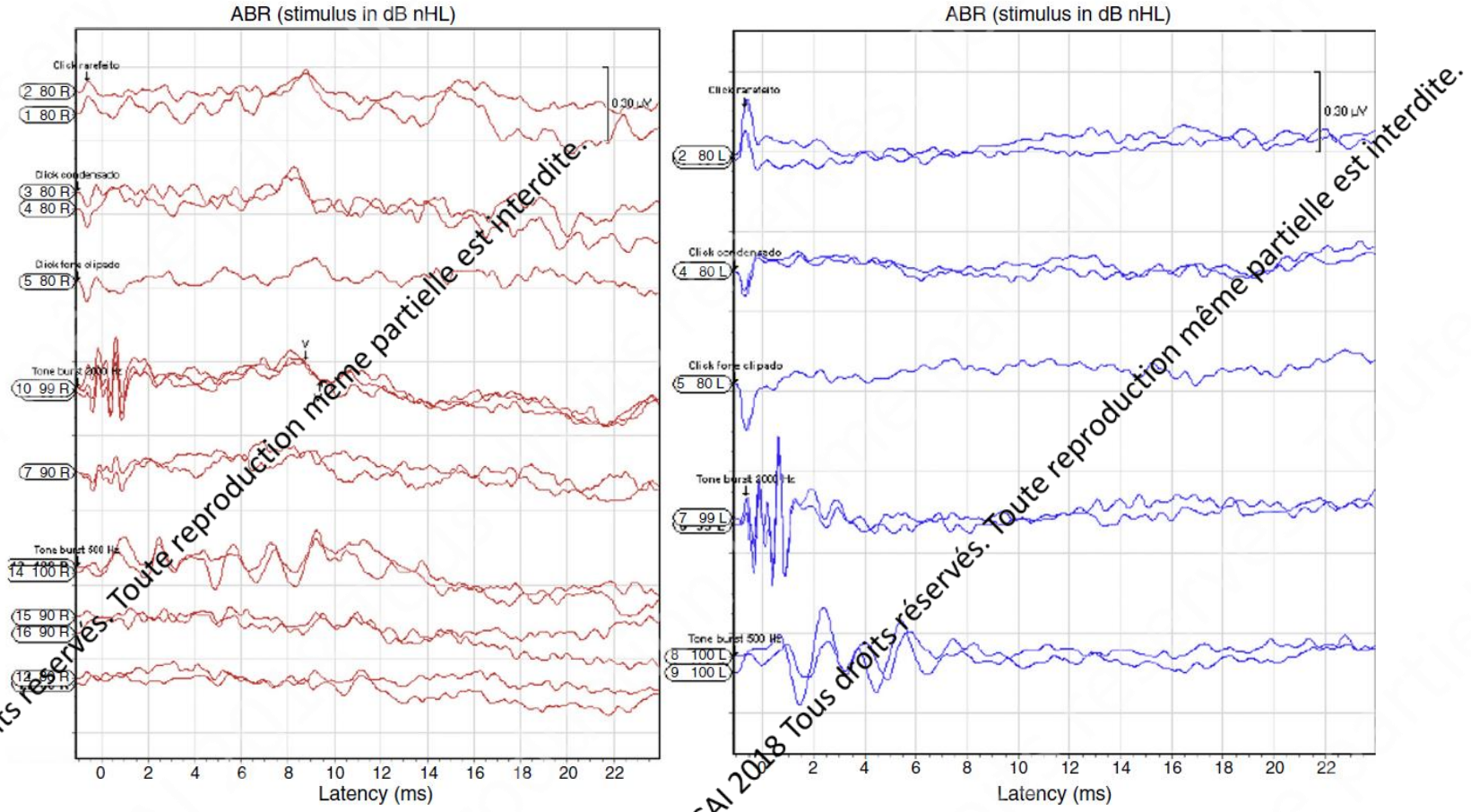


Figure 1 Auditory brainstem evoked responses. Note the bilateral profound deafness.

Leal MC, Braz J Otorhinolaryngol 2016

Sensorineural hearing loss in a case of congenital Zika virus – First case ever reported (3)

- Origin of hearing loss : central?
  - The severity of CNS lesions can be the origin of the auditory impairment
- Origin of hearing loss : peripheral?
  - the absence of optoacoustic emissions indicates that a cochlear damage is more likely to be the cause
- Lessons from TORCH
  - Infants born with rubella and cytomegalovirus congenital infections can also present with microcephaly, but it is well established that in these cases the auditory malfunction is secondary to a peripheral lesion

Leal MC, Braz J Otorhinolaryngol 2016

Données préliminaires des cohortes ZIKA-DFA-BB

- 1003 bébés nés vivants à l'issue d'une grossesse conduite en période d'épidémie
- Tests auditifs réalisés chez 823 bébés
- Anomalies observées chez 45 bébés
  - Cohorte 1 (bébés exposés, cliniquement normaux) 30/644 (4,6%)
  - Cohorte 2 (bébés présentant des anomalies congénitales) 5/27 (18,5%)
  - Cohorte 3 (témoins) 10/152 (6,6%)

Infection congénitale à ZIKV : ce qu'on sait

- Une infection à ZIKV au cours de la grossesse peut entraîner chez le fœtus et le nouveau-né des anomalies malformatives
  - Ces anomalies concernent principalement le SNC
  - Les anomalies congénitales les plus graves résultent d'une infection à ZIKV survenant au cours du 1er trimestre de la grossesse
  - La fréquence des malformations graves après infection à ZIKV est inférieure à 5%
  - Le risque de survenue d'anomalies congénitales après infection à ZIKV n'est pas lié
    - à l'intensité de la virémie maternelle
    - à la présence ou l'intensité des manifestations cliniques

    } au moment de l'infection aiguë
- La microcéphalie
  - est un mauvais indicateur diagnostique et ne résume pas le SICOZ
  - n'a pas la même signification lorsqu'elle est isolée ou intégrée dans un SICOZ
- Le suivi échographique fœtal permet de détecter la quasi-totalité des anomalies et d'aider à la décision d'ITG
- En l'absence de SICOZ, les anomalies sensorielles (vision, audition) sont rares

Infection congénitale à ZIKV : ce qu'on ne sait pas (encore)

- Les enfants ayant développé une infection in utero ont probablement un risque plus important de développer un SICOZ
- Quel est le risque de survenue d'anomalies de développement (neurologique et psychomoteur) des enfants exposés in utero et apparemment indemnes d'anomalies à la naissance ?
- Quelles explorations est-il légitime de proposer à des enfants nés apparemment asymptomatiques de mère ayant eu une infection à ZIKV au cours de la grossesse ?
  - à quelle fréquence ?
  - jusqu'à quel âge ?

Avis relatif à la prise en charge médicale et au suivi des nouveau-nés et nourrissons ayant été exposés au virus Zika *in utero* ou présentant une infection congénitale à virus Zika (complément à l'avis du 21 mars 2016)

Haut Conseil de la Santé Publique

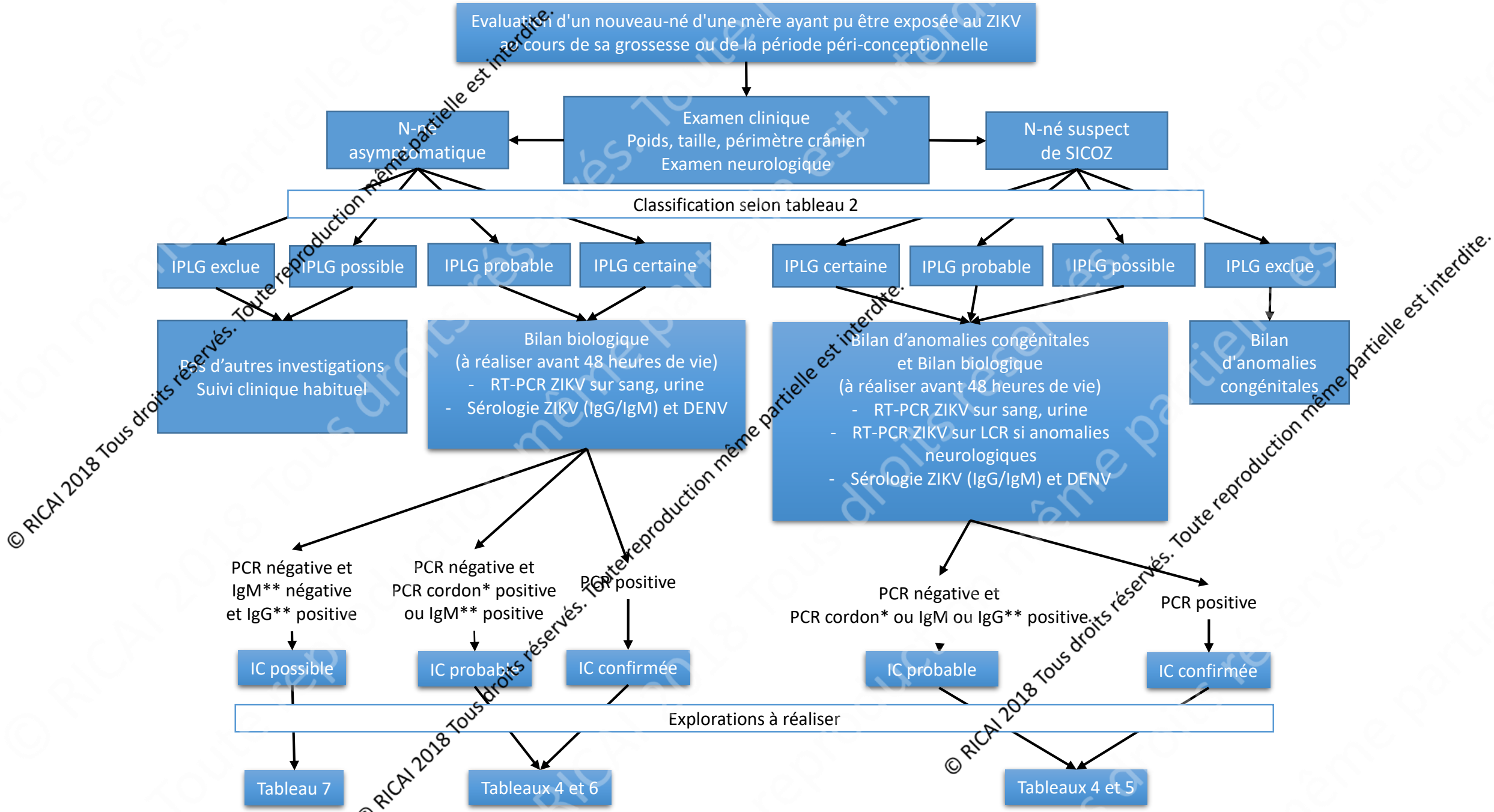
21 décembre 2017

Le HCSP recommande

- une prise en charge des enfants nés de mère infectée ou susceptible d'avoir été infectée par le virus Zika pendant la grossesse
  - tenant compte des résultats d'un premier bilan clinique et biologique,
  - le suivi à long terme étant dépendant des situations clinico-biologiques à la naissance

Diagnostic d'infection à ZIKV pendant la grossesse

Iplg confirmée **(femme infectées par le virus Zika en période péri-conceptionnelle ou durant la grossesse)**	Femme ayant, en période péri-conceptionnelle ou durant la grossesse ou à l'accouchement, un des résultats biologiques suivants : • RT-PCR Zika positive sur le sang, l'urine ou tout autre prélèvement biologique ; • séroconversion en IgM anti-Zika avec négativité des IgM anti-dengue ; • séroconversion en IgG anti-Zika confirmée par séroneutralisation
Iplg probable **(femme susceptible d'avoir été infectées par le virus Zika en période péri-conceptionnelle ou durant la grossesse)**	Femme ayant en période péri-conceptionnelle ou durant la grossesse, rempli une des conditions suivantes : • signes cliniques évocateurs d'infection sans confirmation biologique ; • présence d'IgM anti-Zika (sans IgM anti-dengue) ou d'IgG anti-Zika confirmées par séroneutralisation, sans possibilité de datation de l'infection
Iplg possible **(femme exposée au virus Zika en période péri-conceptionnelle ou durant la grossesse)**	Femme exposée au virus pendant la période péri-conceptionnelle ou durant la grossesse : • sans signe clinique évocateur d'infection ; • ou sans bilan biologique ; • ou avec un bilan biologique non concluant.
Absence d'Iplg	Femme non exposée pendant la grossesse ou biologiquement exclue



Conduite à tenir devant une suspicion post natale d'infection congénitale à virus Zika (1)

- Une infection materno-fœtale par le virus Zika peut parfois être suspectée à distance de la période néonatale, chez des enfants ayant pu être exposés au virus *in utero*. On peut ainsi citer les situations suivantes
  - constatation lors du suivi de l'enfant de signes cliniques évocateurs de SICOZ,
  - apparition de troubles du développement ou des apprentissages,
  - connaissance, après la période néonatale, d'un diagnostic d'infection maternelle confirmée durant la grossesse.
- Il s'agit souvent de nourrissons ou d'enfants chez lesquels on ne dispose pas de diagnostic biologique néonatal

Conduite à tenir devant une suspicion post natale d'infection congénitale à virus Zika (2)

- *Pour les enfants symptomatiques* pour lesquels un diagnostic de SICOZ est évoqué *a posteriori* sur des signes cliniques, et pour ceux ayant des troubles du développement et des apprentissages, le HCSP recommande
  - de rechercher par les moyens appropriés d'autres causes de fœtopathies infectieuses, génétiques ou toxiques
  - de pratiquer, sur le support utilisé pour les dépistages néonataux [s'il est encore disponible (durée de détention du carton variable selon les centres, habituellement de quelques mois)], une RT-PCR et, si possible, un test sérologique Zika. Les résultats des tests pratiqués à partir de ce support doivent être interprétés avec précaution : faux négatifs par quantité réduite de matériel sanguin, détérioration du support au fil du temps..., faux positifs éventuels par souillure du matériel sanguin de l'enfant par d'autres matériels sanguins déposés sur d'autres supports stockés au même endroit
  - de pratiquer les explorations proposées au tableau 4
  - si le diagnostic est finalement retenu, de suivre les enfants comme indiqué tableau 5

Conduite à tenir devant une suspicion post natale d'infection congénitale à virus Zika (3)

- *Pour les enfants asymptomatiques*, chez lesquels un diagnostic d'infection maternelle pendant la grossesse est porté *a posteriori*, le HCSP recommande
  - de s'assurer du bon développement neurologique de l'enfant et de l'absence de signes cliniques de SICOZ
  - de ne pas pratiquer d'exploration biologique ou neuroradiologique complémentaire
  - de suivre les enfants comme indiqué dans le tableau 6

- **Le HCSP préconise** également qu'une étude de cohorte soit mise en place compte tenu notamment des incertitudes à long terme concernant la nature des lésions induites par le virus Zika chez les enfants lorsque l'infection survient *in utero*