



REGIONE DEL VENETO



**AGGIORNAMENTI IN TEMA
DI MEDICINA DEI VIAGGI E
DELLE MIGRAZIONI**

Zikavirus e altre arbovirosi



Venezia, 9 giugno 2016

*Sala Polifunzionale del Palazzo Grandi Stazioni
Regione Veneto, Cannaregio 23*

Zika virus:

**Clinica dei casi non complicati e
definizioni di caso.**

**Sintesi delle evidenze sul rischio di
complicanze: gravidanza, sindrome
di Guillain-Barré, altre?**

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SYMPTOMS OF ZIKA DISEASE ¹



About 1 in 5 people infected with Zika virus actually become ill. ³

Il ~20% delle infezioni è sintomatica:



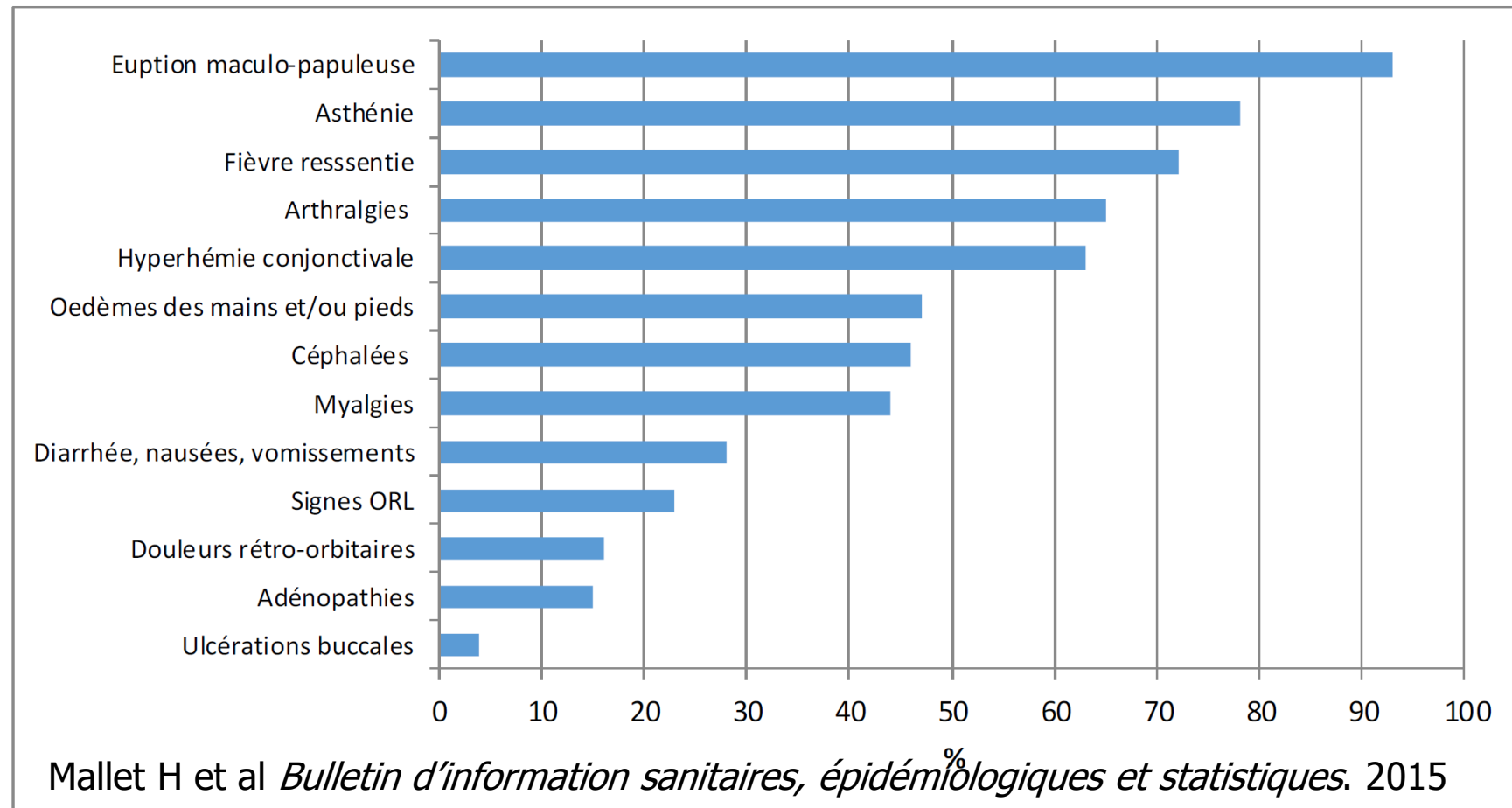
Il periodo di incubazione non è noto con esattezza:

- Probabilmente <14gg
- La maggior parte dei casi importati ha un esordio entro 6 giorni dal rientro
- In casi a trasmissione sessuale: massimo intervallo tra insorgenza sintomi in caso indice e secondario 19 giorni

Frequenza dei sintomi nei casi confermati (Polinesia Francese, 2013-2014)



Figure 1. Fréquence des symptômes chez les cas confirmés (N=297)



Frequenza dei sintomi nei casi confermati (Isola di Yap-Micronesia, 2007)

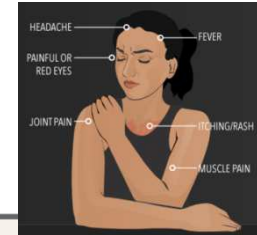


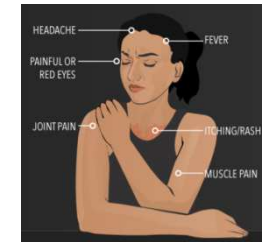
Table 1. Clinical Characteristics of 31 Patients with Confirmed Zika Virus Disease on Yap Island during the Period from April through July 2007.

Sign or Symptom	No. of Patients (%)
Macular or papular rash	28 (90)
Fever*	20 (65)
Arthritis or arthralgia	20 (65)
Nonpurulent conjunctivitis	17 (55)
Myalgia	15 (48)
Headache	14 (45)
Retro-orbital pain	12 (39)
Edema	6 (19)
Vomiting	3 (10)

* Cases of measured and subjective fever are included.

Duffy MR et al *New England Journal of Medicine* 2009

Frequenza dei sintomi nei casi pubblicati in letteratura



Technical Appendix Table 3. Symptoms and sequelae of 195 symptomatic patients with confirmed Zika virus infection reported in Peer-reviewed literature for 1964–2016*

Symptom	No. of patients	% Total patients
Rash	131	67.2
Fever	124	63.6
Arthralgia	56	28.7
Myalgia	46	23.6
Headache	42	21.5
Conjunctivitis	40	20.5
Retroorbital pain	22	11.3
Edema	19	9.7
Pruritus	15	7.7
Fatigue/asthenia	14	7.2

*Data represent reports that included clinical symptoms and sequelae for all symptomatic patients with laboratory-confirmed Zika virus infection (confirmed by serologic testing or RT-PCR, or mode of laboratory testing not specified), with a complete and detailed account of symptoms reported in peer-reviewed literature for January 1, 1964–February 3, 2016 (age range of patients was 4 days–76 years). Reports only for this period included symptoms and therefore met criteria for inclusion in the table. Patients may have experienced ≥ 1 symptom. Less prevalent reported symptoms and sequelae (<5% of patients with reported symptoms) include microcephaly, cerebral calcifications, Guillain-Barré syndrome, prostatitis, hematospermia, hematuria, hypotension, gingival bleeding, hearing loss, pruritus, malaise, diarrhea, nausea/vomiting, constipation, edema, sore throat, cough, stomach pain, anorexia, lightheadedness, dizziness, chills, oral aphthous ulcers, photophobia, lymphadenopathy, rhinorrhea, and burning sensation of palms/soles.

References: (3,7,8,11,23–25,34,36,37,39–41,46,47,56,57,60–62,68,75,87,88,99,101,108,109).

Sintomi in donne in gravidanza, Brasile 2015:

- Gruppo 1: rash insorto <5gg e PCR per ZIKV positiva (urine, saliva, siero)
- Gruppo 2: rash insorto <5gg e PCR per ZIKV negativa (urine, saliva, siero)

Symptoms — no./total no. (%)			
Rash§	72/72 (100.0)	16/16 (100.0)	
Any			0.47†
Median duration	4	5.5	
Range	2–14	2–60	
Macular	37/72 (51.4)	8/16 (50.0)	1.00
Maculopapular	32/72 (44.4)	2/16 (12.5)	0.02
Other	3/72 (4.2)	6/16 (37.5)	0.001
Pruritus	69/72 (95.8)	14/15 (93.3)	0.54
Arthralgia or arthritis	46/72 (63.9)	7/16 (43.8)	0.16
Conjunctival injection	42/72 (58.3)	2/15 (13.3)	0.002
Headache	38/72 (52.8)	9/16 (56.3)	1.00
Fatigue or malaise	35/72 (48.6)	7/16 (43.8)	0.79
Retro-orbital pain	34/69 (49.3)	5/16 (31.3)	0.27
Myalgia	30/72 (41.7)	8/16 (50.0)	0.59
Lymphadenopathy	29/72 (40.3)	1/15 (6.7)	0.015
Localized	15/29 (51.7)	0/1	1.00
Generalized	14/29 (48.3)	1/1 (100.0)	1.00
Paresthesia	27/58 (46.6)	4/10 (40.0)	0.75
Edema	23/64 (35.9)	4/16 (25.0)	0.56



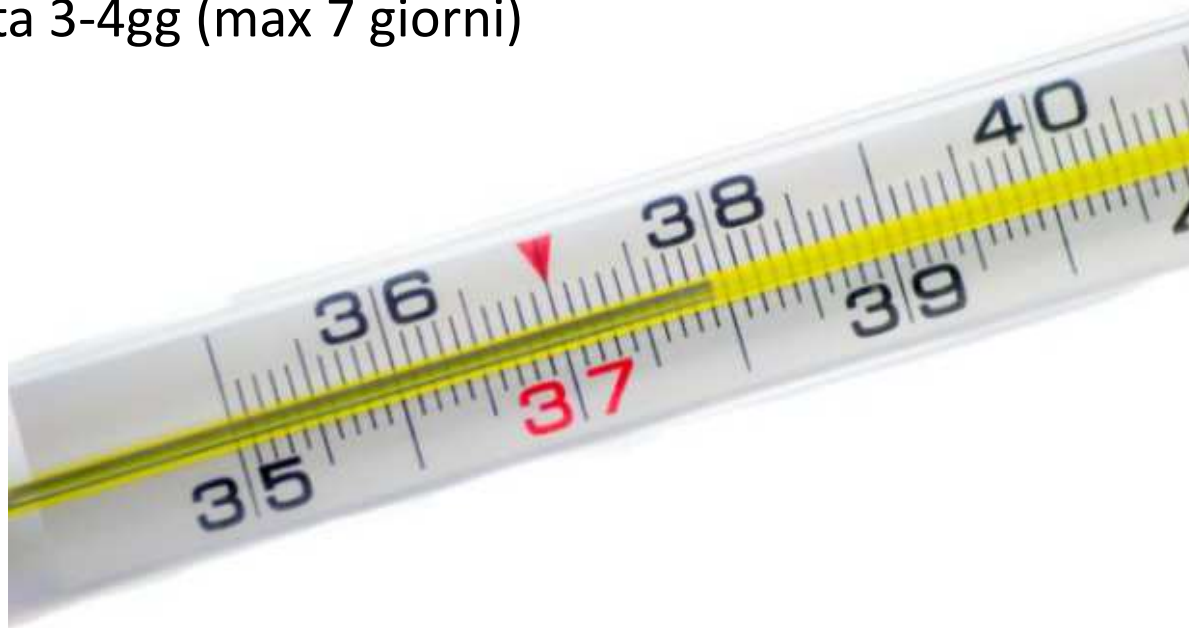
Rash cutaneo

- Presente nel **90-100%** dei casi
- Talvolta preceduto da febbre (1-4 giorni prima)
- Maculare o maculo-papulare
- Pruriginoso nel 10-100% dei casi
- A evoluzione centrifuga (dal tronco alle estremità)
- Durata 4-5 gg (range 2-14)



Febbre

- Quando presente è il primo sintomo ad apparire assieme ad astenia
- Presente nel 65-70% dei casi
- Generalmente $<38^{\circ}\text{C}$
- Durata 3-4gg (max 7 giorni)



Waddel et al *Plos One* 2016

Mallet H et al *Bulletin d'information sanitaires, épidémiologiques et statistiques*. 2015

Artralgie ± Edemi

- Presente **nel 65%** dei casi
- Associate a edemi periarticolari nel 20-45%
- Localizzazioni più frequenti:
 - Mani 30%-40%
 - Piedi 17%
 - Ginocchia 16%
 - Polsi 10%
- Durata ~7gg (max 1 mese)

Mallet H et al
*Bulletin d'information sanitaires,
épidémiologiques et statistiques* 2015



Brazil P *New England Journal of Medicine* 2016



Zanluca C et al *Mem Inst Oswaldo Cruz* 2015

Iperemia congiuntivale

- Presente nel 55-60% dei casi
- Bilaterale
- Non purulenta
- Durata <7gg (max 14gg)



Linfoadenopatie

- Presente del 15-40*%
- Ascellare, inguinale, retroauricolare
- Può persistere fino a 2 settimane
- *casistica di donne in gravidanza in Brasile



Alterazioni esami ematici

- Pochi dati, esami generalmente normali, raramente riportate:
 - Lieve linfopenia
 - Lieve neutropenia
 - Lieve-moderata piastrinopenia
 - Lieve incremento di PCR, ferritina, fibrinogeno, LDH, ALT

Diagnosi differenziale

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

... ma anche: Morbillo, Rosolia, V° malattia, *Streptococcus* B emolitico gruppo A, Leptospirosi, Malaria

CDC. Zika virus-What clinician should know? http://emergency.cdc.gov/coca/ppt/2016/01_26_16_zika.pdf

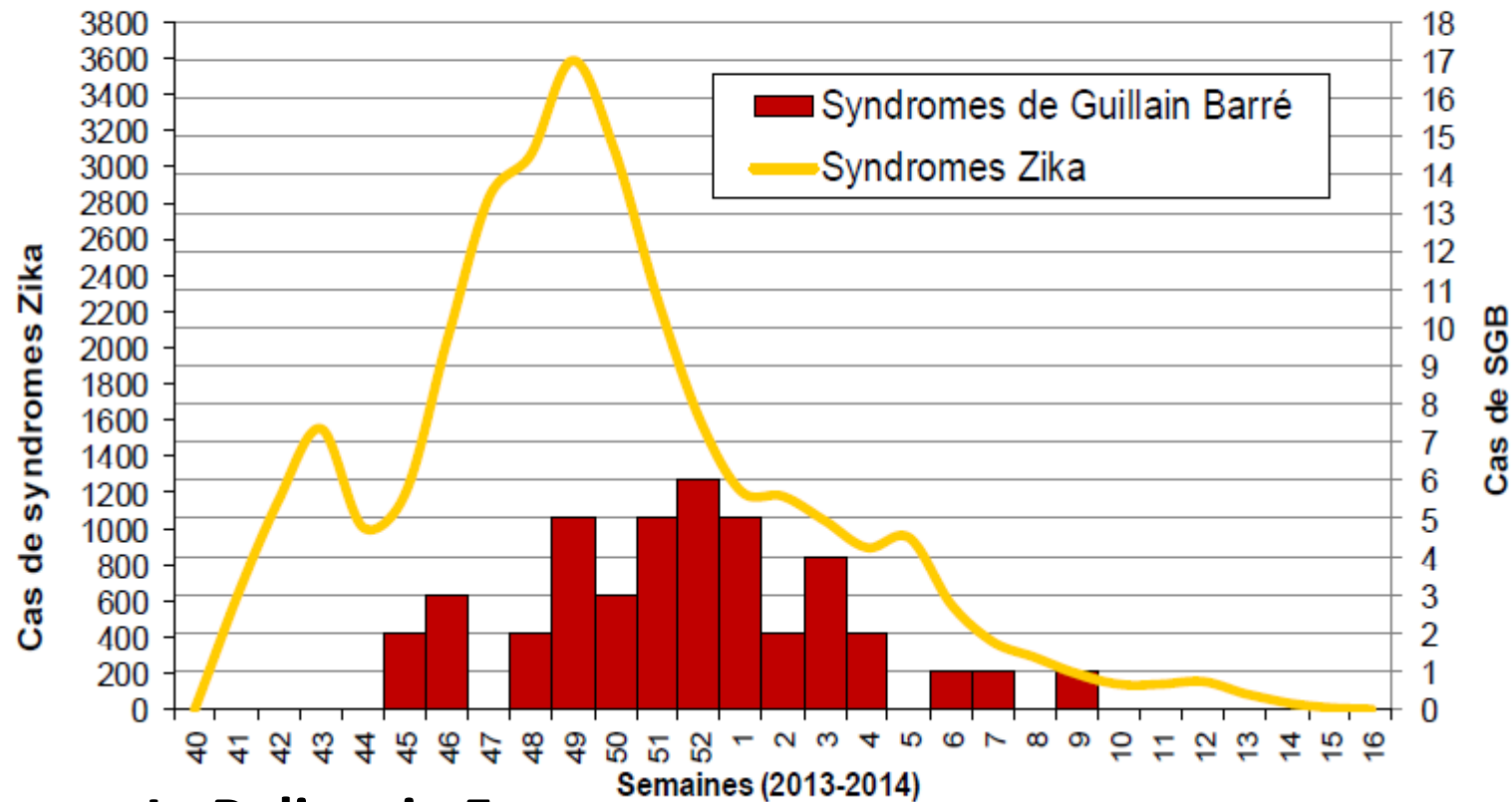
Proposed case definition for surveillance of Zika virus infection

Definition	
Clinical criteria	<p>A person presenting with a rash, with or without fever and at least one of the following signs and symptoms:</p> <ul style="list-style-type: none"> • arthralgia or • myalgia or • non-purulent conjunctivitis/hyperaemia
Laboratory criteria	<p><u>Laboratory criteria for a probable case</u> Detection of Zika-specific IgM antibodies in serum</p> <p><u>Laboratory criteria for a confirmed case</u> At least one of the following:</p> <ul style="list-style-type: none"> • detection of Zika virus nucleic acid in a clinical specimen • detection of Zika virus antigen in a clinical specimen • isolation of Zika virus from a clinical specimen • detection of Zika virus specific IgM antibodies in serum sample(s) and confirmation by neutralisation test; • seroconversion or four-fold increase in the titre of Zika-specific antibodies in paired serum samples
Epidemiological criteria	<p>History of exposure in an area with transmission of Zika within two weeks prior to onset of symptoms or Sexual contact with a male confirmed case of Zika virus infection or Sexual contact with a male who had been in an area with Zika virus transmission in the past four weeks A list of Zika-affected areas is kept updated on the ECDC website (link).</p>
Classification	
Probable case	<p>A person meeting the clinical criteria and the epidemiological criteria. A person meeting the laboratory criteria for a probable case.</p>
Confirmed case	<p>A person meeting the laboratory criteria for a confirmed case.</p>

Sindrome di Guillain Barré



Figure 3. Courbe épidémique des cas de SGB durant l'épidémie de zika en Pf, 2013-2014



In Polinesia Francese:

- 42 casi in 4 mesi
- Prima del 2013: ~5 casi/anno in media

Mallet H et al *Bulletin d'information sanitaires, épidémiologiques et statistiques*. 2015

Sindrome di Guillain Barré in Polinesia Francese



- 100% (di 42) dei pazienti con GBS avevano anticorpi neutralizzanti anti ZIKV vs 54% (di 98) dei controlli [OR=34.1 (5.8–/+∞)]
- 88% sindrome virale 2-23 giorni prima dei sintomi neurologici (mediana 6 giorni)
- EMG: neuropatia assonale motoria acuta (AMAN)
- Assenza dei caratteristici anticorpi anti ganglioside (dubbio su patogenesi autoimmune?? Ruolo diretto di ZIKV??, generalmente intercorrono 3-6 settimane tra infezione e GBS)
- 29% hanno richiesto supporto ventilatorio
- Terapia: immunoglobuline o immunoglobuline+plasmaferesi (1 solo caso)
- Nessun decesso
- Rischio di sviluppare una sindrome di Guillain Barré dopo una infezione da Zika virus: stimato ~2.4% (simile a quello che si ha dopo una infezione da *Campylobacter jejuni*)

Sindrome di Guillain Barré e ZIKV in altri paesi



Table 4. Countries, territories or areas reporting Guillain-Barré syndrome (GBS) potentially associated with Zika virus infection.

Classification	Country / territory / area
Reported increase in incidence of GBS cases, with at least one GBS case with confirmed Zika virus infection	Brazil, Colombia, Dominican Republic, El Salvador*, French Polynesia, Honduras, Suriname, Venezuela (Bolivarian Republic of)
No increase in GBS incidence reported, but at least one GBS case with confirmed Zika virus infection	French Guiana, Haiti, Martinique, Panama, Puerto Rico

* GBS cases with previous history of Zika virus infection were reported by the International Health Regulations (2005) National Focal Point in United States of America.

WHO Situation Report. Zika virus, Microcephaly and Guillain-Barré syndrome. June 2, 2016

Casi di sindrome di Guillain Barré nel periodo gennaio-novembre 2015 (dati WHO 8 Febbraio 2016):

1,708 casi corrispondenti a un incremento percentuale nei seguenti stati: Alagoas (516.7%), Bahia (196.1%), Rio Grande do Norte (108.7%), Piauí (108.3%), Espírito Santo (78.6%), and Rio de Janeiro (60.9%)

Altre sindromi neurologiche nell'adulto

Zika Virus Associated with Meningoencephalitis

TO THE EDITOR: Zika virus (ZIKV) is currently spreading widely, while its clinical spectrum remains a matter of investigation. Evidence of a relationship between ZIKV infection and cerebral birth abnormalities^{1,2} is growing.³ An increased incidence of some peripheral nervous syndromes

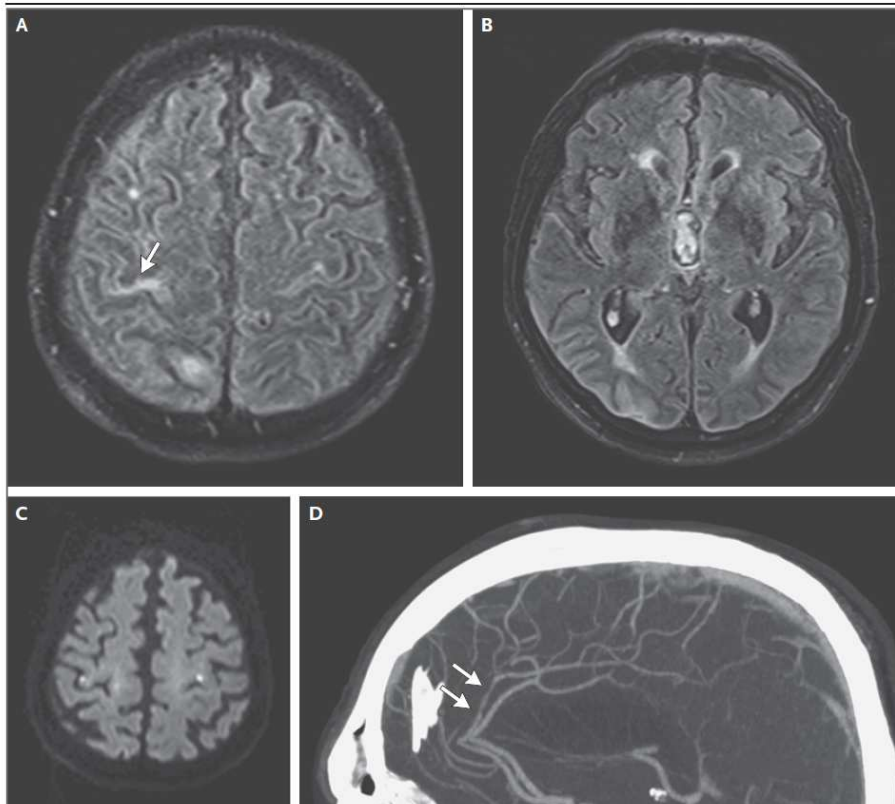


Figure 1. Imaging of the Brain.

MRI with the use of fluid-attenuated inversion recovery (FLAIR) imaging revealed subcortical white-matter hyperintensities in the right frontal region, the right parietal region (Panel A), the right temporo-occipital region (Panel B), and bilateral Rolandic regions (Panel A). The slight hyperintensity of the right Rolandic fissure (Panel A, arrow) is suggestive of meningitis. The multiple punctuated hyperintensities on diffusion-weighted sequences are suggestive of ischemic foci (Panel C). The MRI with FLAIR imaging and diffusion-weighted sequences were performed with the use of a 3T MRI unit (Magnetom Verio, Siemens). The computed tomographic angiogram shows an irregular narrowing of the right callosomarginal artery (Panel D, arrows). Angiography was performed with the use of a Discovery CT750 HD scanning system (GE Medical Systems).

Carteaux NEJM 2016

Acute myelitis due to Zika virus infection

Sylvie Mécharles, Cécile Herrmann, Pascale Poullain, Tuan-Huy Tran, Nathalie Deschamps, Grégory Mathon, Anne Landais, Sébastien Breurec, Annie Lannuzel



In January, 2016, a 15-year-old girl with a history only of an ovarian cyst was admitted to hospital in Pointe-à-Pitre, Guadeloupe, with left hemiparesis. 7 days previously she had presented to the emergency department with left arm pain, frontal headaches, and conjunctival hyperaemia, but no fever, signs of meningeal irritation, or sensory or motor deficits. The day of admission, she developed acute lower back pain, paraesthesia on the left side of her body, and weakness in her left arm. On admission she had slight left-sided weakness and proximal pain of the left arm and leg, exacerbated on movement, but no fever or signs of meningism, and Glasgow Coma Score (GCS) 15. Laboratory analyses were normal except for raised leucocytes ($11.5 \times 10^9/L$) and polymorphonuclear leucocytes ($9.2 \times 10^9/L$). Brain MRI was normal.

On day 2, she developed dysuria and urinary retention needing catheterisation, but no abnormal urinary frequency or urgency. The left-sided hemiparesis and pain worsened, and we noted loss of temperature sensation below the T2 dermatome on the left and T4 on the right, and bilateral Hoffman signs. Spinal MRI showed lesions of the cervical and thoracic spinal cord. The cervical lesion was enlarged, suggesting oedema (figure). Conus medullaris and lumbar roots were normal, suggesting the bladder dysfunction could be linked to spinal damage. Electromyography and cerebrospinal fluid examination (including isoelectric focusing protein profile) were normal. We detected high concentrations of Zika virus on specific real-time reverse PCR (Eurobio, Les Ulis, France) in serum, urine, and cerebrospinal fluid on the second day of her admission (9 days after symptom onset). PCR for varicella zoster and herpes simplex viruses, *Legionella*, and *Mycoplasma pneumoniae* in her cerebrospinal fluid were negative. She had no serological signs of acute infection with cytomegalovirus, Epstein-Barr, chikungunya or dengue viruses, syphilis, or Lyme disease; tests for HIV and human T-cell lymphotropic virus (HTLV) were negative; and aquaporin-4 antibodies, a marker of neuromyelitis optica, were absent.

We started methylprednisolone 1 g daily for 5 days. On the seventh day of admission her neurological condition improved and we could remove the catheter. 1 month after admission she had moderate weakness in both legs but was able to walk unaided. Repeat MRI showed reduced cervical spinal oedema (appendix).

The Zika virus epidemic that started in Brazil in May, 2015, spread to 28 countries in February, 2016, including the French Caribbean Islands of Martinique and Guadeloupe. Like dengue, Zika is an arthropod-borne virus of the Flaviviridae family transmitted by *Aedes* mosquitoes. Until recently, Zika was thought to cause benign infections in humans.¹ The presence of Zika virus in the cerebrospinal fluid of our patient with acute

myelitis suggests that this virus might be neurotropic. In addition to the usual clinical picture of myelitis she had severe pain. Absence of intrathecal immunoglobulins and normal brain MRI excluded acute disseminated encephalomyelitis. The neurotropism of flaviviruses such as dengue, Japanese encephalitis, and West Nile viruses, which might be responsible for invasive encephalitis and transverse or extensive myelitis,^{2,3} is well documented. West Nile virus might also affect lumbosacral nerve roots in addition to the spinal cord,⁴ and retrograde axonal transport from infected peripheral nerves has been shown.⁵ Zika virus infection should be considered in patients with acute myelitis living in or travelling from endemic areas, and further study should clarify the spectrum and incidence of neurological associations.

Contributors

SM, CH, PP, THT, ND, GM, ALand, SB, and ALann managed the patient. ALann, SM, and SB wrote the report. Consent to publication was obtained.

References

1. Pauci AS, Morens DM. Zika virus in the Americas—yet another arbovirus threat. *N Engl J Med* 2016; 374: 601–04.
2. Lariik A, Chiong Y, Lee LC, Ng YS. Longitudinally extensive transverse myelitis associated with dengue fever. *BMJ Case Rep* 2012; published online May 11. DOI:10.1136/bcr.2012.20115783.
3. Verma R, Pralauaj HN, Paul TB, Giti P. Acute transverse myelitis following Japanese encephalitis viral infection: an uncommon complication of a common disease. *BMJ Case Rep* 2012; published online Sept 24. DOI:10.1136/bcr.2012.2007094.
4. Ali M, Saifeld Y, Soli J, Llave A, Weathers S. West Nile Virus Infection: MR imaging findings in the nervous system. *Am J Neuroradiol* 2005; 26: 289–97.
5. Samuel MA, Wang H, Siddharthan V, Morrey JD, Diamond MS. Axonal transport mediates West Nile virus entry into the central nervous system and induces acute flaccid paralysis. *Proc Natl Acad Sci USA* 2007; 104: 17140–45.



Figure: Magnetic resonance imaging (MRI) showing myelitis in Zika virus infection. (A) T2 sequences showing hyperintensity in the thoracic cord T5–T8 (arrow) and enlargement of the cervical spinal cord. (B) Sagittal short time inversion recovery (STIR) sequences showing hyperintensity in the cervical spinal cord C4–C7 (arrow).

Mecharles Lancet 2016



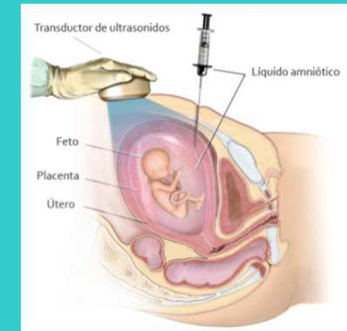
May 2015: Brazil diagnosis of first autochthonous cases (North-Eastern States). The virus probably was circulating since early 2015



September 2015: first reports from physician of an increase in the number of infants born with microcephaly in Zika virus-affected areas



October 2015: Brazil increase of microcephaly cases (North-Eastern States). Risk ↑20 times from estimated incidence of 1/10,000 to 20/10,000



December 2015: Detection of Zika virus RNA from amniotic fluid of 2 fetuses with microcephaly.



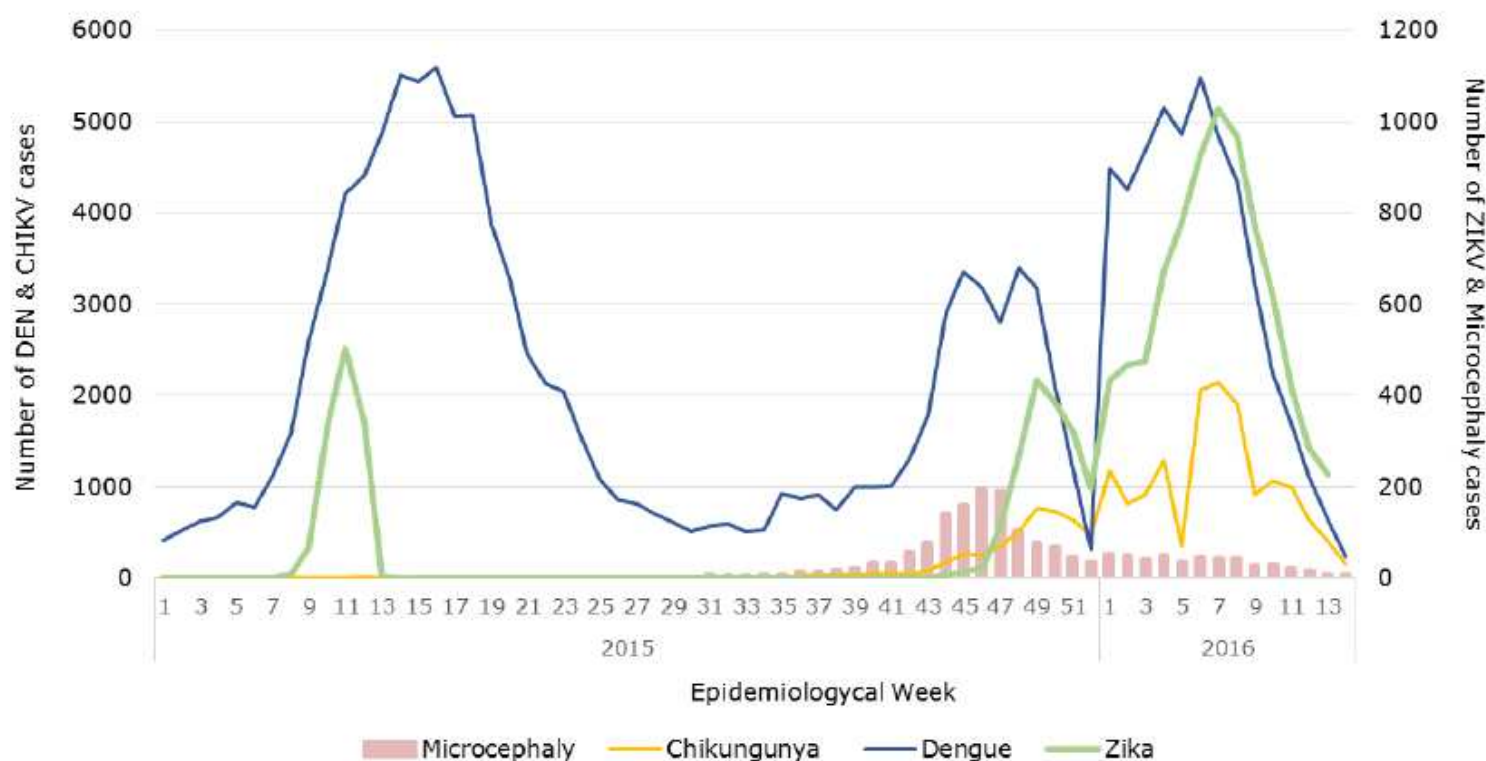
May 2016: 8 countries report CNS and other fetal malformation potentially related to ZIKV



November 2015-February 2016: ECDC, CDC and WHO alerts on possible association between microcephaly and ZIKV

Aumento di casi di microcefalia nello stato di Pernambuco, Brasile. Il picco di incidenza corrisponde a 7-8 mesi dopo il picco di incidenza dell'epidemia di Zika virus

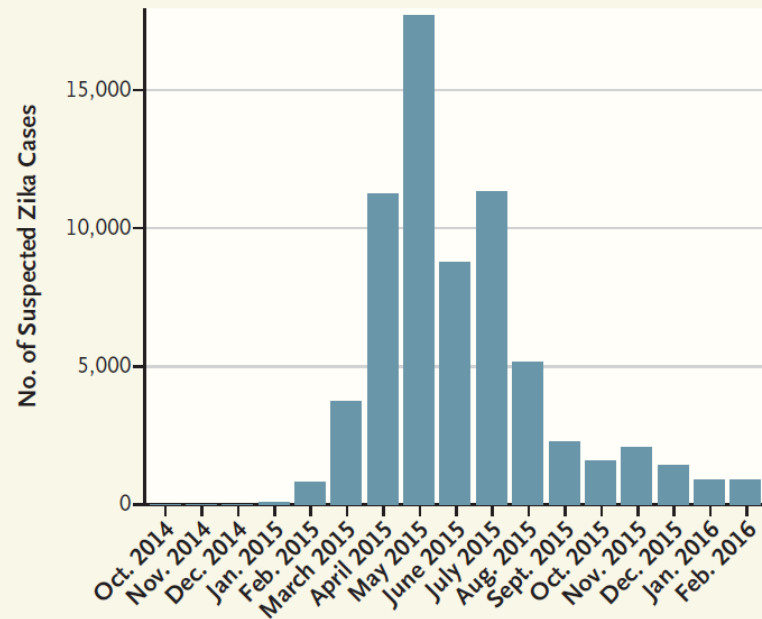
Figure 7. Reported cases of dengue, chikungunya, Zika virus and microcephaly in Pernambuco state, Brazil by EW, 2015 to 2016.



Source: Data published by the Pernambuco State Secretary of Health, Brazil.

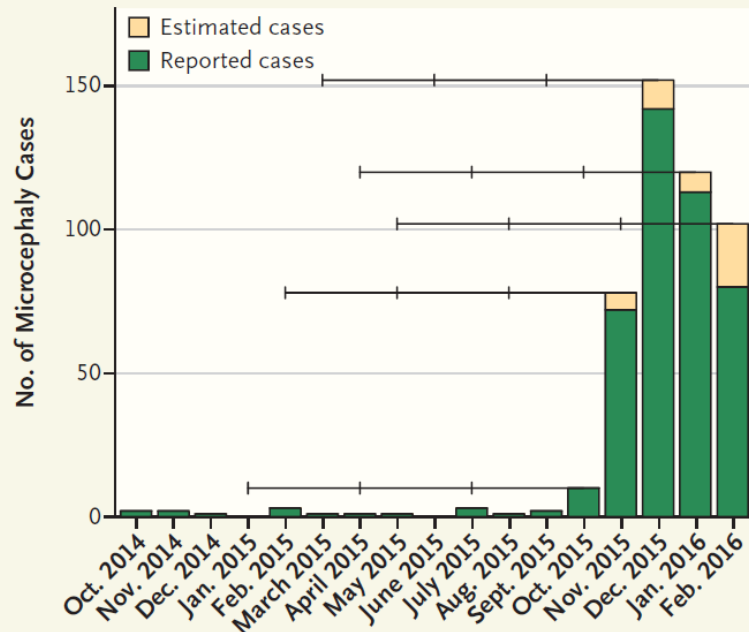
PAHO. Zika Epidemiological Update April 28, 2016

A Suspected Zika Cases



Epidemia di ZIKV e casi di microcefalia nello stato di Bahia, Brasile.

E Microcephaly Cases



Il picco di incidenza corrisponde a 7-8 mesi dopo il picco di incidenza dell'epidemia di Zika virus

Johansson NEJM 2016

Situazione in Brasile

(aggiornamento 21 Maggio 2016)

Da ottobre 2015 al 21 maggio 2016:

Numero casi
microcefalia/anno in
Brasile negli anni
precedenti: 200/anno

7 623 casi sospetti di microcefalia (1)

1 434 microcefalia confermata e suggestiva di infezione congenita (2)

208 con infezione da ZIKV confermata in laboratorio (3)

2 932 microcefalia esclusa (4)

3 257 con indagini in corso

Note:

1) Neonati con circonferenza cranica <33 cm o <32 cm (dal 9/12/2015)

2) Neonati con microcefalia e segni indicativi di infezione congenita, come calcificazioni intracraniche, dilatazione dei ventricoli cerebrali o alterazioni della fossa posteriore identificati con neuroimaging o identificazione del virus Zika nei test di laboratorio.

3) Neonati con test di laboratorio (PCR o sierologia) positiva per ZIKV

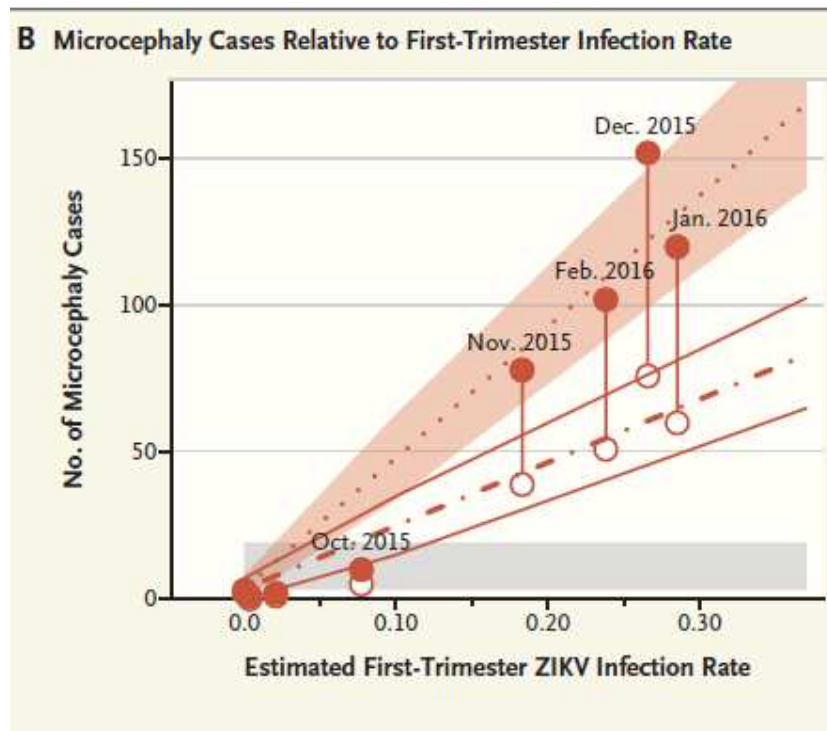
4) Assenza di microcefalia o malformazioni da altra causa confermata

Secretarias de Saúde dos Estados e Distrito Federal (dados atualizados até 21/05/2016).

http://combateaedes.saude.gov.br/images/sala-de-situacao/informe_microcefalia_epidemiologico27.pdf

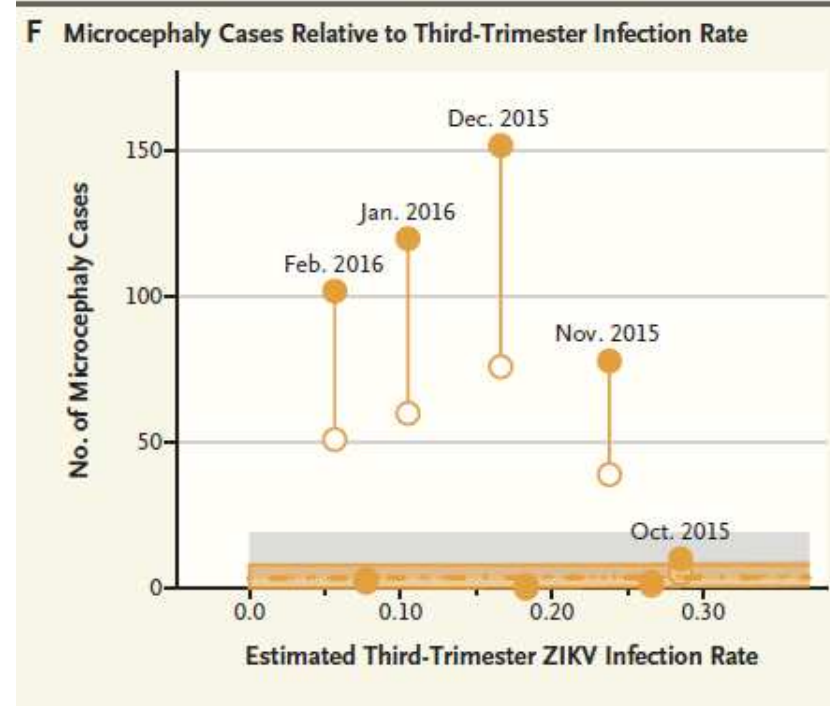
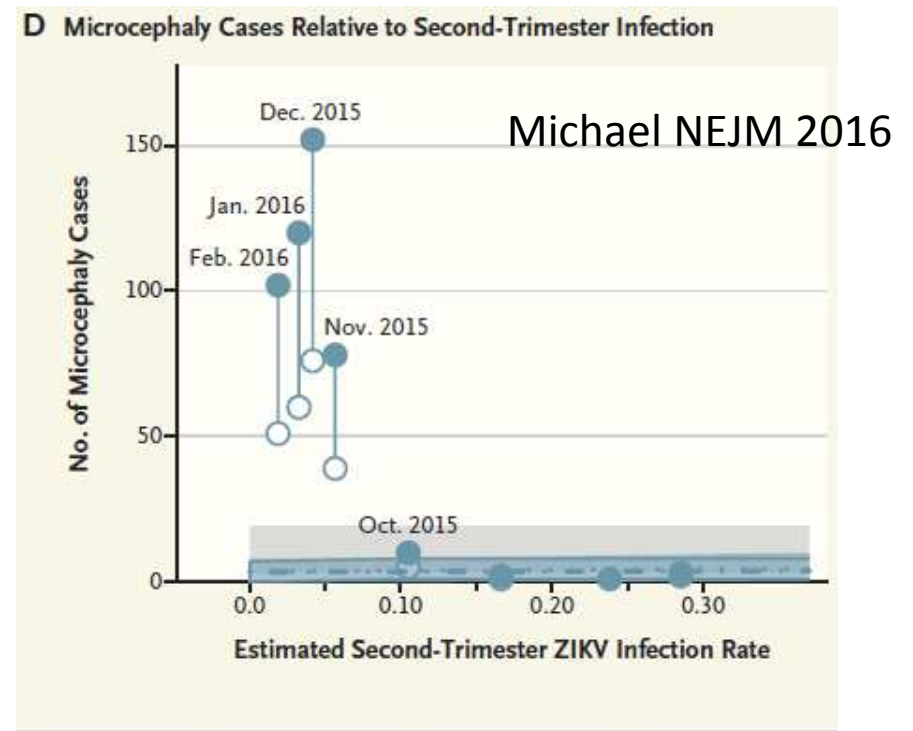
Associazione microcefalia/Zika virus in Polinesia Francese (studio retrospettivo)

- Epidemia Ottobre 2013-Aprile 2014
- 66% della popolazione infettata (32,000 casi)
- Ricerca casi di microcefalia nel periodo settembre 2013-luglio 2015
- 8 casi trovati, 88% (7/8) del quali nel periodo marzo 2014-luglio 2014*
- Tali osservazioni sono consistenti con una infezione avvenuta nel I° trimestre
- **Rischio di microcefalia per infezione materna nel primo trimestre (stimato con modello matematico) ~1% ovvero un incremento della prevalenza di microcefalia nei neonati di donne infette da 2/10,000 a 95/10,000**
- *** solo 7 sottoposti a amniocentesi per ZIKV di cui 4 positivi (Besnard Eurosurveillance 2016)**



Stima del rischio di microcefalia in caso di infezione da ZIKV nello stato di Bahia secondo il trimestre di infezione (con modello matematico): Linearità tra tasso di infezione da ZIKV e casi di microcefalia se l'infezione avviene nel primo trimestre e assenza di correlazione per gli altri trimestri.

Tasso di rischio stimato: **tra 0.88%** (95% credible interval, 0.80 to 0.97), assumendo un rischio di infezione da ZIKV del 80% e una sovrannotifica di microcefalia del 100% e , **e 13.2%** (95% credible interval, 12.0 to 14.4), assumendo un tasso di infezione da ZIKV del 10% e assenza di sovrannotifica di microcefalia.



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

Patrícia Brasil, M.D., Jose P. Pereira, Jr., M.D., Claudia Raja Gabaglia, M.D.,
Luana Damasceno, M.S., Mayumi Wakimoto, Ph.D.,
Rita M. Ribeiro Nogueira, M.D., Patrícia Carvalho de Sequeira, Ph.D.,
André Machado Siqueira, M.D., Liege M. Abreu de Carvalho, M.D.,
Denise Cotrim da Cunha, M.D., Guilherme A. Calvet, M.D.,
Elizabeth S. Neves, M.D., Maria E. Moreira, M.D., Ana E. Rodrigues Baião, M.D.,
Paulo R. Nassar de Carvalho, M.D., Carla Janzen, M.D.,
Stephanie G. Valderramos, M.D., James D. Cherry, M.D.,
Ana M. Bispo de Filippis, Ph.D., and Karin Nielsen-Saines, M.D.

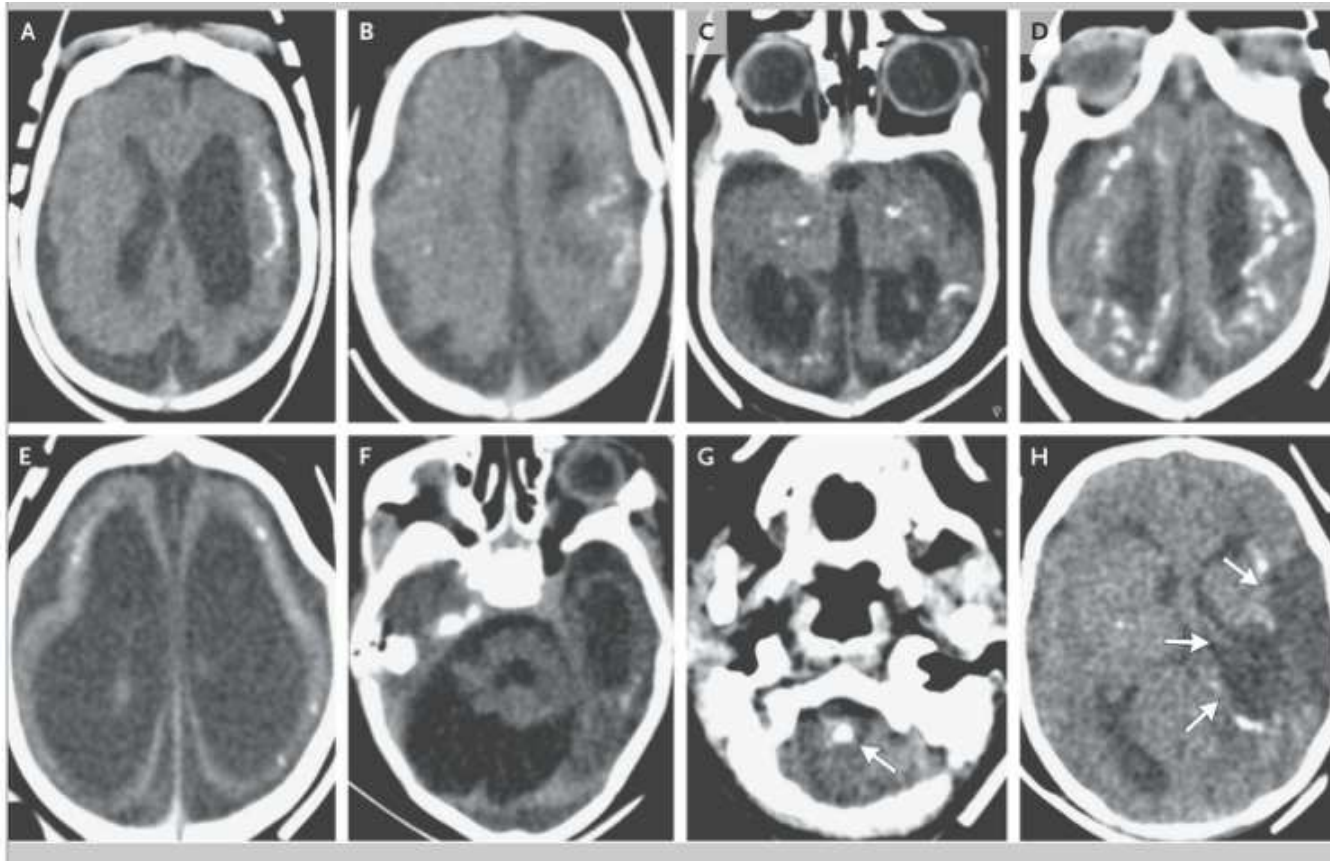
Anomalie fetali nel 29% (12 di 42) delle gestanti con infezione da Zika virus e in nessuna tra le 12 gestanti testate ma risultate negative.

Le anomalie comprendevano morti fetali a 36 e 38 settimane di gestazione (2 feti), restrizione di crescita in utero con o senza la microcefalia (5 feti), calcificazioni ventricolari o altre lesioni del sistema nervoso centrale (7 feti), anomalie del volume del liquido amniotico o del flusso dell'arteria cerebrale o ombelicale (7 feti).

Quadri neuroradiologici nei neonati, Brasile

CT scan findings in 23 infant with probable Zika virus congenital infection (IgM in CSF positive in 7/7 cases with available samples)

- Intracranial calcifications were seen in all the infants
- Ventriculomegaly was found in all the infants
- All the infants had global hypogyration of the cerebral cortex
- Cerebellar hypoplasia was present in 74%



Original Investigation

Ocular Findings in Infants With Microcephaly Associated With Presumed Zika Virus Congenital Infection in Salvador, Brazil

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IMPORTANCE The Zika virus (ZIKV) has rapidly reached epidemic proportions, especially in northeastern Brazil, and has rapidly spread to other parts of the Americas. A recent increase in the prevalence of microcephaly in newborn infants and vision-threatening findings in these infants is likely associated with the rapid spread of ZIKV.

OBJECTIVE To evaluate the ocular findings in infants with microcephaly associated with presumed intrauterine ZIKV infection in Salvador, Bahia, Brazil.

DESIGN, SETTING, AND PARTICIPANTS Case series at a tertiary hospital. Twenty-nine infants with microcephaly (defined by a cephalic circumference of ≤ 32 cm) with a presumed diagnosis of congenital ZIKV were recruited through an active search and referrals from other hospitals and health unities. The study was conducted between December 1 and December 21, 2015.

INTERVENTIONS All infants and mothers underwent systemic and ophthalmic examinations from December 1 through December 21, 2015, in the Roberto Santos General Hospital, Salvador, Brazil. Anterior segment and retinal, choroidal, and optic nerve abnormalities were documented using a wide-field digital imaging system. The differential diagnosis included toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, syphilis, and human immunodeficiency virus, which were ruled out through serologic and clinical examinations.

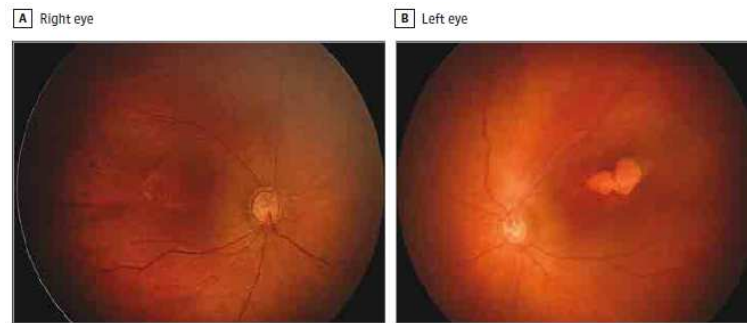
MAIN OUTCOMES AND MEASURES Ocular abnormalities associated with ZIKV.

RESULTS Twenty-three of 29 mothers (79.3%) reported suspected ZIKV infection signs and symptoms during pregnancy, 18 in the first trimester, 4 in the second trimester, and 1 in the third trimester. Of the 29 infants (58 eyes) examined (18 [62.1%] female), ocular abnormalities were present in 17 eyes (29.3%) of 10 children (34.5%). Bilateral findings were found in 7 of 10 patients presenting with ocular lesions, the most common of which were focal pigment mottling of the retina and chorioretinal atrophy in 11 of the 17 eyes with abnormalities (64.7%), followed by optic nerve abnormalities in 8 eyes (47.1%), bilateral iris coloboma in 1 patient (2 eyes [11.8%]), and lens subluxation in 1 eye (5.9%).

CONCLUSIONS AND RELEVANCE Congenital infection due to presumed ZIKV exposure is associated with vision-threatening findings, which include bilateral macular and perimacular lesions as well as optic nerve abnormalities in most cases.

- 29 neonati con microcefalia
- 23/29 madre con sintomi di ZIKV in gravidanza
- 10 bambini (34.5%) alterazioni oculari

Alterazioni oculari: accumulo di pigmento nella retina e atrofia corioretinica, alterazioni del nervo ottico, coloboma dell'iride bilaterale, sublussazione delle lenti



The right eye has granular, pigmentary mottling in the macula (A), and the left eye has a chorioretinal lobulated atrophic lesion and slight pigmentary mottling (B).

Zika virus infection



Grazie per l'attenzione!

SPECIAL REPORT

Zika Virus and Birth Defects — Reviewing the Evidence for Causality

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Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.

...we evaluated available data using criteria that have been proposed for the assessment of potential teratogens. On the basis of this review, we conclude that a causal relationship exists between prenatal Zika virus infection and microcephaly and other serious brain anomalies. ...

Table 1. Shepard's Criteria for Proof of Teratogenicity in Humans as Applied to the Relationship between Zika Virus Infection and Microcephaly and Other Brain Anomalies.*

Criterion No.	Criterion	Evidence	Criterion Met?
1	Proven exposure to the agent at one or more critical times during prenatal development	On the basis of case reports, case series, and epidemiologic studies of microcephaly that are associated with laboratory-confirmed or presumed Zika virus infection, the timing of Zika virus infection associated with severe microcephaly and intracranial calcifications appears to be in the late first or early second trimester. ¹⁴⁻²⁰	Yes

* The criteria listed here were proposed by Shepard.⁹ Criteria 1, 2, and 3 or criteria 1, 3, and 4 are considered to be essential, whereas criteria 5, 6, and 7 are helpful but not essential. Partial evidence is insufficient to meet a criterion. NA denotes not applicable.

2	Consistent findings by ≥ 2 high-quality epidemiologic studies, with control of confounding factors, sufficient numbers, exclusion of positive and negative bias factors, prospective studies if possible, and relative risk ≥ 6	On the basis of data from Brazil, the temporal and geographic association between Zika virus illness and cases of microcephaly is strong. ¹ Two epidemiologic studies have been published. In a study in Brazil ¹⁴ that used a prospective cohort design, 29% of women with Zika virus infection at any time during pregnancy had abnormalities on prenatal ultrasonography, some of which have not been confirmed postnatally. In a study in French Polynesia, ² retrospective identification of eight cases of microcephaly and the use of serologic and statistical data and mathematical modeling suggested that 1% of fetuses and infants born to women with Zika virus infection during the first trimester had microcephaly; the risk ratio in this analysis was approximately 50, as compared with the baseline prevalence of microcephaly. No other epidemiologic studies have examined this association to date.	Partially
3	Careful delineation of clinical cases; a specific defect or syndrome, if present, is very helpful	The phenotype has been well characterized in fetuses and infants with presumed congenital Zika virus infection, including microcephaly and other serious brain anomalies, redundant scalp skin, eye findings, arthrogryposis, and clubfoot. ^{15,20-23} The phenotype in some infants appears to be consistent with the fetal brain disruption sequence, ^{20,22} which has been observed after infection with other viral teratogens. ²⁴	Yes
4	Rare environmental exposure that is associated with rare defect	Reports of fetuses and infants with microcephaly who are born to women with brief periods of travel to countries with active Zika virus transmission are consistent with Zika virus being a rare exposure. ^{16,18,19} The defect, congenital microcephaly, is rare, with a birth prevalence of approximately 6 cases per 10,000 liveborn infants, according to data from birth-defects surveillance systems in the United States. ²⁵	Yes
5	Teratogenicity in experimental animals important but not essential	No results of an animal model with Zika virus infection during pregnancy and fetal effects have yet been published.	No
6	Association should make biologic sense	Findings are similar to those seen after prenatal infection with some other viral teratogens (e.g., cytomegalovirus, rubella virus). ²⁶ Animal models have shown that Zika virus is neurotropic, ^{27,28} which supports biologic plausibility. Evidence that Zika virus infects neural progenitor cells and produces cell death and abnormal growth, ²⁹ along with evidence of Zika virus in brains of fetuses and infants with microcephaly, on the basis of immunohistochemical staining and identification of Zika virus RNA and live virus, ^{16,17,19} provides strong biologic plausibility.	Yes

7	Proof in an experimental system that the agent acts in an unaltered state	This criterion applies to a medication or chemical exposure, not to infectious agents.	NA
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* The criteria listed here were proposed by Shepard.⁹ Criteria 1, 2, and 3 or criteria 1, 3, and 4 are considered to be essential, whereas criteria 5, 6, and 7 are helpful but not essential. Partial evidence is insufficient to meet a criterion. NA denotes not applicable.

Zika virus e danno neurologico: ipotesi patogenetiche (I)

IPOTESI

- Danno diretto e/o Danno immunomediato?

Le attuali ricerche (e quindi le evidenze ottenute) sono state orientate sulla 1° ipotesi

- Nell'uomo: riscontro ZIKV nei tessuti cerebrali di feti con microcefalia (*Mlakar NEJM 2016*)
- Nell'uomo: prolungata viremia in gravidanza (settimane!) (*Driggers NEJM 2016*)
- Nell'uomo: altri flavivirus sono neuropatogeni (per esempio WNV)
- Studi in vitro: ZIKV induce apoptosi (mediata da caspasi) in cellule neuronali in coltura (*Tang Cell Stem Cell 2016*) e disturba la neurogenesi (*Garcez Sciences 2016*). Dengue non provoca le medesime alterazioni.
- Modello animale: ZIKV infetta il sistema nervoso di roditori e lo danneggia (*Bell Arch Gesamte Virusforsch 1971, Way Gen Cell Virol 1976*)

Zika virus e danno neurologico: ipotesi patogenetiche (II)

....continua....

- Modello animale (Lazear Cell Host Microbe 2016): confronto tra:
 - Topi adulti immunocompetenti: non segni di malattia.
 - Topi incapaci di produrre INF α/β : segni neurologici e decesso. ZIKV ritrovato nel cervello e midollo spinale (importanza IFN nel controllo dell'infezione)
 - Topi lattanti immunocompetenti: segni neurologici e decesso (vulnerabilità età dipendente)
- Rossi Am J Trop Med Hyg 2016: risultati simili al precedente
- Alto tasso variazioni fenotipiche dei ceppi appartenenti al lineage Asiatico isolati nelle Americhe: potrebbero indurre una viremia più elevata facilitando la trasmissione transplacentare e l'instaurarsi di epidemie in cui il serbatoio è costituito dall'uomo o potrebbero avere un maggior neurotropismo (Weaver Antiviral Research 2016)

Zika virus e danno neurologico: ipotesi patogenetiche (III)

....continua....

- Modello animale in gravidanza:
 - confermano trasmissione transplacentare
 - ritardo di crescita nei feti infettati
 - morte fetale intrauterina
 - danni placentari
 - alto tasso di apoptosi neuronale nei tessuti cerebrali dei feti
 - Progenitori neuronali come principale target di ZIKV
 - Alterazione della proliferazione e sviluppo neuronale.

Miner *Cell* 2016

Cugola *Nature* 2016

Li *Cell Stem Cell* 2016

Teratogenic effects of the Zika virus and the role of the placenta

Jennifer J Adibi, Ernesto T A Marques Jr, Abigail Cartus, Richard H Beigi

The mechanism by which the Zika virus can cause fetal microcephaly is not known. Reports indicate that Zika is able to evade the normal immunoprotective responses of the placenta. Microcephaly has genetic causes, some associated with maternal exposures including radiation, tobacco smoke, alcohol, and viruses. Two hypotheses regarding the role of the placenta are possible: one is that the placenta directly conveys the Zika virus to the early embryo or fetus. Alternatively, the placenta itself might be mounting a response to the exposure; this response might be contributing to or causing the brain defect. This distinction is crucial to the diagnosis of fetuses at risk and the design of therapeutic strategies to prevent Zika-induced teratogenesis.

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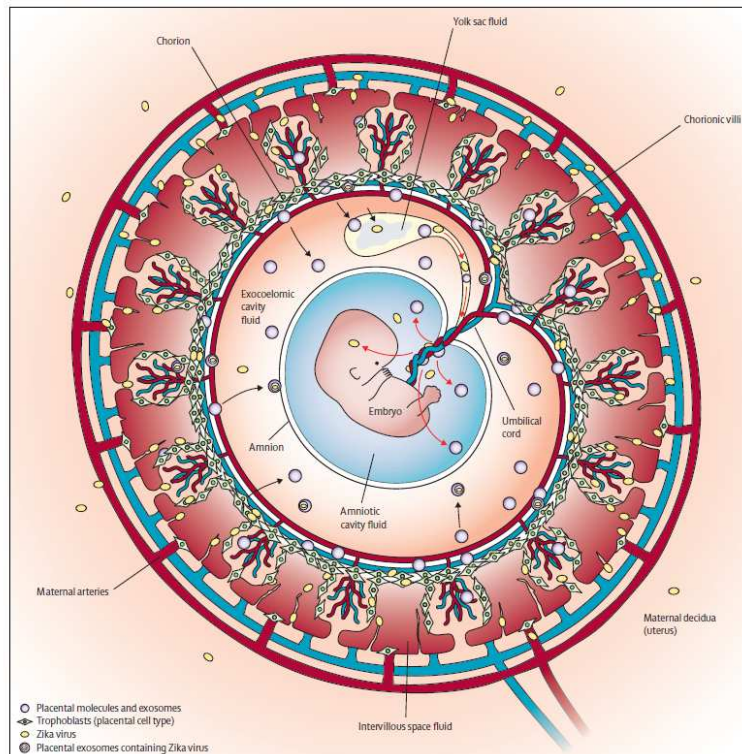


Figure: The gestational sac in the first trimester before the onset of maternal-placental blood flow

The placenta consists of the chorion and the chorionic villi which encircle the embryo and carry out synthesis and secretion of molecules that can enter into the embryo. Different scenarios include: direct transfer of free virus through the trophoblast layers, placental exosome-mediated transfer, or minimal to no transfer.

La placenta potrebbe facilitare l'invasione dei tessuti embrionali e fetali da parte del virus oppure potrebbe indurre una reazione infiammatoria responsabile del danno.