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Zika infection - the clinical problems

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Zika virus

- Typical symptoms
- Asymptomatic infection
- Zika and neurological sequelae
- Zika and other severe sequelae
- Congenital Zika infection

First cases of mystery head-shrinking virus hit Britain

THREE Britons have contracted a mysterious virus linked to babies born with shrunken heads.

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Symptoms of Zika

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 et al, NEJM 2009. **Yap Island**

TABLE. Demographic characteristics, clinical course, and signs and symptoms in 30 patients with Zika virus disease identified by the Puerto Rico Department of Health — Puerto Rico, November 23, 2015–January 28, 2016

Characteristic	Patients: Age/Illness onset (range)	Patients: No. (%)
Median age (yrs)	40 (10–80)	
Median time from illness onset to specimen collection (days)	3 (0–15)	
History of recent travel*		1 (3)
Female		18 (60)
Pregnant		1 (3)
Hospitalized		3 (10)
Signs and symptoms†		
Rash		23 (77)
Myalgia		23 (77)
Arthralgia		22 (73)
Fever		22 (73)
Eye pain		20 (67)
Chills		20 (67)
Headache		19 (63)
Sore throat		12 (40)
Petechiae		10 (33)
Conjunctivitis		8 (27)
Diarrhea		7 (23)
Nausea/Vomiting		5 (17)

* Travel outside of Puerto Rico and the United States in the 14 days before illness onset.
† Signs and symptoms were reported by the patients' clinician.

Thomas et al, MMWR 2016. **Puerto Rico**

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Symptoms of Zika

Zika Virus Outbreak in **Rio de Janeiro, Brazil:** Clinical Characterization, Epidemiological and Virological Aspects.

Brasil et al, PLOS NTD 2016

Table 2. Clinical characteristics of confirmed and unconfirmed* ZIKV infected patients, in the first four days of disease.

Sign/Symptom	Confirmed n(%)	Unconfirmed n(%)
Macular or papular rash	115(97)	113(79)
Itching	94(79)	127(89)
Prostration	87(73)	104(73)
Headache	78(66)	101(71)
Arthralgia	75(63)	105(73)
Myalgia	73(61)	96(67)
Nonpurulent conjuntivitis	66(56)	57(40)
Low back pain	61(51)	70(49)
Retro-orbital pain	53(45)	76(53)
Lymphonodes elargement	49(41)	33(23)
Chills	44(37)	52(36)
Fever	43(36)	71(50)
Anorexia	42(35)	60(42)
Photophobia	41(345)	43(30)
Oropharyngeal pain	38(32)	35(25)
Edema	34(29)	26(18)
Taste alteration	32(27)	33(23)
Nausea	28(24)	43(30)
Enanthema/Petechiae/Bleeding	25(21)	16(11)
Nasal congestion	24(20)	25(18)
Sweating	23(19)	38(27)
Diarrhea	23(19)	21(15)
Abdominal pain	20(17)	29(20)
Cough	19(16)	28(20)
Coryza	18(15)	20(14)
Lipothymia	18(15)	28(20)
Hoarseness	13(11)	13(9)
Earache	11(9)	8(5)
Dysuria	8(7)	5(4)
Choluria	7(6)	8(6)
Dyspnea	7(6)	10(7)
Vomiting	5(4)	10(7)
Hepatomegaly	2(2)	2(1)

* tested ZIKV negative

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Symptoms of Zika

Persistence of Zika Virus in Body Fluids — Preliminary Report.

(150 PCR-diagnosed cases in **Puerto Rico**)

Paz-Bailey et al, NEJM 2017

Signs or symptoms at enrollment — no./total no. (%)†	
Fever	115/146 (78.8)
Red eyes or eye pain	119/146 (81.5)
Rash	135/144 (93.8)
Pruritus	117/145 (80.7)
Photophobia	59/144 (41.0)
Edema	92/145 (63.4)
Arthralgia	120/139 (86.3)
Myalgia	102/125 (81.6)
Headache	115/145 (79.3)
Abdominal pain	73/145 (50.3)
Lymphadenopathy	50/144 (34.7)
Diarrhea	62/145 (42.8)
Nausea	63/145 (43.4)
Vomiting	17/145 (11.7)
Pelvic pain	25/139 (18.0)
Dysuria	25/145 (17.2)
Other‡	129/144 (89.6)

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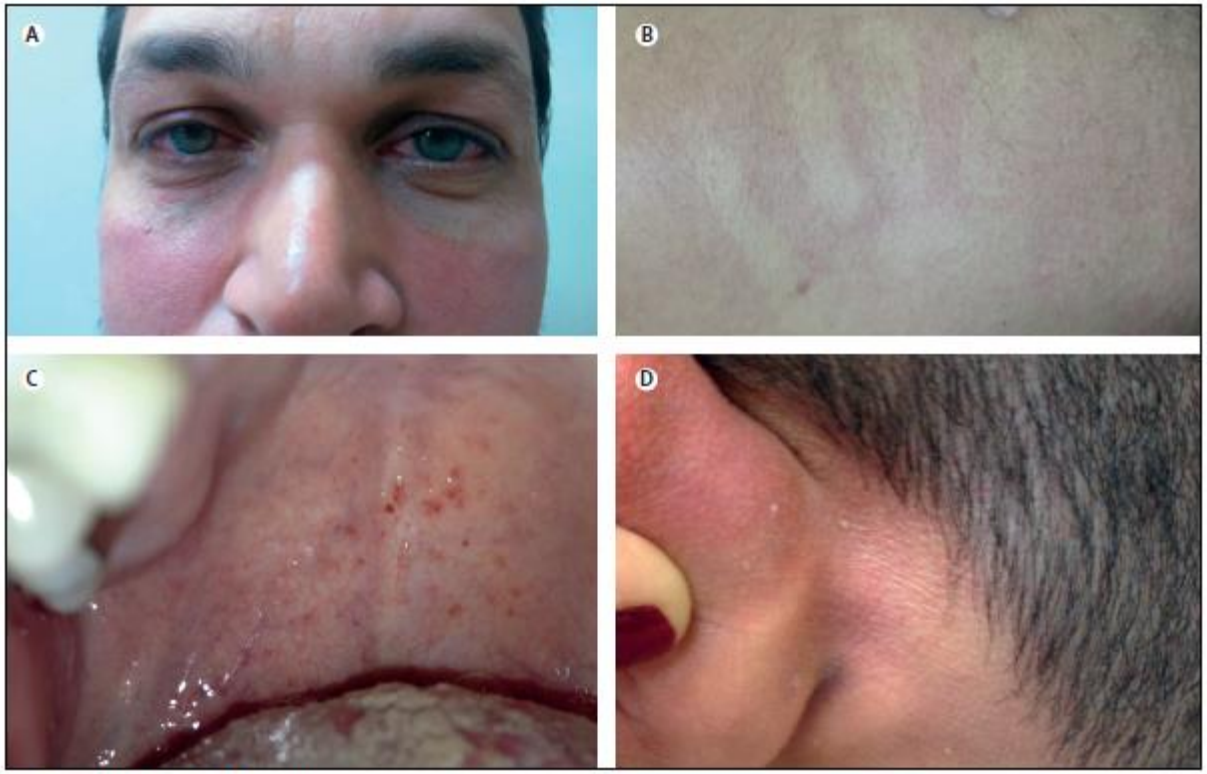

Figure: Presentation of Zika virus infection
(A) Oedema and erythema of the malar region of the face, and conjunctival injection. (B) Macular rash on the abdomen. (C) Hyperaemia and petechiae in the hard palate. (D) Tender, mobile, soft lymph node, about 15 mm in diameter, behind the left ear.

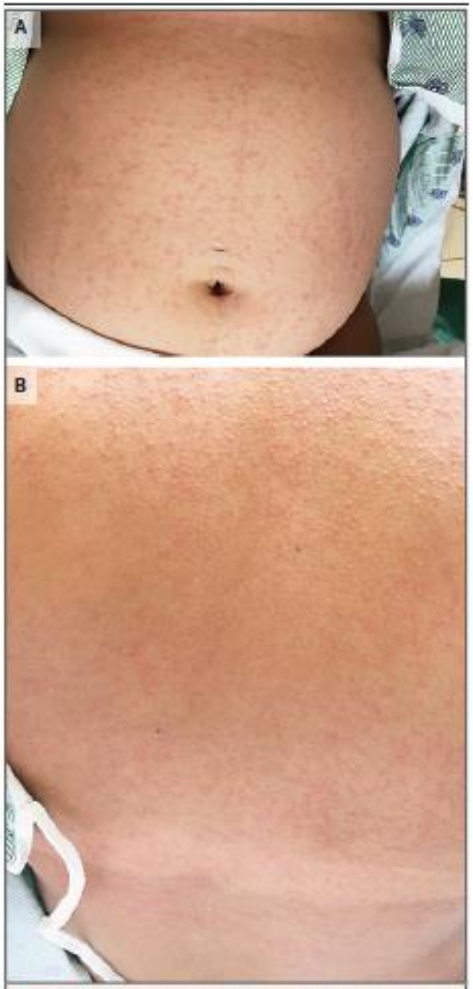

Figure 1. Cutaneous Eruption in a Pregnant Woman with Locally Acquired Zika Virus Infection.
Generalized erythematous macules and papules are shown on the abdomen (Panel A) and back (Panel B) of a pregnant woman with locally acquired Zika virus infection in the United States.

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microcephaly in Brazil

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Asymptomatic infection: 80%?

- Household serological survey during Yap outbreak found that only 19% of Zika IgM + individuals reported rash, joint pains, or conjunctivitis *probably attributable to* Zika virus infection (Duffy, NEJM 2009)

	IgM +ve	IgM -ve	Total
Symptoms	156 (38%)	27 (19%)	183 (33%)
Asymptomatic	258 (62%)	115 (81%)	373 (67%)
Total	414 (100%)	142 (100%)	557 (100%)

- Subsequently, proportion of asymptomatic cases was extrapolated as 100 – (38-19) = 81%

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Proportion of asymptomatic infection?

- Systematic screening of 136 returning travellers from Suriname identified 11 infections, only 3 of which **(27%)** were asymptomatic (De Laval, Lancet 2016)

- In Martinique outbreak, 76 (1.8%) of 4,129 blood donors, although asymptomatic at the time of blood donation, were found positive for ZIKV by PCR
  - of 75, 42 subsequently reported symptoms
  - therefore, proportion asymptomatic was **45%**
  - additional info (from seroprevalence study) suggested that the proportion of population who had infection, but who did not seek medical attention was 80-85% (Gallian, Blood 2017)

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Asymptomatic Zika virus infection in returning travellers

CDC report from USA (Dasgupta, MMWR 2016)

- 2,557 asymptomatic returning travellers who received testing between January and March 2016
  - 2,425 (94.8%) were pregnant women
    - only seven (0.3%) asymptomatic pregnant women had confirmed Zika virus infection
      - 5 of these had been residing in Zika-affected area
      - only 2 were short-term travellers

The likelihood that a short-term asymptomatic traveller has had Zika virus infection is very low

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Asymptomatic Zika virus infection in returning travellers

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You have to test a lot of asymptomatic travellers to find the infected ones

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Zika virus and Guillain-Barre Syndrome

Table 4. Countries and territories that have reported Guillain-Barré syndrome (GBS) potentially associated with ZIKV infection

	WHO Regional Office	Country or territory	Total
Reported increase in incidence of GBS cases, with at least one GBS case with confirmed ZIKV infection	AMRO/PAHO	Brazil, Colombia, Curaçao, Dominican Republic, El Salvador*, French Guiana, Guadeloupe, Guatemala, Honduras, Jamaica, Martinique, Puerto Rico, Suriname**, Trinidad and Tobago, Venezuela (Bolivarian Republic of)	15
	WRPO	French Polynesia	1
No increase in GBS incidence reported, but at least one GBS case with confirmed ZIKV infection	AMRO/PAHO	Bolivia (Plurinational State of), Costa Rica, Grenada, Haiti, Mexico, Panama, Saint Martin	7
Total			23

**GBS cases with previous history of ZIKV infection were reported by the United States of America.*

***One case living in continental Netherlands was diagnosed in January 2016 and reported by the Netherlands.*

WHO Sitrep 10/03/17

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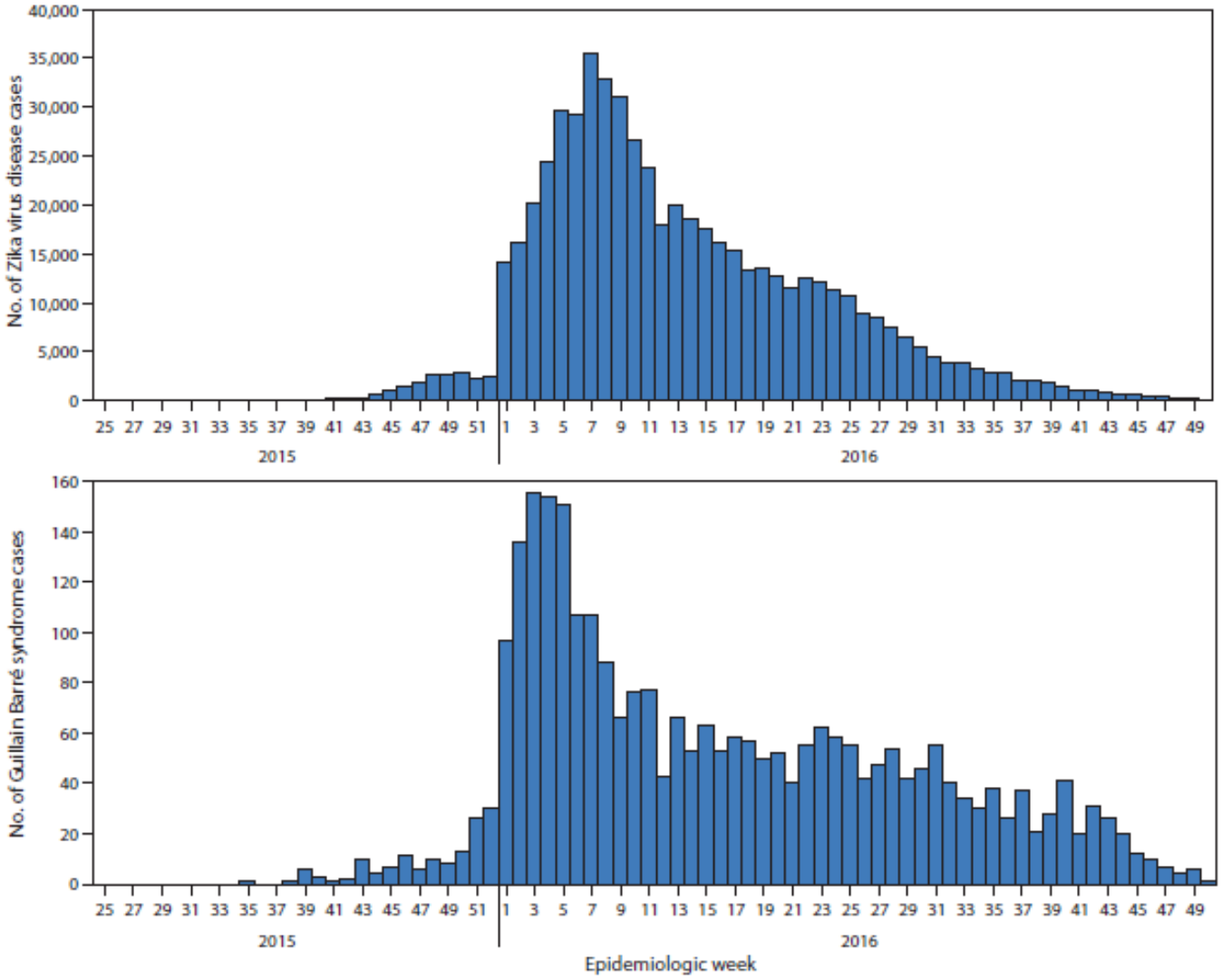
Zika virus and Guillain-Barre Syndrome

Suspected and confirmed cases of Zika virus and Guillain-Barré syndrome, by epidemiologic week — Region of the Americas, May 2015–December 2016

(Ikejezie, MMWR 2017)



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Zika virus and Guillain-Barre Syndrome

- 50 of 66 (76%) GBS cases in **Venezuela** had clinical history consistent with Zika virus infection, and Zika virus detected by PCR in three patients (WHO sitrep 19/2/16)
- Zika RNA detected in CSF of GBS case in **Brazil** on day 6 after onset of rash illness (Brasil, Lancet 2016)
- Of 42 people with confirmed GBS in **French Polynesia**, 37 (88%) reported an illness consistent with Zika virus infection, and 100% had neutralising antibodies against Zika virus. (Cor-Lormeau, Lancet 2016)

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Summary of reviewers' assessments of evidence about Zika virus infection and GBS, by causality dimension.

Zika Virus Infection as a Cause of Congenital Brain Abnormalities and Guillain-Barre Syndrome: Systematic Review

Krauer *et al*, PLOS Med 2017

Causality dimension[a]	Number of items and groups[b]
1. Temporality	31 studies in 26 groups
2. Biological plausibility	6 items in 4 groups
3. Strength of association	7 items in 2 groups
4. Exclusion of alternative explanations	10 items in 7 groups
5. Cessation	8 items in 6 groups
6. Dose–response relationship	0 items
7. Animal experiments	0 items
8. Analogy	Not reported
9. Specificity	0 items
10. Consistency	Not reported

"There is evidence that supports a role for molecular mimicry, a proposed mechanism of auto-immunity, which has been reported in *C. jejuni*-associated GBS. Direct neurotropic effects of ZIKV might also occur."

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Other severe consequences of Zika infection

- **Meningoencephalitis** in 81y man with ZIKV RNA in CSF following Pacific Island cruise. Recovered. (Carteaux, NEJM 2016)
- **Meningoencephalitis** in 36y heart transplant recipient in Brazil. ZIKV RNA in CSF and brain. Died of acute cardiac rejection following withdrawal of immunosuppression. (Schwartzmann, Mayo Clin Proc 2017)
- 15y girl in Guadeloupe developed **acute myelitis** with ZIKV RNA in CSF. Recovered. (Mecharles, Lancet 2016)
- Cases of severe **thrombocytopenia**. (eg Chammard, Emerg Infect Dis 2016)
- Cases of bilateral **uveitis**. (Furtado, NEJM 2016, Kodati, Lancet 2016)
- 45y man developed a transient **myocarditis** alongside other features of acute ZIKV infection after visit to Martinique. (Aletti, Clin Infect Dis 2016)
- Also small numbers of fatal cases reported. (Swaminathan, NEJM 2016)

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Microcephaly…

Known causes: Infections - toxoplasmosis, rubella, herpes, syphilis, CMV, HIV
Toxins – arsenic, mercury, alcohol, radiation, smoking
Genetic – Down Syndrome

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Conclusions

The panel of experts[5] concluded:

1. The most likely explanation of available evidence from outbreaks of Zika virus infection and clusters of microcephaly is that Zika virus infection during pregnancy is a cause of congenital brain abnormalities including microcephaly;
2. The most likely explanation of available evidence from outbreaks of Zika virus infection and Guillain-Barré syndrome is that Zika virus infection is a trigger of GBS.

The expert panel recognizes that Zika virus alone may not be sufficient to cause either congenital brain abnormalities or GBS. It is not known whether these effects depend on as yet uncharacterized co-factors being present. Nor is it known whether dengue virus plays a part; dengue virus is carried by the same species of mosquito and has circulated in many countries during the same period.

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Zika Virus Infection as a Cause of Congenital Brain Abnormalities and Guillain-Barre Syndrome: Systematic Review

Krauer *et al*, PLOS Med 2017

Causality dimension[a]	Number of items and groups[b]
Temporality	35 items in 21 groups
Biological plausibility	28 items in 25 groups
Strength of association	7 items in 3 groups
Exclusion of alternative explanations	28 items in 18 groups
Cessation	6 items in 2 groups
Dose–response relationship	0 items
Animal experiments	20 items in 20 groups
Analogy	Not reported
Specificity	0 items
Consistency	Not reported

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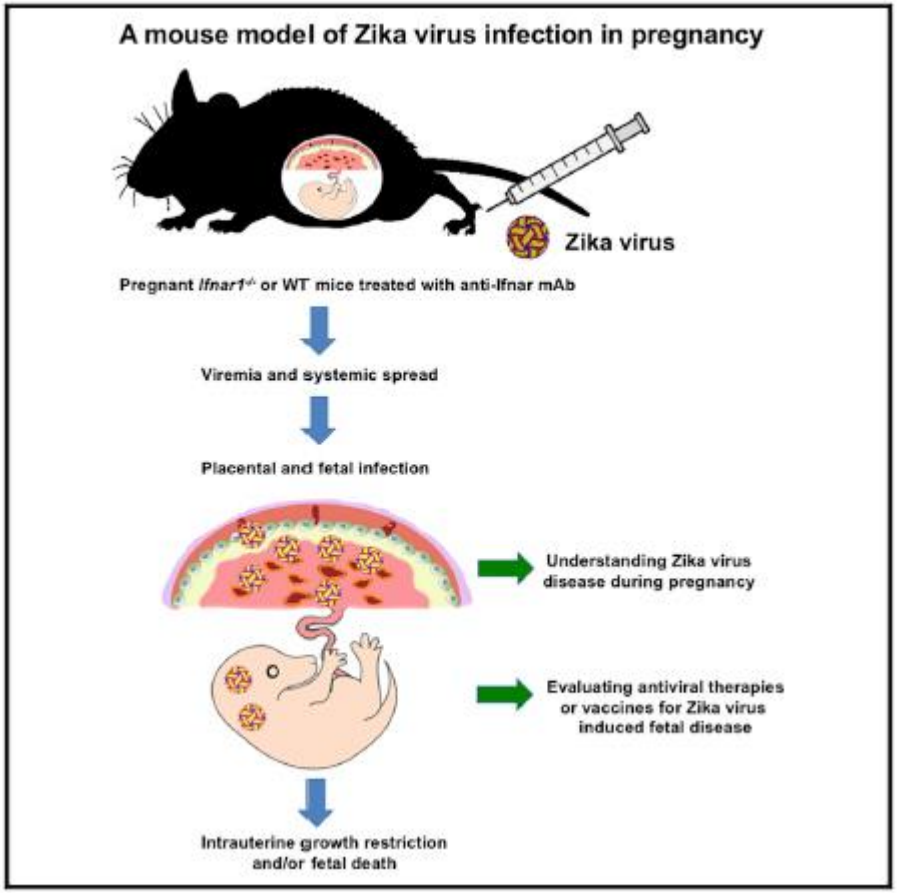
Laboratory evidence - mouse

French Polynesian ZIKV

- infects placental cells and results in intrauterine growth restriction in fetal mice
- infects and causes damage by apoptosis in the fetal mouse brain



Miner *et al*, Zika Virus Infection during Pregnancy in Mice Causes Placental Damage and Fetal Demise. Cell 2016

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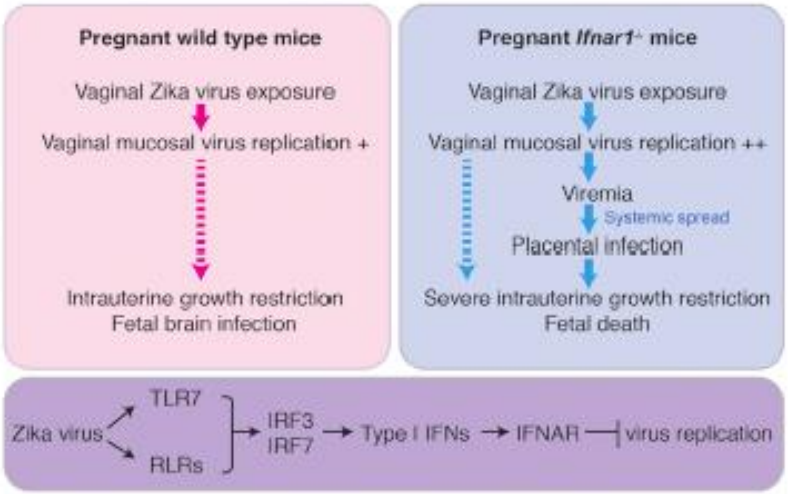
Laboratory evidence - mouse

Cambodian ZIKV

- replicates in the vaginal tract of wild-type virgin and pregnant mice
- infection via the vaginal route in early pregnancy can lead to fetal growth restriction and to fetal brain infection

Yockey *et al*, Vaginal Exposure to Zika Virus during Pregnancy Leads to Fetal Brain Infection. Cell 2016



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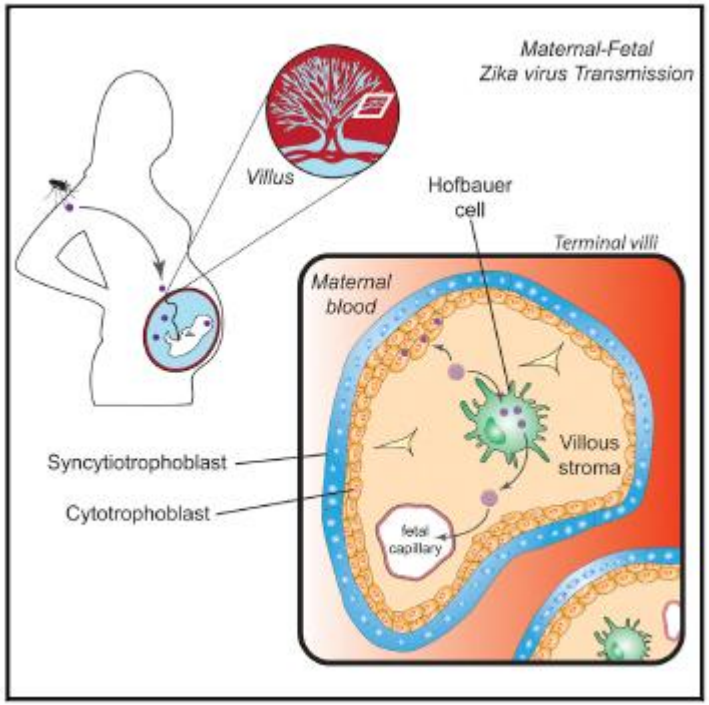
Laboratory evidence – human tissue

Puerto Rico ZIKV

- productively infects human placental fetal macrophages, called Hofbauer cells
- Infection of Hofbauer cells coincides with IFN and antiviral gene induction, but minimal cell death



Quicke *et al*, Zika Virus Infects Human Placental Macrophages. Cell Host & Microbe 2016

Also El Costa *et al*, ZIKA virus reveals broad tissue and cell tropism during the first trimester of pregnancy. Sci Reports 2016

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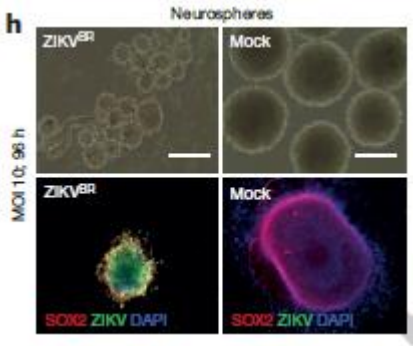
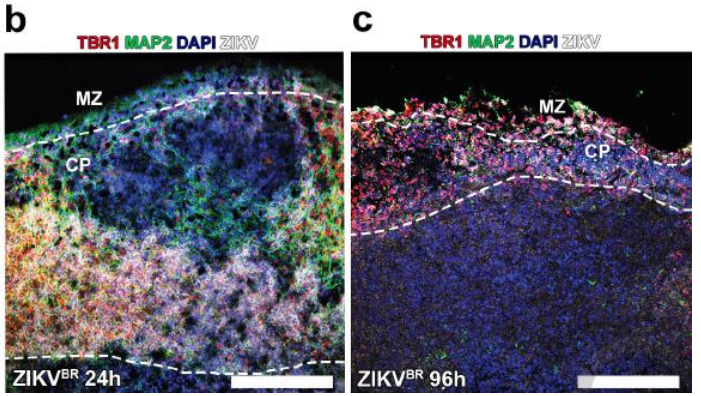
Laboratory evidence – mouse / human

Brazilian ZIKV

- causes intrauterine growth restriction, including signs of microcephaly, in fetal mice
- infects human cortical progenitor cells, leading to an increase in cell death by apoptosis and autophagy
- infection of human brain organoids results in a reduction of proliferative zones and disrupted cortical layers





Cugola *et al*, The Brazilian Zika virus strain causes birth defects in experimental models. Nature 2016

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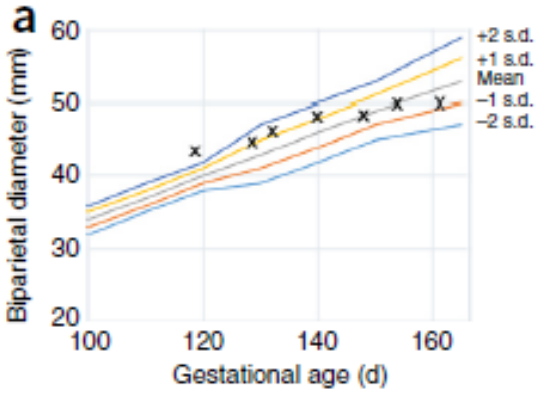
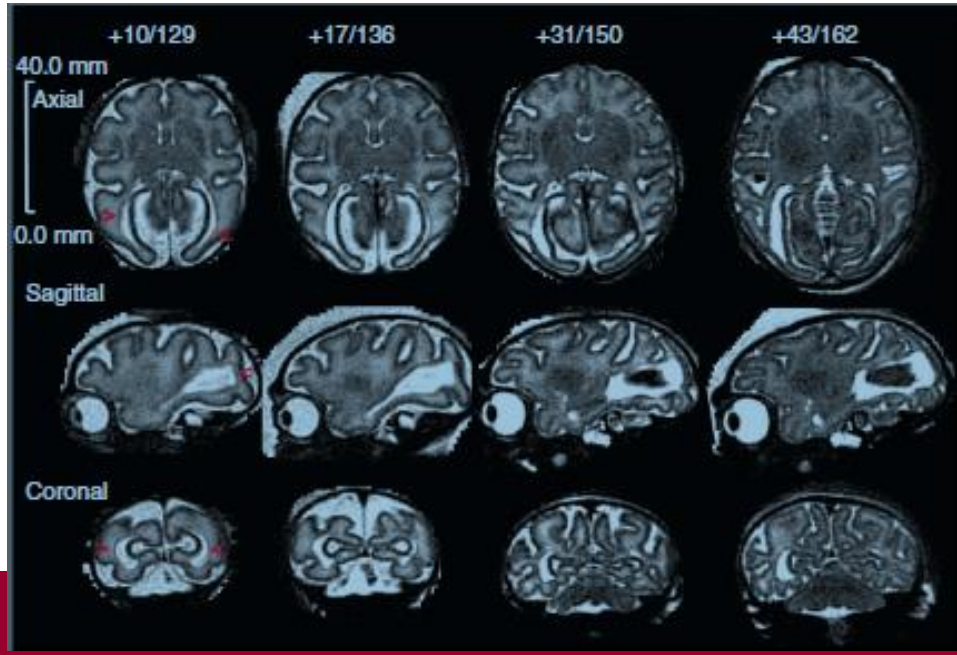
Laboratory evidence - macaque

Cambodian ZIKV

- injected subcutaneously in the forearm of a pregnant pigtail macaque (equivalent to 28/40) resulted in fetal brain lesions
- was detected in fetal brain at autopsy in association with significant cerebral white matter hypoplasia, periventricular white matter gliosis, and axonal and ependymal injury

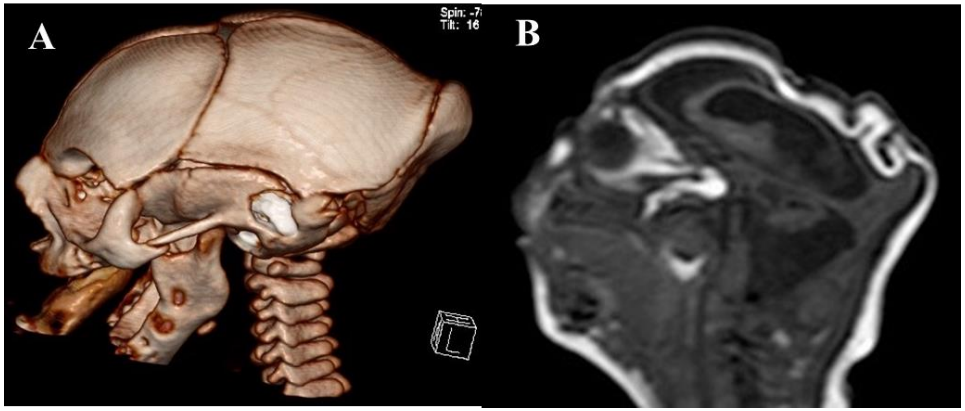




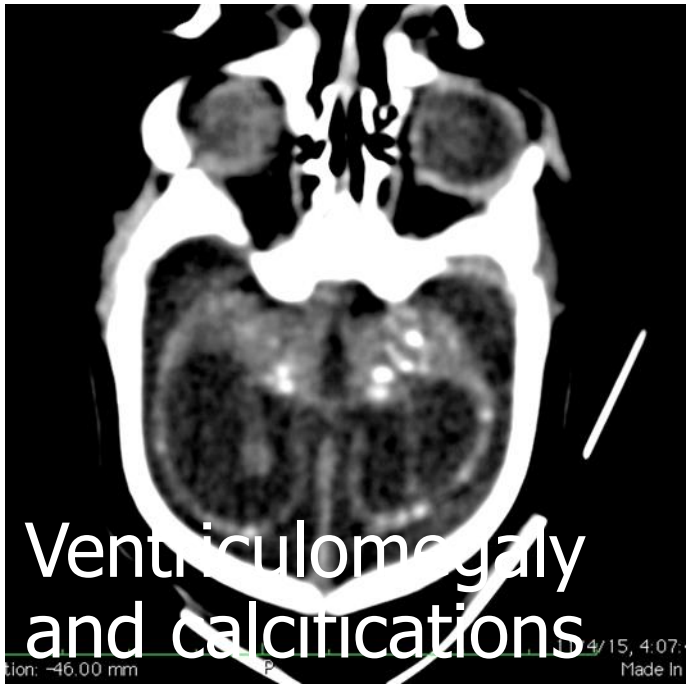
Adams Waldorf *et al*, Fetal brain lesions after subcutaneous inoculation of Zika Virus Iin a pregnant non-human primate. Nature Med 2016

Features of Congenital Zika Syndrome

Thanks to Laura Rodrigues



External occipital protuberance



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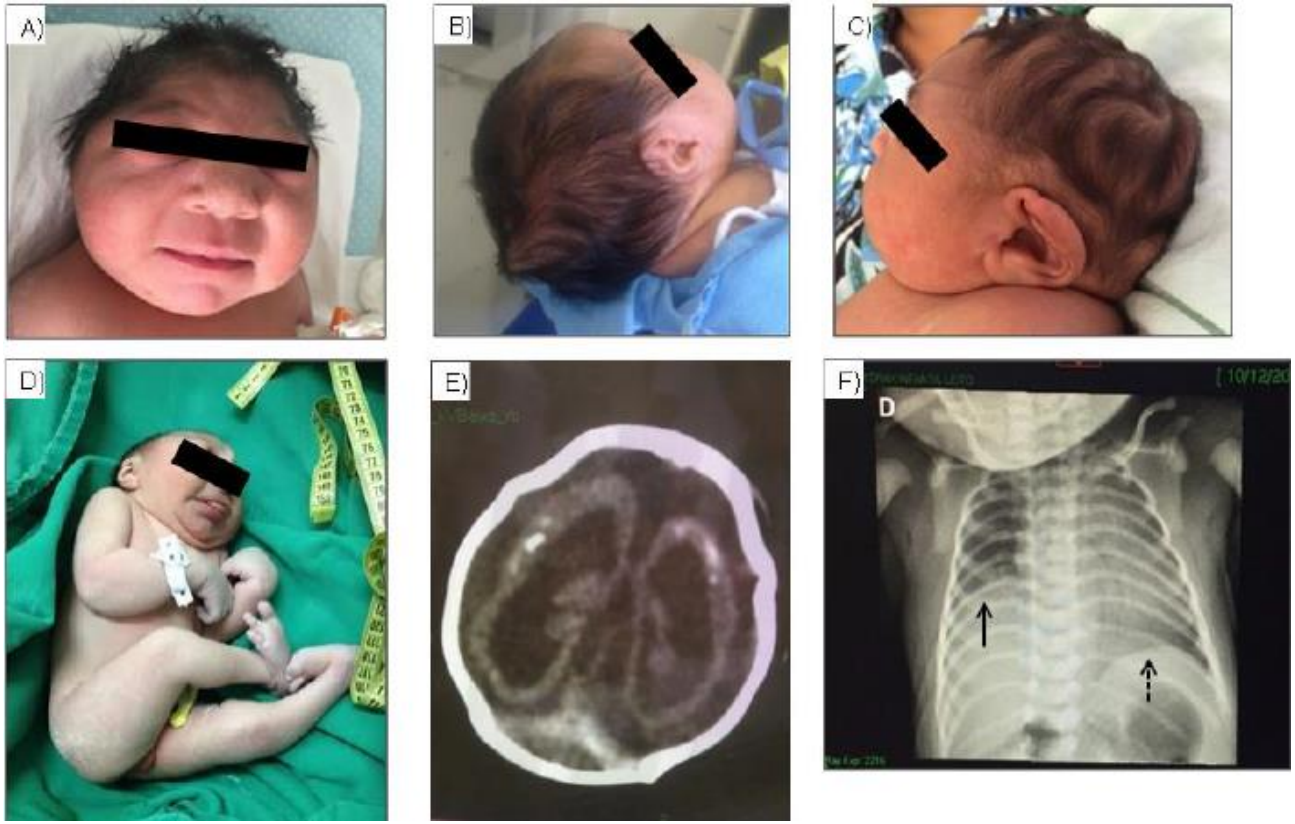
Typical features of CZS



(A) Craniofacial disproportion. (B) Pointed occiput. (C) Redundant scalp skin. (D) Arthrogryposis. (E) Cerebral calcifications in CT scan. (F) Right diaphragmatic paralysis (bold arrow)

(Meneses, Clin Infect Dis 2016)

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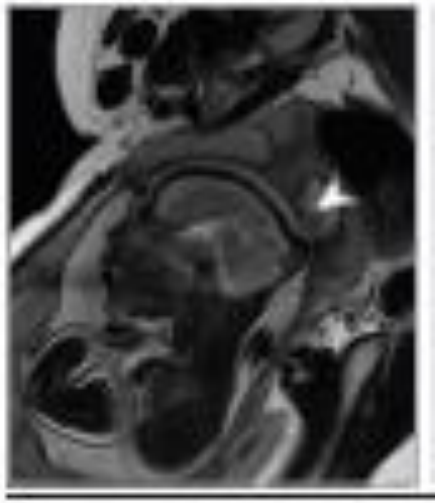
Fetal Brain Disruption Sequence

- Severe microcephaly
- Overlapping cranial sutures
- Prominent occipital bone
- Redundant scalp skin
- Craniofacial disproportion
- Severe neurological impairment

MRI at 29 weeks gestation



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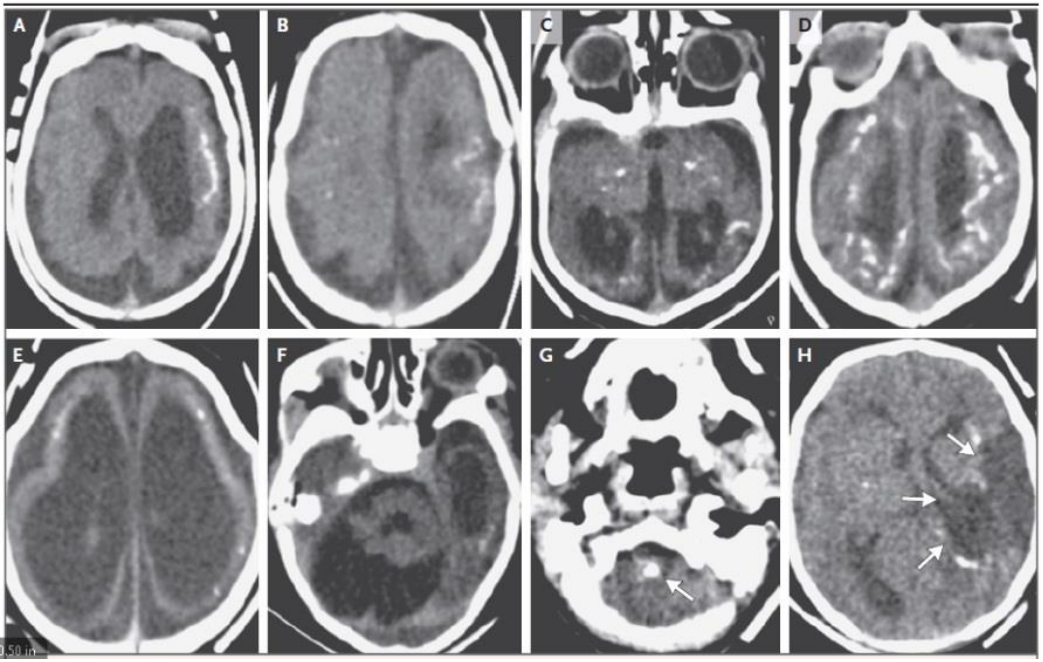
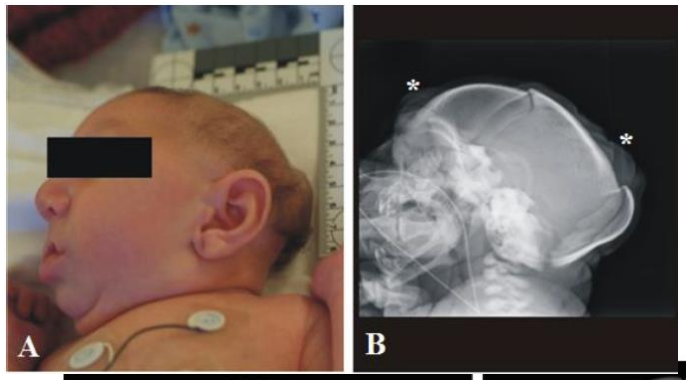
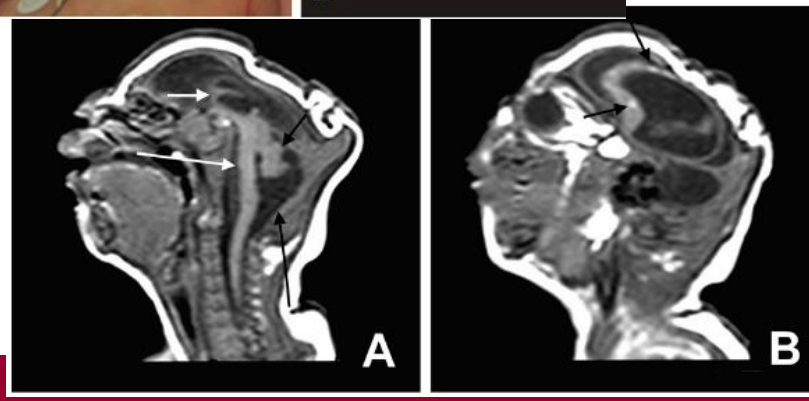
Manifestations of Congenital Zika Syndrome 1

- Brain abnormalities: microcephaly, **subcortical calcifications**, brain atrophy and asymmetry, abnormally formed or absent brain structures, hydrocephalus, and neuronal migration disorders.







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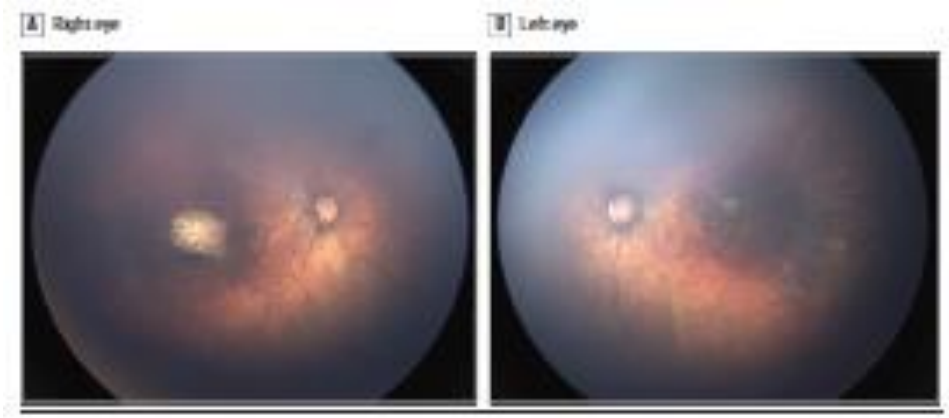
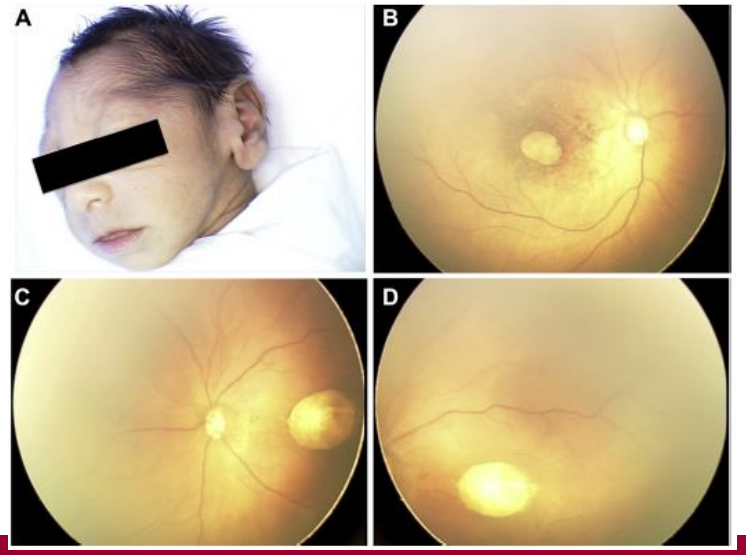
Manifestations of Congenital Zika Syndrome 2

- Neurologic findings: hypertonia, hyperreflexia, irritability, tremors, seizures, brainstem dysfunction, and dysphagia.
- Eye abnormalities: microphthalmia, lens subluxation, cataracts, intraocular calcifications, optic nerve atrophy, optic nerve hypoplasia and pallor, macular pallor, macular chorioretinitis, and chorioretinal atrophy.





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Manifestations of Congenital Zika Syndrome 2

- Neurologic findings: hypertonia, hyperreflexia, irritability, tremors, seizures, brainstem dysfunction, and dysphagia.
- Eye abnormalities: microphthalmia, lens subluxation, cataracts, intraocular calcifications, optic nerve atrophy, optic nerve hypoplasia and pallor, macular pallor, macular chorioretinitis, and chorioretinal atrophy.
- Other anomalies: excessive and redundant scalp skin, arthrogryposis, and clubfoot.

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Unusual persistent viremia

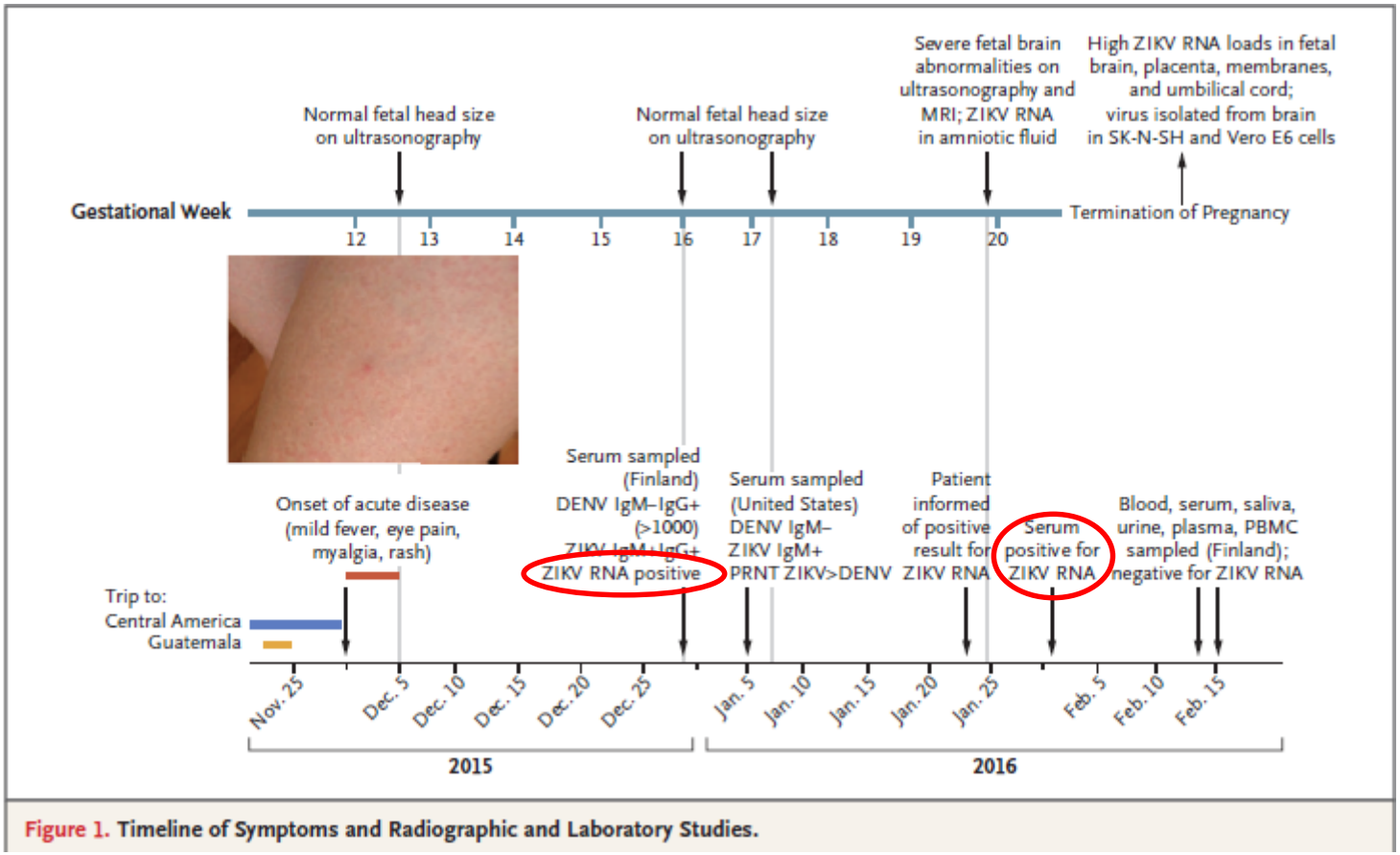


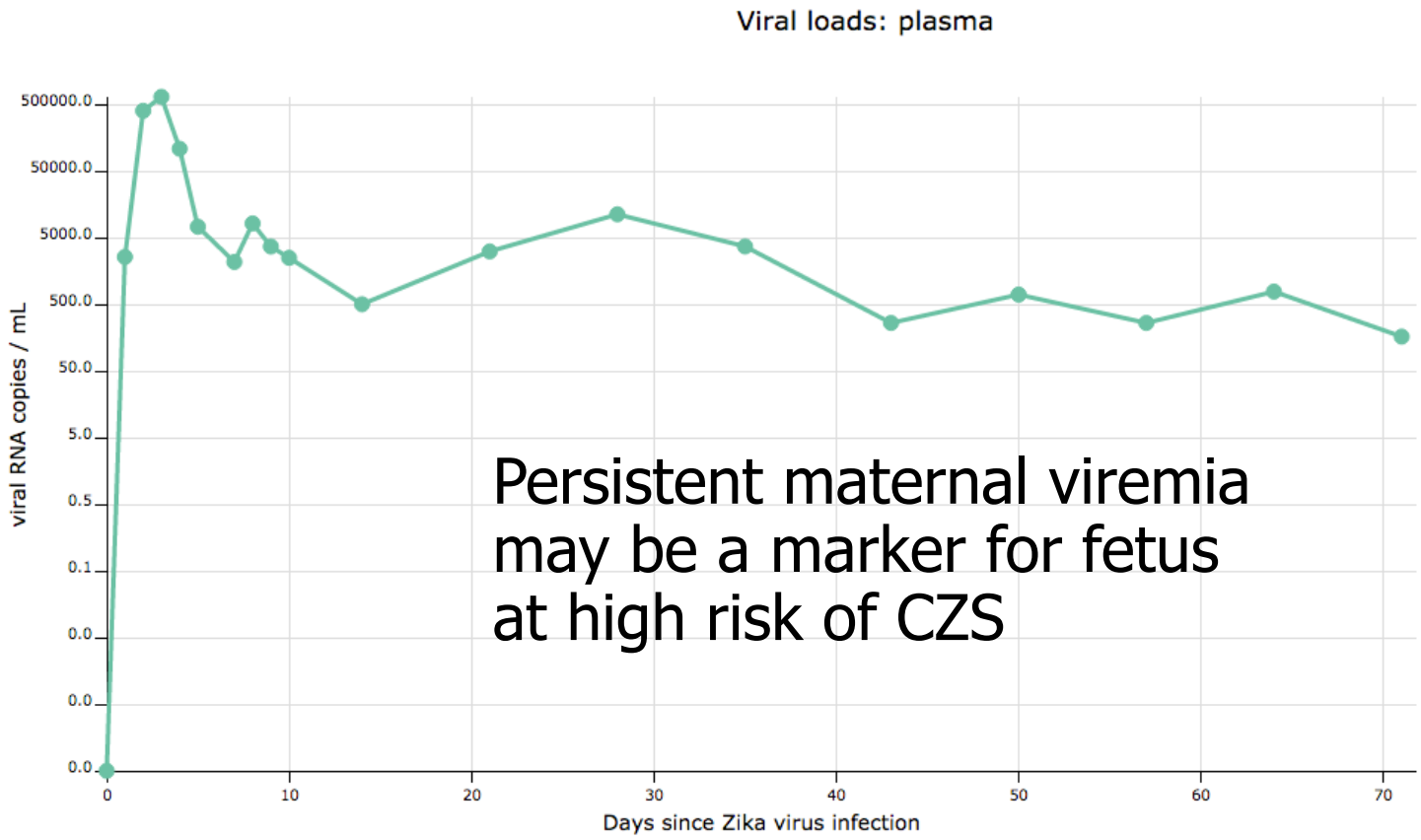
Figure 1. Timeline of Symptoms and Radiographic and Laboratory Studies.

Driggers, NEJM 2016

Public Health England

Placental backspill

The ZIKV-003 pregnant macaque that was infected in her 1st trimester still has low levels of virus detectable in plasma at 71dpi.



O'Connor Lab, University of Wisconsin-Madison / Wisconsin National Primate Research Center

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What's the risk of having a Zika-affected baby?

- Retrospective analysis of data from French Polynesia: risk of microcephaly associated with Zika virus infection was 95 cases (34–191) per 10,000 women infected in the first trimester, i.e. ~1% (**0.3-1.9%**) (Cauchemez, Lancet 2016)
- Preliminary analysis of data from NE Brazil: the estimated risk of microcephaly due to Zika infection in the first trimester ranged from **0.88% to 13.2%** (Johansson, NEJM 2016)
- Among 442 pregnant women with laboratory evidence of Zika infection in USA, 26 (6%) had fetus/infant with microcephaly/brain abnormalities. For 1st trimester infection, **11%** affected (Honein, JAMA 2016)
- Among 117 live infants born to 116 ZIKV RNA+ve women with rash in Rio, 4 (**3.4%**) infants had microcephaly *but a further 45 (38.5%) said to have abnormal clinical or brain imaging findings or both.* (Brasil, NEJM 2016)
- Among 301 Zika-infected pregnancies in French Guiana, 9 (**3%**) had fetus/neonate with confirmed or suspected CZS (Pomar, Ultrasound Obs Gynae 2017)

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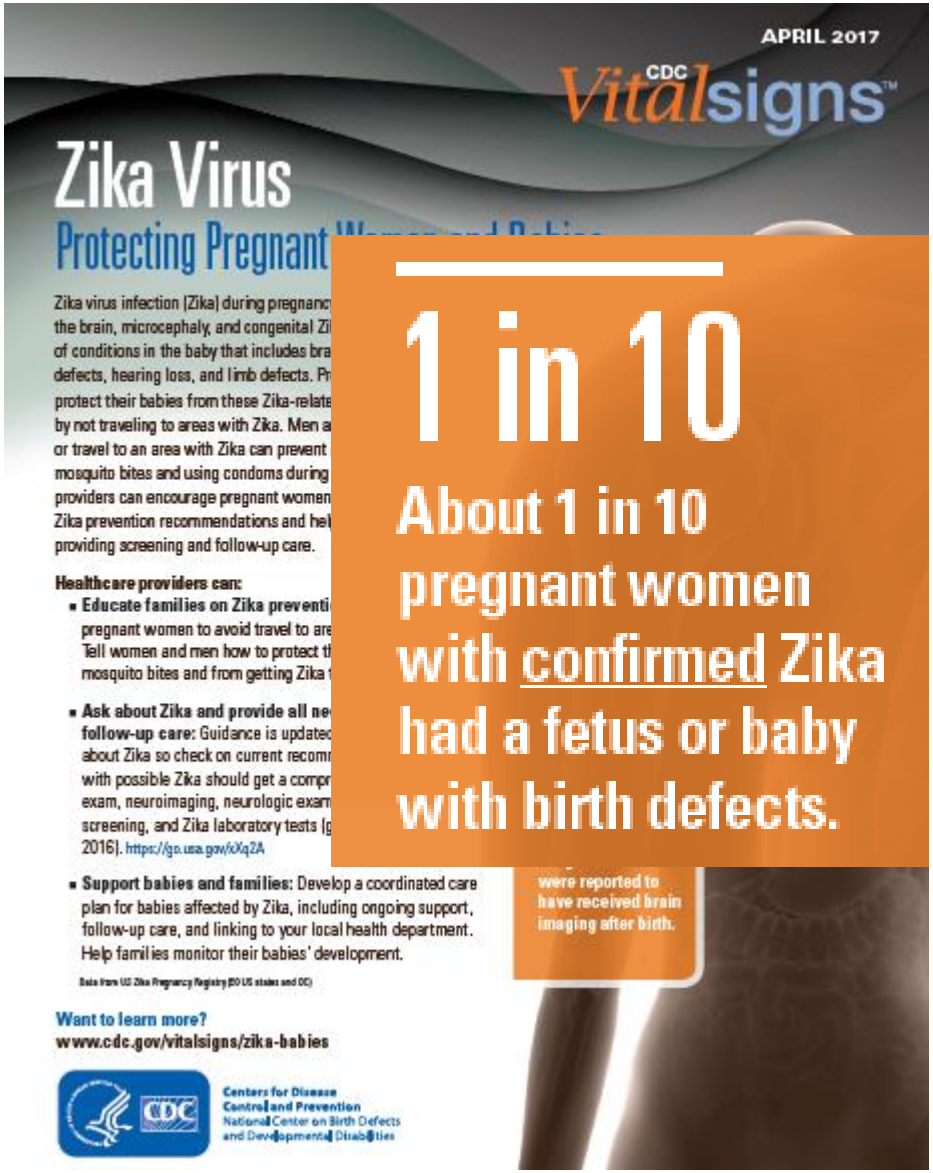
1,297 pregnancies with possible recent ZIKV in USA in 2016 (Reynolds, MMWR 2017)

- Birth defects in 51 (5%) of the 972 completed pregnancies
  - Birth defects in 24 (**10%**) of the 250 cases with confirmed ZIKV
    - Microcephaly and/or brain abnormalities in 18 (75%) of 24



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Summary

- Zika virus infection is typically a (mild) *rash* illness, rather than a febrile illness
- The widely promulgated “80% of infections are asymptomatic” is probably an overestimate
- Diverse evidence indicates that ZIKV infection is a trigger for GBS and a cause of congenital neurological abnormalities, including microcephaly
- Published reports of other severe sequelae (*e.g.* meningoencephalitis) or of fatal infection are remarkably rare
- Clinical features of severe CZS are microcephaly with partial skull collapse, occipital protuberance, redundant scalp skin and arthrogryposis
- The risk of severe CZS for a woman who acquires ZIKV infection in the first trimester may be around 10%

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Acknowledgements

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