



What's *Hot* in Pediatric Infectious Diseases 2015-16

Soren Gantt UBC Peds ID





ZIKA VIRUS!!!





Virus Zika estructura



What is ZIKV?

- ZIKV is a flavivirus, related to dengue, yellow fever, West Nile and Japanese encephalitis
- Discovered in 1947 in the Zika forest of Uganda
 Gets 10 lines in *Field's Virology…*
- Transmitted by *Aedes* mosquitoes (& sex, &...?)
- Incubation period 3-12 days
- Symptoms occur in 20-25% of infections

 Fever, rash, arthralgia, conjunctivitis, HA x ~1 wk
 GBS recognized in French Polynesia outbreak 2013
- Virus detectable in serum and saliva for ~7 d, urine for ~10 d, semen for >60 days

Why is ZIKV hot?

- Huge increase (>20-fold) in microcephaly coinciding with ZIKV outbreak in Brazil
 - >1.5 M ZIKV infections since Feb 2015
 - >5000 cases microcephaly in Brazil
 - Associations also reported widely in Latin America
- ZIKV now accepted to be causal
 - Several affected fetuses/infants positive for ZIKV in brain, CSF, etc
 - Viral loads in amniotic fluid 4 logs higher than in blood of acutely infected adults
- Ocular involvement, hydrops, fetal death, etc.

Figure 3. Notified cases of microcephaly in Brazil from 2010 to 2015, with 14 states under investigation, as of 28 November 2015



DISEASE PREVENTION AND CONTROL

NTRE FOR



ORIGINAL ARTICLE

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.

- Case series of 88 pregnant women with a rash tested for ZIKV
- 72 (82%) were ZIKV+
- Among 42 of ZIKV+ women who had an ultrasound, fetal abnormalities were detected in 29% of cases

NEJM 2016

theguardian

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	ricas asia australia africa middle east	ities development euro	pe US	
Global development	Brazil warns women not as zika virus is linked to i Health authorities examine link between rise in n	to get pregna are birth defe	nt ect	
	Brazil has experienced a nationwide rise in cases of the zika virus.	disease borne by Aedes aegypti moso	Initoes.	

About eight weeks into her pregnancy, Patricia Campassi's body began to ache and she developed a rash. Doctors at her local maternity clinic in Campinas, in the state of São Paulo, put her condition down to a food allergy.

After a few days, she recovered and for the next five months everything appeared to be fine. But in the final weeks before the birth of her son, Lorenzo, the scans



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CDC A-Z INDEX 💙

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EMERGING INFECTIOUS DISEASES[®]

Probable Non–Vector-borne Transmission of Zika Virus, Colorado, USA

Brian D. Foy, Kevin C. Kobylinski, Joy L. Chilson Foy, Bradley J. Blitvich, Amelia Travassos da Rosa, Andrew D. Haddow, Robert S. Lanciotti, and Robert B. Tesh

Author affiliations: Colorado State University, Fort Collins, Colorado, USA (B.D. Foy, K.C. Kobylinski); Poudre Valley Hospital, Fort Collins (J.L.C. Foy); Iowa State University, Ames, Iowa, USA (B.J. Blitvich); University of Texas Medical Branch, Galveston, Texas, USA (A. Travassos da Rosa, A.D. Haddow, R.B. Tesh); and Centers for Disease Control and Prevention, Fort Collins (R.S. Lanciotti)

Clinical and serologic evidence indicate that 2 American scientists contracted Zika virus infections while working in Senegal in 2008. One of the scientists transmitted this arbovirus to his wife after his return home. Direct contact is implicated as the transmission route, most likely as a sexually transmitted infection.

ZIKV in breast milk...

Correspondence

Infectious Zika viral particles in breastmilk

Before 2007, no Zika virus outbreak had been recorded, and Zika virus was deemed to cause mild infections.¹ In 2013–14, an outbreak occurred in French Polynesia associated with an increased rate of Guillain-Barré syndrome following Zika infections.² Zika virus spread in the Pacific region in 2014 and then, in 2015, to Brazil where an association between Zika infection and microcephaly is under investigation.² There is a need for better comprehension of this disease.

Zika virus is transmitted to human beings by mosquitoes (Aedes spp). However, other routes of transmission have been described, such as sexual or perinatal transmission.3 Here, we report the presence of infective Zika virus particles in breastmilk with substantial viral loads. Arbovirus transmission via breastfeeding has been previously suggested for dengue,⁴ West Nile,⁵ and yellow fever,⁶ but more information is needed. Zika infection in woman during pregnancy or during the perinatal period must be considered very seriously by practitioners.

Zika virus infection in French Polynesia

On Feb 1, WHO issued an alert¹ on the potential fetal consequences of the Zika virus outbreak after the Brazilian authorities reported an abnormal increase in the number of cases of neonates born with microcephaly.² Although no causal link could be clearly established, circumstantial evidence was considered worrisome enough for several countries to discourage pregnant women from travelling to Central and South America.³

French Polynesia was affected by an



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This online publication has been corrected. The corrected version first appeared at thelancet.com on March 10, 2016



Published Online March 1, 2016 http://dx.doi.org/10.1016/ S0140-6736(16)00625-5

Current Canadian situation

- Risk of local ZIKV transmission is "very low"
- Travellers to affected regions should take precautions against mosquito bites
 - If possible, pregnant women should not go
 - Women should wait <a>2 months before trying to get pregnant
 - Men should use a condom to prevent pregnancy for <u>></u>6 months or for the duration of the pregnancy with a pregnant partner
- Diagnosed by RT-PCR or serology (>4x dengue)
- No treatment, vaccine development ongoing

Aedes mosquito vectors

- Several *Aedes* spp. can transmit ZIKV and other flaviviruses but primarily *A. aegypti*
- Range is increasing due to climate change
 - Dramatic expansions of *Aedes albopticus*
 - Reproduction rates and survival highly sensitive to temperature and precipitation
 - Increased temps can also increase viral infectivity
 - Linked to increased infections spread of dengue
- Aedes rarely found in southeastern Canada
- *A. japonicus* recently discovered in BC



Countries experiencing Zika virus outbreaks Updated 26th Feb 2016



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Life | Thu Mar 3, 2016 4:08pm EST

Related: HEALTH, BRA

Research indicates another common mosquito may be able to carry Zika (Culex quinquefasciatus) RIO DE JANEIRO | BY PAULO PRADA

Malaria incidence is decreasing

Figure 8.5 Proportion of children aged 2–10 years infected with *P. falciparum*, comparison between a) 2000 and b) 2013

WHO.org

No malaria vaccine yet in use

- Still ~200 million clinical cases and >500,000 child deaths/year
- RTS,S/AS01 (Mosquirix, GSK) is the most extensively tested *P. falciparum* vaccine
- Consists of circumsporozoite protein (CSP) repeats fused to HBsAg, adjuvanted with AS01
- Targets the sporozoite and intrahepatic stages
- 3 doses (0,1,2 months) +/- a booster 18 months later tested in ~15,000 children placebo-controlled RCT

RTS,S efficacy

- Efficacy to prevent clinical malaria was only ~25% in infants 6-12 weeks and ~35% in those 5-17 months at first vaccination
 - Lower protection against severe malaria

- Efficacy also wanes over time

- However, estimated to have prevented an average of >1 clinical case during the follow up period per child who received all doses
 - 983 cases/1000 in the 6-12 wk group over 3 yrs
 - 1774 cases/1000 in the 5-17 mo group over 4 yrs

RTS, S Clinical Trials Partnership Lancet 2015

Figure 3: Vaccine efficacy against clinical and severe malaria by study site in the 5-17 months age category

Figure 5: Vaccine efficacy against clinical and severe malaria by study site in the 6-12 weeks age category

Vaccine-Resistant Malaria ?

The NEW ENGLAND JOURNAL of MEDICINE

- Recent study investigated whether RTS,S efficacy is related to parasite genotype
- Next-gen sequencing performed on CSP gene PCRed from blood of RTS,S trial participants
- Performed a "sieve" analysis on ~5000 children
- The efficacy of RTS,S to prevent parasites with the identical CSP sequence was 50% versus 33% for mismatched parasites in older children
 - No difference in infants

Figure S1. Sieve Analysis Schematic.

RTS,S controversies

- Efficacy is relatively low, especially in infants
 - No effect on mortality
 - Booster dose is critical but logistically difficult...
- Even lower for mismatched parasites
 - Broad RTS,S could select for mismatched variants, further reducing protective efficacy
- Higher incidence of meningitis in RTS,S group (21 vs 1 in control)
- WHO announced in late 2015 that RTS,S/AS01 will be piloted in up to 1 million children

PATH Malaria Vaccine Initiative

Azithromycin to prevent severe LRTI?

 Severe wheezing with respiratory infections is common in preschool kids

- Asthma therapy is suboptimal

- Usually viral, but bacteria (e.g. pneumoccocus, *Moraxella*) often found in NP samples
- Unlike traditional asthma, IL-8 and neutrophilic inflammation is seen in RSV bronchiolitis and rhinovirus infection
- Macrolides may have benefits for wheezing related to antimicrobial and/or anti-inflammatory effects

Original Investigation

Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses A Randomized Clinical Trial JAMA November 17, 2015 Volume 314, Number 19

"APRIL"

- Children 1-6 yrs old with recurrent severe wheezing with LRTI
- Randomized 1:1 to placebo or azithromycin 12 mg/kg once daily for 5 days (double blind)
- Treatment started at start of usual trigger during an RTI according to the parent
- All children got albuterol QID for 48h and PRN

APRIL

APRIL's cold showers?

- NNT to prevent one severe LRTI was:
 - 33 kids with 1 treated RTI
 - 14 with 2 RTIs
 - 10 with 3 RTIs
 - 7 with 4 RTIs
- No difference in urgent care, ED visits, or hospitalization
- No clear benefit for any subgroup
- Potential for widespread use outside of the eligibility criteria
 - Bad recurrent wheeze, but not too bad?
- Concern for macrolide resistance, effects on microbiome, etc...

"Gent synergy"

- In vitro studies show synergistic effects of gentamicin with cell wall agents against enterococci
- Combination therapy with low-dose (3 mg/kg/day) gent is the standard of care and improves outcomes for enterococcal endocarditis
- Unclear whether gent is beneficial for enterococcal bacteremia without endocarditis
- Increasing evidence that risks of acute kidney injury from AG combination therapy may outweigh the benefits for some Gram+ infections

Clinical Infectious Diseases Advance Access published July 4, 2015

MAJOR ARTICLE

Low-dose Gentamicin for Uncomplicated *Enterococcus faecalis* Bacteremia May be Nephrotoxic in Children

Sarai Little Ibrahim,¹ Long Zhang,² Tammy M. Brady,³ Alice J. Hsu,⁴ Sara E. Cosgrove,⁵ and Pranita D. Tamma⁶

¹Campbell University College of Pharmacy and Health Sciences, Buies Creek, North Carolina; ²Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health, ³Department of Pediatrics, Division of Pediatric Nephrology, The Johns Hopkins University School of Medicine, ⁴Department of Pharmacy, Division of Pediatric Pharmacy, The Johns Hopkins Hospital, ⁵Department of Medicine, Division of Infectious Diseases, and ⁶Department of Pediatrics, Division of Pediatric Infectious Diseases, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Low-dose gent in kids

- Included patients 1-18 yrs old at Johns Hopkins with positive blood cx for *E. faecalis* and clinical evidence of infection
- Excluded if:
 - Polymicrobial bacteremia
 - Endocarditis, thrombophlebitis
 - High-dose gent (7.5 mg/kg/day)
 - E. faecalis resistant to prescribed regimen
 - Renal replacement therapy prior to episode
- Total N=313
 - 163 cases got amp + gent (all Q8h), 150 got amp alone
 - Median duration of gent was 9.6 days

Table 1	Ampicillin and Gentamicin, n = 163 (52%) n, Percent	Ampicillin, n = 150 (48%) n, Percent	<i>P</i> Value
Age in years, mean (SD)	4.9 (4.6)	5.8 (6.1)	<.01
Severity of illness			
Pitt bacteremia score, mean (SD)	1.66 (1.2)	1.56 (1.4)	.48
ICU on day 1 of bacteremia	88 (54.3)	39 (26.2)	<.001
Vasopressors	38 (23.6)	20 (13.4)	.02
Mechanical Ventilation	73 (45.4)	38 (25.5)	<.001
Preexisting medical conditions			
Immunocompromised ^b	49 (32.7)	25 (15.3)	<.001
Short-gut syndrome	64 (39.3)	65 (43.3)	.47
End-stage liver disease	12 (7.3)	8 (5.3)	.49
Chronic kidney disease	11 (6.8)	22 (14.7)	.03
Baseline creatinine clearance			
>60 mL/min/1.73 m ²	154 (94.5)	130 (86.7)	.02
30–60 mL/min/1.73 m ²	7 (4.3)	14 (9.3)	.06
10–29 mL/min/1.73 m ²	2 (1.2)	6 (4.0)	.16
<10 mL/min/1.73 m ²	0	0	1.00
Source of bacteremia			
Central line	100 (61.3)	103 (68.6)	.19
Urinary source	16 (9.8)	15 (10.0)	.87
Intra-abdominal	42 (25.8)	29 (19.3)	.44
Deep wound	5 (3.1)	3 (2.0)	.73

Low-dose gent associated with AKI

- Time to clearance was 10 hours faster in the gent group (p=0.04)
 - Adjusted for removing central line/ draining intraabdominal collections within 72 hrs
- No difference in relapse of bacteremia
- Risk of Acute Kidney Injury was 2x higher in the gent group
 - Even after adjusting for additional nephrotoxins

- HR = 2.29 (95% CI 2.14-8.63)

- No child developed endocarditis
- Could not evaluate once-daily dosing

Initial Low-Dose Gentamicin for *Staphylococcus aureus* Bacteremia and Endocarditis Is Nephrotoxic

Clinical Infectious Diseases 2009;48:713-21

Sara E. Cosgrove,¹ Gloria A. Vigliani,² Marilyn Campion,^a Vance G. Fowler, Jr.,⁵ Elias Abrutyn,^{7,b} G. Ralph Corey,^{5,6} Donald P. Levine,⁸ Mark E. Rupp,⁹ Henry F. Chambers,¹⁰ Adolf W. Karchmer,³ and Helen W. Boucher⁴

Research Original Investigation | COMPARATIVE EFFECTIVENESS RESEARCH JAMA Pediatr. 2013;167(10):903-91 Less Is More Combination Antibiotic Therapy for the Treatment of Gram-Negative Bacteremia in Pediatric Patients Pranita D. Tamma, MD, MHS; Alison E. Turnbull, DVM, MPH; Anthony D. Harris, MD, MPH; Aaron M. Milstone, MD, MHS; Alice J. Hsu, PharmD, BCPS; Sara E. Cosgrove, MD, MS

MAJOR ARTICLE

- Given the risk of AKI, use of combination therapy with gentamicin for definitive treatment of bacterial infections should be limited to indications with proven benefit
 - Not enterococcal bacteremia without endocarditis

Probiotics to prevent NEC

- NEC occurs in 5-10% of VLBW infants
- Mortality is high (~25%) and survivors often have long-term morbidity secondary to bowel resection
- Thought to be due to gut dysbiosis
 - Associated with antibiotic use
 - Human milk is protective
- Probiotics appear to be beneficial, but quality/heterogeneity of trials and probiotic products used complicate clinical translatability

Bifidobacterium breve BBG-001 in very preterm infants: a randomised controlled phase 3 trial

Kate Costeloe, Pollyanna Hardy, Edmund Juszczak, Mark Wilks, Michael R Millar, on behalf of The Probiotics in Preterm Infants Study Collaborative Group*

- PiPs phase 3 multicenter double-blinded RCT
- Infants $23 30^6/7$ gest age within 48 h of birth
- Given QD *B. breve* BBG-001 8.3 8.8 log₁₀
 CFU or placebo in elemental formula

B. breve manufactured/regulated as a pharmaceutical product

- Continued until 36 wk gest age or d/c home
- Outcomes: NEC Bell stage 2-3, sepsis at <a>>72 h, and death before d/c home

Figure 1: Trial profile

*Of the eight infants who received no intervention, seven died within the first week and the eighth was transferred on the first day of life to a hospital without the necessary regulatory approvals to give the intervention. †These five cases are excluded from all analyses. ‡These three cases remained on paediatric wards at the time of the analysis, they are included in the analyses as survivors and were later all discharged from hospital.

W Not all probiotic strains prevent necrotising enterocolitis in premature infants

Thomas R Abrahamsson

to everybody's disappointment, the PiPS trial was negative for all clinical outcomes.

Lancet 2015

Controversy!

- ProPrems was largest previous trial showed a benefit for NEC but not sepsis or mortality
 - No effect in neonates <28 wks gest?</p>
 - Used B. infantis, B. lactis, and Streptococcus thermophilius: called "ABC Dophilus"
- Cochrane review (meta-analysis included ProPrems) found a significant benefit for NEC
- Most studies were small and many were of poor quality; used different probiotics and dosages
- Generally safe... but ABC Dophilus recalled
- Still unclear what (if?) probiotics are effective
 - What dose, when to start, for how long???

Gut bacteria dysbiosis and necrotising enterocolitis in very low birthweight infants: a prospective case-control study

Barbara B Warner, Elena Deych, Yanjiao Zhou, Carla Hall-Moore, George M Weinstock, Erica Sodergren, Nurmohammad Shaikh, Julie A Hoffmann, Laura A Linneman, Aaron Hamvas, Geetika Khanna, Lucina C Rouggly-Nickless, I Malick Ndao, Berkley A Shands, Marilyn Escobedo, Janice E Sullivan, Paula G Radmacher, William D Shannon, Phillip I Tarr

- Case-control microbiome study
- Compared stool in infants that went on to develop NEC vs. controls
- Infants that developed NEC had
 - More Gram-neg facultative bacteria
 - Fewer obligate anaerobic bacteria
 - Lower gut diversity
- Differences apparent after 1 month of age
- No difference in *B. breve*
- Probiotic interventions may need to be individualized

THANK YOU!

