Coming to a Shore Near You: Zika and other Emerging Infectious Diseases

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EIDs — Two Major Categories

Newly emerging:
- Newly recognized in human hosts

Remerging — have historically infected humans:
- Appear in new locations
- Appear in drug-resistant forms
- Reappear after control/elimination

But don’t forget the following:
- MERS-CoV
- Chikungunya virus
- Influenza H7N9
- Ebola virus in West Africa
- Avian influenza H5N2 and others
- Zika virus
- Yellow fever (Angola, Brazil)

Factors in the Emergence of Infectious Diseases

1992
- Microbial adaptation and change
- Economic development and land use
- Human demographics and behavior
- International travel and commerce
- Technology and industry
- Breakdown of public health measures

2003
- Microbial adaptation and change
- Human susceptibility to infection
- Climate and weather
- Changing ecosystems
- Human demographics and behavior
- Economic development and land use
- International travel and commerce
- Technology and industry
- Breakdown of public health measures
- Poverty and social inequality
- War and famine
- Lack of political will
- Intent to harm

Challenges of Newly Emerging Infections

Need to rapidly learn about:
- Transmission, e.g. incubation period, communicability
- Clinical presentations and consequences
- At-risk populations
- Treatments
- Prevention, e.g. vaccines
- IP&C measures
- Risk assessment
- Communication
- Education, training
Our globally inter-connected reality

- The frontlines of infectious disease surveillance and response are not border-crossings/ports-of-entry.
- They are:
  - Primary care/urgent care
  - Emergency departments/hospitals
  - EMS
  - Community care
  - LTC

Transmission and Incubation Period

- Transmitted by *Aedes aegypti* mosquitoes
- Incubation period - 3 to 12 days (may be up to 14 days)
- Usually causes a mild, self limiting illness
  - Maculopapular rash
  - Low grade fever
  - Conjunctivitis
  - Arthralgia

Acute Zika Virus Infection: Clinical Management

- Supportive management
  - No antiviral therapy available for Zika virus infection.
  - Rest, fluids to avoid dehydration
  - Antipyretics, analgesics
- Do not take aspirin and other non-steroidal anti-inflammatory drugs (NSAIDS) until dengue ruled out, and do not use them in pregnant patients.
- Avoid mosquito bites until a week after symptom onset (to prevent spread to others)
Testing Modalities Available

- Molecular detection: real-time RT-PCR (PHOL)
- Blood/urine up to 14 days post-symptom onset
- Combined with CHIKV and dengue PCRs if symptomatic
- Serology (NML)
  - ELISA IgM
  - Plaque reduction neutralization titre (PRNT)
- Antigen detection
  - Immunohistochemistry (CDC only)
  - Immunochromatographic tests
- Virus Culture

Zika virus IgM serology

- Zika virus IgM reactive specimens are considered indicative of a recent flavivirus infection.
- IgM antibodies against Zika, dengue, West Nile and other flaviviruses have strong cross reactivity in serological assays
- Current assays cannot reliably distinguish between Zika and dengue virus infections.
  - IgM reactive specimens will be further investigated by neutralization assays (PRNT).

Asian lineage detected in French Polynesia, 2014 and Suriname, 2015

Worldwide spread of Zika virus

Zika Virus in the Americas – Why now, why here?

- International spread eastward over past 10-12 years
- Immunologically naïve populations
- Ample competent mosquito vectors, especially Ae. aegypti + Ae. albopictus
- Socio-economic determinants:
  - Poverty
  - Population density
  - Housing
  - Healthcare/public health systems capacity/access
- Viral mutations – changes to transmissibility and/or virulence?
  - Co-factors?
    - Previous/concurrent flavivirus infections, especially dengue
    - Environmental exposures
    - Bovine-like diarrheal virus (BVDV)

Challenges in Assessing/Understanding Emerging Zika Epidemiology

- Healthcare/public health system capacity in areas most affected
- Competing priorities in Zika-affected areas
- Concurrent epidemics of dengue fever and chikungunya virus infections
- Non-specific nature of clinical signs and symptoms:
  - Fever, rash, conjunctivitis, arthralgias
Challenges in Assessing/Understanding Emerging Zika Epidemiology

- Short period of viremia + capacity to detect via PCR
- Cross-reactivity of serological tests for antibodies with other flaviviruses:
  - Dengue
  - Yellow fever
  - West Nile virus
- High proportion of asymptomatic infections
- Evolving understanding of routes of transmission/clinical consequences
Congenital Zika virus syndrome in Brazil: a case series of the first 3501 births with complete investigation

**Summary**

In November 2015, an epidemic of microcephaly was reported in Brazil, which was later attributed to congenital Zika virus infection. This report presents cases that were reported to the Brazilian Ministry of Health until June 4, 2016, and discusses the implications for public health.

**Figure 4.** Distribution of suspected and confirmed cases of Zika and GBS by EW. Region of the Americas, 2015–2017 (as of EW 16).18

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**Early Growth and Neurologic Outcomes of Infants with Probable Congenital Zika Virus Syndrome**

We report the early growth and neurologic findings of 48 infants in Brazil diagnosed with probable congenital Zika virus syndrome and followed to age 1–4 months. Most of these infants had microcephaly (86.7%) and craniofacial dysmorphia (86.8%). The clinical pattern included poor head growth with increasingly negative z-scores, pyramidal extrapyramidal symptoms, and epilepsy.

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**Association between Zika virus infection and microcephaly in Brazil, January to May, 2016: preliminary report of a case-control study**

**Summary**

In Brazil, microcephaly, which occurred in 2015, was declared a Public Health Emergency of International Concern. We report preliminary results of a case-control study investigating the association between microcephaly and Zika virus infection during pregnancy.
The EC originally recommended a PHEIC in February 2016 on the basis of an extraordinary cluster of microcephaly and other neurological disorders reported in Brazil, following a similar cluster in French Polynesia and geographic and temporal association with Zika virus infection which required urgent and coordinated research. Because research has now demonstrated the link between Zika virus infection and microcephaly, the EC felt that a robust longer-term technical mechanism was now required to manage the global response.

As a result, the EC felt that Zika virus and associated consequences remain a significant enduring public health challenge requiring intense action but no longer represent a PHEIC as defined under the IHR. Many aspects of this disease and associated consequences still remain to be understood, but this can best be done through sustained research. The EC recommended that this should be escalated into a sustained programme of work with dedicated resources to address the long-term nature of the disease and its associated consequences.
Abstract

Background. In collaboration with state, tribal, local, and territorial health departments, CDC conducted a U.S. Zika Pregnancy Registry (USZPR) in early 2016 to monitor pregnant women with laboratory evidence of possible recent Zika virus infection and their infants.

Methods. This report includes an analysis of completed pregnancies (which include live births and pregnancy losses, regardless of gestational age) in the U.S. state and the District of Columbia (DC) with laboratory evidence of possible recent Zika virus infection reported to the USZPR from January 1 to December 27, 2016. Both defects potentially associated with Zika virus infection during pregnancy include lipoatrophy in affected microcephaly cases and other caudal anomalies, isolated brain defects, and other early ultrasonographic findings.

Results. Through analysis of 1,484 women with at least one gestational test result for Zika virus RNA, 1,377 pregnant women had at least one gestational test result for Zika virus RNA. Among these 1,377 pregnant women, 1,041 (76%) had at least one positive result. Among positive cases, the proportion was higher when a clinical or laboratory diagnosis of Zika virus infection was confirmed (55% vs. 76%).

Conclusions. The proportion of congenital anomalies detected was higher among women with laboratory-confirmed Zika virus infection than among those with a diagnosis of probable Zika virus infection. The proportion of congenital anomalies detected was higher among women with laboratory-confirmed Zika virus infection than among those with a diagnosis of probable Zika virus infection.
**Severe microcephaly**

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Linda Trueman, RN, The Hospital for Sick Children, Toronto

**Background:**  
Microcephaly is an anomaly of the central nervous system. It is a condition in which an infant or child is born with a smaller than normal head circumference. The head circumference is measured by circling the head near the temples and comparing it to norms for the child’s age. Microcephaly is usually a result of brain abnormalities, which may be caused by abnormalities during fetal development or acquired brain injury. Many microcephalic infants and children experience developmental delays, ranging from mild to severe. Children with microcephaly also present with undernutrition of the brain health, impaired motor skills, speech impairments, and other long-term, developmental, and social impairments.

**Congenital Zika syndrome (CZS) in infants in Canada**

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**Background:**  
Zika virus can cause microcephaly and other congenital defects. The virus is transmitted to humans through the bites of infected mosquitoes. Zika virus can also be transmitted through sexual contact, and there is evidence suggesting that the virus can be transmitted from an infected mother to her fetus. Children born with Zika virus infection may experience developmental delays, ranging from mild to severe. Children with microcephaly also present with undernutrition of the brain health, impaired motor skills, speech impairments, and other long-term, developmental, and social impairments.

**Prevention of Sexual Transmission**

- **Abstinence**
- **Male/female condoms:**
  - For vaginal, oral and anal sex
  - For entirety of sexual contact
  - Dental dams for oral to vagina/anal contact
- **Condoms for males with symptomatic or asymptomatic illness:**
  - Six months post-symptom onset
  - Based on earlier evidence of virus persistence in semen + precaution factor
- **Recent evidence of PCR positivity for 180+ days post-symptom onset**

**Sexual Transmission of Zika Virus**

- **Substantial evidence of symptomatic male→female/male transmission**
- **Limited evidence of transmission from:**
  - Asymptomatic males
  - Females→males/females
  - Sex toys
- **What is still unknown/uncertain?**
  - Persistence of pattern of shedding of infectious virus in semen
  - Persistence of pattern of shedding in vaginal fluids/cervical secretions
  - Differences in the above in symptomatic vs. asymptomatic cases
Prevention of Sexual Transmission

- Symptomatic or asymptomatic females require 8 weeks of transmission precautions:
  - Shorter duration of viral persistence in vaginal fluids/cervical secretions
  - Avoid sharing of sex toys

Other Potential Exposures/Modes of Transmission

- Urine:
  - No reports of transmission
  - Use of routine practices
- Breastmilk:
  - No reports of transmission
  - No restrictions on breastfeeding
- Saliva/tears:
  - No reports of transmission
  - Use of routine practices
- Blood screening/blood supply:
  - CBS donor deferral for 21 days

Reportability of Zika Virus Infection

- Zika virus infection not designated reportable in Ontario
- Limited data elements from PHO laboratories collected by/shared with CMOH/PHAC
- Why isn’t Zika reportable?
  - Limited PH actions requiring reporting/collection of personal health info
  - Prevention of sexual transmission via public education vs. case/contact follow-up
  - Priorities for lab testing: dependence on clinical diagnosis/reporting
  - Non-specific clinical signs and symptoms ➔ Zika, chikungunya, dengue, other
  - High proportion of asymptomatic infections
  - Pregnancy complications/ZCS reporting/assessment via PHAC/CPS voluntary system

Preliminary Findings from an Investigation of Zika Virus Infection in a Patient with No Known Risk Factors — Utah, 2016
Managing Occupational Exposures

- No documented evidence to date of transmission to HCWs, one lab transmission via needlestick injury
- Use of routine practices
- If exposed, within 8 wks of source patient exposure?
- If risk factors, testing of source patient
- Initial testing/counselling re. Zika symptoms
- If transmission occurs, pregnancy/sexual transmission follow-up
- No exclusion from work

Rapid Risk Assessment: The risk of Zika virus to Canadians (third update) – Appendix 1

Table 1: Core questions in risk assessment for communicable diseases

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<tr>
<th>Core questions in risk assessment for communicable diseases</th>
<th>Example of information needed</th>
<th>Risk factors</th>
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<tbody>
<tr>
<td>Assessing likelihood of transmission:</td>
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<tr>
<td>1. Is human exposure and transmission likely within Ontario?</td>
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<td>2. Is the population highly susceptible?</td>
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<td>3. Is the agent highly infectious?</td>
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<tr>
<td>Assessing probability of impact:</td>
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<td>4. Is the agent likely to cause severe disease?</td>
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<td>5. Will a significant proportion of the population be affected?</td>
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<td>6. Are effective treatments and/or control measures available?</td>
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Zika Virus Infection: Information and guidance for health care providers

Obtained October 5, 2016

Public Health Ontario has been working with the Ontario Ministry of Health and Long-Term Care, the Public Health Agency of Canada (PHAC) and other partners on monitoring and assessing the epidemiology, clinical impacts, prevention and control of Zika virus (ZIKV) infection. Where possible, PHAC refers to the latest advice from the Public Health Agency of Canada (PHAC), the World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC) when more up-to-date guidance is available.
PAHO and Zika Risk Communication

- With uncertain health risks, what is known, what not?
- Timely, transparent, accurate, accessible information
- Coordinating messages across health organizations
- Prioritize the messages → those with greatest impact
- Adapt information for different audiences
- Avoid over-interpretation and over-confidence
- Things will change as more is learned
- Link with/mobilize community leaders/educators
- Keep media informed

Zika Virus Commercial Assays

Press Release

Altona Diagnostics confirms launch of commercially available CE-IVD marking for detection of Zika Virus

Hamburg, January 27, 2016

The RealStar® Zika Virus RT-PCR Kit 1.0 is an in vitro diagnostic assay based on real-time Reverse Transcriptase/Polymerase Chain Reaction (RT-PCR) technology, for the identification of Zika virus. RealStar® Kits are reliable CE-IVD marked assays for detection and quantification of various viruses, bacteria and parasites. The assays meet all requirements of the IVD Directive 98/79/EC. With the development of the RealStar® Zika Virus RT-PCR Kit 1.0, Altona Diagnostics enlarges its panel of CE-IVD marked ready-to-use kits for tropical pathogens.

Source: http://www.who.int/diagnostics_laboratory/ce-zika-virus-160211invitation_to_mx_of_Zika_virus_diagnostics_v2.pdf?ua=1

Source: http://www.nature.com/nm/journal/v22/n8/full/nm.824.html

OpenZika: An IBM World Community Grid Project to Accelerate Zika Virus Drug Discovery

Abstract

The OpenZika project was a World Community Grid project to accelerate Zika virus drug discovery. The OpenZika project was designed and implemented by the Global Open Access to Antiviral Drug Discovery (GOAAV) initiative, a partnership between the World Health Organization, the International Alliance for the Development of AIDS Drug Resistance, the Global Alliance for Health and Development, and the World Bank. The project used a distributed computing approach to identify potential drugs that could be repurposed to treat Zika virus infection. The project was successful in identifying several potential drug candidates, including a drug that was later confirmed to be effective against Zika virus in clinical trials. The results of the project were published in the journal *PLoS Negl Trop Dis*.

From Drug Re-Purposing to Clinical Treatments

- In-vitro studies re. mechanism of action, toxicity
- Prioritization among drug candidates
- Phase 1, 2 and 3 clinical trials:
  - Clinical end-points: infection, transmission, protection of fetus?
  - Dose, route, duration of treatment?
  - Capacity to set-up/undertake vs. competing priorities?
- Drug approvals
- Manufacturing, distribution, clinical guidelines
- Phase 4 post-marketing capacity
ZIKV Vaccines
Options for vaccine development:
- Inactivated whole virus
- Subunit vaccines
- Live attenuated
- Chimeras, using existing viral platforms
- DNA vaccines → virus-like particles

Challenges of developing/testing a vaccine for women in reproductive years/pregnant:
- Outcomes of Zika in pregnancy not fully characterized
- Ethical challenges – risks vs. benefits mother/fetus, consent
- Research design – vaccination prior to/early pregnancy
- Baseline outcome rates (e.g. miscarriage), across geographies

Potential vaccine complications:
- Association of GBS with ZIKV infection
- Antibody-dependent enhancement with previous dengue infections
- Phase 3 and 4 detection/monitoring

Issues in ZIKV Vaccine Development (cont’d)
- Testing in animal models, phase 1, 2 and 3 studies
- WHO Emergency Assessment and Listing procedure for the use of experimental products during an epidemic:
  - Accelerated assessment process
  - Ensure products meet acceptable levels of quality, safety and efficacy, even if evaluation fast-tracked
- Regulatory approvals, manufacturing and distribution
- Funding, education, infrastructure, delivery, Phase 4 capacity
Mosquito Vector Control

- Personal protection measures → acceptability? compliance? effectiveness?
- Larviciding → myriad breeding sites
- Adulticiding:
  - Magnitude of applications
  - Aedes lives/feeds indoors
  - Reduction of adult mosquito populations
  - Impact on disease transmission/impacts?
  - Cost/sustainability

Mosquito Vector Control (cont’d)

- Eradication of breeding sites:
  - El Nino and rainfall patterns
  - Scale of what would be required, given Aedes breeding capacity
  - Huge community capacity/compliance
- Release of genetically-modified adult male mosquitoes:
  - WHD-supported
  - Evidence of impact on mosquito populations
  - Impact on incidence and complications, especially pregnancy-related?
  - Scale up, sustainability, cost-effectiveness?
  - Potentially part of the answer, not THE answer
  - Emergence of need to monitor for insecticide resistance
- Resistance to permethrins – impregnated clothing
Zika virus management, Florida

- Local transmission started in June 2016
- 285 confirmed cases in 2016
- Aedes aegypti responsible
- Intensive management program put in place

Local Zika virus transmission, Texas

- First evidence of local transmission at end of November 2016
- 6 confirmed cases
- Likely Aedes aegypti is vector
- Intensive management program initiated
- Active testing of residents near index case

Aedes albopictus – pre 2016, Ontario

- 2005 – Ottawa, August 28
- 2005 – Peel, September 1
- 2005 – Toronto, August 10
- 2012 – Windsor-Essex, June 12
- Likely detected from adventitious individuals hitching ride in vehicles from south
- WNV surveillance not designed to detect these mosquitoes, but if there is a local population, our traps will detect it
Aedes *albopictus* detected in Ontario

- Late September and early October 2016
- Adult mosquitoes collected in CDC traps at single location in Windsor (index site)
- Mid-October, intense collection of eggs, larvae and pupae from container habitats near index site
- BGS traps set up to collect adults, designed specifically for *Aedes albopictus* and *Aedes aegypti*

Results:
- Immature forms reared to adulthood identified as *Aedes albopictus* and *Aedes aegypti*
- Female and male adult *Aedes albopictus* collected by BGS traps
The face of Zika is not often seen in the air-conditioned shopping malls of upscale Rio neighbourhoods or on the beaches of Ipanema. Rio has its fair share of cases, but so far the heaviest burden has been borne by the northeast region of Brazil, where poverty, poor infrastructure, and lack of access to health services are rampant, and the penetration of Aedes aegypti is high. A large proportion of the population in that region is of African descent—indeed, the face of Zika is often that of a darker-skinned person. And because most cases are asymptomatic, and the most dramatic signs of the disease appear through congenital Zika syndrome, the face of Zika is that of a woman or a small child. That is at least what we are able to outline, because in spite of the need for disaggregated epidemiological data to understand transmission patterns and evaluate interventions in vulnerable populations, there is no reliable count of Zika cases by sex and ethnicity.
Zika and Global Health Security – Some Facts

WHO strategic response plan needs until end-2017: $122 million!

International funds raised by WHO to mid-August 2016: $14.5 million

WHO emergency contingency fund for all health threats: $31.5 million

World Bank estimates of economic losses, Latin America, to date: $3.5 billion

World Bank offsetting loans to mid-August 2016: $155 million

CDC spending on Zika response activities by end-August 2016: $194 million of $222 million allocated

UNDP Report Conclusions

• The current Zika epidemic will have a long-term impact, and countries will incur high direct and indirect costs as a result.
• There is a profound equity challenge at the core of the Zika epidemic. The impact is disproportionate on the poorest countries of the region, as well as on the poorest and most vulnerable groups, especially poor women in peri-urban communities.
• Regional and national preparedness and response strategies require strengthening and must involve communities.

UNDP Report Recommendations

Given that Zika is likely to become endemic, budgetary plans should be established accordingly.

Integrate efforts aimed at multiple mosquito-borne viruses, allowing room to tailor approaches to each disease’s unique effects.

Put equity considerations at the forefront of Zika strategies and provide adequate social protection mechanisms for those affected.

Promote public policies that support gender equality and promote sexual and reproductive health and rights, targeting affected communities.

Develop a multi-sectoral approach to mosquito-borne diseases both nationally and regionally.


Source: WHO/Institut Pasteur Draft

Figure 1: Timeline for the development and implementation of standardized research protocols for ZIKV.
Our globally inter-connected reality

- The frontlines of infectious disease surveillance and response are not border-crossings/ports-of-entry.
- They are:
  - Primary care/urgent care
  - Emergency departments/hospitals
  - EMS
  - Community care
  - LTC