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Zika virus outbreak: Challenges for research

Michel Counotte - Veterinary epidemiologist, Institute for Social and Preventative Medicine, University of Bern, Switzerland.

Zika virus was discovered in Uganda in 1947 and is primarily transmitted by mosquitoes (1). Infection with the virus can cause mild symptoms, such as rash and fever. However, most infected individuals do not have any symptoms. Over the past six decades, Zika virus only caused sporadic outbreaks. Endemic circulation was confined to regions in Africa and Asia where mosquitoes of the *Aedes* species were present; the same mosquitos that are responsible for the transmission of Dengue virus and Chikungunya. Zika virus spread to Yap Island in the Pacific Ocean in 2007 and to French Polynesia in 2013. From there, the virus spread to Brazil in 2014. In a short time span, the virus covered much of the American continent that harboured the *Aedes* vector (2).

The introduction of the virus on the American continent allowed the virus to spread in a large immunologically naïve population with attack rates, the percentage of the population infected during the outbreak, of up to 70%. During the outbreak, and for the first time in the history of the virus, adverse outcomes that appeared to be linked with the outbreak were seen on a large scale: clusters of babies born with microcephaly, a congenital malformation resulting in smaller than normal head size for age and sex, and older children and adults with acute autoimmune neurological symptoms. The size and impact of these adverse outcomes led the World Health Organization (WHO) to declare the outbreak as a Public Health Emergency of International Concern (PHEIC) on February 1, 2016 (3).

Besides transmission through mosquitos, it appeared that Zika virus could be transmitted by sexual contact as well (4), a feature not observed in any other flavivirus before. Sexual transmission increases the geographic reach of the virus, since the virus is not bound anymore to regions that harbour the right species of mosquito. Travellers infected with Zika virus returning to regions without endemic spread of the virus can transmit the virus to their sexual partners, and potentially spread the disease further within their sexual networks.

From the onset of an infectious disease outbreak, there is a need for public health guidance. In order to inform public health guidance, one needs to understand the potential risks that are associated with the outbreak. At this stage, however, large scale studies providing robust evidence are lacking, and evidence only slowly accumulates as the outbreak expands. Here I discuss how our research group from the Sexual and Reproductive Health Group of the Institute for Social and Preventive Medicine of the University of Bern approached two challenges that the Zika virus outbreak presented, as a newly re-emerging infectious disease about which very little research about infection in humans had been done. First, establishing causality in the absence of high quality epidemiological studies. Second, establishing the risk of sexual transmission in the presence of multiple transmission routes.

Causality between Zika virus and adverse neurological outcomes

Causal inference is the process of drawing the conclusion that an outcome derives from an identified mechanism or cause. Our aim was to determine whether Zika virus causes adverse neurological outcomes. Large scale randomized controlled trials (RCTs) are regarded as the best study design to answer causal questions. There are, however, no vaccines or treatments for Zika at present and hence no RCTs conducted. Observational studies, such as cohort studies or case-control studies, provide evidence about epidemiological associations. However, this is prone to biases or factors that might complicate the interpretation of causality. Early during the Zika virus outbreak, none of these types of studies was available, and we had to rely on evidence from case reports, case series, modelling studies and laboratory studies.

We used the approach outlined by Bradford Hill to examine the evidence for causal associations between Zika virus infection and the congenital abnormalities and Guillain-Barré syndrome (5). Bradford Hill listed nine 'viewpoints' from which to study associations between exposure and disease. These viewpoints are not strict rules, but can be used to decide if there is any other more likely explanation than cause and effect. We used these viewpoints as the basis for a causality framework, which enabled us to assess the full body of evidence and keep adding to it as new data emerges (6). We addressed specific questions in the domains of temporality, biological plausibility, strength of association, exclusion of alternative explanations, cessation, dose–response relationship, animal experimental evidence, analogy, specificity and consistency of findings (Box 1). A systematic review of the evidence led to

the conclusion that Zika virus was the cause of microcephaly and Guillain-Barré syndrome (6). On September 7, 2016, the WHO published their causality statement based on this assessment. At present, we are keeping track of the evidence to see if our conclusions stay valid over time (7).

Box 1. Dimensions of causality, based on Bradford Hill, applied to an infection (cause) with a named outcome (effect)

1. *Temporality: Does the infection precede the outcome?*
2. *Biological plausibility: Do underlying biological mechanisms explain that the infection results in the outcome?*
3. *Strength of association: How strong is the association between the infection and the outcome?*
4. *Exclusion of alternative explanations: Can the observed outcome be explained by alternative causes?*
5. *Cessation: Does a reduction in the number of infections result in a reduction in the number of outcomes?*
6. *Dose-response relationship: Does the severity of the outcome depend on the infectious dose or titre?*
7. *Animal experimental evidence: Does the infection in animal models produce a similar outcome?*
8. *Analogy: Do analogous infections cause similar outcomes?*
9. *Specificity: Does the infection cause a specific outcome or syndrome?*
10. *Consistency: Does the relation between infection and outcome occur consistently in different settings (populations, study designs, geographic settings)?*

Risk of sexual transmission of Zika virus

Unravelling the proportion that sexual transmission contributes to the total transmission of Zika virus is complicated by coexistence of multiple transmission routes. In a region where Zika virus is endemic, it is difficult to identify sexual transmission as the cause of an infection, or whether the infection may be explained by the presence of mosquitoes. To assess the risk of sexual transmission in absence of mosquitoes, we can use data from travellers; people visiting countries that have active transmission of Zika virus who then return back to their sexual partners in countries without Zika virus. Fitting a transmission model to data from such cases in the US enabled us to estimate the risk of transmission per sex act (8). We estimated that the probability of sexual transmission of Zika virus was 1.6% (95% CI: 1.1-2.4%) per sex act. This parameter can then be used to help infer the risk of transmission or the proportion of cases due to sexual transmission in endemic regions.

Informing mathematical models with the most up to date parameters is crucial to keep modelling estimates current and relevant. To this end, we established a framework that divides transmission into its key parameters: susceptibility to infection, incubation period following sexual transmission, serial interval between the onset of symptoms in a primary and secondary case, duration of infectiousness, basic reproduction number R_0, probability of transmission per sex act, and transmission rate (9). Combining the available evidence on sexual transmission of Zika virus has led to the conclusion that sexual transmission of Zika virus poses a small risk, that sexual transmission is more likely to happen from men to women than from women to men, and that sexual transmission alone will not be sufficient to sustain an outbreak. By continually updating the parameters with the most recent data, we ensure that the estimates are up to date.

In conclusion, applying conceptual frameworks supports the systematic assessment of the limited evidence base during disease outbreaks. The causality framework based on Bradford Hill's viewpoints and the sexual transmission framework allows taking into account the full spectrum of the evidence and help inform guidance. Mathematical modelling helps filling knowledge gaps by making efficient use of the available data. The generalisability of both the frameworks and the modelling makes them excellent tools to tackle similar challenges during future outbreaks of emerging infectious diseases.

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Michel Counotte *- Veterinary epidemiologist, Institute for Social and Preventative Medicine, University of Bern, Switzerland. Research interests: zoonotic and emerging diseases including the Zika virus outbreak.* michel.counotte@ispm.unibe.ch

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