

# Zika virus, the new kid on the block

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According to Tolstoy, happy families were all alike, whereas unhappy families were each unhappy in their individual ways. So it is with the emergence of new virus infections. Each new virus epidemic brings misery to affected human populations, in unique ways. In the last 15 years, we have experienced the emergence and spread of Severe Acute Respiratory Syndrome (SARS), H5N1 and H7N9 influenza A viruses, pandemic influenza A(H1N1)pdm09, Middle Eastern Respiratory Syndrome (MERS) and Ebola virus disease, and most recently in 2015–16, Zika virus. The wider societal impact that such infectious disease events can cause has been amply demonstrated with Ebola virus in West Africa, which was responsible for over 11,000 deaths and has inhibited economic growth in this war-torn region of the world [1].

Each of the viruses mentioned above occupies a different ecological niche, with diverse impact on the human population (magnitude of the epidemic, disease severity) as a result of transmission characteristics, host immune response and disease pathogenesis. Serious complications and deaths from Zika virus infection have not been common: most infections are asymptomatic or very mild, although there is an association with neurological complications such as Guillain–Barré syndrome. The key issue, however, is the impact of infection on pregnancy.

For most emerging viruses, classical control measures of contact tracing and quarantine will eventually break chains of transmission between humans following zoonotic infection, when human-to-human transmission occurs and infectiousness is related to symptomatic illness. However, when infection is through a vector-borne route and sexual transmission can occur from a minimally symptomatic person, such as with Zika virus infection, additional population-based control measures must be undertaken. Vector control requires sustained and determined efforts to achieve a measurable impact and may involve a range of interventions at a personal level (e.g. avoidance, mosquito nets and insecticide) and at population level (e.g.

breeding genetically resistant mosquitoes). Steering towards other rational interventions requires evidence from well-documented individual case studies.

Zika virus disease (ZVD) is a mosquito-borne infection caused by Zika virus, a member of the genus *Flavivirus* and family *Flaviviridae*. It was first isolated from a monkey in the Zika forest in Uganda in 1947. For those with symptoms, Zika virus generally causes a mild, short-lived (2–7 days) disease. Typical symptoms include: rash, itching/pruritus, low-grade fever, joint pain (with possible swelling mainly in the smaller joints of the hands and feet), conjunctivitis/red eyes, headache, muscle pain, lower back pain and eye pain – some of which were described in two of the case studies in this issue of *Eurosurveillance* [2,3]. However, the majority of people infected either do not have symptoms or have a very mild illness, and therefore the identification of symptom-free, but infectious individuals becomes much more problematic, particularly when coupled with consideration of sexual transmission of the virus, as described in the case report on sexual transmission in asymptomatic returning travellers [4]. In Brazil, a country heavily and early affected by the current Zika virus epidemic, an upsurge of cases of ZVD in women has been noted, with the underlying hypothesis that sexual transmission may be more important than hitherto recognised [5]. This may be consistent with modelling estimates that suggest that the  $R_0$  for transmission is lower than calculated for dengue, inferring that modes of infection other than *Aedes aegypti* bites might be involved [6]. The three articles in today's *Eurosurveillance* add to the accumulating body of evidence of persistence of virus in seminal fluids and emphasise the sexual transmission of Zika virus, including sexual transmission between completely asymptomatic individuals [4].

While the exact relationship of detection of viral genome by reverse transcription-polymerase chain reaction (RT-PCR) and virus infectivity and transmissibility from seminal fluid remains uncertain, the current European advice from the European Centre for Disease

Prevention and Control (ECDC) about prevention of sexual transmission of viral infection through the use of safer sex with condoms for several months in returning symptomatic and asymptomatic travellers from endemic areas [7] seems prudent and proportionate. The longest time for recovery of infectious virus from semen occurred at around 19–25 days post illness [8,9], the longest estimated time to sexual transmission following onset of illness is 32 to 41 days [10], whereas detection of viral genome to 60 days or more, previously noted in [8] is also noted in [2]. All of these estimates are subject to some uncertainties, but strongly suggest viral persistence in an immunologically privileged site. The kinetics of antibody response indicate that neutralising antibody will be present by this stage after illness onset. We should not be too surprised by this, following the demonstration of exactly this phenomenon in survivors of Ebola virus disease [11]. Even though these are different groups of viruses with different pathogenesis, both have a viraemic phase with possible replication in vascular and reticuloendothelial tissue. As further data develop about duration of persistence of viral material in the testes, pragmatic public health advice about condom use, for a reasonable period beyond last known documented virus detection, may be a more rational and cost-effective approach than country-specific advice that returning travellers should routinely undergo laboratory testing.

There is scientific consensus that Zika virus is a cause of microcephaly and other congenital anomalies, also referred to as congenital Zika virus syndrome, the full definition for which continues to evolve as case-based information develops. The World Health Organization has thus started coordinating efforts to define congenital Zika virus syndrome and has issued an open invitation to all partners to join in this effort [12]. The combination of widespread asymptomatic infection, seminal fluid infectiousness, transmission from men to women and infection in early pregnancy, with a linkage to congenital anomaly, is an unfolding horror story, which we are ill-equipped to deal with. The current scenario is a true global public health emergency, which requires an urgent raft of measures to minimise the impact. We should be under no illusions – it will take several years to find permanent solutions, such as vaccination.

The current response to Zika virus in mainland European countries is centred on limited numbers of cases of returning travellers. There will be a close watch in Europe in the coming summer season for any autochthonous transmission in areas where *Ae. aegypti* or *Ae. albopictus* is established [13], although the risks are considered to be low [7].

Disease control programmes start with awareness and accurate diagnosis. The symptoms of Zika virus infection can be similar to those of dengue, caused by a related flavivirus, or chikungunya, an alphavirus, which are often co-circulating in affected areas where Zika

virus is present. Testing of symptomatic infections for individual case management is most needed in pregnancy. On the other hand, reliance on clinical diagnosis will not be sufficient to provide accurate estimates of disease burden in the affected countries and where laboratory capacity is limited. Laboratory testing of a proportion of all clinical cases is essential for feeding accurate information into predictive transmission modelling. During the first five to seven days after onset of clinical illness during the acute viraemic phase, serum can be used for detection of viral genomic material by real-time RT-PCR. Body fluids such as urine or oral fluid may extend the window for genome detection during acute illness, and urine is already recommended for testing by some public health agencies [14]. These fluids were useful in the limited case studies reported in *Eurosurveillance* [2,3]. As more data become available from cohort studies, information about the reliability of virus detection in different body compartments during the acute phase of illness would be very welcome. Further partial genome sequencing may be helpful to confirm strain variation, and in any case will be important to track the relationship between strain variation and clinical outcome.

Overall laboratory capacity and cost of testing will raise barriers to providing widespread diagnostic support in affected areas, but is less of an issue in Europe. There is an urgent need to develop low-cost, simple point-of-care tests for viral antigen detection, as has been possible for dengue virus. It has taken many decades to realise the potential contribution of self-sampling, using non-invasive body fluids, to support disease control efforts. The detection of substantial amounts of Zika virus in urine and oral fluids suggests that detection of early infection could be attempted from these fluids. If dipsticks or similar simple devices can be developed for antibody detection, with sufficient sensitivity either for capillary blood finger prick testing and urine or for oral fluid sampling, the desirable goal of specific testing linked to self-sampling can provide some additional capacity within severely constrained health systems in affected countries.

Limited data from a small number of cases are currently available on the serological responses to Zika virus. There is antibody cross-reactivity with other flaviviruses, especially dengue virus and yellow fever virus or, less frequently, with West Nile virus. Serology focussing on the detection of viral E antigen, a key viral structural protein involved in virus receptor binding, is likely to demonstrate cross-reactivity between flaviviruses, as there is a high degree of conservation of the human immune response to this viral protein. Tests based around virus neutralisation need to be interpreted with caution and may not be useful as

first-line screening tests, although they may have a role in confirmation of antibody status. The application of serological tests (ELISA or immunofluorescence) to detect specific IgM or IgG against Zika virus can be positive five to six days after the onset of symptoms. In line with classical antibody responses to infection, increased antibody titres are seen in paired samples, with an interval of about two weeks. The results of serological tests are much easier to determine in populations, such as returning European travellers, who mostly do not have a background of exposure to multiple co-circulating dengue subtypes or other flaviviruses. Interpretation of serology in flavivirus-exposed populations will be much more challenging. There is an urgent necessity for Zika virus-specific IgG serological tests that can deliver a very high negative predictive value, and distinguish past infection with other flaviviruses, when applied in sero-epidemiological studies, as this will define the extent of susceptibility in the population, to inform wide-scale control measures. On the other hand, there is a need for serological tests that will deliver a high positive predictive value for Zika virus IgM detection following acute illness, where the narrow window for detection of the viral genome by PCR has been missed. It is particularly challenging to ensure that the correct individual diagnosis is made and pregnant women are not subjected to inappropriate procedures for an infection that they do not have. Considerations of anamnestic response to diverse flaviviruses and original antigenic sin may be relevant in highly exposed populations and may give rise to positive serological test results, following acute illness, as a result of lack of specificity. The complexity of serological responses to Zika virus in light of previous multiple diverse flavivirus infections or vaccinations will require careful elaboration and comparison and pooling of datasets internationally, as well as consideration of whether the risk of congenital anomaly is enhanced or reduced in the presence of pre-existing flavivirus antibody.

It may be some years before we have serology that is highly reliable at both the individual patient and population level. There is a notable gap between the application of serology to carefully studied individual cases, with confirmed genome detection and knowledge of dates of onset of illness, and the application of serology to address the wider disease control questions, at scale, in diverse populations.

The development of serological tools for emerging infections inevitably lags behind the availability of accurate molecular diagnostic tools. The experience of SARS a decade ago, showed that even a year after the first serological tools were developed for detection of this infection, the number of laboratories that could reliably perform serology globally was severely limited [15]. The development of serological tools for MERS is also highly restricted. Urgent attention is required for the development and standardisation of serological tools for Zika virus. It is entirely appropriate that

international efforts are directed towards collaborative serological studies, international standards and reagents for serology and study of the relationships between antibody responses to Zika virus and other flaviviruses, to define the protein epitopes involved in cross-reactivity, and address the potential for antibody-dependent enhancement between different groups of flaviviruses.

In summary, it will be crucial to provide support to affected countries to enable the development of robust serological tools, with the goal of ensuring safe pregnancies. Serological tests and algorithms for Zika virus-specific serological testing are in their infancy. Achieving reliability of testing will require sharing of data and reagents, a cooperative working approach to develop international standards and a hierarchy of serological algorithms. The current situation requires that we manage expectations and acknowledge uncertainties to patients, physicians and politicians in this unhappy circumstance. Individual case reports, as published in *Eurosurveillance* today, have an important role in providing evidence to reduce uncertainties.

## Conflict of interest

None declared.

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