HHS Public Access

Author manuscript

Lancet Infect Dis. Author manuscript; available in PMC 2021 December 15.

Published in final edited form as:

Lancet Infect Dis. 2020 March ; 20(3): 270–272. doi:10.1016/S1473-3099(19)30686-3.

Balancing sensitivity and specificity of Zika virus case definitions

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In a study published in *The Lancet Infectious Diseases*, Raquel Burger-Calderon and colleagues[1] characterise the clinical profile of Zika virus infection and assess the performance of WHO and Pan American Health Organization case definitions in a large paediatric cohort from Nicaragua. They show that Zika disease primarily manifests with undifferentiated fever or afebrile rash, and that the occurrence of symptoms increases with age. As a result, Zika in children is likely to be missed by recommended case definitions more frequently than in adults. Sensitivity improved with age, as older cases presented with more symptoms, but at most, only half of the symptomatic cases were captured. The most commonly presenting symptom was rash; other symptoms, such as arthralgia and periarticular oedema, were equally rare in cases with and without Zika. The study testing algorithm helped identify that previous dengue infection did not change the clinical presentation of Zika. Cases only identified by serology were milder than were PCR positive cases, suggesting that studies that only used PCR positivity to confirm cases might be more aligned with recommended case definitions. In summary, these definitions missed most cases and mainly captured cases in older children with dengue-like illness. The authors call for case definitions to be revised to better capture the full clinical spectrum of Zika virus.

Previous work supports that age is a key determinant of arboviral clinical presentation. In dengue, leukopenia was identified as an early predictor of disease among adults aged 20 years and older, but not among children. Leukopenia is common in viral childhood infections and as children can have an average of between six and eight viral infections annually, it can be a non-specific indicator of dengue in this population.[2] Researchers from our group have also found a trend towards increasing Zika symptomatology among older children,[3] and arthralgia and myalgia are more common in adults than in children.[4] Studies from Brazil also showed better performance of the WHO case definition among adults than in children.[5] Separate clinical definitions or diagnostic algorithms could be appropriate for children and adults; however, this might not be feasible for large scale surveillance.

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We declare no competing interests.

Zika surveillance moving forward will be challenging. First, most cases are mild or asymptomatic, and the percentage of asymptomatic cases can vary in different populations. For example, although in Yap it was estimated that 27% of Zika infections were symptomatic, in Puerto Rico, 50% of Zika infections were symptomatic.[6] Furthermore, only 55% of people with symptoms from Zika in Puerto Rico sought care, and a fifth of these cases were reported to authorities.[7] Similar under-reporting has been suggested for dengue.[8] Second, symptoms of Zika are similar to symptoms of other common infections. Laboratory confirmation is required, especially in children, given Zika's mild non-specific presentation. Laboratory capacity in many countries is limited and only a subset of samples are tested. Additionally, cross-reactivity complicates serological diagnosis. PCR diagnosis is only useful at the early stages of disease progression.[9] Finally, transmission in the Americas is low, and with high immunity (25–80%),[10] whether Zika virus will return (and when) remains unclear. Additionally, increased dengue transmission has been recorded in many locations. During periods when Zika transmission is low, the performance of case definitions will be worse than when transmission is high. Immunity among older children and adults will change future monitoring of the epidemiology of Zika, with more cases occurring among children, in whom presentation is milder and more difficult to recognise.

The optimal balance between sensitivity and specificity for case definitions is different for research and surveillance. Research can benefit from hospitals and clinics capturing as many cases as possible. Surveillance systems must consider several factors: probability of detecting transmission should it occur (sensitivity), avoidance of false-positives requiring interventions (specificity), and the resources needed for conducting surveillance. A modelling comparison of Zika surveillance systems found that no strategy was likely to detect even 5% of infections.[11] The probability of detecting at least one Zika infection was highest when surveillance was done by testing individuals presenting to health facilities with rash, compared with surveillence among pregnant women or blood donors.[11] To closely monitor for Zika re-emergence, countries would need to maintain sentinel surveillance and routinely test patients with rash for arboviruses. Beyond the needs for research projects, the question that results from Burger-Calderon and colleagues[1] study is how sensitive does surveillance need to be to guide public health action? Increased sensitivity must be balanced against loss of specificity and resource implications. The most important feature of surveillance is not the ability to detect all cases, but the ability to detect at least one locally transmitted case in a timely manner and thus prompt enhanced surveillance and appropriate prevention measures.[11]

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