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Title:

Zika Virus in Saliva – New Challenges for Prevention of Human to Human Transmission

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The ongoing Zika virus (ZIKV) outbreak in South-and Central America has rapidly focused global attention due to its association with clusters of congenital malformations and neurological disorders (1), and because of the impending 2016 Olympic Games in Rio de Janeiro, Brazil (2). The ZIKV outbreak was quickly declared a Global Emergency by the World Health Organization and the ensuing flurry of research is focused on the defining the complex epidemiology and pathogenesis of ZIKV. The main mode of ZIKV virus transmission to humans is through the bite of an infected *Aedes* spp. mosquito. However the unexpected rapid spread and transmission of the ZIKV in the Americas has raised questions as to whether secondary human to human transmission can occur after primary infection. ZIKV has been isolated in cell culture from semen samples of patients and cases of sexual transmission of ZIKV infection from males to their female partners have been documented (3,4). More recent reports of detection of ZIKV in saliva (5,6), emphasizes the need to resolve the relative importance of human to human transmission through intimate contact during kissing or sexual intercourse.

ZIKV has been cultured from saliva obtained from a patient during acute ZIKV infection (5) on day 6 after symptom onset, and prolonged viral shedding was observed for up to 29 days (6). Musso et al. (5) studied biological samples collected from 855 ZIKV-infected patients in French Polynesia and found that ZIKV was more frequently detected in saliva compared to blood. During the acute phase of the infection, the use of saliva as a sample compared to blood, for molecular detection of ZIKV increased detection rates by approximately 20% indicating higher viral load concentrations. ZIKV has also been detected in urine (7). These observations provide opportunities for developing rapid diagnostic tests for ZIKV infection using saliva or urine which are easily available non-invasive clinical samples which could be invaluable for development of point of care rapid diagnostic tests for identification of ZIKV cases, and for conduct of large scale epidemiological studies.

Oral-genital contact is known to transmit several sexually transmitted infections (STIs) including viral infections such as human immunodeficiency virus (HIV) (8). It is difficult to measure the exact risk of ZIKV transmission through oral sex because people who practice oral sex may also concurrently practice other forms of sex during the same encounter. Current guidelines developed by the Centers for Disease Control (CDC) (9) for minimizing risk of human to human transmission of ZIKV through infected semen and saliva are regularly updated. Specific recommendations for: a) women who are pregnant and living in an area with ZIKV; or b) women who are trying to get pregnant and their male partner lives in, or has traveled to, a ZIKV endemic country, and vice versa. CDC guidelines recommend: a) use of condoms when having vaginal, anal, or oral sex during pregnancy; or b) avoiding sex with male partner during pregnancy (9). Whilst these are prudent and practical recommendations, there is no specific evidence base for them.

The risk of human to human ZIKV transmission by saliva, urine and semen through intimate contact or sexual intercourse is difficult to quantify. Important questions remain to be answered: 1) Can ZIKV be spread from other body fluids, such as saliva and vaginal fluids and are they important in the current ZIKV outbreak epidemiology? How long does ZIKV persist in the bodily fluids in people with ZIKV infection? Are asymptomatic men with ZIKV infection have the virus in their semen and are they able to spread ZIKV through oral, anal or vaginal sex? Specific studies on the viral kinetics of ZIKV, viral load concentrations in bodily fluids and duration of infectivity are urgently required for developing prevention guidelines. Genomic studies on ZIKV isolated from any bodily fluid both primarily infected donor and the contact recipient are urgently required to establish transmission dynamics and the importance of various modes of transmission. Whilst the evidence base is being developed, the vital question that remains to be answered is whether women planning to get pregnant, or those who are pregnant in ZIKV endemic areas should be advised to avoid kissing or having intimate contact anyone in ZIKV endemic areas? These research studies should be conducted in parallel with, and should not divert attention from ongoing efforts on control of *Aedes spp* and research on vaccines.

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