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Systematic Review

Sexually acquired Zika virus: a systematic review

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ABSTRACT

Background: Zika virus (ZIKV) is transmitted to humans primarily by *Aedes* mosquito bites. However, circumstantial evidence points to a sexual transmission route.
Objectives: To assess the sexually acquired ZIKV cases and to investigate the shedding of ZIKV in genital fluids.
Data sources: PubMed, Scopus, Pro-MED-mail and WHO ZIKV notification databases from inception to December 2016.
Selection criteria: Reports describing ZIKV acquisition through sex and studies reporting the detection or isolation of ZIKV in the genital fluids were included.
Risk-of-bias assessment: The risk of bias was assessed using the National Institute of Health Tool.
Results: Eighteen studies reporting on sex-acquired ZIKV and 21 describing the presence of ZIKV in genital fluids were included. The overall risk of bias was moderate. Sexual transmission was male–female (92.5%), female–male (3.7%) and male–male (3.7%). Modes of sexual transmission were unprotected vaginal (96.2%), oral (18.5%) and anal (7.4%) intercourse. The median time between onset of symptoms in the index partner and presumed sexual transmission was 13 days (range 4–44 days). ZIKV RNA was detected in semen as late as 188 days (range 3–188 days) following symptom onset, and infectious virus was isolated in semen up to 69 days after symptom onset. No study reported ZIKV isolation from female genital samples, but detection did occur up to 13 days after symptom onset.
Conclusions: ZIKV is potentially sexually transmitted and persists in male genital secretions for a prolonged period after symptom onset.
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Introduction

Zika virus (ZIKV) is an emerging flavivirus belonging to the family *Flaviviridae*, which is currently responsible for a major outbreak in the Americas [1]. As of 7 December 2016, a total of 69 countries and territories have reported evidence of vector-borne ZIKV transmission since the start of the outbreak in 2015 [2].

The disease usually presents as a self-limited febrile illness, but mounting data have established an association between ZIKV infection and adverse pregnancy and fetal outcomes, with microcephaly being the most prominent, as well as other neurological syndromes, especially Guillain–Barré syndrome [3,4]. By these close associations, in February 2016 WHO declared that the situation represented a Public Health Emergency of International Concern [5]. Recently, during the fifth meeting of the Emergency Committee on ZIKV convened by WHO, the team felt that ZIKV no longer represented a Public Health Emergency of International Concern, but emphasis was made that it remains a significant enduring public health challenge that requires a long-term response mechanism [6].

The main mode of transmission of Zika virus disease (ZVD) in urban and suburban environments is by mosquito bite—*Aedes aegypti* and, to a lesser extent, *Aedes albopictus* [1]. Non-mosquito transmission does occur but the magnitude of the contributions

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of different ZIKV transmission routes to initiate or maintain the epidemics in different regions remains unclear [7]. Here we summarize the current evidence about sexually acquired ZIKV infection. Second, we assess the shedding of ZIKV in genital fluids. We hope that by assembling the available data we will be able to contribute much-needed evidence to support WHO's interim guidance regarding the prevention of the sexual transmission of ZIKV. Furthermore, we highlight the gaps in the current knowledge that should be addressed to improve our understanding of the transmission of ZIKV through sex.

Materials and methods

Search strategy

This study is a systematic review, and the PRISMA guidelines were followed [8] The PubMed and Scopus databases from inception to 8 December 2016, were searched to identify published clinical reports describing ZIKV infection acquired through sex, and studies reporting the presence of ZIKV in genital fluids. The following keywords were used in search engine: 'Zika', 'Zika infection', 'Zika fever', 'Zika virus disease', 'Sex' and 'Semen'. Additionally, we searched for unpublished sexually acquired ZIKV cases that were notified to WHO by National International Health Regulations Focal Points and the PROMED-mail database. Neither time nor language restrictions were imposed. Manual searches were also performed from the reference lists of the included articles. The study is registered at PROSPERO (CRD42016041475).

Study criteria

Published observational studies (i.e. case series and case reports) were considered for inclusion. Studies lacking primary data were excluded. Sexually acquired infections were considered for individuals without a history of residing in or travelling to areas of active ZIKV transmission who acquired ZIKV infection from a sex partner with ZIKV infection, as defined by WHO ZIKV disease interim case definitions [9]. For the sake of clarity, index subjects were those who were the likely source of infection with suspected, probable or confirmed ZIKV infection residing in or with a history of travel to areas of active ZIKV transmission or a recent ZIKV outbreak. Non-human cases were excluded. Moreover, eligible studies could include individuals in whom the presence or persistence of ZIKV was evaluated in the genital fluids throughout the disease process. Two review authors (JM, TP) independently screened the titles and abstracts of studies based on the inclusion criteria. If there was a disagreement, a consensus was arrived at through discussion with a third reviewer.

Data extraction

We extracted the following key information from the included studies: study design, country and date of publication, modes of sexual transmission, age and clinical manifestations relative to the index patients, diagnostic workout of ZVD, secondary incubation period relative to the other sex partner, presence of other sexually transmitted infections, country of ZIKV acquisition, timing of sexual intercourse in relation to disease onset in the index case (i.e. before, during or after the symptom onset), and the investigations used to exclude other non-sexual transmission routes.

For the studies that evaluated ZIKV shedding in genital fluids, we extracted the timing and the viral load of ZIKV in genital fluids in relation to other specimens tested (i.e. serum, saliva, urine, cerebrospinal fluid).

Aims

The primary aim was to assess the number of suspected, probable or confirmed sexually acquired ZIKV cases. The secondary aim was to describe the number of ZIKV-infected cases in which ZIKV shedding in genital fluids was documented.

Risk-of-bias assessment

Two independent review authors (JM, TP) assessed the quality of the individual case reports or case series using a modified National Institute of Health Tool [10].

Results

Our initial search result yielded 88 records, but only 33 articles were considered for the qualitative analysis (Fig. 1). A total of 18 reports described sexually acquired ZIKV cases, whereas 21 described the kinetics of ZIKV in genital fluids. Six articles described both outcomes.

Risk-of-bias assessment

Four studies were of low quality, 27 of medium quality and two of high quality, indicating a moderate risk of bias for the total analysis (see Supplementary material, Tables S1 and S2).

Transmission of ZIKV through sexual intercourse

We found 18 studies reporting person-to-person transmission of ZIKV through sexual intercourse, corresponding to 27 episodes of probable or confirmed sexual transmission of ZIKV [11–28]. Table 1 describes the probable or confirmed cases of sexually acquired ZIKV. Fig. 2 shows the countries reporting sexual transmission of ZIKV. The median index case age was 41 years (range 20–61 years). Fifteen studies reported male to female transmission in 25 couples; one reported male to male transmission [19], and another reported female to male transmission [24]. Modes of sexual transmission were unprotected vaginal intercourse in 96.2% (26/27), oral intercourse in 18.5% (5/27) and anal intercourse in 7.4% (2/27). Time of sexual intercourse concerning index case symptom onset was reported in 13/27 (48%) couples. Sexual intercourse occurred before, during and after the index's symptom onset in five (38.4%), seven (53.8%) and one (7.6%), respectively.

The most commonly reported signs and symptoms in the index partner were, fever (83.3%), rash (79.1%), arthralgia (58.3%), conjunctivitis hyperaemia (33.3%) and headache (25%). Fever was absent in four patients, and three were entirely asymptomatic [14,20,26]. Laboratory evidence of ZIKV infection in the index patient included positive serological test results in 20 (74%) cases and positive RT-PCR in nine (33.3%) cases. ZIKV RT-PCR was detected in seminal plasma (1/27, 3.7%), serum (2/27, 7.4%), urine (5/27, 18.5%) and semen (6/27, 22.2%). In six (22.2%) cases ZIKV was confirmed through both serology and RT-PCR. In four cases (reported in three studies), ZIKV was suspected in the index patient, and probable sexual transmission was defined based on the epidemiological and clinical history of the participants [13,14,18].

Among the 15 symptomatic index cases with known travel dates, patients reported becoming ill a median of 1 day after returning home (range 3 days before return to 6 days after return). The most frequently reported regions with active ZIKV transmission visited by index cases were the Caribbean ($n = 5$), Central America ($n = 5$) and one each for the Maldives, Senegal, Thailand and Pacific islands.