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Can dengue virus be sexually transmitted?

Martin P. Grobusch[a,b,*], Karin S. van der Fluit[a], Cornelis Stijnis[a], Cornelis A. De Pijper[a], Thomas Hanscheid[c,d], Philippe Gautret[e,f], Patricia Schlagenhauf[g], Abraham Goorhuis[a]

[a] Centre of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Amsterdam University Medical Centres, Amsterdam Public Health, Amsterdam Infection & Immunity, Amsterdam, the Netherlands
[b] Institute of Tropical Medicine, University of Tübingen, Tübingen, Germany
[c] Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal
[d] Instituto de Microbiologia, Faculdade de Medicina, Universidade de Lisboa, Avenida Prof. Egas Moniz, 1649-028, Lisboa, Portugal
[e] Aix Marseille University, IRD, AP-HM, SSA, VITROME, Marseille, France
[f] IHU-Méditerranée Infection, Marseille, France
[g] University of Zürich Centre for Travel Medicine, WHO Collaborating Centre for Travellers' Health, Department of Public and Global Health, Institute for Epidemiology, Biostatistics and Prevention, Zürich, Switzerland

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ABSTRACT

It has been well documented that Zika virus (ZIKV) can be sexually transmitted. Dengue virus (DENV) shows many similarities with ZIKV; both belong to the genus *Flavivirus* and share the same main vector route of transmission. Moreover, they share overall architectural features on a molecular level, with a highly similar structure and distinctive insertions, deletions and mutations of their respective E proteins, and it has been suggested that they use a common pathophysiological pathway. In view of similarities with other sexually transmissible viruses, the question arises as to whether DENV could also be sexually transmissible.

Limited animal model data do not suggest otherwise. The presence of dengue virus in - and human-to-human, non-vector transmission from - various bodily fluids other than semen or vaginal secretions has been documented anecdotally.

Several anecdotal reports described prolonged presence of DENV in semen, urine and vaginal secretions. In 2019, two cases of likely sexual transmission were reported from Spain and South Korea, respectively.

We discuss the evidence for and against a relevant DENV sexual transmission potential, highlight controversies and propose a future research agenda on this issue.

1. Introduction

Today, about 3.9 billion people, 52% of the world's population in over 100 countries, live in dengue virus (DENV) endemic areas. It is estimated that there are around 390 million DENV infections annually [1,2]. Over the past decades, population growth, urbanisation and globalisation have allowed DENV to spread and dramatically increase in incidence [3,4]. Apart from vector control measures, interventions against dengue have shown low efficacy.

Behavioural aspects of populations at risk may play a critical role in control strategies [4]. To optimise control and intervention strategies, potential routes of transmission of DENV need to be identified.

DENV is primarily transmitted via mosquito vectors: predominantly *Aedes aegypti*, and to a lesser extent *Aedes albopictus*. However, other modes of transmission have been anecdotally documented: via mucocutaneous transmission, via needle stick injury in patient care and laboratory accidents, via blood transfusion, via bone marrow transplantation, via organ transplantation, as well as peripartal, perinatal and via breastfeeding [5–7].

There are two striking recent examples for the 'discovery' of sexual transmissibility of viruses not known before to have this potential.

First, during the large West-African Ebola virus disease (EVD) outbreak, the potential of this filoviral disease for sexual transmission was recognised for the first time [8]. By now, it is established that live Ebola virus (EBV) can be transmitted by male individuals up to years after their clinical recovery from EVD [9].

Secondly and relevant here, in early 2015, ZIKV spread epidemically across the tropical and subtropical parts of the Americas and it soon became clear that ZIKV can be sexually transmitted [10]. To date, more than 35 cases of sexual transmission have been documented [11].

* Corresponding author. Centre of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Amsterdam University Medical Centres, Amsterdam Public Health, Amsterdam Infection & Immunity, Amsterdam, the Netherlands.
E-mail address: m.p.grobusch@amsterdamumc.nl (M.P. Grobusch).

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DENV shares many similarities with Zika virus (ZIKV); both belong to the genus *flavivirus* and share the same main route of transmission. They share the same *Aedes* mosquito vectors and show similarity of the overall structural architecture on a molecular level [12,13], with a highly similar structure but distinctive insertions, deletions and mutations of the E proteins [14]. Both ZIKV and DENV show inhibition of the extracellular matrix (ECM) pathway, which suggests there is a common pathophysiological pathway [15]. In view of these similarities, the question whether DENV is sexually transmissible, too, is evident.

Furthermore, there were two reports of detection of other flaviviruses including chikungunya virus and yellow fever virus in semen up to 30 days and 21 days after symptom onset, respectively [16,17].

All this raises the question if there is more to explore with relation to sexual transmission of arboviruses as a recent publication eloquently put it [18].

2. Evidence for and against DENV sexual transmission potential

2.1. Sexual transmission potential of viruses in general

Salam and Horby reviewed the sexual transmission potential of a broad range of viruses pathogenic to man [19]. Their search identified 27 viruses (from 13 families) which were shown to be detectable in semen, 13 of which had also been isolated. Evidence for actual sexual transmission was found for HIV, hepatitis A (HAV), B (HBV) and C (HCV), herpes simplex viruses (HSV) 1 and 2; cytomegalovirus (CMV), ZIKV, and EBOV. In men having sex with men (MSM), HAV, HBV, HCV transmission are of particular importance [20,21]. Counotte et al. also summarised some evidence for anecdotal West Nile virus (WNV) sexual transmission [11].

2.2. DENV structural considerations

With DENV and ZIKV sharing structural and biochemical properties [12–15], Goo and colleagues [22] assessed the relative stability of ZIKV, DENV and WNV, by measuring changes in infectivity following prolonged incubation at physiological temperatures. Their findings suggest that whilst the half-lives of the flaviviruses differ (ZIKV 11.8 h; DENV 5.2 h), structural E-protein variations had no measurable impact on the stability of the respective viruses in the experiments. Overall, the similarities of the viruses indicate that perhaps DENV can survive the same harsh environments (semen, vaginal fluid) as ZIKV, which is a prerequisite for virus viability and replicability following sexual transmission.

2.3. Evidence from animal models

To the best of our knowledge, data derived from animal models are scarce. Some abstracts, but otherwise unpublished data, describe a small cohort of pigtail macaques experimentally infected with DENV-3 and demonstrate virus recovery from prostate glands and seminal vesicles [23].

2.4. Presence of DENV in human body fluids other than blood, and alternative routes of transmission of DENV

Back in 2004, Chen and Wilson [5] reported a case of dengue fever in a US healthcare worker who had no recent history of travel outside Northeastern United States. The source of infection was presumed to be a febrile traveller who had recently returned from Peru. The health care worker was transferring the blood of the traveller from a syringe to a blood culture bottle when the needle dislodged from the syringe, splashing blood onto her face. Although molecular proof was lacking, sequential serologic testing of index and secondary patient, in conjunction with circumstantial evidence, rendered nosocomial transmission from blood onto mucous membranes as the only plausible route of transmission.

In the same paper, the authors summarised, and later updated [7], published information on non-vectorial DENV transmission; highlighting that, except for sexual transmission, albeit only anecdotally, merely all routes of non-vector borne transmission of DENV have been shown to exist, from mucocutaneous to percutaneous to intrapartum or vertical transmission, and via bone marrow and solid organ transplantation [11].

In 2017, Iannetta et al. [24] reported on a woman returning to Italy from Sri Lanka with confirmed dengue fever. DENV RNA could be isolated from all body fluids tested (urine, saliva, vaginal secretion), with DENV remaining detectable in vaginal secretions up to 18 days after onset of symptoms.

In 2018, Lalle et al. [25] reported on a man returning to Italy from Thailand, where he had been diagnosed with dengue, using a commercial rapid test. This diagnosis was confirmed in Italy on day 9 following symptom onset (FSO), by detection of dengue RNA and specific IgM and IgG in serum. Virological follow-up was performed on semen and urine samples that were positive at admission (day 9). Urine samples were negative after day 24, while semen samples remained positive until day 55.

Molton and colleagues [26] examined semen specimen obtained between days 4 and 6 FSO, in a cohort of five male dengue patients from Singapore, all diagnosed between 3 and 6 days FSO (with the diagnoses based on clinical findings, NS1 positivity, and in 3/5 cases a positive serum PCR). Semen specimen from all 5 men were qualitative DENV-PCR negative. This was not surprising, since virus kinetics data suggest a later appearance in, and disappearance from, urine than in blood [27]. It could be argued that the same holds true for semen. In the study by Molton et al., all patients fell ill shortly before specimen collection; moreover, the viral loads were undetectable in the two serum PCR-negative individuals and allegedly low in the three others. Thus, the timing of semen collection could have been too early to detect virus, which means that a study with a longer period of follow-up is warranted, to conclude whether or not DENV is able to appear and survive in semen.

Virus kinetics suggest that after an early viraemia peak in blood, followed by rapid clearance after a couple of days, DENV is detectable with an ill-defined delay in urine, which can be as early as from two days FSO to more than a month later. Based on dengue virus recovery studies from urine samples by real-time PCR in a small cohort of patients from Belgium, it is suggested that, in general, DENV RNA concentrations are higher in serum than in urine during the first week FSO. Thereafter, virus concentrations in urine might exceed those in serum, peaking around day 10 FSO and then fading away, becoming undetectable between three and four weeks in most cases. This line of reasoning suggests that one would expect a delay between the blood viraemia peak and the appearance of virus in other body fluids, including semen. This implies that a systematic study of presence or absence of DENV from semen during or after a dengue fever episode in male patients should encompass sequential serum, (urine) and semen testing by (ideally quantitative) PCR for a prolonged period of at least 3–4 weeks.

2.5. Evidence of human-to-human sexual transmission

At the end of 2019, a report from Spain, described likely sexual transmission of dengue between men who have sex with men (MSM) and provided epidemiological, clinical and molecular diagnostic evidence (the latter not reported in detail) for sexual transmission [28]. The index patient had travelled to Cuba and afterwards to the Dominican Republic for about a week in total. He became ill immediately after return to Spain. Having had sex with the index patient on day 4 FSO, the second patient fell ill about a week after exposure. From both patients, semen samples tested DENV positive; and sequencing, according to the report, yielded genetically fully identical viruses. With the second

Table 1
Evidence in support of, and against, DENV sexual transmission.

Evidence supporting sexual transmission of DENV	Evidence against relevant sexual transmission of DENV
Strong: MSM transmission in Madrid [28]	*Strong:* Large numbers of returned viremic travellers do not seem to transmit DENV further[a]
Strong: Female-to-male transmission in South Korea [29]	*Weak:* Singapore study methodology may not have been appropriate [26]
Weak: Some limited supportive data from a macaque animal model [23]	

[a] Note the complete absence of reports of dengue sexual transmission other than [28,29] in the travel medicine literature.

patient not having visited a dengue-endemic area within the incubation period, in conjunction with other circumstantial evidence, it was concluded that sexual transmission was by far the most likely mode of DENV transmission.

Finally, a recent report from South Korea [29] offered anecdotal but strong epidemiological, clinical and molecular diagnostic evidence for female-to-male sexual transmission of DENV in a couple from South Korea. In this case, the index patient had visited Indonesia, fell ill around the time of return, and had sex with a partner who had not visited a dengue-endemic area recently, falling ill nine days after the sexual intercourse. From both patients, DENV type 1 was isolated from serum, and genotyping demonstrated identical virus. With alternative routes of transmission (e.g. blood-mucosa contact) being impossible to be entirely excluded; as in the case reported from Spain, sexual transmission was considered most likely, if not definitive.

3. Controversies

The evidence, presented above, clearly shows possible sexual transmission of dengue. But to what extent does this occur and is this of public health significance? Table 1 summarises the evidence to date. In view of the fact that sexual transmission of dengue to partners of ill-returning travelers to non-endemic countries has so rarely been reported and given the considerable number of dengue cases in returning travelers [30], it is highly unlikely that such a route of transmission of relevance would have slipped notice on a global scale until recently. On the other hand, reports and data now begin to accumulate, which support the sexual (genital) transmission of DENV virus amongst partners, in line with reports on other alternative (non-vectorial) modes of transmission.

Perhaps it is useful to put this risk into perspective by comparing it to the transmission efficacy of known viral STDs, such as HBV, HCV or HIV. Heterosexual transmission of HBV outside a sex work context reaches 40% for non-immune partners and around 0,5%–2% per year of relationship for HCV [31]. The risk for HIV is estimated to be in the region of 0.4–1.4% per sexual exposure [32]. Furthermore, it is well known, certainly from the case of HIV-infection, that certain risk factors may increase sexual transmission [33]. However, information on this is scarce from the two well-documented cases of DENV sexual transmission where such risk factors were not identified in both cases but where the paucity of data renders any conclusions speculative.

Virological data aiming at deducing the sexual transmission propensity from biochemical and molecular structural characteristics are not contradicting the DENV potential to be transmitted via genital contact. Transmission of virus material does not equal transmission of 'viable' virus able to reproduce after transmission as pointed out in an editorial on a publication on ZIKA virus, where only 4% of RNA-positive semen was found to be infectious, with a minimum of $\log_{10}$ RNA copies/mL [34].

4. Future research

Animal experimental data demonstrating sexual transmission of viable DENV capable of reproduction in the receiving partner are lacking, and data suggesting this route of transmission in humans are to date, confined to two anecdotal reports. Epidemiological studies on human-to-human transmission in this area will be very challenging to perform. Perhaps, the best way forward would be a well-designed, prospective, long-term, multicentre study amongst collaborating travel clinics looking systematically into DENV expression in semen and vaginal fluid during and after an acute disease episode. This would be an appropriate approach to address the controversy of DENV sexual transmission potential.

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Declaration of competing interest

All authors declare no conflict of interest.

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