Clinical Infectious Diseases

BRIEF REPORT

Male-to-Female Sexual Transmission of Zika Virus—United States, January–April 2016

Kate Russell,[1,2] Susan L. Hills,[3] Alexandra M. Oster,[4] Charsey Cole Porse,[5] Gregory Danyluk,[6] Marshall Cone,[7] Richard Brooks,[1,8] Sarah Scotland,[9] Elizabeth Schiffman,[10] Carolyn Fredette,[11] Jennifer L. White,[12] Katherine Ellingson,[13] Allison Hubbard,[14] Amanda Cohn,[15] Marc Fischer,[3] Paul Mead,[3] Ann M. Powers,[3] and John T. Brooks[4]

[1]Epidemic Intelligence Service, [2]Influenza Division, National Center for Immunization and Respiratory Diseases, [3]Division of Vector-Borne Diseases, and [4]Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; [5]California Department of Public Health, Sacramento; [6]Florida Department of Health, Polk County, Winter Haven; [7]Florida Department of Health, Tallahassee; [8]Maryland Department of Health and Mental Hygiene, Baltimore; [9]Massachusetts Department of Public Health, Jamaica Plain; [10]Minnesota Department of Health, Saint Paul; [11]New Hampshire Department of Health and Human Services, Concord; [12]New York State Department of Health, Albany; [13]Oregon Public Health Division, Portland; [14]Virginia Department of Health, Richmond; and [15]Office of the Director, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

We report on 9 cases of male-to-female sexual transmission of Zika virus in the United States occurring January–April 2016. This report summarizes new information about both timing of exposure and symptoms of sexually transmitted Zika virus disease, and results of semen testing for Zika virus from 2 male travelers.

Keywords. Zika; Zika virus; sexual transmission; semen.

Recent outbreaks of Zika virus disease in the Pacific Islands and the Americas have identified new and underrecognized clinical manifestations and modes of transmission, including sexual transmission. Sexual transmission of Zika virus was first recognized in 2008 [1]. Recent outbreaks have further reinforced the risk of sexual transmission of Zika virus. As of 19 May 2016, cases of sexually transmitted Zika virus infection had been reported from 10 countries [2]. Replication-competent virus (ie, from virus culture) may have been isolated from semen of infected men up to 70 days after symptom onset [3, 4], and Zika virus RNA has been detected at least 188 days after symptom onset [5]. A case report described possible male-to-female sexual transmission at least 32 days and perhaps up to 41 days after symptom onset; however, both people traveled and a long incubation period or prolonged detection of viral RNA following mosquito-borne transmission in the female partner could not be ruled out [6]. The majority of published cases have involved virus transmission to female and male sex partners through condomless vaginal, anal, or oral sex with symptomatic men who traveled to areas of active Zika virus transmission. A case of female-to-male sexual transmission has been reported, as well as transmission from asymptomatically infected man to female sexual partners who had not traveled [7, 8].

As of 7 May 2016, the US Centers for Disease Control and Prevention (CDC) had received reports of 10 confirmed cases of sexually transmitted Zika virus disease occurring during January–April 2016 in the continental United States (http://www.cdc.gov/zika/). One of these cases has been described elsewhere and involved transmission from a male traveler who had visited Venezuela to his male nontraveling sex partner [9]. This report summarizes information about 9 additional cases.

METHODS

Zika virus disease cases are reportable to ArboNET, the national surveillance system for arboviral diseases (http://www.cdc.gov/westnile/resourcepages/survResources.html). Suspected cases of sexually transmitted Zika virus disease were identified and interviewed by state and local health departments as part of Zika surveillance activities and reported to ArboNET. Clinical criteria to define a case were according to the interim national surveillance case definition for Zika virus disease [10], with laboratory results confirming a recent Zika virus infection [11]. A case of Zika virus disease was considered sexually transmitted if the only known risk factor for Zika virus exposure was sexual contact with a person who had traveled to an area with active Zika virus transmission. For each case, health department staff collected information about the infected travelers' dates of travel, countries visited, symptoms, and dates of symptom onset and resolution. Nontravelers were asked about symptoms, dates of symptom onset, and other possible exposures to Zika virus (ie, history of recent travel, blood transfusions, or organ or tissue transplant). Partners were asked to provide the dates of sexual contact after the traveler's return to the United States and until the nontraveler's symptom onset, types of sexual contact (ie, vaginal sex, anal sex, and fellatio), and whether condoms were used. Clinical and epidemiologic information was obtained as part of arboviral disease surveillance activities, and institutional review board review was not required.

Methodology for serum real-time reverse-transcription polymerase chain reaction (rRT-PCR), immunoglobulin M (IgM) antibody capture enzyme-linked immunosorbent assay (MAC-ELISA), and plaque reduction neutralization testing (PRNT) performed at the CDC Division of Vector-Borne

Received 29 August 2016; editorial decision 23 September 2016; accepted 14 October 2016; published online December 15, 2016.

Correspondence: K. Russell, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS A-32, Atlanta, GA 30329–4027 (vnt0@cdc.gov).

Clinical Infectious Diseases® 2017;64(2):211–13

DOI: 10.1093/cid/ciw692

Diseases laboratory has been described elsewhere [12, 13]. The Florida, Massachusetts, Maryland, and New York State public health laboratories each performed IgM serology and rRT-PCR testing for specimens collected from one couple (both traveler and nontraveler) using Emergency Use Authorization–approved CDC assays, or by methods slightly modified from CDC protocols. The California Viral and Rickettsial Disease Laboratory performed IgM immunofluorescence assays for Zika and dengue virus IgM antibodies for specimens collected from one couple. Specimens from all other cases were tested at the CDC Division of Vector-Borne Diseases laboratory. Testing of semen and urine was performed at the Florida public health laboratory using the same rRT-PCR method as that used for serum.

RESULTS

Cases were reported from January through April 2016 from 9 states where no local mosquito-borne transmission of Zika virus had been identified. Travelers ranged in age from 20 to 55 years; all were male and had recently traveled to areas with active Zika virus transmission, including Colombia, Costa Rica, El Salvador, Haiti, Puerto Rico, and Suriname. Symptom onset among travelers ranged from 8 days before return to 10 days after return to the United States. All developed at least one symptom consistent with Zika virus disease during travel or within 2 weeks of return to the United States: 8 (89%) reported rash, 8 (89%) fever, 5 (56%) arthralgia, and 3 (33%) conjunctivitis. Among 8 male travelers queried about genitourinary symptoms, none reported hematospermia or dysuria. The nontravelers ranged in age from 19 to 55 years; all were female and all developed at least one symptom consistent with Zika virus disease: 9 (100%) reported rash, 7 (78%) fever, 6 (67%) arthralgia, and 4 (44%) conjunctivitis. Three nontravelers were pregnant at the time of infection.

Symptom onset for all nontravelers occurred after sexual contact with travelers. Time from the date of first sexual contact with the returned traveler to date of the nontraveler's symptom onset was 8–21 days. Time between the returned traveler's onset of symptoms and the nontraveler's onset of symptoms was 10–19 days. All couples reported condomless vaginal sex. Four couples also reported condomless oral sex (fellatio) and one couple also reported condomless anal sex. Sexual contact occurred before, during, and after the travelers' symptom onset. One couple reported that their only sexual contact was 3 days after resolution of the traveler's symptoms.

All travelers had laboratory evidence of a recent Zika virus or unspecified flavivirus infection. One of the travelers had laboratory evidence of Zika virus infection by rRT-PCR, 5 had evidence of recent Zika virus infection by IgM and neutralizing antibody testing, and 3 had evidence of recent flavivirus infection by IgM and neutralizing antibody testing. All nontravelers had laboratory-confirmed Zika virus infection; 4 had serologic evidence of recent Zika virus infection and 5 were positive by rRT-PCR.

Additionally, 2 travelers had Zika virus testing performed on semen and urine specimens (Table 1). Male 1 provided a urine specimen at day 41 and a semen specimen at day 42 after illness onset; both were Zika rRT-PCR negative. Male 2 provided a urine specimen at day 27 and 4 serial semen specimens on days 28–60 after illness onset. The urine was equivocal by rRT-PCR whereas the semen was positive at 28 and 39 days after illness onset, equivocal at 46 days, and negative at 60 days. Culture of virus from semen was not attempted.

DISCUSSION

Sexual contact has been confirmed as a mode of transmission of Zika virus during the current epidemic in the Americas. To the best of our knowledge, sexual transmission between humans of other flaviviruses has not been definitively documented. As of 7 May 2016, 10 of the 482 (2%) Zika virus disease cases reported in residents of US states were sexually transmitted, including 9 of the 301 (3%) cases in females (CDC, unpublished data). Travel-associated cases of sexually transmitted Zika virus infection diagnosed in nonendemic

Table 1. Laboratory Results for 2 Male Travelers With Testing of Serum, Urine, and Semen Samples

	Serum		Urine		Semen	
Patient	Collection (Days After Illness Onset)	Serological Result	Collection (Days After Illness Onset)	Zika Virus rRT-PCR Result	Collection (Days After Illness Onset)	Zika Virus rRT-PCR Result
Male 1	22 days	Zika virus infection[a]	41 days	Negative	42 days	Negative
Male 2	27 days	Unspecified flavivirus infection[b]	27 days	Equivocal[c]	28 days	Positive
					39 days	Positive
					46 days	Equivocal[c]
					60 days	Negative

Abbreviation: rRT-PCR, real-time reverse-transcription polymerase chain reaction.

[a]Zika virus immunoglobulin M (IgM) antibodies in serum with Zika virus neutralizing antibody titers ≥10 and dengue virus neutralizing antibody titers <10 [11].

[b]Zika virus IgM antibodies in serum with neutralizing antibody titers ≥10 for both Zika virus and dengue virus [11].

[c]Positive on single RNA primer/probe set and negative on the second RNA primer/probe set.

areas present a unique opportunity to characterize the epidemiology of infections transmitted by this route. In areas with local Zika virus transmission, it is typically impossible to determine whether an infection follows mosquito-borne or sexual transmission of Zika virus. The extent to which sexual transmission may be contributing to the epidemic in these areas is unknown.

We found that symptoms of Zika virus disease associated with sexual transmission were similar to those reported previously among mosquito-borne cases [14]. Although hematospermia has been reported in published case reports of men with laboratory-confirmed Zika virus infection [1, 15], none of the male travelers in our case series reported any genitourinary signs or symptoms. This confirms that hematospermia does not reliably identify men who might transmit Zika virus sexually.

Case reports indicate that Zika virus can be detected by rRT-PCR in semen after it is no longer detectable by rRT-PCR in blood [8, 15, 16]; however, our understanding of the incidence, persistence, and pattern of shedding of Zika virus in semen remains limited. Two cases of sexual transmission of Zika from asymptomatically infected men have been reported, in one case 10-14 days and in the other 39 days after potential exposure [7, 8]. Such cases appear to be rare but are also less likely to be recognized.

Based on the reports published to date, CDC has issued guidelines to prevent sexual transmission of Zika virus for couples in which one or both partners have traveled to or reside in an area with active Zika virus transmission [17]. Of particular importance is prevention of sexual transmission of Zika virus to pregnant women; therefore, CDC recommends that couples in which a woman is pregnant use barrier methods (eg, male condoms, female condoms, or dental dams) correctly and consistently or abstain from sex for the duration of pregnancy after return from areas of Zika virus transmission. For other couples, the recommended duration of a barrier method against infection or abstinence from sex depends on whether the sex partner has a confirmed infection or clinical illness consistent with Zika virus disease and whether the sex partner is male or female; updated CDC guidance is available electronically (http://www.cdc.gov/zika/transmission/sexual-transmission.html). These prevention modalities should be used in tandem with mosquito protection and vector control measures to help reduce the risk of Zika virus transmission.

Notes

Acknowledgments. We thank all of the contributing state and local health departments and the CDC Division of Vector-Borne Diseases laboratory.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflict of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Foy BD, Kobylinski KC, Chilson Foy JL, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg Infect Dis **2011**; 17:880–2.
2. World Health Organization. Prevention of sexual transmission of Zika virus. Interim guidance. **2016**. WHO/ZIKV/MOC/16.1Rev.2. Geneva, Switzerland: WHO. Available at: http://apps.who.int/iris/bitstream/10665/204421/1/WHO_ZIKV_MOC_16.1_en. Accessed 19 May 2016.
3. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. Emerg Infect Dis **2015;** 21:359–61.
4. Arsuaga M, Bujalance SG, Diaz-Menendez M, Vazquez A, Arribas JR. Probable sexual transmission of Zika virus from a vasectomised man. Lancet Infect Dis **2016;** 16:1107.
5. Barzon L, Pacenti M, Franchin E, Lavezzo E, Trevisan M, Sgarabotto D, et al. Infection dynamics in a traveller with persistent shedding of Zika virus RNA in semen for six months after returning from Haiti to Italy, January 2016. Euro Surveill. 2016 Aug 11;21(32).
6. Turmel JM, Abgueguen P, Hubert B, et al. Late sexual transmission of Zika virus related to persistence in the semen. Lancet **2016;** 387:2501.
7. Brooks RB, Carlos MP, Myers RA, White MG, Bobo-Lenoci T, Aplan D, et al. Likely Sexual Transmission of Zika Virus from a Man with No Symptoms of Infection - Maryland, 2016. MMWR Morb Mortal Wkly Rep **2016;** 65:915–6.
8. Fréour T, Mirallié S, Hubert B, et al. Sexual transmission of Zika virus in an entirely asymptomatic couple returning from a Zika epidemic area, France, April 2016. Euro Surveill **2016**; 21.
9. Deckard DT, Chung WM, Brooks JT, et al. Male-to-male sexual transmission of Zika virus—Texas, January 2016. MMWR Morb Mortal Wkly Rep **2016**; 65:372–4.
10. Council of State and Territorial Epidemiologists. Zika virus disease and congenital Zika virus infection interim case definition and addition to the Nationally Notifiable Disease List. Atlanta, GA: Council of State and Territorial Epidemiologists, **2016**. https://www.cste2.org/docs/Zika_Virus_Disease_and_Congenital_Zika_Virus_Infection_Interim.pdf. Accessed 19 May 2016.
11. Rabe IB, Staples JE, Villanueva J, et al; MTS. Interim guidance for interpretation of Zika virus antibody test results. MMWR Morb Mortal Wkly Rep **2016**; 65:543–6.
12. Lanciotti RS, Kosoy OL, Laven JJ, et al. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. Emerg Infect Dis **2008**; 14:1232–9.
13. Calisher CH, Karabatsos N, Dalrymple JM, et al. Antigenic relationships between flaviviruses as determined by cross-neutralization tests with polyclonal antisera. J Gen Virol **1989**; 70(pt 1):37–43.
14. Armstrong P, Hennessey M, Adams M, et al; Zika Virus Response Epidemiology and Laboratory Team. Travel-associated Zika virus disease cases among U.S. residents—United States, January 2015–February 2016. MMWR Morb Mortal Wkly Rep **2016**; 65:286–9.
15. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. Emerg Infect Dis **2015**; 21:359–61.
16. Atkinson B, Hearn P, Afrough B, et al. Detection of Zika virus in semen. Emerg Infect Dis **2016**; 22:940.
17. Petersen EE, Meaney-Delman D, Neblett-Fanfair R, et al. Update: Interim Guidance for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus for Persons with Possible Zika Virus Exposure — United States, September 2016. MMWR Morb Mortal Wkly Rep 2016;65:1077–81.