International Journal of Infectious Diseases xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

Unexpected and Rapid Spread of Zika Virus in The Americas - Implications for Public Health Preparedness for Mass Gatherings at the 2016 Brazil Olympic Games

Eskild Petersen [a,*], Mary E. Wilson [b], Sok Touch [c], Brian McCloskey [d], Peter Mwaba [e], Matthew Bates [e], Osman Dar [d], Frank Mattes [f], Mike Kidd [f], Giuseppe Ippolito [g], Esam I. Azhar [h], Alimuddin Zumla [h,i]

[a] The Royal Hospital, Muscat, Oman, and Insititute of Clinical Medicine, Aarhus University, Aarhus, Denmark
[b] School of Medicine, University of California, San Francisco, USA; Harvard T.H. Chan School of Public Health, Boston, MA, USA
[c] Communicable Disease Control Department, Ministry of Health, Cambodia
[d] Global Health Department, Public Health England, London, United Kingdom
[e] UNZA-UCLMS Project, University Teaching Hospital, and Ministry of Health, Lusaka, Zambia
[f] Dept of Virology, University College London Hospitals NHS Foundation Trust, London, UK
[g] National Institute for Infectious Diseases Lazzaro Spallanzani, Rome, Italy
[h] Special Infectious Agents Unit, King Fahd Medical Research Centre, and Medical Laboratory Technology Department, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia
[i] Division of Infection and Immunity, University College London, and NIHR Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London, United Kingdom

ARTICLE INFO

Article history:
Received 2 February 2016
Accepted 2 February 2016

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:
Arboviruses
Mass Gatherings
Sporting events
Olympics
Zika virus
Brazil

SUMMARY

Mass gatherings at major international sporting events put millions of international travelers and local host-country residents at risk of acquiring infectious diseases, including locally endemic infectious diseases. The mosquito-borne Zika virus (ZIKV) has recently aroused global attention due to its rapid spread since its first detection in May 2015 in Brazil to 22 other countries and other territories in the Americas. The ZIKV outbreak in Brazil, has also been associated with a significant rise in the number of babies born with microcephaly and neurological disorders, and has been declared a 'Global Emergency by the World Health Organization. This explosive spread of ZIKV in Brazil poses challenges for public health preparedness and surveillance for the Olympics and Paralympics which are due to be held in Rio De Janeiro in August, 2016. We review the epidemiology and clinical features of the current ZIKV outbreak in Brazil, highlight knowledge gaps, and review the public health implications of the current ZIKV outbreak in the Americas. We highlight the urgent need for a coordinated collaborative response for prevention and spread of infectious diseases with epidemic potential at mass gatherings events.

1. Mass gatherings and transmission of infectious diseases

Sporting events attract millions of international travelers and residents from the host country. These mass gatherings of people are put at risk of acquiring imported and locally prevalent infectious diseases.[1,2] Brazil is to host the 2016 Olympic and Paralympic Games in Rio De Janeiro in August 2016 [3] where millions of people from within Brazil and from all over the world, are expected to attend. Recent media and World Health Organization (WHO) attention has focused on the unexplained rapid spread of the mosquito-borne Zika Virus (ZIKV) across South and Central America and the Caribbean Islands.[4] On February 1st 2016 the WHO announced that the ZIKV outbreak constitutes a '*Public Health Emergency of International Concern*'.[5] The term 'public health emergency of international concern (PHEIC)' is defined in the International Health Regulations as "an extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease and to potentially require a coordinated international response".

* Corresponding author.
E-mail address: eskildp@dadlnet.dk (E. Petersen).

http://dx.doi.org/10.1016/j.ijid.2016.02.001

Please cite this article in press as: Petersen E, et al. Unexpected and Rapid Spread of Zika Virus in The Americas - Implications for Public Health Preparedness for Mass Gatherings at the 2016 Brazil Olympic Games. Int J Infect Dis (2016), http://dx.doi.org/10.1016/j.ijid.2016.02.001

The first ever case of ZIKV disease in Brazil was reported in May 2015,[6] and since then, the virus has rapidly spread within Brazil[7] and across 22 other countries and territories in the region.[8,9] The ZIKV outbreak in Brazil is unusual, in that, alarmingly it has been associated with a large rise in the number of babies born with microcephaly and other neurological complications.[4,5,7,10–12] The rapid spread of ZIKV in Brazil and the Americas is also of great concern since it joins the growing list of re-emerging infectious diseases[13], and its epidemic potential poses challenges for public health preparedness and surveillance for the 2016 Olympics and Paralympic Games. We review the epidemiology and clinical features of the current ZIKV outbreak in Brazil, highlight knowledge gaps, and highlight the need for enhanced public health preparedness for the 2016 Olympic Games.

2. ZIKV epidemiology and global spread

ZIKV is a single stranded RNA arbovirus member of the genus Flavivirus and is related to other mosquito-borne viruses such as Dengue, Yellow Fever, Japanese B encephalitis, and West Nile Fever viruses. ZIKV was named as such because it was first identified in a rhesus monkey in the Zika Forest of Uganda in 1947.[14] ZIKV was later found in humans with febrile illnesses in West Africa[15] in 1954. It then to spread to Indonesia[16], Micronesia[17], Thailand,[18] the Philippines,[19] French Polynesia,[20] and Easter Island-South Pacific in 2014.[21] ZIKV was not documented on mainland South America until the first report of autochthonous transmission in Brazil in May 2015.[6] The conclusion at that time was that ZIKV was introduced into Brazil during the 2014 World Cup Football.[6] This was not supported due to the fact that no Pacific countries with documented ZIKV had competed in the World Cup competition. However, Pacific countries had participated in the August 2014 Va'a World Sprints canoe championship which was held in Rio de Janeiro, suggesting that introduction of ZIKV into Brazil could have occurred then.[23,23] Another possibility was the introduction of ZIKV to Brazil by travelers from Chile.[24] Since its introduction into Brazil in May 2015, ZIKV has subsequently spread rapidly across Brazil and the Americas. As of January 28th 2016, autochthonous cases of ZIKV infection have been reported from 26 countries in the Americas: Barbados, Bolivia, Brazil, Cabo Verde, Colombia, Curaçao, Dominican Republic, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Martinique, Mexico, Nicaragua, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, Thailand, Venezuela, Virgin island.[11] No autochthonous ZIKV transmission has been reported from EU countries, and a heightened state of global alert is in place in Europe and USA to screen for ZIKV in travelers with fever returning from ZIKV-endemic countries.[4,5]

The first travel-associated ZIKV disease case among U.S. travelers was reported in 2007. From 2007 to 2014, a total of 14 returning U.S. travelers had positive ZIKV testing performed at UC-Centers for Diseases Control (CDC). In 2015 and 2016 at least eight U.S. travelers have had positive ZIKV testing performed at CDC.[25]

3. Mode of transmission of ZIKV

The primary mode of transmission of ZIKV between humans is through the bite of an infected female mosquito of the *Aedes* species.[4,5] Apart from mosquitos, other non-vector means of transmission of ZIKV have been suggested: a) via sexual intercourse[26,27], b) blood transfusions[28], c) perinatal transmission from mother to foetus at time of delivery.[29–31]

Although it is possible that ZIKV could be passed from mother to fetus during any trimester of pregnancy[30], limited data from one study[31] has indicated that ZIKV maternal infection in the first trimester might carry a greater risk of fetal microcephaly. Of 35 infants with microcephaly, 26 (74%) of the mothers reported having had a rash; 21 in the first trimester, 5 in the second trimester. Other fetal brain abnormalities that have been reported in association with clinical maternal ZIKV infection are ventriculomegaly, cell migration abnormalities, and congenital contractures secondary to central or peripheral nervous system involvement.[29–31] There have been no reports yet of ZIKV postnatal transmission to babies through breastfeeding. Further studies are required to delineate the importance of these modes of transmission.

3.1. Mosquito-borne ZIKV transmission

Aedes spp mosquitoes are present throughout the tropics. They Q4 are known to transmit other important arboviruses that affect humans such as Chikungunya Virus, Dengue Virus and Yellow Fever Virus.[32–37] The main vector associated with transmission of ZIKV is *Aedes aegypti*. Transmission can also occur via other *Aedes* species[38] such as: *Ae.albopctus, Ae.africanus*, *Ae.luteocephalus*, *Ae.vitattus*, *Ae.furcifer*, *Ae.hensilii* and *Ae.apicoargenteus*. *Aedes aegypti* lives and breeds near people and their homes, laying their eggs in stagnant water which collects in puddles, buckets, flower pots, empty cans and other containers. They bite humans mainly during daytime, either outside or inside their houses. *Aedes aegypti* mosquitoes are widely distributed in the Americas (except for Chile) and the suitable climatic breeding conditions is partly responsible for the current ZIKV epidemic, with over a million cases reported.[4,5] *Aedes albopictus*[39] is found in the USA[40] as far north as New York and Chicago, and in parts of southern Europe. It is expected that the current ZIKV transmission will increase throughout the Americas with possibility of local transmission within the USA. Since the *Aedes* mosquito species that spread ZIKV are found in many locations throughout the world, it is likely that outbreaks will spread to new countries.

3.2. Sexual transmission

ZIKV has been isolated from semen[26,27] and possible sexual transmission has been reported.[26] Studies are needed to assess how frequently and for how long ZIKV persists in semen (or other privileged sites in the body) and whether precautions to prevent sexual transmission of ZIKV are warranted.

3.3. Blood transfusion and transmission of ZIKV

Given that the majority (80%) of persons with ZIKV infection are asymptomatic[4] and among them are blood donors, transmission of ZIKV via blood transfusion is of concern.[28] It has a parallel in the introduction of West Nile Virus in the United States and Canada, which led to the need for screening of donated blood.[41] The outbreak of Chikungunya Virus (CKV) which started in Reunion[42] and spread throughout Asia, also prompted screening of blood products. After the introduction of CKV in Italy, systematic screening by blood banks was considered, but a laboratory test for routine testing was not available[43] so blood donations from people living in the affected municipalities were discontinued. A 21-day deferral policy was introduced nationwide for blood donors who had visited the affected areas, even for a few hours. The predonation questionnaire was modified for an early detection of CKV infections. All stocked blood components collected from donors living in the affected area, after the identification of the first case, even those already delivered to the pharmaceutical industry, were eliminated. The impact of the CKV outbreak in Italy was later evaluated[44] with the conclusion that "Even a relatively small outbreak in Italy resulted in considerable adverse impact on blood

Please cite this article in press as: Petersen E, et al. Unexpected and Rapid Spread of Zika Virus in The Americas - Implications for Public Health Preparedness for Mass Gatherings at the 2016 Brazil Olympic Games. Int J Infect Dis (2016), http://dx.doi.org/10.1016/j.ijid.2016.02.001

collections and economic consequence". It is likely that blood transfusion related infection does occur in ZIKV endemic areas. To prevent blood transfusion related ZIKV infection, blood donations must also be screened for ZIKV.

4. Clinical Features

4.1. Symptoms and signs

The incubation period is not known but the first symptoms of ZIKV disease can develop between 3 to 12 days after the mosquito bite and they resolve within 7 days in most cases. ZIKV causes predominantly a mild illness and therefore over 80% of cases may go unnoticed.[4] In one in five cases who are symptomatic the clinical spectrum of disease overlaps with that caused by other arbovirus infections such as Dengue and Chikungunya.[4,9,45] These include fever, malaise, skin rashes (maculo-papular rash is considered immune mediated), conjunctivitis (red eye), muscle and joint pain and headache. These symptoms are usually mild and last for between 2 to 7 days.[4] Severe disease is uncommon and most cases do not require hospitalization.

4.2. Diagnosis

The US-CDC has recommended specific diagnostic algorithms for ZIKV diagnosis in adults and children.[46,47] The diagnosis of ZIKV can be confirmed by amplification (RT-PCR) of viral genome. Commercial diagnostic tests for ZIKV detection are under development but not yet available. The ZIKV outbreak in the Americas has generated significant interest in development of new rapid diagnostics, drugs and vaccines for ZIKV. Ongoing efforts in diagnostics include: a) Standardizing PCR methods for comparative purposes, b) Development of rapid specific serologic tests for clinical and epidemiological studies, c) Determining the role of viral load in pathogenesis and *in utero* transmission and d) Validating the use of non-blood specimens. Due of the kinetics of the ZIKV viraemia, the clinical utility of RT-PCR is limited to testing blood samples collected less than one week after onset of symptoms. Since ZIKV virus is excreted for a longer time in urine, such samples can be usefully tested up to three weeks after onset. RT-PCR can also be performed on amniotic fluid, although the positive and negative predictive values for either fetal infection or development of fetal pathology are uncertain. For detection of past or recent infection, serum antibody testing is not reliable because of extensive cross-reactivity against Dengue Fever and Yellow fever, two diseases which are co-located geographically and have wide vaccine coverage. This diagnostic limitation to demonstrating seroconversion to ZIKV in pregnancy hampers the retrospective investigations into the temporal relationship between the Brazilian epidemic and increase in congenital malformations.

4.3. Congenital malformations and Neurological complications

During the large ZIKV outbreaks in 2013 in French Polynesia[48] and in Brazil[7] in 2015, neurological complications such as the Guillain Barré syndrome were reported. According to the Ministry of Health of Brazil epidemiological update[49] of 27th January, 2016, there were 4,180 reported cases of microcephaly with suspected associated with ZIKV infection, of which 732 (17.5%) have been investigated and classified. Of the 270/732 (37%) confirmed cases with central nervous system malformations, 6/270 (2.2%) were positive for ZIKV infection. The risk of developing a microcephalic baby following ZIKV infection in pregnancy cannot be quantified and will require case control studies. ZIKV testing in newborns has several challenges and case controlled studies using more sensitive diagnostics are required. RT-PCR tests may not detect ZIKV RNA in a newborn who acquired ZIKV infection *in utero* if the period of viremia has passed.

Serologic tests for ZIKV can often be falsely positive because of cross-reacting antibodies against other endemic flaviviruses such as Dengue Fever and Yellow Fever. Plaque-reduction neutralization testing (PRNT) can be performed to measure virus-specific neutralizing antibodies to ZIKV, but neutralizing antibodies may still yield cross-reactive results in newborns due to maternal antibodies that were transferred to the infant. Cases of microcephaly following ZIKV infection have not been reported from Southeast Asia, but could easily have been missed due to lack of clinical awareness, and because investigation for ZIKV is not usually part of the investigations for a short, febrile illness. Interim Guidelines for the Evaluation and Testing of Infants with possible congenital ZIKV Infection have been recently introduced by the US-CDC.[47]

5. Knowledge gaps on the current Brazil ZIKV outbreak

It is not clear what are the factors underlying the rapidity and intensity of ongoing ZIKV outbreak in Brazil. Furthermore the association of ZIKV with microcephaly and neurological disorders requires further study.[50]

One hypothesis is that the ZIKV has undergone recombination in nature and that a loss of the N154 glycosylation site in the envelope protein as a possible adaptive response to the *Aedes dalzieli*, a zoophilic vector in Africa.[51]

It is also possible that the link between sporadic cases of microcephaly in Zika endemic areas were being missed due to low numbers and poor surveillance mechanisms. Thus it was only when the massive outbreak occurred in Brazil, which has a good live birth surveillance system, that the link between ZIKV and microcephaly was recognized.[7,49,52]

The Chikungunya Virus (CKV) responsible for the outbreak in Italy in 2007 showed a specific mutation in the E1 gene, A226 V, which probably increased the adaption to *Aedes albopictus* allowing more efficient transmission.[53–55] A recent study of the *Aedes albopictus* found that certain flavivirus sequences were integrated into the *A. albopictus* genome, indicating a long co-existence and mutual adaptation.[56]

Another parallel to draw here is the introduction of West Nile Virus to North America in 1999 which seems to be explained by ecological and environmental factors (an abundance of suitable vectors and a huge reservoir in non-immune birds) creating a biological niche in a pristine environment.[57] Since the introduction the original NY99 genotype has been replaced by the SW/WN03 genotype.[38] Similar detailed analysis of the ZIKV which is now rapidly spreading throughout Central and South America is now required.

6. Protecting the health of attendees of the 2016 Olympics

Given the increase of congenital anomalies, Guillain-Barré syndrome, other neurological and autoimmune syndromes associated with ZIKV,[5,10,50] the WHO recommends that all Member States establish and maintain heightened awareness and capacity to detect and confirm ZIKV cases, have healthcare facilities prepared to respond to a possible increased demand for specialized care for microcephaly and neurological syndromes, strengthen antenatal care, and introduce public health measures to reduce risk of ZIKV spread and infection.[4,5]

6.1. Reducing risk of acquiring ZIKV

Several recommendations are available for reducing risk of acquiring ZIKV.[56–58] Measures to avoid mosquito bites[61] include wearing long sleeved shirts, use of insect repellant and staying in

Please cite this article in press as: Petersen E, et al. Unexpected and Rapid Spread of Zika Virus in The Americas - Implications for Public Health Preparedness for Mass Gatherings at the 2016 Brazil Olympic Games. Int J Infect Dis (2016), http://dx.doi.org/10.1016/j.ijid.2016.02.001

screened or air conditioned accommodations. US-CDC[58] and ECDC[10] recommend that any travelers who are pregnant (any stage/ trimester) or planning to become pregnant, should avoid travelling to areas with ZIKV outbreaks. If travel cannot be avoided or postponed, or if people live in areas where ZIKV transmission is known to occur, scrupulous measures to avoid mosquito bites during both daytime and nighttime hours must be taken. Pregnant women in Zika-affected areas should wear protective clothing, apply a U.S. Environmental Protection Agency (EPA)-approved insect repellent, and sleep in a screened room or under a mosquito net. *Aedes spp* mosquitoes predominantly bite during the day, especially around dawn and dusk, and thus the correct timing and use of mosquito repellents and other personal protection measures are key to preventing any vector-borne infection.

6.2. Reducing other health risks

There are several other health risks that attendees of the 2016 Olympic games will face[1,2] and all travelers to the 2016 Olympic games should seek travel health advice from their family doctors or a travel medicine providers, well in advance of their travel. They should also consult the National Travel Health Network and Centre[56], the Latin American Society for Travel Medicine (SLAMVI)[58] guidelines or their relevant local public health agency for up to date country information on requirements for pre-travel vaccinations (eg Yellow Fever) and malaria prophylaxis. Travelers should also be educated on safe eating and drinking habits such as choosing bottled water over tap water, making sure meat and seafood are cooked fully, and avoiding raw unpeeled fruits and vegetables, and wearing appropriate footwear and avoiding skin contact with sand to prevent worm infections, such as cutaneous larva migrans. Sex education for prevention of sexually transmitted diseases and the use of condoms is also important.

Transmission of the arboviruses ZIKV, CKV and Dengue virus in Brazil can occur during all months of the year.[63,64] In 2014 a major outbreak of CKV infections (>1000 cases reported), occurred in August-and September in a completely susceptible population in Bahia.[64] This suggests the potential for transmission of ZIKV, outside of periods typical for Dengue Virus outbreaks in a population lacking immunity to ZIKV. The WHO[5] Emergency Committee on Zika virus has emphasized that 'A coordinated international response is needed to improve surveillance, the detection of infections, congenital malformations, and neurological complications, to intensify the control of mosquito populations, and to expedite the development of diagnostic tests and vaccines to protect people at risk, especially during pregnancy.' Ongoing vector control efforts by the Brazilian government prior to the Games will reduce the risk of outbreaks of ZIKV and other vector borne diseases amongst attendees and the local population. The Brazilian authorities have in put in place intense vector control programs which are eliminating breeding sites for *Aedes spp* to prevent the spread of the ZIKV at the impending August 2016 Rio de Janeiro Olympic Games. Brazil hosted the 2014 Fédération Internationale de Football Association (FIFA) World Cup and the event went without any major infectious diseases incidents.[65] Our hope is that the Olympic Games will not be plagued by infectious diseases outbreaks, and the perceived anticipated threat of international spread of ZIKV from Brazil[66] will not materialize.

7. Conclusions

ZIKV has been present for many decades in Africa and Asia; since 2007 it has caused major outbreaks in Micronesia, French Polynesia, and recently reached Brazil in 2015. In the Americas ZIKV is spreading and is a potential threat to the attendees of the 2016 Rio Olympics. A previously unreported linkage has been identified in Brazil, that of microcephaly in babies and other neurological disorders leading to the WHO declaring ZIKV a 'Global emergency' Molecular analyses of ZIKV are urgently needed to understand whether a change in the virus can explain the rapid spread and the serious consequences of infection. In the absence of a ZIKV vaccine, control efforts so far rests entirely on mosquito vector control both at community and household levels and prevention of mosquito bites by individuals. Strategies for preventing spread by blood transfusions, via sexual contact (if confirmed), other tissue and organ transplantation and are required. Travel restrictions to ZIKV endemic areas for pregnant women, and postposing pregnancy for women living in areas experiencing ZIKV outbreaks have been recommended. The development and availability of specific and rapid diagnostic tests for ZIKV will allow enhanced surveillance and assessing level of risk for microcephaly, Guillain-Barre, and other complications. There is no specific treatment or vaccine available. Research into rapid diagnostics, treatments and vaccine are underway. The emergence of ZIKV soon after the Ebola outbreak, is yet another reminder for the urgent need for a coordinated Global effort to have sufficiently resourced Rapid Response Groups for proactive surveillance and conduct of priority research in emergency situations.

Conflicts of interest: Authors declare no conflicts of interest

Author roles and contributions: Professors Alimuddin Zumla, Eskild Petersen and Mary Wilson developed the first draft. All authors contributed to subsequent drafts and finalized the manuscript.

Uncited references

[22,59,60,62].

References

1. McCloskey B, Endericks T, Catchpole M, Zambon M, McLauchlin J, Shetty N, et al. London 2012 Olympic and Paralympic Games: public health surveillance and epidemiology. *Lancet* 2014;**383**:2083–9.
2. Smallwood CA, Arbuthnott KG, Banczak-Mysiak B, Borodina M, Coutinho AP, Payne-Hallström L, et al. Euro 2012 European Football Championship Finals: planning for a health legacy. *Lancet* 2014;**383**:2090–7.
3. Rio 2016 Organizing Committee for the Games of the XXXI Olympiad. The official website of the 2016 Rio Olympic Games. http://www.rio2016.com/en/olympic-games -accessed January 16th 2016.
4. World Health Organization 2016. Zika virus. http://www.who.int/mediacentre/factsheets/zika/en/- accessed January 23rd 2016.
5. WHO 2016. WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/ -accessed February 1st 2016.
6. Zanluca C, de Melo VCA, Mosimann ALP, dos Santos GIV, dos Santos CND, Luz K. First report of autochthonous transmission of Zika virus in Brazil. *Mem Inst Oswaldo Cruz* 2015;**110**:569–72. http://dx.doi.org/10.1590/0074-02760150192
7. Ministério da Saúde (Brazil). Microcefalia - Ministério da Saúde divulga boletim epidemiológico [Internet]. Brasília: Ministério da Saúde; 2015 [updated 2015 Nov 17; cited 2015 Nov 17]. Available from: http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/20805-ministerio-da-saudedivulga-boletim-epidemiologico –accessed January 16th, 2016.
8. European Centre for Disease Prevention and Control. Zika virus infection outbreak, Brazil and the Pacific region: ECDC; 2014 [updated 2015 May 26]. Available from: http://ecdc.europa.eu/en/publications/Publications/rapid-risk-assessment-Zika%20virus-south-america-Brazil-2015.pdf –accessed January 16th, 2016.
9. Centers for Disease Control and Prevention. Zika Virus. http://www.cdc.gov/zika/ accessed January 25th 2016. –accessed January 26th, 2016.
10. European Centre for Disease Prevention and Control. Microcephaly in Brazil potentially linked to the Zika virus epidemic [Internet]. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1407 –accessed January 26th, 2016.
11. European Centre for Disease Prevention and Control Epidemiological update: Outbreaks of Zika virus and complications potentially linked to the Zika virus infection. http://ecdc.europa.eu/en/press/news/_layouts/forms/News_

Please cite this article in press as: Petersen E, et al. Unexpected and Rapid Spread of Zika Virus in The Americas - Implications for Public Health Preparedness for Mass Gatherings at the 2016 Brazil Olympic Games. Int J Infect Dis (2016), http://dx.doi.org/10.1016/j.ijid.2016.02.001

DispForm.aspx?ID=1342&List=8db7286c-fe2d-476c-9133-18ff4cb1b568– accessed January 29th 2015 –accessed January 29th, 2016.
12. European Centre for Disease Prevention and Control. 10 December 2015: Rapid Risk Assessment: Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barré syndrome. Available at: http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1413 –accessed January 16th, 2016.
13. Al-Tawfiq JA, Zumla A, Gautret P, Gray GC, Hui DS, Al-Rabeeah AA, Memish ZA. Surveillance for emerging respiratory viruses. *Lancet Infect Dis* 2014;**14**: 992–1000.
14. Dick GW, Kitchen SF, Haddow AJ. Zika virus. I. Isolations and serological specificity. *Trans R Soc Trop Med Hyg* 1952;**46**:509–20.
15. Macnamara FN. Zika virus: a report on three cases of human infection during an epidemic of jaundice in Nigeria. *Trans R Soc Trop Med Hyg* 1954;**48**: 139–44.
16. Olson JG, Ksiazek TG. Suhandiman, Triwibowo. Zika virus, a cause of fever in Central Java, Indonesia. *Trans R Soc Trop Med Hyg* 1981;**75**:389–93.
17. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009;**360**:2536–43.
18. Buathong R, Hermann L, Thaisomboonsuk B, Rutvisuttinunt W, Klungthong C, Chinnawirotpisan P, et al. Detection of Zika Virus Infection in Thailand, 2012-2014. *Am J Trop Med Hyg* 2015;**93**:380–3.
19. Alera MT, Hermann L, Tac-An IA, Klungthong C, Rutvisuttinunt W, Manasatienkij W, et al. Zika virus infection, Philippines, 2012. *Emerg Infect Dis* 2015;**21**:722–4.
20. Baronti C, Piorkowski G, Charrel RN, Boubis L, Leparc-Goffart I, de Lamballerie X. Complete coding sequence of Zika virus from a French Polynesia outbreak in 2013. *Genome Announc* 2014;**2**:e00500–514. http://dx.doi.org/10.1128/genomeA. 00500-14
21. Tognarelli J, Ulloa S, Villagra E, Lagos J, Aguayo C, Fasce R, et al. A report on the outbreak of Zika virus on Easter Island, South Pacific, 2014. *Arch Virol* 2015 Nov 26 [Epub ahead of print].
22. Musso D. Zika virus transmission from French Polynesia to Brazil. *Emerging Infect Dis* 2015;**21**:10.1887.
23. Musso D, Nilles EJ, Cao-Lormeau V-M. Rapid spread of emerging Zika virus in the Pacific area. *Clin Microbiol Infect* 2014;**20**:O595–6.
24. Salvador FS, Fujita DM. Entry routes for Zika virus in Brazil after 2014 world cup: New possibilities. Travel Med Infect Dis 2015 Nov 14. pii: S1477-8939(15)00173-8. http://dx.doi.org/10.1016/j.tmaid.2015.10.004.
25. US-CDC 2016: Transcript for CDC Telebriefing: Zika Virus Travel Alert http://www.cdc.gov/media/releases/2016/t0116-zika-virus-travel.html -accessed 29th January, 2016.
26. Foy BD, Kobylinski KC, Foy JLC, Blitvich BJ, Travassos Da Rosa A, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. *Emerg Infect Dis* 2011;**17**:880–2.
27. 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.
28. Marano G, Pupella S, Vaglio S, Liumbruno GM, Grazzini G. Zika virus and the never-ending story of emerging pathogens and transfusion medicine. *Blood Transfus* 2015;1–6. http://dx.doi.org/10.2450/2015.0066-15
29. Besnard M, Lastère S, Teissier A, Cao-Lormeau VM, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. Euro Surveill 2014; 19(13):pii=20751.
30. Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis M. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound in Obstetrics & Gynecology* 2016;**47**:6–7.
31. Schuler-Faccini L, Ribeiro EM, Feitosa IM, Horovitz DD, Cavalcanti DP, Pessoa A, et al. Brazilian Medical Genetics Society–Zika Embryopathy Task Force. Possible Association Between Zika Virus Infection and Microcephaly - Brazil, 2015. *MMWR Morb Mortal Wkly Rep* 2016;**65**:59–62.
32. Roth A, Mercier A, Lepers C, Hoy D, Duituturaga S, Benyon E, et al. Concurrent outbreaks of dengue, chikungunya and Zika virus infections an unprecedented epidemic wave of mosquito-borne viruses in the Pacific, 2012-2014. Euro Surveill 2014; 19:pii: 20929.
33. Terzian ACB, Auguste AJ, Vedovello D, Ferreira MU, Silva-Nunes MD, Speranca MA, et al. Isolation and characterization of Mayaro virus from a human in Acre, Brazil. *Am J Trop Med Hyg* 2015;**92**:401–4.
34. Gautret P, Simon F. Dengue, chikungunya and Zika and mass gatherings: What happened in Brazil, 2014. *Travel Med Infect Dis* 2015 Dec 24. pii: S1477-8939(15)00205-7.
35. Musso D, Cao-Lormeau VM, Gubler DJ. Zika virus: following the path of dengue and chikungunya? *Lancet* 2015;**386**:243–4.
36. Marcondes CB, Ximenes MF. Zika virus in Brazil and the danger of infestation by Aedes (Stegomyia) mosquitoes. *Rev Soc Bras Med Trop* 2015 Dec 22. pii: S0037-86822015005003102. [Epub ahead of print]..
37. Hayes EB. Zika virus outside Africa. *Emerging Infectious Diseases* 2009;**15**:1347–50.
38. Calvez E, Guillaumot L, Millet L, Marie J, Bossin H, Rama V, Faamoe A, Kilama S, Teurlai M, Mathieu-Daudé F, Dupont-Rouzeyrol M. Genetic Diversity and Phylogeny of Aedes aegypti, the Main Arbovirus Vector in the Pacific. *PLoS Negl Trop Dis* 2016 Jan 22;**10**(1):e0004374. http://dx.doi.org/10.1371/journal.pntd.0004374. eCollection 2016 Jan.
39. Wong PS-J, Li MY, Chong CS, Ng LC, Tan CH. Aedes (Stegomyia) albopictus (Skuse): A Potential Vector of ZIKV in Singapore. *PLoS NEGL Trop Dis* 2013;**7**:e2348.
40. CDC. Information for vector control programs. http://www.cdc.gov/chikungunya/pdfs/CHIKV_VectorControl.pdf-accessed January 29th 2016.
41. Centers for Disease Control and Prevention (CDC). Investigations of West Nile virus infections in recipients of blood transfusions. *MMWR Morb Mortal Wkly Rep* 2002;**51**:973–4.
42. Brouard C, Bernillon P, Quatresous I, Pillonel J, Assal A, De Valk H, et al. Estimated risk of Chikungunya viremic blood donation during an epidemic on Reunion Island in the Indian Ocean, 2005 to 2007. *Transfusion* 2008;**48**:1333–41.
43. Liumbruno GM, Calteri D, Petropulacos K, Mattivi A, Po C, Macini P, et al. The Chikungunya epidemic in Italy and its repercussion on the blood system. *Blood Transfus* 2008;**6**:199–210.
44. Petersen LR, Stramer SL, Powers AM. Chikungunya virus: possible impact on transfusion medicine. *Transfus Med Rev* 2010;**24**:15–21.
45. Cardoso CW, Paploski IAD, Kikuti M, Rodrigues MS, Silva MMO, Campos GS. Outbreak of exanthematous illness associated with Zika, chikungunya, and dengue viruses, Salvador, Brazil. *Emerg Infect Dis* 2015;**21**:2274–6.
46. CDC (2016) Zika Virus diagnostic testing. http://www.cdc.gov/zika/hc-providers/diagnostic.html -accessed January 30th 2016.
47. Staples JE, Dziuban EJ, Fischer M, Cragan JD, Rasmussen SA, Cannon MJ, et al. Interim Guidelines for the Evaluation and Testing of Infants with Possible Congenital Zika Virus Infection - United States, 2016. *MMWR Morb Mortal Wkly Rep* 2016;**65**:63–7.
48. Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastere S, Valour F, et al. Zika virus infection complicated by Guillain-Barre syndrome–case report, French Polynesia, December 2013. *Euro Surveill* 2014;**19**:20720.
49. Brazilian Ministry of Health. 12 January 2016: Weekly epidemiological update on suspected microcephaly cases (12 January 2016) Available at: http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/21677-novos-casos-suspeitos-de-microcefalia-sao-divulgados-pelo-ministerio-da-saude –accessed January 26th, 2016.
50. Pan American Health Organization. 17 January 2016: Neurological syndrome, congenital malformations, and Zika virus infection. Epidemiological Update. Available at: http://www.paho.org/hq/index.php?option=com_content&view=article&id=11552&Itemid=41672&lang=en.causes –accessed January 26th, 2016.
51. Faye O, Freire CC, Iamarino A, Faye O, de Oliveira JV, Diallo M, et al. Molecular evolution of Zika virus during its emergence in the 20(th) century. *PLoS Negl Trop Dis* 2014;**8**:e2636.
52. Gatherer D, Kohl A. Zika virus: a previously slow pandemic spreads rapidly through the Americas. *J Gen Virol* 2015 Dec 18. http://dx.doi.org/10.1099/jgv.0.000381 [Epub ahead of print].
53. Bordi L, Carletti F, Castilletti C, Chiappini R, Sambri V, Cavrini F, et al. Presence of the A226 V Mutation in Autochthonous and Imported Italian Chikungunya Virus Strains. *Clin Infect Dis* 2008;**47**:428–9.
54. Bordi L, Meschi S, Selleri M, Lalle E, Castilletti C, Carletti F, et al. Chikungunya virus isolates with/without A226 V mutation show different sensitivity to IFN-a, but similar replication kinetics in non human primate cells. *New Microbiol* 2011;**34**:87–91.
55. Weaver SC, Lecuit M. Chikungunya virus and the global spread of a mosquito-borne disease. *N Engl J Med* 2015;**372**:1231–9.
56. Chen XG, Jiang X, Gu J, Xu M, Wu Y, Deng Y, et al. Genome sequence of the Asian Tiger mosquito, Aedes albopictus, reveals insights into its biology, genetics, and evolution. *Proc Natl Acad Sci U S A* 2015;**112**:E5907–15.
57. Brinton MA. The molecular biology of West Nile Virus: a new invader of the western hemisphere. *Annu Rev Microbiol* 2002;**56**:371–402.
58. NaTHNaC. Zika virus: update and advice for pregnant women (updated 19 January 2016). http://travelhealthpro.org.uk/zika-virus-update-and-advice-for-pregnant-women/.
59. Petersen EE, Staples JE, Meaney-Delman D, Fischer M, Ellington SR, Callaghan WM, Jamieson DJ. Interim Guidelines for Pregnant Women During a Zika Virus Outbreak - United States, 2016. Jan 22;65(2):30-3 MMWR Morb Mortal Wkly Rep 2016;65:30-3.
60. Centers for Disease Control and Prevention (CDC). Interim Guidelines for Pregnant Women During a Zika Virus Outbreak — United States, 2016. http://www.cdc.gov/mmwr/volumes/65/wr/mm6502e1.htm –accessed January 26th, 2016.
61. CDC. 2016. http://wwwnc.cdc.gov/travel/yellowbook/2016/the-pre-travel-consultation/protection-against-mosquitoes-ticks-other-arthropods – accessed January 26th, 2016.
62. Gallego V, Berberian G, Lloveras S, Verbanaz S, Chaves TS, Orduna T, et al. The 2014 FIFA World Cup: communicable disease risks and advice for visitors to Brazil–a review from the Latin American Society for Travel Medicine (SLAMVI). *Travel Med Infect Dis* 2014;**12**:208–18.
63. Aguiar M, Coelho GE, Rocha F, Mateus L, Pessanha JE, Stollenwerk N. Dengue transmission during the 2014 FIFA World Cup in Brazil. *Lancet Infect Dis* 2015;**15**:765–6.
64. Campos GS, Bandeira AC, Sardi SI. Zika virus outbreak, Bahia, Brazil. *Emerg Infect Dis* 2015;**21**:1885–6.
65. Wilson ME, Chen LH, Han PV, Keystone JS, Cramer JP, Segurado A, et al. The GeoSentinel experience and implications for the 2014 World Cup and the 2016 summer Olympic Games. *Clin Infect Dis* 2014;**58**:1347–56.
66. Bogoch II, Brady OJ, Kraemer MU, German M, Creatore MI, Kulkarni MA, Brownstein JS, Mekaru SR, Hay SI, Groot E, Watts A, Khan K. Anticipating the international spread of Zika virus from Brazil. *Lancet* 2016 Jan 14. pii: S0140-6736(16)00080-5 [E-pub ahead of print].

Please cite this article in press as: Petersen E, et al. Unexpected and Rapid Spread of Zika Virus in The Americas - Implications for Public Health Preparedness for Mass Gatherings at the 2016 Brazil Olympic Games. Int J Infect Dis (2016), http://dx.doi.org/10.1016/j.ijid.2016.02.001