Non-vector transmission of flaviviruses, with implications for the Zika virus

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Abstract

Objective - To assess available evidence on non-vector modes of transmission of relevant flaviviruses to inform on potential transmission risks and preventive measures for Zika virus.

Methods - MEDLINE was searched for publications related to non-vector transmission of dengue, West Nile, Japanese encephalitis, yellow fever and Zika viruses, available before March 2016. The titles and abstracts were reviewed to select articles for full text reviews. The reference list of the articles chosen for full-text review were examined for other potentially relevant publications.

Findings - Vertical transmission has been demonstrated for dengue, Japanese encephalitis and Zika virus. Transmission through infected blood products and possibly through transplants has been reported for dengue and West Nile virus. Transmission in the healthcare setting through needle stick injuries and other blood exposures has been reported for dengue, West Nile, yellow fever viruses and most recently with Zika. Transmission through sexual contact has been reported only for Zika virus.

Conclusion - The findings concerning non-vector transmission has major implications for daily lives of hundreds of thousands of people living in areas where Zika may become endemic and for travellers to the affected countries. The respective countries should improve surveillance and data collection to report these deviant cases and institute relevant policies and guidelines informed by those already available for other flaviviruses, customizing it to their settings.
Introduction

Zika virus (ZIKV) was first identified in Uganda in 1947 in rhesus monkeys. Only sporadic human cases were reported in the next sixty years, until the outbreaks in Yap Island of Micronesia in 2007, followed by an epidemic in French Polynesia in 2013. As of 28th April 2016, autochthonous transmission of Zika has been reported in 35 countries/territories in the Americas. The explosive spread is highlighted by the fact that before 2014, it was reported in humans, mosquitoes and primates in only 14 different countries. The clinical presentation in most cases was asymptomatic or mild self-limiting febrile illness until the epidemic in French Polynesia, when a number of cases were diagnosed with neurological complications, including Guillain-Barré Syndrome (GBS). A case-control study from the same epidemic showed a strong association between ZIKV infection and GBS.

Furthermore, clusters of cases of microcephaly were detected in Northeast Brazil along with unusual increase of GBS in El Salvador and Brazil. These cases were temporally and spatially associated with the ZIKV. This prompted the World Health Organization to declare the clusters of microcephaly and neurological disorders a Public Health Emergency of International Concern.

The recent reports of sexual transmission in Dallas, United States (US) alongside previous evidence highlights an important issue in making policies and recommendations for the general public. Secondary modes of transmission, including sexual, vertical, and via blood transfusion and organ transplants, have to be considered as they have been reported for other flaviviruses. This underscores the public health dilemma in formulating recommendations for sexual partners, potential parents, blood donors, transplant patients, travellers and their families in order to prevent transmission and possibly introduction into naïve populations.

The ZIKV belongs to the Flavivirus genus of Flaviviridae family, comprised of 73 different viruses. The most important human pathogens among them are dengue virus (DENV), West Nile virus (WNV), Japanese encephalitis virus (JEV) and yellow fever virus (YFV). These viruses have distinct geographic distributions according to their vectors and different natural hosts. They differ in their pathogenicities with clinical syndromes ranging from being asymptomatic, mildly febrile illnesses to severe neurological and haemorrhagic diseases. There are also a number of similarities like the transmission to humans principally through mosquito bites, a major proportion of infections being asymptomatic and no effective treatment existing for any of them. Moreover, they have shown to be surprisingly emergent in previously naïve regions and non-vector transmissions have been reported.

The rapid spread coupled with a causal link with microcephaly and GBS has tremendous implications for public health systems. It is therefore prudent to create an evidence base for the potential threats. Non-vector transmission is an important facet as other viruses in the Flaviviridae family have shown a capacity for this. Hence, we performed a systematic review to look at evidence of non-vector modes of transmission of WNV, DENV, JEV and YFV to find features that can guide us in predicting the behaviour of ZIKV and also help institute relevant preventive methods.
Transmission of Flaviviruses.

The *Aedes* mosquitoes (most commonly *A. aegypti* and *A. albopictus*) are responsible for the spread of DENV, YFV and ZIKV; whereas *Culex* species (particularly *Culex quinquefasciatus*) are responsible for transmission of WNV and JEV. These viruses, especially during epidemics have been known to be transmitted through other non-vector modes.

**DENGUE VIRUS.**

**Vertical Transmission**

There have been reports from many countries providing strong evidence that intrauterine transmission of dengue is possible. The presence of DENV in the foetal tissue, placenta and newborn serum of dengue confirmed mothers along with a spectrum of dengue presentations in newborns were evidence used to demonstrate transmission.

There is limited evidence of miscarriages, perinatal deaths and low birth-weight babies among mothers with dengue infection. A case-control study showed that recent dengue infections were more common in women with miscarriages than with controls with viable pregnancies. Two case series have shown that dengue infection in first and second trimester has the potential to increase risk of abortions. A retrospective study showed that infection increases the risk of preterm labour and birth. There have not been any reports of congenital deformities or abnormalities in viable infants and foetuses born to DENV infected mothers.

Furthermore, there are case series suggesting no evidence of transmission in early pregnancy contrary to evidence of transmission near term. It is notable that peripartum infection of the child might increase the possibility of symptomatic infection and reports have shown that the spectrum of illness in these neonates range from acute febrile illness alongside thrombocytopenia to severe illness with haemorrhage, circulatory failure and pleural effusions.

One report was identified showing presence of DENV in breast milk, with viral load similar to blood during an acute infection, raising the possibility of post-natal transmission through breastfeeding.
Blood Transfusion

We found four reports suggesting transfusion associated transmission of DENV. The first case was reported in non-endemic Hong Kong.65 Thereafter, two have been reported from Singapore, the first to three recipients from a single infected donor followed by a recent report resulting in prolonged hospitalization.36,37 Furthermore, in 2015, suspected cases were reported from endemic Puerto Rico and Brazil.38,39

Transfusion transmitted (TT) DENV could be under-reported given the high overall incidence of infection in some populations, leading to difficulty in distinguishing TT DENV from mosquito-borne infection. Also, the presence of DENV antibodies can have a role in reducing the presentation of these cases as clinically significant.40 Furthermore, enhanced immunogenicity involving the mosquito bite could lead to a more severe form in comparison to milder presentation in TT infections.41

It has been shown that asymptomatic DENV viremia is a potential risk to the blood supply system especially in endemic regions.38,40,42 The rate of dengue viremic donors ranged from 0.19% in Puerto Rico to 0.4% in Ribeirao Preto, Brazil.38,43 Although TT DENV might form only a small fraction of the total burden, the screening policies in endemic countries should be guided by the prevalence of TT DENV and availability of resources.44

Organ Transplantation

There have been three reports on possible transplant-related transmission of DENV. A case of dengue haemorrhagic fever was reported after a renal transplant but without any comparative samples from the donor.45 A liver transplant recipient acquiring it and a possible transmission through bone marrow transplant have also been reported.46,47 This points towards a possibility and mandates vigilance on the physician’s part in areas of endemcity and during epidemics.

Occupational Exposure

The early phases during acute dengue fever have the highest levels of viremia.46 Haemorrhage being a potential complication makes the exposure risk higher. Transmission has been reported in healthcare workers (HCWs) through needle stick injuries during the earlier acute phase.49–52 Furthermore, a case reported a HCW contracting dengue following splash of blood onto her face.53 These cases were possibly detected as they occurred in non-endemic settings and the detection in endemic settings could be comparatively more challenging.

Table 1 Non-vector transmission of dengue virus

<table>
<thead>
<tr>
<th>Summary Notes</th>
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<tbody>
<tr>
<td><strong>Vertical transmission</strong></td>
</tr>
<tr>
<td>Reported in neonates of mothers who have had acute infection in the peripartum period. In case of early pregnancy, there is no evidence for vertical transmission. In case of late pregnancy, there is some confirmative evidence.</td>
</tr>
<tr>
<td>A case with DENV in breast milk poses questions about the risk of breastfeeding and post-natal transmission of DEV.</td>
</tr>
<tr>
<td><strong>Blood transfusion</strong></td>
</tr>
<tr>
<td>There was a cluster of blood transfusion associated dengue infections in endemic Singapore along with a case found in non-endemic Hong Kong. Suspected cases also reported from Brazil and Puerto Rico.</td>
</tr>
<tr>
<td><strong>Transplant</strong></td>
</tr>
<tr>
<td>Transmission reported in a renal and liver transplant case along with a suspected bone marrow transplant in a 6-year-old child who subsequently died.</td>
</tr>
<tr>
<td><strong>Needle stick injury</strong></td>
</tr>
<tr>
<td>Dengue has been confirmed in some cases of needle stick injury.</td>
</tr>
<tr>
<td><strong>Mucocutaneous</strong></td>
</tr>
<tr>
<td>The patient’s blood splashed onto the face, including eye, nose, and mouth of the HCW, who later developed dengue.</td>
</tr>
<tr>
<td><strong>Sexual</strong></td>
</tr>
<tr>
<td>Not reported</td>
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West Nile Virus

Vertical Transmission

The first case of intrauterine transmission of WNV was reported in 2002, with WNV-specific IgM detected in both mother and child. The mother was infected in the second trimester and the infant developed severe cerebral abnormalities and bilateral chorioretinitis. An observational study suggested possible congenital infection with three reported neonatal infections. One child developed lissencephaly and WNV encephalitis on the 17th day of life. Another observational study did not show evidence of congenital infection from pregnant mothers.

Furthermore, probable post-natal transmission through breast milk from a mother with TT-WNV has been demonstrated with detection of WNV-specific IgM in breast milk and serum from asymptomatic infant. A review has concluded that transmission through breast milk may rarely occur.

Blood Transfusion

A WNV epidemic started in 1999 in the US and by 2002, 23 cases of TT-WNV infection had been detected along with other cases in multiple blood donation recipients. Following this, the estimated mean risk of transmission through transfusions ranged from 2.12 to 4.76 per 10000 donations. Although this was hundreds of times higher than for other routinely screened diseases like HIV, HCV or HBV we have to remember that this was at the peak of the epidemic. This prompted the authorities to institute routine WNV screening of blood products. The institution of nucleic acid amplification testing (NAAT) led to identification and removal of almost 1500 potentially infectious blood products in 2003.

About 43% of the TT-WNV infection in a report were high-risk immunocompromised patients and 35% were 70 years or over. Similar screening methods has potentially prevented cases in other affected countries like Italy.

Haemodialysis

A cluster of three patients using the same dialysis machine were diagnosed with WNV infection suggesting transmission in the dialysis centre. As patients undergoing dialysis are immunocompromised and have multiple exposure to invasive procedures, infection control protocols should be thoroughly monitored and strictly followed.

Organ Transplantation

In 2002, the Centers for Disease Control (CDC) reported that three of four recipients of organs from a single donor developed meningoencephalitis and were positive for WNV. Transmission has been reported in liver, lung, heart and renal transplant patients in US and Italy, with presentation ranging from asymptomatic to severe WNV encephalitis. The risk of neuroinvasive disease in transplant patients is 40 times higher than in general population. Furthermore, 30% patients with organ-derived WNV infections have either died or were in a coma suggesting high morbidity and mortality in this group.

Needle Stick injury

In 2002, two microbiologists were exposed to percutaneous inoculation with laboratory samples resulting in WNV infection in both. This emphasizes that HCWs have to be educated regarding the risk posed by these pathogens and infection control guidelines reinforced.
### Table 2  Non-vector transmission of West Nile virus

<table>
<thead>
<tr>
<th>Summary Notes</th>
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<tbody>
<tr>
<td><strong>Vertical transmission</strong></td>
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<tr>
<td><strong>Blood transfusion</strong></td>
</tr>
<tr>
<td><strong>Haemodialysis</strong></td>
</tr>
<tr>
<td><strong>Transplant</strong></td>
</tr>
<tr>
<td><strong>Needle stick injury</strong></td>
</tr>
<tr>
<td><strong>Mucocutaneous</strong></td>
</tr>
<tr>
<td><strong>Sexual</strong></td>
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</tbody>
</table>

### JAPANESE ENCEPHALITIS VIRUS

During an epidemic of JEV in India (1978) acute infection was observed in five pregnant women. Two had healthy babies, two aborted and one was lost to follow-up. JEV was isolated from one of the aborted foetal tissues suggesting intrauterine transmission and possibly spontaneous abortion due to the infection. The abortions occurred in mothers infected in second trimester whereas mothers infected in third trimester had normal delivery. Another epidemic (1980) saw abortions in two pregnant women infected in first trimester while other two infected in the third trimester delivered normal babies. Although a link between early infection and spontaneous abortion can be suspected, which is in line with the evidence for DENV, more evidence is required to confirm.

### Table 3  Non-vector transmission of Japanese encephalitis virus

<table>
<thead>
<tr>
<th>Summary Notes</th>
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<tbody>
<tr>
<td><strong>Vertical transmission</strong></td>
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<tr>
<td><strong>Blood transfusion</strong></td>
</tr>
<tr>
<td><strong>Transplant</strong></td>
</tr>
<tr>
<td><strong>Needle stick injury</strong></td>
</tr>
<tr>
<td><strong>Mucocutaneous</strong></td>
</tr>
<tr>
<td><strong>Sexual</strong></td>
</tr>
</tbody>
</table>

### YELLOW FEVER VIRUS

Vertical transmission has been reported only once, from a mother infected in late pregnancy, with the infant presenting with symptoms on the third day and later succumbing to the disease. In 2009, an infant was diagnosed with the first confirmed case of yellow fever (YF) vaccine-associated neurologic disease transmitted through breast milk followed by further cases adding to the evidence.

A report in 1931 described a lab technician coming in contact with blood from a YF patient and subsequently dying. Furthermore, instances of lab technicians and scientist acquiring YF after coming in contact with blood or other tissues of infected animals/humans have been reported.
**Table 4  Non-vector transmission of Yellow fever virus**

<table>
<thead>
<tr>
<th>Summary Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vertical transmission</strong></td>
</tr>
<tr>
<td>One case report suggesting probable vertical transmission. Also suggestions</td>
</tr>
<tr>
<td>of YF vaccine virus transmission through breast milk.</td>
</tr>
<tr>
<td><strong>Blood transfusion</strong></td>
</tr>
<tr>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Transplant</strong></td>
</tr>
<tr>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Unclear contact transmission</strong></td>
</tr>
<tr>
<td>Transmission through contact with blood and other tissues were</td>
</tr>
<tr>
<td>circumstantially related to the subsequent YF infections in lab staff.</td>
</tr>
<tr>
<td><strong>Sexual</strong></td>
</tr>
<tr>
<td>Not reported</td>
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</tbody>
</table>

**ZIKA VIRUS**

**Sexual Transmission**

The first reported non-vector transmission of ZIKV was a probable case of sexual transmission based on serologic and circumstantial evidence from a scientist returning from Senegal. In other cases, ZIKV-RNA and replicative ZIKV was detected in semen samples. ZIKV-RNA has been detected in semen upto 62 days after onset of illness. Along with a recent case in Texas, the CDC has reported two confirmed and four suspected cases of sexual transmission from symptomatic male partners with recent history of travel to the Caribbean and Central America to their female partners with no history of travel outside continental US. Furthermore, the first case of male-to-male transmission has also been reported from Texas. Our search did not find any reports of sexual transmission of any other aforementioned flaviviruses.

**Vertical Transmission**

After the outbreak in French Polynesia, vertical transmission from two mothers to their infants was reported. ZIKV RNA was detected in the serum sample of both mothers and infants and peripartum transmission was suspected. ZIKV RNA was also detected in the breast milk of both these mothers suggesting a possible post-natal route of transmission. Also, ZIKV infection was demonstrated by RT-PCR in two miscarriages and the brain tissue of two neonates with microcephaly who died in Brazil. ZIKV RNA was also detected in the brain samples of another case in Slovenia where the foetus was terminated. The virus being isolated from brain tissue in all these fatal cases with abnormalities points to a link between microcephaly and ZIKV and the neurotropic nature of the virus.

The mother from the report in Slovenia was living in Natal, Brazil, an area of ongoing transmission, when she was infected around the 13th week of gestation. Although the mothers of more than half the microcephaly cases from Northeast Brazil reported maternal rashes during first trimester, as Zika was not confirmed in either the mothers or babies during reporting, further evidence regarding the period of pregnancy with the worst prognosis is necessary.

**Breastfeeding**

ZIKV RNA was detected in breast milk and saliva of infected mothers in French Polynesia suggesting a possible route of infection. The significant viral load shown in breast milk of a mother with acute dengue infection along with transmission shown with WNV and the YF-vaccine virus points towards the plausibility of transmission of ZIKV through this route.

However, clinical presentation of an infant infected by the ZIKV by breast feeding has not been described and the consequences are not known so far. It would be helpful to study the presence of viral RNA and replicative virus in breast milk of infected mothers to introduce guidelines regarding this mode of transmission.
**Blood Transfusion**

During the outbreak in French Polynesia, remarkably 2.8% (42/1505) of the asymptomatic blood donors were found positive for ZIKV by PCR.\(^8^7\) There is considerable risk in transfusion transmissibility due to asymptomatic viremia and especially so during huge epidemics.\(^8^8\) Although transfusion poses little risk to start or expand epidemics, there is a potential of introducing novel agents into a naïve population. There are principally two factors of primary concern over the transfusion-transmitted (TT) infections. The first is the public health impact, more specifically the frequency, severity and secondary transmission rate of an infection. The second being the public reaction to the disease.\(^8^9\) In case of Zika, a proven association with microcephaly or GBS justifies the serious public health impact. Also, given this association, the public concern is nonetheless very significant. Another important factor is that the most susceptible group affected by this route is the immunocompromised and elderly.\(^5^9\)

**Occupational exposure**

A case of needle stick injury associated ZIKV transmission has been reported from the US in a laboratory personnel.\(^9^0\) This is in line with other flaviviruses as mentioned above.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Non-vector transmission of Zika virus</th>
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<tbody>
<tr>
<td><strong>Summary Notes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Sexual transmission</strong></td>
<td>There are confirmed cases of sexual transmission from symptomatic males to female and male partners. ZIKV was isolated from the semen of a patient in Tahiti presenting with hematospermia and evidence shows persistence of ZIKV-RNA up to 62 days in semen.</td>
</tr>
<tr>
<td><strong>Vertical Transmission</strong></td>
<td>Two newborns with ZIKV infection born to infected mothers in an outbreak in French Polynesia first suggested intrauterine transmission. ZIKV RNA was also detected in their breast milk. Also, detection of ZIKV RNA in amniotic fluid of women with foetuses suspected of microcephaly, brain tissue of neonates with congenital defects and in miscarriage foetuses point towards vertical transmission of this virus.</td>
</tr>
<tr>
<td><strong>Blood Transfusion</strong></td>
<td>Almost 3% of blood samples from asymptomatic donors were found positive for ZIKV RNA in French Polynesia.</td>
</tr>
<tr>
<td><strong>Transplant</strong></td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Needle stick injury</strong></td>
<td>One case reported from the United States</td>
</tr>
<tr>
<td><strong>Mucocutaneous</strong></td>
<td>Not reported</td>
</tr>
</tbody>
</table>

**Discussion**

This review has shown evidence supporting vertical transmission of DENV, JEV and ZIKV. However, unlike ZIKV, the review does not show an increased risk of congenital abnormalities associated with DENV, WNV, YFV or JEV.\(^2^8,5^5,7^5,7^7\) The evidence from DENV and JEV points towards early infection leading to spontaneous abortion, preterm labour and birth.\(^2^7,2^8,3^0,7^5,7^6\) Also, the review has shown transmission near delivery resulting in infection with a spectrum of illness in newborns ranging from asymptomatic to cases of death.\(^2^0,2^3,3^2\) The association of gestational age of maternal infection with the outcomes is an important factor that has to be kept in mind while designing studies for Zika.

Post-natal transmission through breast milk although suggested, has rarely been reported. The risk shown by the YF-vaccine virus infection through breastfeeding raises a question about postpartum vaccination which should be kept in mind if a live-attenuated vaccine for Zika is to be rolled-out.
However, there isn’t any evidence suggesting transmission from breastmilk and hence, refraining from breastfeeding for mothers infected with ZIKV is not recommended. The evidence from aforementioned cases alongside demonstration of replicative ZIKV in semen presents sexual transmission as a feature unique to Zika among clinically relevant flaviviruses and arboviruses. Reports detecting significant viral load in semen along with persistence up to 62 days point towards possibility of this mode being more common than reported in regions of autochthonous transmission. Hence, more information is required regarding the persistence in the male genito-urinary tract, infectivity whilst being asymptomatic, transmission from females to male and the transmission rates. The sexual transmission of ZIKV along with potential intrauterine infection and severe foetal outcome mandates pertinent preventive measures for exposed people in high-risk areas. Therefore, we recommend following the interim guidelines set forth for HCWs to advise women with possible exposure alongside the guidelines to prevent sexual transmission.

Also, the evidence corroborating transmission of WNV and DENV through blood transfusion raises serious concerns. Asymptomatic donors carrying viral RNA with a potential to transmit points towards the precarious position we are with Zika. After TT-WNV was reported in the US, there were a series of systematic interventions implemented in order to reduce the transmission risk. The blood supply system of the respective countries should contemplate instituting similar guidelines and screening in case of suspected infection. We suggest evaluating the transmissibility of ZIKV through this route and then modelling the potential threat to the health system would be a way forward. Currently, the systems can be screened to establish prevalence and the potential for transmission using techniques used for WNV in the US and ZIKV in French Polynesia.

The addition of WNV screening to routine donor screening in the US prevented thousands of cases of TT-WNV infection. From this experience we surmise that institution of NAATs in epidemics might be a useful tool to ponder upon. However, TT–ZIKV infection might not be a priority given the possibility of transmission by the ubiquitous mosquitoes and that most affected countries are developing, leading to other health services being of higher priority than ZIKV screening. Hence, instituting similar measures as for WNV should be discussed thoroughly taking into account the associated morbidity and opportunity costs of such interventions in developing economies.

Transplant associated transmission has been reported for DENV and WNV. Screening of organs to be transplanted is not feasible as this will delay transplants and deferral in case of infections might narrow the already small pool of donors. Hence, for transplant related transmissions, clinicians should bear in mind the potential of transmission in transplant cases along with the possibility of increased severity of disease, especially in endemic regions.

HCWs have frequent exposure to blood products through a range of procedures. Hence, needle-stick injuries and mucocutaneous exposure is a common problem in most healthcare institutions. Transmission of DENV and WENV through needle-stick injuries and mucocutaneous route has been discussed along with a recent report of transmission of ZIKV. With the current spread, laboratory workers and HCWs will potentially have more exposure, conceding the fact that this isn’t a haemorrhagic fever and exposure to blood might be lower than with other viruses. Hence, all HCWs should be aware of the possibility of transmission and adhere to standard guidelines of infection control and prevention.

An important approach for effective preparedness and surveillance could be engaging with collaborative studies such as the REDS–III study in Brazil, which looks at epidemiology and emerging infections like DENV and issues pertaining to safety and adequacy of transfusion medicine. The data collection tools and availability of sample repositories will be invaluable for research into the potential risk posed by Zika. The collaborative work between blood supply systems, regulatory bodies, healthcare facilities and public health actors in endemic states will be the backbone for preparedness, solving this crisis and tackling similar emergence in the future.
**Limitations**

As most of the studies reviewed are case reports and series along with few comparative studies, the quality of evidence is low. This is because we are looking at the most infrequent modes of transmission. Furthermore, the ubiquity in transmission through mosquitoes in endemic areas will mask the detection of these modes. Also, lack of proper diagnostic facilities in developing states precludes finding and reporting of these cases.

Furthermore, there will definitely be differences in the transmission rates of different viruses due to multiple reasons. However, the evidence listed here is only for guidance and precaution in this time of uncertainty and thus will have to be interpreted with this consideration. These will have to be updated as new evidence on these viruses emerge.

**Conclusion**

This review shows that these viruses can transmit by routes other than their normal mosquito-borne transmission. Non-mosquito modes of transmission have been reported repeatedly with other pathogens in the same family. Hence, many of these routes are likely to be a risk for Zika. The countries facing the current spread will have to take these modes into account to devise pertinent guidelines. They can use and modify guidelines already in place for the other viruses according to the setting, resources and prevalence. Furthermore, an effective surveillance system to monitor and record transmission dynamics will provide valuable information for an efficient preventive strategy and go a long way in controlling this disease. This highlights the need for standardised clinical data collection alongside serial sampling using good diagnostics and all of which requires early funding.

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**Box 2 General recommendations**

- Case-control and cohort studies have begun in some of the affected countries e.g. cohorts of symptomatic pregnant women with long-term follow up of their babies. Harmonisation of protocols and associated data collection tools is crucial to allow for later comparison of the data.

- Sub-groups to study shedding profiles is clearly advisable as reports of sexual transmission are occurring on a weekly basis. Research on establishing the infectivity, transmissibility through sexual contact and persistence of virus in semen is necessary. The gestational age of infection and the associated outcomes is an important area for research.

- Some work on pathogenesis and neuroinvasiveness of ZIKV has been published and further work is ongoing.\(^{101}\) This needs to be linked to the immune response and could be used to inform drug and vaccine development.

- Diagnostic, therapeutic and vaccine development are ongoing. These will pose a challenge in the pregnant patient with new or repurposed potential treatments and/or vaccines. Also, consideration has to be given to the context of co-circulating flaviviruses where immune enhancement deserves consideration.

- Monitoring impact of current public health advice and adapt guidance accordingly as more evidence arises.

- Maintain public messaging & address key concerns of the public promptly e.g insecticides, GM mosquitoes.
Box 3 Transmission specific recommendations

- As sexual transmission is possible, abstinence and use of condoms consistently and correctly for high-risk individuals living in the areas with ongoing outbreak and the one’s traveling to these areas is advised. The persistence in semen has not been established, hence these measures should be instituted at least 6 months following an illness or 28 days after returning from affected areas without an illness.  

- Pregnant women, those planning pregnancy and their male partners should take advice from their physicians or concerned healthcare professional about the risk of traveling to these areas and if the travel is unavoidable, should take thorough preventive measures against mosquito bites.

- Potential transmission through infected blood products is possible. We recommend further studies to establish the prevalence of ZIKV in the blood supply system. Also, economic modelling and evaluations should be undertaken to elicit the cost and benefit of instituting screening measures and donor deferral systems before rolling these out at the national levels.

- Transplant associated transmission has been reported for flaviviruses. The immunocompromised state and elderly nature of majority of these patients predispose them for poorer outcomes if infected. Hence, the clinician should be vigilant about transmission through this route in areas of outbreaks.

- HCWs should be vigilant of the high risk of transmission in current epidemic state and especially in the acute infectious periods through needle-stick injuries or mucocutaneous exposures. Standard infection control procedures should be followed individually and reinforced on an institutional level.

- The cases related to transfusion, transplant and nosocomial transmission should be suspected and reported to strengthen the evidence base for these modes.
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