Non-Vector Transmission of Dengue and Other Mosquito-Borne Flaviviruses

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Abstract

A number of mosquito-borne viruses in the family Flaviviridae, genus Flavivirus, cause significant illnesses in humans. These diseases include dengue, yellow fever, West Nile fever, Japanese encephalitis, St. Louis encephalitis and Murray Valley encephalitis. The viruses cause syndromes that can be generally classified as one of three types: haemorrhagic fever, fever with rash and arthralgia, and encephalitis. Transmission of dengue virus following mucocutaneous exposure has recently been documented. Transmission of West Nile virus (WNV) without a mosquito vector has also been reported. We review the literature and summarize reported cases and routes of non-vector transmission of the six medically most important mosquito-borne flaviviruses. We also compare the biological characteristics of the viruses in humans and discuss how this could influence the probability of non-mosquito transmission.

Keywords: Dengue, flavivirus, West Nile virus, virus transmission.

Introduction: Flavivirus Transmission

The genus Flavivirus, which belongs to the family Flaviviridae, contains 73 RNA viruses[1]. Among these viruses, 34 are mosquito-borne, 17 are tick-borne and 22 are zoonotic agents; 22 of the 34 mosquito-borne and 13 of the 17 tick-borne flaviviruses are associated with human disease[1]. There are three serological groups – dengue serological group, Japanese encephalitis serological group and yellow fever virus group[1-2]. Non-vectored flaviviruses are probably maintained in nature by animal-to-animal transmission via saliva and urinary shedding.

Flavivirus infection in mosquito occurs when the mosquito ingests a blood meal containing the virus, which infects the midgut epithelial cells and subsequently the salivary gland[3]. Some days after the initial blood meal (extrinsic incubation period), the virus is...
secreted in the saliva and reaches a new host when the mosquito takes another blood meal. Infection of salivary gland leads to lifelong infection in the mosquito\(^3\). Some enzyme processing may occur in the mosquito’s midgut, for example by trypsin, and may exert an impact on the infectivity of the virus\(^4\). Following a mosquito bite, which inoculates dengue virus into skin, the virus appears to target skin Langerhans cells, and replicates in local tissues and regional lymph nodes, then disseminates via lymphatics to the blood stream\(^1,5,6\). Similarly, after inoculation from an infected mosquito, the West Nile virus (WNV) may infect fibroblasts, vascular endothelial cells or the reticuloendothelial system, leading to viraemia, and then reach the central nervous system to infect the host cells\(^2,3\). The recent study that documents the infection of uninfected mosquitoes co-feeding with WNV-infected mosquitoes on the same host (mouse) shows that some local diffusion/dispersal of the virus from bite site must occur as the mosquito is feeding\(^7\).

For a mosquito-borne infection, the amount of virus in the mosquito saliva, the frequency of bites and the duration of feeding by infected mosquitoes would determine the amount of virus inoculated. The amount of WNV secreted in mosquito saliva has been measured by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) in *Culex pipiens quinquefasciatus*, a vector of WNV; mosquitoes infected with WNV could transmit about $10^{4.3}$ plaque-forming units of virus\(^8\). Furthermore, mosquitoes inoculate about 1% of their total virus content when they take a blood meal, thus each mosquito could transmit at least 100 infective doses of virus\(^8\).

The level of viraemia in humans depends on the rate of clearance by macrophages, and viraemia ceases with the production of humoral antibodies in the host\(^1\). In vertebrate hosts, dengue viraemia titers usually are $>10^5$/ml, although virus can be below detectable levels by conventional laboratory techniques\(^9\). The time of onset, duration and level of viraemia varies with different flaviviral infections and may vary from one subtype or strain of a specific virus to the other.

Analogous to mosquito-borne infection, a non-vector transmission depends on the amount of virus in the inoculum and volume of material that reaches a receptive site. Additional factors that may influence the likelihood of direct transmission include stability of shed virus in the environment, the immune status of those potentially exposed, the size of the inoculum and the route of virus contact and entry\(^9\). Virus shedding may vary among the flaviviruses, may be different in humans as compared to experimental animals, and may occur in irregular patterns. Many reports of infection follow blood exposure, but some flaviviral infections are associated with virus in cerebrospinal fluid (CSF), urine, or other fluids that clinicians and caretakers could potentially be exposed to. A patient who is critically ill and who has haemorrhage is more likely to be a source of blood exposures in the hospital setting or at home. An important variable in the level of risk is the time of viraemia relative to the presence of severe illness and haemorrhage.

The viability of viruses in the environment also may differ. For example, WN and yellow fever viruses appeared to have prolonged survival at room temperature in an experiment where the viruses dried on filter paper were tested for infectivity by culture, titration in Vero cells and assessed by RT-PCR for viral RNA\(^10\). WNV was recovered up to 60 days after the procedure and yellow fever up to 90 days\(^10\). The survival of Japanese encephalitis virus (JEV) appeared to be inversely related to relative humidity whereas the yellow fever virus infectivity remained longer at higher relative humidity\(^9\).
Dengue Virus

Dengue viruses can be associated with haemorrhage, which can increase health care workers’ exposure to blood, and presumably lead to a greater risk for direct or nosocomial transmission. Dengue virus transmission without mosquito vector has been reported to occur via different routes, including needlestick, intrapartum, bone marrow transplant and mucocutaneous exposure\(^{11-21}\) (Table 1).

Among the reported cases of dengue virus infection from non-mosquito transmission, most source patients did not have haemorrhagic manifestations. Specifically, the reported health care workers who acquired dengue infection were not exposed to haemorrhagic source patients. One case of intrapartum/vertical transmission occurred in an infant born to a mother who was diagnosed with dengue haemorrhagic fever just before delivery\(^{18}\).

Yellow Fever

Yellow fever is the prototype virus amongst the flaviviruses. Because yellow fever virus is associated with haemorrhage, there may be a greater potential for transmission through blood exposure in health care workers, compared to flaviviruses that do not cause haemorrhage. A review of literature identified numerous cases of non-vector transmission in the pre-vaccine era, where scientists and laboratorians became infected with yellow fever virus after contact with blood or tissues of infected laboratory animals or handling experimentally-infected animals\(^{23,24}\). One case that occurred in 1930 in a hospital technician who analysed the blood of a yellow fever patient in London was described again recently; the route of transmission was unclear\(^{25}\) (Table 1).

Experimentally, monkeys have become infected with yellow fever virus that was introduced through a gastric catheter\(^{26}\). Intranasal transmission and mucocutaneous transmission via conjunctival sac has also been documented in monkeys in the laboratory\(^{27-29}\). Furthermore, yellow fever virus rubbed on intact abdominal skin of monkeys has led to infection\(^{30}\) (Table 2).

West Nile Virus

Human infections with WNV have been reported to occur from needlestick, breastfeeding, blood transfusion, organ transplants, haemodialysis and intrauterine or transplacental routes\(^{31-38}\). Two cases of West Nile fever occurred in turkey breeders where the route of transmission was unknown, but was speculated to have been by aerosol, fecal-oral or percutaneous exposure\(^{37}\). A seroprevalence survey conducted on the workers from six turkey farms showed that 18% had recent infection with WNV; seroprevalence was highest (55%) from the farm where the two cases worked\(^{37}\) (Table 1).

Among the reported cases of non-mosquito transmission, many source patients were asymptomatic. In fact, asymptomatic viraemic donors of blood products and organs were the most likely contributors to non-mosquito transmission. This shows that asymptotically-infected individuals are viraemic.
### Table 1. Reported routes of transmission in humans without vector

<table>
<thead>
<tr>
<th>Virus</th>
<th>Route of transmission</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue</td>
<td>Percutaneous</td>
<td>Several health care workers acquired dengue virus infection after needlestick injuries sustained while caring for febrile returned travellers diagnosed with dengue.</td>
</tr>
<tr>
<td></td>
<td>Intrapartum/congenital</td>
<td>Dengue infections have been documented in newborns whose mothers had acute dengue infections in the peripartum period. One newborn had intracerebral haemorrhage and died. One mother was diagnosed with dengue haemorrhagic fever just prior to delivery.</td>
</tr>
<tr>
<td></td>
<td>Bone marrow transplant</td>
<td>A 6-year-old child from Puerto Rico acquired DENV-4 from bone marrow transplant and died.</td>
</tr>
<tr>
<td></td>
<td>Mucocutaneous</td>
<td>DENV-3 virus was transmitted to a health care worker after being splashed in the face by blood from a febrile returned traveller diagnosed with dengue.</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Unclear contact transmission</td>
<td>A lab technician became infected with yellow fever after obtaining blood and performing a blood count on a yellow fever patient; he died subsequently. At least 30 other scientists and laboratorians acquired yellow fever after contact with mouse or monkey blood or tissues or handling infected animals.</td>
</tr>
<tr>
<td>West Nile</td>
<td>Breast-feeding</td>
<td>A nursing mother who acquired WNV infection postpartum was found to have WNV in breast milk, and the asymptomatic infant tested seropositive.</td>
</tr>
<tr>
<td></td>
<td>Percutaneous</td>
<td>2 microbiologists had laceration or needlestick injuries in lab and acute WNV infection was documented.</td>
</tr>
<tr>
<td></td>
<td>Intrauterine</td>
<td>A 20-year-old pregnant woman had acute WNV infection at 27 weeks; live infant delivered 5 weeks later had chorioretinitis and cerebral abnormalities.</td>
</tr>
<tr>
<td></td>
<td>Transfusion</td>
<td>Numerous recipients of blood products have been confirmed to acquire WNV through transfusion.</td>
</tr>
<tr>
<td></td>
<td>Organ transplant</td>
<td>Transmission of WNV to transplant recipients from kidneys, liver, and heart of an infected donor has been documented.</td>
</tr>
<tr>
<td></td>
<td>Aerosol, oral-fecal, or percutaneous in turkey farm workers</td>
<td>High incidence of WNV in turkey breeder farm workers suggested possible non-vector transmission.</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Intrapartum</td>
<td>A cluster of 3 haemodialysis patients diagnosed with WNV infection suggested transmission through a common dialysis machine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 pregnant women were infected during an epidemic in Uttar Pradesh, India. Two delivered normal infants, one was lost to follow up. Two women miscarried in the first or second trimesters, and virus was isolated from one fetus.</td>
</tr>
</tbody>
</table>
Infected blood has, however, been the most frequently documented source of non-mosquito transmission. WNV RNA has been identified by reverse transcriptase-polymerase chain reaction in the urine of a patient with encephalitis on the 8th day of illness[39]. It is not yet clear whether the WNV RNA in urine is infectious, and whether viruria plays a significant role in human WNV transmission.

Similarly, an experiment in hamsters found WNV to persist in the brain and kidneys, leading to chronic renal infection with persistent viruria[40]. Although transmission from urine exposure has not been documented in literature, infectious WNV was cultured from hamster urine for up to eight months and could possibly spread to other animals by aerosol or by ingestion[41]. WNV can also infect mice by the oral route[42]. In hamsters, investigators compared the pathogenesis of WNV following infection by mosquito bite, needle inoculation and ingestion; infection occurred by all three routes, resulting in similar levels of viraemia, duration of viraemia, clinical manifestations, pathology and antibody response[43]. The onset of viraemia was delayed following oral infection and mortality was lower, but the importance of oral route in the transmission of WNV in nature remains unclear[43] (Table 2).

Flaviviruses are sensitive to acid pH and bile, but their transmission via ingestion of infected milk has been demonstrated with tick-borne encephalitis, another flavivirus infection[7,44]. It is conceivable that virus entry could occur at other parts of oropharynx rather than in the stomach or duodenum. With breastfeeding humans, one could postulate that virus potentially could enter via mucosa of oropharynx.

Japanese Encephalitis

No nosocomial cases in humans have been reported. However, intrapartum, transplacental or congenital infection has been documented[45,46]. A study of five pregnant women infected during an epidemic in Uttar Pradesh, India, found that two women delivered normal infants, two women miscarried in the first or second trimesters, and the virus was isolated from one aborted fetus[46] (Table 1).

Experiments in animals have demonstrated direct transmission of JEV. One study showed that a bat that ingested infected mosquitoes became infected[47]. Two experiments showed possible aerosol transmission[48,49]. Macaques inoculated intranasally with JEV developed symptoms 11-14 days later; viral antigen was identified by immunofluorescent staining and histopathological changes were found in the nervous system[48]. Investigators speculated that JEV probably entered the blood stream following aerosol infection and seeded the central nervous system. A study in mice infected with aerosolized JEV showed lesions in olfactory bulb, frontal lobe and olfactory portions of cerebrum initially, followed by necrotic lesions in olfactory bulb, cerebrum, brain stem and spinal cord; the suggested spread was from nasopharynx across the cribriform plate to the olfactory bulb[49]. Oral infection in mice of JEV led to antibody production and protection against intracerebral challenge of JEV[50]. JEV has also been isolated from mouse urine after infection; in addition, JE viruria was shown to persist longer than viraemia (days 5–9 versus days 1–2 after infection)[51] (Table 2).

St. Louis Encephalitis

Direct, non-mosquito transmission of this virus in humans has not been reported. However, a study on mice exposed to aerosolized St. Louis encephalitis virus in a closed chamber demonstrated intranasal/aerosol transmission[52].
Table 2. Potential routes of transmission in animals*

<table>
<thead>
<tr>
<th>Virus</th>
<th>Route of transmission</th>
<th>Animal model</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow fever</td>
<td>Oral/intragastric</td>
<td>Monkey</td>
<td>Intragastric exposure to virus led to infection in monkeys[296].</td>
</tr>
<tr>
<td></td>
<td>Intransal/aerosol</td>
<td>Monkey</td>
<td>Monkeys sprayed intransally with yellow fever 17D vaccine became viraemic and immune; separately caged monkeys in single room became infected[277-278].</td>
</tr>
<tr>
<td></td>
<td>Cutaneous</td>
<td>Monkey</td>
<td>Rubbing virus on intact as well as abraded abdominal skin transmitted infection; conjunctival exposure to virus was followed by death but necropsy was inconclusive[106].</td>
</tr>
<tr>
<td></td>
<td>Conjunctival sac</td>
<td>Monkey</td>
<td>Intillation of virus in conjunctival sac led to infection[296].</td>
</tr>
<tr>
<td>West Nile</td>
<td>Oral</td>
<td>Hamster, mice</td>
<td>Infection occurred after ingestion, and resulted in similar levels of viraemia, duration of viraemia, clinical symptoms, pathology, and antibody response; suspension of WNV fed to mice caused fatal infection[42,43].</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Intransal</td>
<td>Macaque</td>
<td>Intransal inoculation led to symptoms 11–14 days later[48].</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>Mice, bat</td>
<td>Oral feeding of JEV led to antibody production and protection against intracerebral challenge of JEV; a bat was infected after ingesting infected mosquitoes[47,50].</td>
</tr>
<tr>
<td></td>
<td>Aerosol</td>
<td>Mice, hamsters, guinea pigs, rats, squirrel monkeys</td>
<td>Aerosol exposures led to infection of several species of experimental animals[39].</td>
</tr>
<tr>
<td></td>
<td>Percutaneous</td>
<td>Bat</td>
<td>Subcutaneous inoculation with JEV led to viraemia but no clinical illness[47].</td>
</tr>
<tr>
<td>St. Louis encephalitis</td>
<td>Aerosol/intransal</td>
<td>Mice</td>
<td>Animals exposed to SLE virus via aerosol in a chamber became infected[50].</td>
</tr>
</tbody>
</table>

*WNV and St. Louis encephalitis virus have been isolated from urine of experimentally infected hamsters[40,41] and JEV from urine of mice[51], but no reports documenting transmission from urine were found in the published literature.

Patients with St. Louis encephalitis were found to have viral antigen in urine by indirect immunofluorescence, electron microscopy and immune electron microscopy, although virus was not isolated from urine[53]. Recent studies show that hamsters experimentally infected by subcutaneous injection of St. Louis virus can shed the virus in urine for at least four months[41].
Murray Valley Encephalitis

Direct, non-mosquito transmission of this virus in humans has not been reported, which may reflect the small number of human infections as compared to the other flaviviruses.

Viraemia

The levels of viraemia among the flaviviruses are difficult to compare because measurements are described in different terms. These measurements include median mosquito infectious doses per millilitre (MID$_{50}$/ml), copies of RNA per millilitre, plaque-forming units per millilitre (pfu/ml), and intracerebral median lethal dose per millilitre (LD$_{50}$/ml) (Table 3).

Yellow fever virus is readily isolated during the first four days of illness, but may be recovered from serum up to 17 days[54]. Yellow fever viraemia in a human case showed that virus titres were 10$^{4.6}$ LD$_{50}$ at 5 days after the onset of symptoms and 10$^{2.7}$ LD$_{50}$ at 7 days after the onset of illness[53]. Experience with Japanese encephalitis also shows that viraemia can persist following resolution of symptoms and in recurrently symptomatic patients[55,56].

In natural infection with dengue virus, the duration and level of viraemia varied among different strains and serotypes[57]. The duration of viraemia ranged from 1–7 days (2–12 days as per Gubler, 1981), with a mean of 4.5 days, median of 5 days[58]. The duration of viraemia is underestimated in the study because some of the children were still viraemic on the last blood draw. The duration is longer in primary infection (5.1 days), compared to secondary infection (4.4 days), and the peak virus titre was 10$^{9.2}$ MID$_{50}$/ml (median mosquito infectious doses per millilitre)[58]. Patients with primary infections had persistent viraemia until 1.6 days after defervescence whereas those with secondary infections cleared viraemia by 0.6 days after defervescence[59]. Higher levels of viraemia correlated with the severity of disease, and the rate of virus clearance in the two days before defervescence was greater in dengue haemorrhagic fever than in dengue fever[59].

The measurement of plasma RNA by quantitative competitor (RT-PCR) derived a range of 10$^{5.5}$ to 10$^{9.3}$ copies/ml, which correlated with MID$_{50}$ by a geometric mean number of 0.15 RNA copies per MID$_{50}$[60]. These RNA levels peaked two days before defervescence and declined to below detection in two thirds of patients by defervescence[66]. Therefore, one third of patients had detectable dengue RNA at defervescence and they were possibly infectious after defervescence[60]. A study of adult patients infected with DENV-3 in southern Taiwan in 1998 using the quantitative RT-PCR method showed that during defervescence, viral RNA remained high in DHF patients but was undetectable in DF patients; viraemia in DHF patients persisted for up to six days after defervescence[61].

Since the level and duration of viraemia appear to correlate with the severity of the disease, it is likely that asymptomatic dengue infection would have lower levels and shorter duration of viraemia than DF or DHF. Likewise, other flavivirus infections are expected to have lower levels of viraemia in asymptomatic infections, compared to that in symptomatic infections. Cases of WNV acquired through transfusion demonstrate viraemia in asymptomatic donors. Estimated viral loads in blood donations that led to transfusion-associated transmission of WNV were 0.8–75 pfu/ml for 2002 and 0.06–0.5 pfu/ml in 2003[34]. Because RNA titres are higher than plaque-forming units by about 400[62], the RNA levels would range from 24–30 000 copies/ml.

In West Nile infections, viraemia is present during the two days before until about four days after the onset of illness[63]. Rarely the
### Table 3. Population at risk and viraemia

<table>
<thead>
<tr>
<th>Virus</th>
<th>Endemic regions: population at risk</th>
<th>Estimated incidence</th>
<th>Symptomatic : asymptomatic cases</th>
<th>Level of viraemia</th>
<th>Duration of viraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow fever</td>
<td>Tropical South America, sub-Saharan Africa&lt;sup&gt;1,29,34&lt;/sup&gt;</td>
<td>200 000/year</td>
<td>1/3.8–1/7.4 in West African outbreaks</td>
<td>$10^{4.5}$ day 5 to $10^{5.2}$ day 7 LD&lt;sub&gt;50&lt;/sub&gt;/ml</td>
<td>Usually 4 days; up to 17 days; peak on day 2–3</td>
</tr>
<tr>
<td>Dengue</td>
<td>Tropical and subtropical regions worldwide. Especially common in South-East and South Asia; population is 2.5 billion at-risk areas&lt;sup&gt;32,40,73&lt;/sup&gt;</td>
<td>50–100 million/year</td>
<td>1/6.7</td>
<td>$10^{7.4} – 10^{8}$ MDC&lt;sub&gt;50&lt;/sub&gt;/ml or $10^{5.3} – 10^{6.1}$ RNA copies/ml</td>
<td>4–5 days</td>
</tr>
<tr>
<td>West Nile</td>
<td>Middle East, Africa, North America, parts of Europe and former Soviet Union, tropical Asia. Entered eastern US in 1999 and has already spread throughout US and to Canada, Mexico, Central America and Caribbean&lt;sup&gt;1,2,34,64,74,75,76&lt;/sup&gt;</td>
<td></td>
<td>Outbreaks cause hundreds to thousands of symptomatic infections.</td>
<td>1/5 symptomatic; 1/150 meningoencephalitis</td>
<td>6.5 days; &gt;12 days in 10% of cancer patients</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Asia (including East, South, and South-East Asia); far eastern former Soviet Union, Papua New Guinea, Torres Strait and far northern Australia&lt;sup&gt;32,45,46,56,74,77&lt;/sup&gt;</td>
<td>30 000–50 000/year in Asia</td>
<td>1/25 in nonimmune person to 1/250 in Asians</td>
<td>3.3 dex/ml; as low as 0.06–0.5 pfu/ml in blood donations in 2003</td>
<td>Up to 3–7 days; viraemia has been shown 8 months after initial infection; virus has also been isolated from CSF 117 days after onset of symptoms</td>
</tr>
<tr>
<td>St. Louis encephalitis</td>
<td>Most often found in North America; virus also found in Central and South America and Caribbean&lt;sup&gt;1,74,78&lt;/sup&gt;</td>
<td></td>
<td>Less than 50 cases during most years; occasional outbreaks up to 2800</td>
<td>1/806 in children to 1/85 in adults</td>
<td></td>
</tr>
<tr>
<td>Murray Valley encephalitis</td>
<td>Australia; Papua New Guinea&lt;sup&gt;27,46&lt;/sup&gt;</td>
<td>40 cases in 25 years</td>
<td>Outbreaks typically cause up to ~50 cases</td>
<td>1/700 to 1/1200</td>
<td>No data?</td>
</tr>
</tbody>
</table>
virus is isolated from the CSF in patients with meningoencephalitis. The virus has also been isolated from organs such as liver, spleen, lung and pancreas, with a high concentration of reticuloendothelial cells. In immunocompromised patients intentionally infected with West Nile virus as part of a study to examine novel approaches to cancer treatment, the virus could be recovered from blood up to 28 days after inoculation.

In the case of percutaneous or mucocutaneous exposure, the viral load would depend on the amount of blood in contact. Assuming a mean volume of blood inoculated via needlestick to be 1 ul, the viral load after a needlestick exposure would be in the range of 10 to 10^7 RNA copies/ml for dengue virus and up to 300 RNA copies/ml for West Nile virus. Despite the minuscule amount of blood transferred, needlestick transmission has been documented for both dengue and West Nile.

**Quantification of Risk**

The risk of transfusion-associated transmission of West Nile virus in Queens, New York, in 2002, was estimated to be 1.8/10 000 donations (mean) up to 2.7/10 000 donations (peak) (or 1 in 3700 to 1 in 5555 donations). These estimates were based on the findings that 80% of West Nile virus infections are asymptomatic, that the incubation period lasts 2–6 days, and that the virus is detected in blood 1–2 days after mosquito inoculation; therefore an asymptomatic donor may have a mean of three viraemic days before the onset of symptoms. In comparison, the estimated frequency of transfusion-associated hepatitis B virus (HBV) infection in the United States with currently available testing technologies is 1/30 000–250 000 units, hepatitis C virus (HCV) infection is 1/30 000–150 000 units, and human immunodeficiency virus (HIV) infection is 1/200 000 to 2 000 000 units.

A recent report of HCV transmission associated with saline flushes (re-use of disposable syringes and contamination of shared saline bags) showed an attack rate of 27%, and the dose leading to infection of 50% of exposed population for patients was three flushes (30–60 ml of saline). Given the relative rates, one could estimate that WNV could be transmitted from up to 5% of viraemic contacts if similar breaches in sterile techniques occurred with saline flushes.

Health care workers (HCWs) regularly encounter occupational exposure to blood and body fluids, and the risk of injury is related to precautions taken. A study in a community hospital found that one-quarter of HCWs had mucocutaneous blood exposure in the three months prior to the survey, whereas one third of HCWs had percutaneous injury in the same period. Another study that assessed the risk of sharps injuries in nurses caring for diabetic patients found nearly 80% of nurses experienced at least one needlestick; the American Nursing Association reported 600 000 to 1 000 000 sharps injuries in HCWs each year. The frequency of exposure in HCWs illustrates the vulnerability to blood-borne transmission of infections, including flaviviruses. Health care workers in developing countries face a substantially riskier environment because of inadequate supplies of sterile needles, masks, gloves and goggles that could protect them from blood exposures, though few studies are available to document the magnitude of these risks.

**Conclusion**

Multiple routes of non-mosquito transmission of flaviviruses in humans have been described recently. Infections with dengue and West Nile viruses have been the most commonly documented. These two viruses can be associated with asymptomatic infection, febrile
illness with rash and arthralgia, or more severe illnesses such as dengue haemorrhagic fever/dengue shock syndrome and West Nile meningoencephalitis. The asymptomatically infected persons appear to be particularly important as sources in the transfusion-associated and transplant-associated transmission of West Nile virus.

Syndromes with haemorrhage may increase the risk of exposure to blood-borne pathogens, possibly due to higher level of viraemia, greater difficulty in avoiding accidental contact and more intense contact needed to care for the severely ill patients. In spite of the fulminant course and haemorrhagic sequelae of yellow fever infection, the only documented and published cases of possible direct transmission of yellow fever virus were reported before the availability of the yellow fever vaccines. Vaccination probably has provided significant protection to health care workers and laboratorians. It is also possible that health care workers take greater personal protective measures in caring for severely ill patients (for example, those with haemorrhagic symptoms) and therefore minimize their exposure.

Risks of non-mosquito transmission of flaviviruses may differ among the viruses for many reasons. These include the size of the population exposed to the infection (which may vary from year to year and change over time), the availability and state of medical resources (e.g. adequacy of infection control, testing of donated blood, availability of organ transplantation), biological characteristics of the virus and immunity of the human population because of prior infection or vaccination. As discussed, the level of viraemia, the duration of viraemia and peak viraemia differ among the flaviviruses. The infective dose of virus may also differ among the flaviviruses. Finally, the period of clinical illness and the period of viraemia may have different patterns of overlap. Persistent shedders of virus would pose a greater risk of transmission to their contacts. Infection may not be detected in an endemic population where the majority of individuals have previously been infected or vaccinated. For example, non-immune youngsters are more likely to be infected by dengue virus, but an association with non-mosquito transmission may not be apparent to them. Furthermore, WNV is the only flavivirus documented in the literature to be transmitted by transfusion of blood products. One possible explanation is that youngsters, in whom flavivirus infections such as dengue occur at a higher incidence, are less likely to donate blood. Another explanation is that non-mosquito transmission is unlikely to be recognized in an area where an infection is endemic. In addition, many flavivirus infections result in mild or asymptomatic illness and may not prompt any work-up, so could not be recognized as transfusion-acquired infections.

Adequacy of infection control education and materials will influence risks in the health care setting. In many countries endemic for JE, dengue and yellow fever, resources for infection control are lacking and adherence to precautions may be difficult or impossible. Diagnostic laboratories and technologies to document infections and their sources may be unavailable in many endemic countries. It is most difficult to differentiate between non-mosquito transmission and mosquito-borne infection in endemic areas where the vector is widespread. Hence, most cases of non-mosquito flavivirus transmission in humans have been documented in developed countries. Our review would suggest that nosocomial transmission of these infections probably does occur in endemic areas, and health care workers should be aware of the these risks.

The authors searched Medline/Pubmed for viraemia, nosocomial transmission and mucocutaneous transmission of flaviviruses as well as yellow fever, dengue, West Nile, Japanese encephalitis, St. Louis encephalitis and Murray Valley encephalitis for pertinent information on the topic.
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