Arboviruses of human health significance in Papua New Guinea

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SUMMARY

Arboviruses (arthropod-borne viruses) are important emerging pathogens in many tropical and developing countries of the world. The Southeast Asian and Western Pacific regions have recently experienced large outbreaks of dengue, Japanese encephalitis and chikungunya fever. In Papua New Guinea (PNG) serological surveys and mosquito isolation experiments suggest that arboviruses are prevalent throughout the country. However, the lack of surveillance and clinical reporting means that the distribution and prevalence of these diseases is unknown. In this paper we review the most important arboviruses with regard to human health in the PNG region.

Introduction

The word arbovirus is an ecological term that is used to define the heterogeneous collection of viruses which are transmitted by haematophagous arthropods. The term is a contraction of the phrase ‘arthropod-borne virus’ and thus has no taxonomic significance. The arboviruses include a wide variety of virus taxa, representing eight family groups and 14 genera (1). However, most arboviruses of human health significance belong to only three RNA viral families: Flaviviridae, Togaviridae and Bunyaviridae. The Centers for Disease Control (International Catalogue for Arboviruses) have registered over 530 viruses. However, only approximately 130 of these viruses have been associated with human disease and a much smaller number implicated in serious illnesses (2,3).

Arboviruses are among the most common agents of febrile illnesses worldwide and are important emerging pathogens. The last three decades have seen a dramatic increase in the incidence of epidemics due to arboviruses, in particular dengue virus (DENV), chikungunya virus (CHIKV), yellow fever virus (YFV), Japanese encephalitis virus (JEV) and West Nile virus. The reasons behind the emergence (or re-emergence) of these diseases are complex and multifactorial, yet aspects such as increased international travel, habitat destruction and global climate change probably play an important role (4). Countries worldwide are becoming more aware of the increased threat that emerging arboviral diseases present to the health of their people.

This paper will review the impact of arboviral diseases in Papua New Guinea (PNG) and surrounding regions and discuss the possible threat from exotic arboviruses.

Clinical disease

Arboviral infections cause a broad range of disease, including asymptomatic infections and acute self-limiting febrile illnesses. Some viruses are also associated with severe secondary conditions such as meningoencephalitis and haemorrhagic fever which may result in disabling sequelae and death. Generally, arboviral infections can be classified into four main clinical syndromes (Table 1): 1) acute, undifferentiated fever; 2) meningoencephalitis; 3) haemorrhagic fever; and 4) polyarthritis (3,5). Arboviral infections are commonly confused with other illnesses such as malaria, typhoid and dysentery due to their non-specific clinical symptoms and therefore remain undiagnosed in many developing countries (6).

Transmission and life cycles

Arboviruses are transmitted between
TABLE 1

ARBOVIRAL SPECIES OF POSSIBLE HUMAN HEALTH SIGNIFICANCE IN PAPUA NEW GUINEA

<table>
<thead>
<tr>
<th>Virus name</th>
<th>Distribution</th>
<th>Disease</th>
<th>Principal vectors</th>
<th>Vertebrate host</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flaviviridae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dengue virus 1-4 (DENV1-4)</td>
<td>Worldwide tropics and subtropics</td>
<td>FI, HF</td>
<td>Ae. aegypti</td>
<td>Humans, primates</td>
</tr>
<tr>
<td>Japanese encephalitis virus (JEV)</td>
<td>Asia and Australasia</td>
<td>FI, ME</td>
<td>Cx. tritaeniorhynchus, Cx. annulirostris</td>
<td>Birds, pigs</td>
</tr>
<tr>
<td>Murray Valley encephalitis virus (MVEV)</td>
<td>Australia, New Guinea, Indonesia</td>
<td>FI, ME</td>
<td>Cx. annulirostris</td>
<td>Birds</td>
</tr>
<tr>
<td>Kunjin virus (KUNV)</td>
<td>Australia, New Guinea, Indonesia</td>
<td>FI, ME, PA</td>
<td>Cx. annulirostris</td>
<td>Birds</td>
</tr>
<tr>
<td>Sepik virus (SEPV)</td>
<td>New Guinea</td>
<td>FI</td>
<td>Ficalbia spp.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Togaviridae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ross River virus (RRV)</td>
<td>Australia, New Guinea</td>
<td>FI, PA</td>
<td>Cx. annulirostris, Ae. vigilax, Ae. camptorhynchus</td>
<td>Marsupials</td>
</tr>
<tr>
<td>Chikungunya virus (CHIKV)</td>
<td>Africa, Asia</td>
<td>FI, PA, HF</td>
<td>Ae. aegypti, Ae. albopictus</td>
<td>Humans, primates</td>
</tr>
</tbody>
</table>

FI = febrile illness
HF = haemorrhagic fever
ME = meningoencephalitis
PA = polyarthritis
Ae. = Aedes
Cx. = Culex

Arboviruses display several types of life cycle, but generally most arboviruses can be classified into two main transmission cycles (Figure 1). In the sylvatic cycle (also called the enzootic or jungle cycle), the virus in transmitted from mosquitoes to a wild vertebrate host, with humans usually being a dead-end host when infected. In the urban (or epidemic) cycle, the virus cycles between vertebrate hosts through the bite of haematophagous, or blood-sucking, arthropods. Mosquitoes are the primary vectors associated with arbovirus transmission, although other biting arthropods such as ticks, sandflies and midges may also transmit viruses. All known arbovirus transmission occurring in PNG and the surrounding region is through mosquito vectors, and therefore this review will focus on mosquito-borne arboviruses of public health significance in the region.

The majority of arboviruses are maintained in a sylvatic cycle between mosquitoes and a wild vertebrate host, and are therefore regarded as zoonotic diseases when humans are infected (8). The natural vertebrate host for arboviruses varies greatly between viral species. However, in terms of human arboviral diseases the most important primary hosts are birds, rodents and non-human primates; but many other species such as pigs, horses and marsupials may also play an important role as primary hosts for specific arboviruses (1).
after a period of replication in the arthropod tissues the virus can be transmitted during subsequent feedings. The arthropod host usually remains infectious throughout the rest of its life (6). If the vertebrate host cannot act as a reservoir or sufficiently replicate the virus for the reinfection of other vectors, this vertebrate becomes a dead-end host. This happens when the vertebrate is not the normal host, resulting in a low viraemia, and consequently transmission chances are very low (3,9). The infection of a dead-end host can often lead to more severe clinical disease (10). Humans are dead-end hosts for almost all arboviruses except for DENV, YFV and CHIKV (11-13).

Epidemiology of arboviral infections

Despite the increased incidence of large outbreaks of arboviral diseases and the public health impact in many tropical countries, little is known about the geographical distribution, risk factors and disease burden associated with these diseases. This is particularly pertinent in many developing countries such as PNG. It is clear that the health risks of arboviral infections are significant and the factors that influence the transmission and emergence of arboviruses need to be elucidated. Social and economic factors play an important role in the incidence and prevalence of arboviral diseases. For instance, industrialized countries are better able to prevent the transmission of many arboviruses through proper window screens, treated mosquito nets, air conditioning and safe water supplies (14). In developing countries poor housing and living conditions are the major cause of disease outbreaks. In

JEV = Japanese encephalitis virus
MVEV = Murray Valley encephalitis virus
KUNV = Kunjin virus
DENV = Dengue virus
CHIKV = Chikungunya virus
addition, better health services can reduce or eliminate mortality associated with many of these illnesses (14,15).

Historically, the geographical distribution and existence of arboviruses was determined by the ecological parameters governing their transmission cycles. The majority of arboviruses are found in the tropical regions, where the climatic conditions are highly favourable, allowing year-round transmission (3). However, global demographic and societal changes have influenced and thus facilitated the expansion of these diseases beyond their natural (historical) boundaries. Increased population density, urbanization, socioeconomic development, increased travelling made possible by modern transportation, increased animal husbandry and climate change are some of the leading factors that have also influenced arboviral distribution (3,4).

**Arboviral activity within the PNG region**

Over 65 arboviruses have been reported in the Australasian region alone (16), which is approximately 12% of the viruses registered in the International Catalogue of Arboviruses. However, only a few of these viruses are of medical importance. In Southeast Asia and Western Pacific, the most significant arboviral species include DENV types 1-4 (DENV1-4), JEV, Murray Valley encephalitis virus (MVEV), kunjin virus (KUNV), CHIKV, Ross River virus (RRV) and Barmah Forest virus (BFV) (16-18).

A number of studies have been conducted over the years which have indicated that there is a high prevalence of arboviral infections in PNG (19-21). Although research in this area has been limited, serological evidence and mosquito isolations suggest that there are two groups of arboviruses in PNG: the flaviviruses, including DENV1-4, JEV, MVEV, KUNV, Sepik virus (SEPV) and kokobera virus; and the togaviruses, including RRV. Thus far, there are no data available on the detection of bunyaviruses in PNG, simply because little or no research has been done on this group of arboviruses, their vectors and activities in the region. Trevett and Sanders (22) in their paper on arbovirus disease in PNG explained that in all of the areas where surveys have been carried out, antibodies to both flaviviruses and togaviruses were prevalent, mostly among inhabitants of lowland regions, with the disappearance of antibodies 1500 m above sea level. However, the absence of flavivirus and togavirus activity in the highland plateau does not necessarily rule out the introduction of these viruses from the coastal lowlands (23).

A large variety of mosquito species are known to be present in PNG. Of particular concern are the species which are commonly associated with arboviral transmission such as *Aedes aegypti*, *Culex annulirostris*, *Ae. vigilax*, *Ae. albopictus*, *Ae. camptorhynchus* and many other species that have been implicated as efficient vectors for arboviruses (24). The large lowland swamps, abundant birdlife and year-round tropical temperatures indicate that arboviral activity may be very high in PNG.

Below we will review some of the most important arboviruses that are known to circulate in PNG and also discuss some of the important viral species that may be a threat to PNG in the future.

**Dengue virus**

Dengue is currently considered the most important arboviral infection in the world in terms of morbidity and mortality. The worldwide incidence of dengue has increased dramatically in recent decades. Thus more than half of the world’s population (3.5 billion people) are at risk of the disease and up to 100 million cases occur each year (15,25,26). This virus is distributed throughout most of the tropical regions of the world and presents serious public health problems in Southeast Asia, Africa, the Caribbean, Pacific Islands and Latin America (27). Dengue is endemic throughout many countries in Southeast Asia and the Western Pacific, including Papua New Guinea, Indonesia, Malaysia, The Philippines, Thailand, Cambodia and Vietnam (28,29).

Dengue fever (DF) is caused by any of 4 antigenically distinct serotypes of DENV, which display only 62-67% amino acid sequence similarity (26). Nonetheless, the four viruses are nearly identical in terms of epidemiology and clinical presentation. Infection with DENV provides life-long protection to that particular serotype, but does not provide cross-protective immunity against the other serotypes (27). DF is manifested as a sudden onset of fever with headache, myalgia and arthralgia, with or without retro-orbital pain and rash (15).
Classical DF lasts for about two to seven days and milder cases are often misdiagnosed for influenza or other viral infections. In more severe cases, DENV infections may proceed to dengue haemorrhagic fever (DHF), which is characterized by haemorrhaging and thrombocytopenia that may lead to dengue shock syndrome (DSS) as a result of excessive plasma leakage (30,31). DHF and DSS are potentially deadly complications, but early and appropriate treatment can greatly reduce the mortality rate associated with these diseases (28). The factors that influence the progression of disease to DHF and DSS are currently unknown. Many hypotheses have been proposed, which include immunological, host genetic and viral virulence factors (32-34).

The principal vector of dengue is the mosquito *Ae. aegypti*, which is highly adapted to the urban environment and breeds in water-filled containers. The widespread tropical distribution of dengue is attributed to the gradual invasion of *Ae. aegypti* throughout the world (35). DENV can be maintained in both sylvatic and urban cycles. In some African and Southeast Asian countries the virus is transmitted between mosquitoes and non-human primates in a sylvatic cycle. However, the virus can also be maintained in an urban cycle between *Ae. aegypti* mosquitoes and humans. Distinct genetic differences between sylvatic and urban strains of dengue suggest that the two cycles are now epidemiologically independent (30).

Dengue is believed to be endemic in PNG. However, information about the distribution and prevalence of these viruses is limited. The first major outbreak to be documented in this country was in Rabaul in 1971. Over a 5-month period over 1100 cases of dengue-like illness were recorded, with DENV2 identified as the causative agent (36). Further outbreaks were recorded in PNG in 1976 and 1983 (37). Thus the presence of DENV in PNG is evident from the reported clinical cases yet very little information is known about its epidemiology in the country. A recent study at Modillon Hospital, Madang Province detected DENV in 8% of febrile cases enrolled into the study (38), thus confirming that DENV is an important pathogen in PNG.

Although DHF is a leading cause of hospitalization and death in children in Southeast Asia (27), there have only been rare reports of DHF in PNG. However, three cases of DHF were reported in Vanimo in February 2011 (unpublished data). The lack of DHF and DSS cases in PNG is interesting due to the high level of infection believed to occur in PNG and the presence of multiple serotypes. Host susceptibility or viral virulence factors may play a role in the low numbers of cases observed in this country. Alternatively, the paucity of DHF reports in PNG may be an indication of the lack of surveillance and reporting rather than a true absence of cases.

**Japanese encephalitis virus**

JEV is the most important cause of human encephalitis in Southeast Asia, with an estimated 175,000 cases occurring in this region annually (39). Japanese encephalitis (JE) is characterized by a variety of neurological symptoms including headaches, convulsions, seizures, photophobia, reduced levels of consciousness and coma (40,41). Clinical cases of JE are fatal in approximately 25% of cases and severe disabling sequelae occur in up to 50% of cases. However, the majority of JEV infections are asymptomatic with only between 1 in 50 and 1 in 1000 infections resulting in clinical encephalitis (39). JEV may also be an under-appreciated cause of undifferentiated fever in Southeast Asia and other endemic areas. A study in Thailand found that infections with JEV were the apparent cause of fever in 14% of acute febrile cases (42).

*Culex* species of mosquito, in particular *Culex tritaeniorhynchus*, are the major vectors of JEV. The principal vector in PNG and the Torres Strait region of Australia is thought to be *Cx. annulirostris* (24). The natural vertebrate hosts for JEV are the ardeid wading birds, such as egrets and herons. However, over 90 species of wild and domestic birds have been reported with JEV seroconversion or viraemia (39). Pigs also play an important role as amplifying hosts for JEV, and most epidemics occur where there is a high pig population. Pigs are the main vertebrate species that are associated with transmission cycles with respect to human infections due to the close association of pigs with human settlements in JEV-endemic areas and the high viraemia that results in porcine infections (39). Humans are considered a dead-end host for JEV transmission because they do not develop high levels of viraemia sufficient to infect a mosquito for subsequent transmission of the
virus (43).

JE was first reported in PNG from 3 cases in the upper Fly area of Western Province between 1997 and 1998 (17). Subsequent serological studies have shown that JEV has been present in Western Province since at least 1989 (44). Human and porcine serological evidence suggests that JEV is now endemic across much of this area (44). In addition, numerous isolations of JEV from *Culex* species of mosquitoes have been made from a wide area of Western Province (24) and the nearby Torres Strait (45,46). There are concerns that JEV is spreading across a wider region of PNG with human seroconversion detected in the Gulf and Southern Highlands Provinces of the country (17). Clinical cases of JE have also been reported from Normanby Island and Alotau and a case was imported from the Port Moresby region to Australia (18,47). A recent study into the aetiology of febrile encephalopathy at Port Moresby General Hospital detected IgM antibodies to JEV in the cerebrospinal fluid of three patients (48).

**Murray Valley encephalitis virus**

Murray Valley encephalitis (MVE) is characterized by symptoms similar to JE. The clinical presentation of MVE may be variable but features such as sudden onset of fever, headache, nausea and vomiting may be observed, followed by neurological symptoms such as drowsiness, confusion and seizures (49). MVE is fatal in approximately 25% of cases, with a further 25% of cases resulting in severe disabling sequelae. Similarly to JEV, only a small proportion of infections with MVEV are symptomatic (<1 in 1000) and mild febrile illnesses are also common (17).

Although MVEV antibodies have been detected in many species of birds and mammals, the main vertebrate hosts are believed to be the ardeid wading birds (8). The major mosquito vector of MVEV is *Cx. annulirostris*, but many other species may be involved in transmission cycles (49). Serological evidence suggests that MVEV has an enzootic focus in north-western Australia, with epidemic activity occurring throughout much of northern Australia (50). MVEV is also found in PNG (51) and probably in the eastern islands of the Indonesian archipelago (16). One case of MVE was reported in PNG in 1956, and this case was confirmed after MVEV was isolated from the brain tissue of the deceased patient (52). In 1960, a second case from Dutch New Guinea (West Papua) was confirmed serologically (53). MVEV was also detected in mosquitoes collected from the Balimo area in 1998 (24). Sequence analysis of MVEV isolates has revealed that four distinct lineages of the virus exist in Australasia; lineages 1 and 2 have been detected in Australia, and lineages 1, 3 and 4 in PNG (54-56).

**Kunjin virus**

KUNV is very similar to MVEV in terms of vectors, vertebrate hosts and distribution (17). However, kunjin encephalitis is generally milder and non-life-threatening. Similarly to MVEV and JEV infections, KUNV infections are often asymptomatic. Acute febrile illness with polyarthralgia has also been associated with infections from this virus (57). KUNV antibodies have been detected in humans from Australia, PNG, Indonesia, Malaysia, Thailand, Laos and Cambodia (8,21,58). Although neither kunjin encephalitis nor febrile illness have been reported in PNG, this is probably due to the non-specific nature and low severity of the illnesses.

**Sepik virus**

SEPV was first isolated from several species of mosquitoes in the Sepik area in 1966 (59). Subsequently, the virus was isolated from a pool of *Culex sitiens* subgroup mosquitoes in Balimo, Western Province (24). The geographical and temporal distance between these two isolations suggests that SEPV may have a wide distribution around PNG. High neutralizing antibody titres have been detected in the blood of a patient recovering from a febrile illness, which suggests that SEPV is a potential human pathogen (59). To date, SEPV has only been detected in PNG (60).

**Ross River virus**

Ross River fever is the most frequently reported arboviral disease in Australia, with approximately 5000 cases occurring in the country every year (61). The disease is also endemic in PNG (20,21,62,63), but the distribution and prevalence is unknown due to the lack of surveillance in this country. In 1979 a large outbreak of Ross River fever spread
throughout many Pacific island nations, including Fiji, New Caledonia, Samoa and the Cook Islands. This epidemic was the largest outbreak of Ross River fever ever recorded with more than 50,000 people infected (17,64).

The symptoms of Ross River fever (or epidemic polyarthritis) include headache, fever, lethargy, maculopapular rash, arthralgia and arthritis (65,66). Although most patients make a rapid recovery from the infection, a significant proportion of people report arthritic symptoms lasting more than a year and in some cases symptoms have been reported to persist for up to three years (67). The arthritic symptoms observed in cases of Ross River fever are thought to be due to viral replication in the joint tissues and evidence to support this has been provided by antigen staining and RT-PCR (68). Interestingly, clinical disease is only rarely reported in children, which is probably due to their reduced ability to produce arthrogenic cytokines (TNF-α and TNF-γ) and therefore lower susceptibility to immune-induced damage to the synovial joints (69).

RRV has been detected in at least 30 species of mosquito from six genera. However, three species are considered the major vectors for this virus: Cx. annulirostris, Ae. vigilax and Ae. camptorhynchus (17,49). Many other species may be involved in transmission cycles and vector importance seems to be closely linked to environmental conditions. Various marsupials such as kangaroos and wallabies are believed to be the major vertebrate hosts for RRV. However, many other species of marsupial and placental mammals have been identified as competent hosts for the virus (70-73). Indeed, during the large Pacific islands outbreak much of the transmission was thought to be between mosquitoes and humans alone (16).

Although it is generally accepted that RRV is widely distributed and endemic in PNG, only limited research and reports of clinical disease have been published. Tesh and associates (20) conducted a comprehensive serological survey for various arboviruses throughout the Pacific island and Southeast Asian regions. RRV antibodies were detected in adult populations across most of PNG, including Southern Highlands, Eastern Highlands, Sepik, New Britain, Louisiade Archipelago, Bougainville, Port Moresby, Morobe and New Ireland. In some areas, such as Sepik and Port Moresby, neutralizing antibodies to RRV were detected in over 60% of samples. More recent mosquito trapping studies have also detected RRV virus in Western Province (24). The role of RRV in cases of infectious arthritis in PNG was confirmed by Scrimgeour et al. (62) with serological confirmation of infection in three cases of polyarthritis from Port Moresby. The same authors also attributed 14% (182 patients) of arthritis cases at Port Moresby General Hospital, Goroka Base Hospital and Nonga Base Hospital (Rabaul) between 1977 and 1982 to RRV infection (63). Hii and associates (23) detected RRV antibodies in 59% of people tested in the Southern Highlands. This study found that antibody prevalence increased with age, which suggests that RRV is endemic in this region. Unfortunately, no recent studies have been conducted to investigate the distribution and clinical importance of RRV in PNG.

**Chikungunya virus**

Historically, chikungunya fever was known as an enzootic and endemic disease of tropical Africa and Asia. However, since 2004 widespread outbreaks of the disease have occurred throughout the Indian Ocean and in Italy, India, Malaysia, Indonesia, East Timor, Thailand and New Caledonia (74-78). Chikungunya fever is characterized by high fever, maculopapular rash on the trunk and limbs, painful arthritis in the extremities (79) and in some severe cases haemorrhagic manifestations and encephalitis (75). A major contribution to the sudden, widespread outbreaks of CHIKV is a recent mutation in the E1 envelope glycoprotein which has enhanced the replication and transmission of the virus in Ae. albopictus mosquitoes (4). Although chikungunya fever has not so far been reported in PNG, two serological studies conducted in the 1970s found a wide distribution of CHIKV antibodies throughout PNG (20) and West Papua (21). Considering the widespread distribution of this virus throughout the region it is likely that chikungunya is already present in PNG, but has not been identified due to similarities with the clinical presentation of Ross River fever, dengue and malaria.

**Conclusions**

It is evident that arboviruses and their associated diseases are common and widespread throughout PNG. However, the absence of surveillance and clinical reporting,
coupled with the non-specific symptoms of many arboviral diseases, has resulted in limited data being available for these viruses. Serological evidence suggests that the distributions of DENV, JEV and RRV are widespread throughout the country. Less is known about other pathogens of potential significance in PNG such as MVEV, KUNV, SEPV and CHIKV.

Identification of the prevalence and distribution of arboviruses in PNG will not alter the treatment of these diseases. The benefit will be at the population level with the realization that febrile illnesses can be caused by pathogens other than malaria and typhoid. Control strategies that are in line with the current bednet distribution programs taking place for malaria may have a positive effect on the impact and distribution of many arboviruses. However, for some arboviruses such as dengue, which are transmitted by day-biting mosquitoes, the impact may not be as extensive.

PNG is rapidly changing in terms of agriculture, increased urbanization and habitat destruction. These activities may allow endemic and exotic arboviruses to spread and establish in new geographical areas. Unfortunately, PNG does not have an active arboviral disease surveillance program linked to specialized laboratories with the capacity to detect these viruses.

REFERENCES

26. Kyle JL, Harris E. Global spread and persistence of


35 **Diaollo M, Ba Y, Sall AA, Diop OM, Ndiaye JA, Mondo M, Girault L, Mathiot C.** Amplification of the sylvatic cycle of dengue virus type 2, Senegal, Mondo M, Girault L, Mathiot C. *Amplification of* *Diallo M, Ba Y, Sall AA, Diop OM, Ndione JA,* *408.*


