The risks to Australia from emerging and exotic arboviruses

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The recent pandemic spread of mosquito-borne arboviruses across multiple continents, as exemplified by West Nile (WNV)[1], chikungunya (CHIKV)[2], and Zika (ZIKV)[3] viruses, together with the continuing disease burden of epidemic dengue viruses (DENVs)[1], multiple importations of yellow fever virus (YFV) into populous areas of Asia[4], and the potential threat of some other, possibly unknown, emerging arboviral threat, constitute a wake-up call for governments to strengthen surveillance programmes and enhance research into mosquito-transmitted diseases[5–7]. Rift Valley fever[8] (RVFV) and Japanese encephalitis[1,9] (JEV) viruses are also important examples of threats to human and/or livestock health. Australia is vulnerable to these arboviral diseases, with risk of importation and outbreak potential varying between viruses[10]. The risk of exotic arboviral diseases establishing transmission cycles in Australia is dependent on the availability of competent vectors and suitable vertebrate hosts. Therefore, knowledge of the vector competence of Australian mosquito species for exotic arboviruses, potential for the introduction and establishment of exotic vector species, and suitability of vertebrate hosts, are essential components of understanding and mitigating these arboviral threats.

Mechanisms of emergence and spread

The factors involved in the emergence and spread of these viruses are complex and multi-factorial, but are clearly associated with human influences, such as unchecked urbanisation and changes in land use, inadequate water and waste management that leads to a proliferation of larval habitats, as well as increased global movement of humans and trade through air and sea travel[1,11]. Importation of arboviruses can occur via viraemic travellers, or by the introduction of infected mosquitoes on aircraft or other vessels[1]. Virus dissemination can also occur through the movement of vertebrate hosts, such as birds and bats, or infected mosquitoes transported by wind currents.

Vectors and vertebrate hosts of endemic arboviruses, and introduction of exotic vector species

Over 75 arboviruses occur in Australia[12], although relatively few are human or animal pathogens. Transmission cycles of endemic pathogenic viruses inform the likelihood that their vertebrate hosts and vector species may participate in transmission cycles of exotic viruses. This is the case of WNV[13] and probably JEV[14], viruses related to Murray Valley encephalitis virus, for which wading birds and *Culex annulirostris* are important hosts and vectors, respectively.

YFV, DENV, ZIKV and CHIKV have developed human-to-human transmission cycles predominately involving urban *Aedes aegypti* and, in some cases, *A. albopictus* transmission. *A. aegypti* is currently restricted to northern Queensland, but was historically widely distributed in Western Australia and New South Wales[15]. *A. albopictus* is currently absent from mainland Australia, but was recognised in the Torres Strait (TS) in 2005 and, due to a very effective control strategy, has been prevented from spreading to the mainland[16]. In addition to exotic viruses, *A. albopictus* may also become involved in transmission of endemic Australian alphaviruses, Ross River and Barmah Forest viruses[17]. There is an ongoing risk of these two species expanding their range in Australia or being introduced from overseas by air or sea transport. To help mitigate the risk, active surveillance is in place at international seaports and airports to detect introductions (see Sly and Mack, this issue).

Exotic arboviruses: specific examples

The exotic viruses believed to present a potential threat to Australia are described briefly below. YFV, DENV, JEV, WNV and ZIKV are all flaviviruses; CHIKV is an alphavirus; and RVFV is a bunyavirus.

Yellow fever virus

Recent epidemic activity of YFV in Africa and South America, and the importation of cases of YFV into China from Angola[4], have highlighted the vulnerability of SE Asia and Oceania to the introduction of YFV[18]. Vector competence studies with Australian mosquitoes have confirmed that Australian *A. aegypti* are efficient vectors of YFV, but of greater concern, have shown that *A. notoscriptus*, a relatively common species found widely across Australia, including urban areas, may also be a potential vector for both African and South American strains of YFV[19]. Why YFV has not emerged in Asia previously remains an enigma, but with a susceptible population of two billion people and extremely limited infrastructure to respond effectively[18], the risks of emergence are enormous, presenting an increased threat to Australia. It is essential that surveillance of incoming travellers from endemic areas and the requirement for current YFV vaccination is maintained to reduce the risk of a viraemic traveller introducing the virus into receptive areas, particularly north Queensland.

West Nile virus

The risk of an exotic and pathogenic strain of WNV entering Australia are believed to be low[20,21]. The nearest land mass with a pathogenic strain of WNV is the United States, so the most likely route of introduction would be via an infected mosquito carried on aircraft. Current disinsection procedures for aircraft make this unlikely. Nevertheless, endemic Australian mosquito species are competent WNV vectors[22], and Australian avifauna would almost certainly be able to participate in transmission cycles.

Japanese encephalitis virus

JEV is widely dispersed across southern and eastern Asia, including Indonesia, and PNG[9]. Outbreaks of JEV have occurred in Australia, with human cases and widespread swine infection in the TS, and on Cape York Peninsula[9,14]. Sentinel pig and mosquito surveillance conducted between 1995 and 2005 suggested that the virus had become endemic in the TS, but not on mainland Australia[14]. Its inability to become established on the mainland may be due to the presence of different lineages of *C. annulirostris*, which vary in vector competence or limited mosquito feeding on pigs, which are major JEV hosts[14]. However, this may not reflect the potential for establishment elsewhere in northern Australia. There is little doubt that JEV remains a threat to human and animal health in northern Australia.

Dengue viruses

There are four distinct, but closely related, serotypes of the virus that cause dengue (DENV-1, DENV-2, DENV-3 and DENV-4). It is estimated that there are 390 million DENV infections annually around the world, of which 100 million are symptomatic[5]. The highest burden of disease is in Asia, which accounts for 70% of infections[23]. The disease is now endemic in more than 100 countries in tropical and subtropical regions of the world, and is the most common arbovirus disease of humans. Australia has had regular outbreaks of DENVs in north Queensland over the past three decades, each initiated by an infected traveller to the region. This is discussed in more detail in an accompanying article (see paper by Pyke, this issue). Dengue is the most common arboviral disease imported into Australia by travellers.

Zika virus

ZIKV emerged from obscurity in 2007 with an outbreak on Yap in the Federated States of Micronesia[3,24] (see paper by Jamal I-ching Sam, this issue). Previously described as a mild self-limiting fever, ZIKV has become associated with major complications, including foetal developmental defects and Guillain-Barré syndrome in adults. ZIKV then appeared in French Polynesia in 2013–14 where severe complications were first reported. In 2015, the virus jumped from the Pacific to Brazil causing a widespread epidemic which involved large numbers of microcephaly cases. The epidemic spread to other countries and peaked in 2016, when it was declared a public health emergency of international concern (PHEIC) by the World Health Organization (WHO)[24,25]. In April 2017, WHO reported 84 countries or territories with current or previous ZIKV transmission[24]. Of Australian mosquitoes, *A. aegypti* is the primary potential vector, so the receptive zone is restricted to north Queensland[26]. However, multiple non-vector routes of transmission have been reported for ZIKV[27]. Of these, sexual transmission is of particular concern with respect to assessing risk of entry of ZIKV, particularly because live virus can persist in semen for over 60 days[27].

Chikungunya virus

CHIKV causes a rapid-onset febrile illness characterised by moderate to severe joint pain, and is often mistaken for dengue.

Three related lineages occur: the East, Central and South Africa lineage (ECSAL), the Asian lineage (AL), and most recently, the Indian Ocean lineage (IOL)[2]. Since 2004, all lineages have shown a propensity to spread and establish in new areas[2,25]. The epidemic vector is *A. aegypti*. However, a mutation in the E1 envelope glycoprotein gene in a circulating ECSAL strain in East Africa around 2005 resulted in the ability of the virus to replicate efficiently in *A. albopictus*, giving rise to the IOL. Significant CHIKV outbreaks caused by this new lineage then occurred on Indian Ocean islands and southern and SE Asia, resulting in millions of infected persons, with infected travellers spreading the virus to many regions of the world, including Italy in 2007 and southern France in 2011. The AL spread from SE Asia or Oceania to the Caribbean in 2013, followed by much of Central and South America. CHIKV-infected travellers have frequently imported the virus into Australia, although there has been no evidence of local transmission[28]. Despite native Australian species, particularly *A. vigilax*, *A. procax*, and *Coquillettidia linealis*, being highly competent vectors[29], the blood feeding behaviour of *A.aegypti* and *A. albopictus*, incriminates these two species as the primary CHIKV vectors[30].

Rift Valley fever virus

RVFV infection of sheep and cattle causes severe and often fatal illness, which can occasionally result in spill over infection of other domestic animals and humans. In 1–2% of infected humans, severe disease manifestations occur, including hepatitis, encephalitis, retinitis, blindness, and/or a haemorrhagic fever; the case fatality rate is approximately 10–20%[8]. The combination of competent vectors in many countries, high level viraemia in domestic animals, and globalisation of travel and trade, make RVFV a considerable worldwide threat to both human and animal health. This was exemplified in 2000-01, when RVFV spread out of Africa for the first time to cause a major epidemic in the Arabian Peninsula. While the risk of RVFV introduction to Australia is low, importation via an infected human could occur, and several mosquito species could play a role in epidemic transmisson[31].

Other exotic viruses

There are several additional exotic arboviruses of which we need to be vigilant for, although they may not represent an immediate threat to either humans or animals. These include Tembusu[32] and related flaviviruses, which cause widespread disease in poultry in Asia, especially ducks, in China, Thailand and Malaysia; and Mayaro virus, an alphavirus from South America which is closely related to CHIKV, and appears poised for urban spread[6].

Will a novel or unexpected arbovirus emerge to surprise the world, a little like ZIKV has done? New arboviruses continue to emerge, but so far none of them have any indication of pathogenic potential. One virus which could yet cause a surprise is the flavivirus Sepik from PNG[33], the closest known virus to YFV. Only time will tell.

Conclusions

There is little doubt that exotic arboviruses constitute a significant risk to human and/or animal health in Australia. To help prevent or mitigate the consequences of their importation, it is critical that ongoing surveillance be maintained and strengthened at all levels, from border protection to human and animal health. Continued strategies to prevent the entry of *A. albopictus* and *A. aegypti* are essential, both across the TS and through border entry points. Finally, research into exotic arboviruses and their vectors needs to be supported and enhanced.

For brevity, this short review has not included the possible emergence of a hitherto unrecognised mosquito-borne arboviral disease, although novel arboviruses are regularly described in the literature. Nor have we examined additional problems associated with the arrival of infected travellers, where there is not only the risk of local virus transmission, but the also the threat to blood safety[28,34]. Similarly, establishment of a veterinary arbovirus could have implications for Australia's livestock disease-free status.

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