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Influence of Hosts on the Ecology of Arboviral Transmission: Potential Mechanisms Influencing Dengue, Murray Valley Encephalitis, and Ross River Virus in Australia

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Abstract

Ecological interactions are fundamental to the transmission of infectious disease. Arboviruses are particularly elegant examples, where rich arrays of mechanisms influence transmission between vectors and hosts. Research on host contributions to the ecology of arboviral diseases has been undertaken within multiple subdisciplines, but significant gaps in knowledge remain and multidisciplinary approaches are needed. Through our multidisciplinary review of the literature we have identified five broad areas where hosts may influence the ecology of arboviral transmission: host immunity; cross-protective immunity and antibody-dependent enhancement; host abundance; host diversity; and pathogen spillover and dispersal. Herein we discuss the known and theoretical roles of hosts within these topics and then apply this knowledge to three epidemiologically important mosquito-borne arboviruses that occur in Australia: dengue virus (DENV), Murray Valley encephalitis virus (MVEV), and Ross River virus (RRV). We argue that the underlying mechanisms by which hosts influence arboviral activity are numerous and attempts to delineate these mechanisms further are needed. Investigations that focus on hosts of vector-borne diseases are likely to be rewarding, particularly where the ecology of vectors is relatively well understood. From an applied perspective, enhanced knowledge of host influences upon vector-borne disease transmission is likely to enable better management of disease burden. Finally, we suggest a framework that may be useful to identify and determine host contributions to the ecology of arboviruses.

Key Words: Arbovirus(es)—Transmission—Vector-borne—Zoonosis—Zoonotic.

Introduction

In an era of emerging and resurging infectious diseases, understanding ecological interactions that underpin pathogen activity is critical (Russell and Kay 2004). For most emerging vector-borne diseases, scientists have identified the pathogens, vectors, and in the case of zoonoses, the primary animal reservoirs. However, owing to the challenges of studying hosts, research often neglects empirical investigations of mechanisms by which hosts influence transmission and neglects hosts not considered primary reservoirs (Keesing et al. 2006, Kuno and Chang 2005). Arboviruses are primarily zoonotic and transmission typically alternates between a single or few species of vectors and, with the exception of dengue and yellow fever, a variety of host species (Kuno and Chang 2005, Weaver 2005, 2006).

Herein we discuss both known and potential roles of hosts in arbovirus transmission and identify promising areas for future research. From an applied perspective, clarifying mechanisms whereby hosts influence the transmission of arboviruses will assist with forecasting arboviral activity, disease risk, and development of targeted strategies for disease reduction/control. We focus on the details of three epidemiologically important mosquito-borne arboviruses that occur in Australia: dengue virus (DENV; Flaviviridae: *Flavivirus*), Murray Valley encephalitis virus (MVEV; Flaviviridae: *Flavivirus*), and Ross River virus (RRV; Togaviridae: *Alphavirus*). Because ecological counterparts to these arboviruses—such as West Nile virus in the United States, Africa, and Europe; St. Louis encephalitis in the United States; and Venezuelan equine encephalomyelitis in North, South, and Central America (Hubalek 2000, Komar 2003, Kuno and

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Chang 2005)—exist elsewhere, we expect our review to be widely applicable.

Twelve mosquito-borne arboviruses, comprising three viral families (Togaviridae, Flaviviridae, and Bunyaviridae), cause human disease in Australia, with arguably the most significant being DENV, MVEV, and RRV (Russell 1995, Russell and Kay 2004). To a degree, there are shared vectors and hosts among these arboviruses (Carley et al. 1973, Gubler 1981, Harrington et al. 2001, Russell 1995, 2002, Russell and Dwyer 2000). For example: *Culex annulirostris* is a vector of MVEV and RRV; *Aedes aegypti* can potentially vector RRV and DENV; and humans are a host of all three arboviruses (Gubler 1981, Russell 1998). Despite these similarities, all three have distinctive transmission systems. While the biology of vectors has been a major focus, in all three cases, research on hosts is not as advanced.

We have identified five broad areas where hosts may influence arboviral transmission: host immunity; cross-protective immunity and antibody-dependent enhancement; host abundance; host diversity; and pathogen spillover and dispersal. For each topic area we review theoretical ideas and empirical evidence from other arboviruses, then examine the dynamics of DENV, MVEV, and RRV. We conclude with a brief summary and recommendations for future research. Our focus is primarily ecological, and humans are treated as hosts, like other vertebrate species. We define technical terms in Table 1.

Natural History

DENV

Dengue virus is the most significant arbovirus in terms of global morbidity and mortality, with humans being the only host species involved in transmission (Kuno 1995). Each year there are 50–100 million dengue fever cases and 500,000 cases of dengue hemorrhagic fever with an average fatality of 5% (20,000 deaths) (WHO 2000). Infections can be symptomatic or asymptomatic, and clinical infections take two forms: uncomplicated (nonfatal) dengue fever, and dengue hemorrhagic fever, which occurs after secondary infection and can cause mortality (Kawaguchi et al. 2003, Vaughn et al. 1997). Occasionally the latter also results in dengue shock syndrome. There are four antigenically related DENV serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) (Zanotto et al. 1996). We discuss host influences on DENV transmission in Australia and globally. In Australia, DENV cycles between humans and *Ae. aegypti* (Harrington et al. 2001). Dengue virus activity is recorded almost annually in northern Queensland, but it is not endemic (Russell and Kay 2004).

MVEV

Murray valley encephalitis virus exists in northern Australia, Papua New Guinea, and Indonesia, but is occasionally recorded in southern Australia (Johansen et al. 2007, Marshall 1988, Marshall et al. 1982c). *Culex annulirostris* is the major vector in Australia, feeding on a variety of vertebrate species (Kay et al. 1985a, van den Hurk et al. 2003). Most human MVE infections are subclinical, but clinical cases can be fatal (Mackenzie et al. 1993, Marshall 1988). Symptoms include convulsions, brainstem disease or respiratory failure in severe and fatal cases, and involvement of the spinal cord, cranial nerves, or cerebellum in moderate cases (Mackenzie et al. 1993).

RRV

Ross River virus is responsible for the greatest number of human arboviral notifications in Australia (approximately 5000 per year) and occurs across the country (Russell 2002). Three vector species principally transmit RRV—*Cx. annulirostris*, *Ae. vigilax*, and *Ae. camptorhynchus*—but other species can also be involved (Harley et al. 2001, Russell 2002). Numerous vertebrate species are fed upon by vectors of RRV (Frances et al. 2004, Gard et al. 1973, Kay et al. 2007, Ryan et

Table 1. Definitions of Arboviral Terms Used in This Paper

Term	*Definition*
Focal host	The host under consideration, often the reservoir host
Secondary host	A host species that serves as a source of infection but is less important than the reservoir host as a source of infection; often synonymous with spillover host
Amplification host	A host species that serves as a source of infection and can increase the prevalence of a circulating pathogen; often synonymous with reservoir host
Secondary amplification	Enhanced prevalence of a circulating pathogen, due to infection of a secondary host
Nonviremic transmission	Transmission of a pathogen from a host to a vector without detectable viremia in the host
Nonpropagative viremia	Presence of viruses in the blood, but without viral replication
Transmissibility	Probability a pathogen will successfully infect a susceptible host or vector upon contact
Spillover	Process by which a host species becomes infected with a pathogen, but where that host species has limited potential for indefinitely maintaining the pathogen in the population in the absence of an external source of reinfection
Seasonal forcing	Any intraspecific and interspecific interactions that respond to seasonal environmental drivers
Cross-protective immunity	A phenomenon whereby antibodies raised in response to a particular pathogen convey partial or complete immunity to other antigenically similar pathogens
Antibody-dependent enhancement	A phenomenon whereby antibodies raised in response to a particular pathogen interact with antigenically similar pathogens and facilitate infection

al. 1997, Vale et al. 1991). Symptoms of RRV disease include joint pain, joint effusion, rash, and pyrexia (Stocks et al. 1997).

Host Immunity

Vertebrate hosts depend on a combination of their innate and acquired immune systems to fight arboviral infections (Kuno and Chang 2005). Research on host immunity and arboviral ecology has tended to focus on herd immunity and host viremia. Within these research foci a number of assertions are made:

Herd immunity: abundant susceptible hosts provide permissive conditions for arboviral transmission (Scherer et al. 1959, Scott 1988); the susceptibility of juvenile hosts to infection may be enhanced because they are less defensive toward vector contact than adults are (Edman and Spielman 1988, Kale et al. 1972); where immunity wanes, a host may contribute to transmission more than once in a lifetime (Anderson and May 1982); and vertical transmission in hosts does not significantly contribute to arboviral ecology (Scott 1988).

Host viremia: viremia is generally essential to enable infection of vectors (Kuno 2001); the intensity and duration of viremia are short (generally 1–7 days), differ among arboviruses, and are variable among host species (Kuno and Chang 2005); in some cases, viremia may make hosts more attractive to vectors by influencing body temperature and respiration (Mahon and Gibbs 1982, Turell et al. 1984); nonviremic transmission (Table 1) due to vector cofeeding on hosts may contribute to transmission, but whether this is actually nonviremic or nonpropagative (Table 1) in nature remains controversial (Higgs et al. 2005, Jones et al. 1987, Lawrie et al. 2004, McGee et al. 2007, Reisen et al. 2007); and evidence of long-term infection and recurrent viremia in hosts is widespread among arboviruses (Kuno 2001).

DENV

Declines in DENV transmission have been linked to increased population immunity. For example, notifications during an outbreak in Trinidad declined from 5.05/1000 people to 0.49/1000 post-outbreak (Chadee et al. 2007). Conversely, vector control in Singapore resulted in decreased population immunity and increased dengue fever and hemorrhagic fever outbreaks (Egger et al. 2008, Kuno 1995). Transmission of DENV can be cyclical and this may be partially explained by host immunity (but also by vector abundance). For example, immunity of humans is suggested to partially account for alternating patterns in DENV serotypes and epidemics in Bangkok (Adams et al. 2006).

Susceptibility to dengue infection is independent of host age (Kuno 1995). Infection with one serotype leads to lifelong immunity to that serotype, but not necessarily other DENV serotypes (Gubler 1998, Gubler and Kuno 1997). Potentially a person can obtain up to four dengue infections in a lifetime (see Cross-protective immunity and antibody-dependent enhancement) (Mackenzie et al. 2004). In children, viremia lasts 1–7 days, and has a longer duration associated with a primary infection than with a secondary infection (Vaughn et al. 1997).

Nonviremic transmission of DENV is undocumented. Whether vectors are differentially attracted to infected hosts is also unknown. Persistence of DENV IgM and IgA antibodies in tissues (8.5 and 6 months, respectively) has been observed (Chen et al. 1991, Summers et al. 1984), but long-term infections have not been reported.

MVEV

Antibodies to MVEV have been detected in many vertebrate species, including ciconiiforms (herons and egrets), pelecaniforms, placental and marsupial mammals (Anderson et al. 1952, Boyle et al. 1983b, Fraser et al. 1986, Gard et al. 1976, Kay et al. 1987a, Liehne et al. 1976, Marshall et al. 1982a). Ciconiiforms appear to be the reservoirs of MVEV, owing to high antibody prevalence, association with human clinical cases, infection studies, relatively rapid reproductive rates, and consequent generation of susceptible hosts (Anderson et al. 1952, Boyle et al. 1983a, 1983b, Broom et al. 2002, 2003, Marshall 1988, Russell 1995). While studies indicate MVEV is not vertically transmitted in mice (Aaskov et al. 1981a), it is unknown if vertical transmission occurs in other host species.

Host age and immunological influences on MVEV transmission remain understudied. Age-related susceptibility to MVEV infection has not been demonstrated, but does occur for hosts of some flaviviruses (Kuno and Chang 2005). MVEV activity has been associated with avian and mammalian immunity (Broom et al. 1995, Marshall 1988, Marshall et al. 1982c). For example, following epidemic activity in 1974–1975, antibody prevalence rates in ciconiiforms were 44% and 96% for juvenile and adult birds, respectively; in the 2 years following the epidemic, antibody prevalence among waterbirds remained high while human clinical cases ceased (Marshall et al. 1982a). In another supporting example, human infection rates were high (50%) in southeast Kimberley following rainfall in 1993, but low in the following year despite high rainfall (see Pathogen spillover and dispersal) (Broom et al. 2002, 2003). Research on host immunity and MVEV activity may be complicated where other flaviviruses cocirculate (see Cross-protective immunity and antibody-dependent enhancement). The possibility of inherited resistance among some host species should also be considered (Sangster et al. 1998).

Viremia in ciconiiforms lasts 3–5 days, with maximum viral titer tending to be higher in younger birds (1983a) challenged herons with secondary homologous infection up to 152 days after initial infection, without detecting a second viremia. However, Marshall (1988) speculated that, due to the long lifespan of herons in nature and waning of antibodies, a second viremia may still be possible. Thus, seronegative ciconiiforms may not necessarily indicate lack of past exposure, suggesting serosurveys may underestimate previous MVEV activity. Investigations of the competence of probable secondary hosts (Table 1) found that galahs, sulfur-crested cockatoos, corellas, and black ducks produced moderate viremias for 1–9 days, and infected 0%–50% of feeding *Cx. annulirostris* (Kay et al. 1985b). Horses maintained a trace viremia for 1–5 days with 2% of *Cx. annulirostris* becoming infected (Kay et al. 1987a). Western gray kangaroos and rabbits developed high levels of viremia in most individuals, infecting 0%–22% of *Cx. annulirostris* (Kay et al. 1985c). Pigs, dogs, and chickens developed moderate viremia, in some instances, and up to 5% of *Cx. annulirostris* became infected (Kay et al. 1985c). Calves, lambs, and agile

wallabies occasionally developed weak viremia, infecting 0%–11% of *Cx. annulirostris* (Kay et al. 1985c). Wild mice also developed a low-grade viremia for 1–4 days (Kay et al. 1985b).

It is unknown if viremia to MVEV influences host attractiveness or defensive behavior toward vectors, and this warrants investigation. Certainly ciconiiforms exhibit defensive behaviors toward biting mosquitoes (Webber and Edman 1972). Additionally, transmission of MVEV without detectable viremia has been observed in western gray kangaroos, agile wallabies, and chickens (Kay et al. 1985c, Maguire and Miles 1965, Marshall 1988). This may contribute to MVEV transmission and be nonviremic or nonpropagative in nature, but the relative importance of this phenomenon is unknown. It is also unknown if persistent infections of hosts occur in nature. Murray Valley encephalitis virus was detected in tissues of immunosuppressed chickens 28 days after infection (Maguire and Miles 1965), suggesting that recurrent viremia and long-term infection can potentially occur in hosts.

RRV

Rising herd immunity to RRV is likely to influence viral prevalence. This occurrence could explain why fewer notifications of human disease occur in the 2–4 years following epidemics in southwest Western Australia, despite favorable weather and mosquito populations in some interepidemic years (Johansen et al. 2005, Lindsay et al. 1996, Lindsay et al. 2005). In another example, fewer than 25% of western gray kangaroos (the probable RRV reservoir) had antibodies to RRV prior to the 2003–2004 human epidemic (Lindsay et al. 2005; Gordon, unpublished data). However, >75% had seroconverted by the time the epidemic was two thirds to completion. The western gray kangaroo appears to be the reservoir of RRV in this region and decreased immunity is thought to be necessary for human epidemics (see Pathogen spillover and dispersal). The duration of immunity to RRV is undocumented, but interepidemic years in southwest Western Australia support the argument for persistent antibodies (Lindsay et al. 1996, Lindsay et al. 2005). Reductions in herd immunity of western gray kangaroos may result from either waning of immunity or replacement of immune hosts by susceptible recruits, but notwithstanding the mechanism, a loss in herd immunity appears necessary for RRV epizootics and epidemics.

Some RRV hosts, such as sheep, domestic fowl, and possibly laboratory mice, produce a detectable viremia as juveniles, but are not susceptible to infection as adults (Aaskov et al. 1981a, Marshall and Miles 1984, Spradbrow 1973, Whitehead 1969, Seay et al. 1981). This pattern of age-dependent susceptibility may be more widespread among placental mammals and birds and influential on RRV transmission, but has not been studied. For example, RRV transmission may predominate when juvenile recruitment is high. It is unknown whether innate or age-dependent susceptibility occurs in marsupials, or if maternal immunity can be passed to offspring.

The infection of hosts, immune responses, and antibody prevalence to RRV have been studied in a variety of placental mammals, marsupials, and birds and reviewed elsewhere (see Harley et al. 2001, Russell 2002 and references therein). The main conclusions are: marsupials, particularly macropods, have the longest and most intense viremia and high antibody prevalence; placental mammals vary in their competence for RRV, but are generally less competent that marsupials (flying foxes, rodents, horses, juvenile sheep, and pigs have moderate competence); and birds generally develop low or no viremia, but have not been studied extensively (Azuolas 1998, Boyd et al. 2001, Boyd and Kay 2002, Kay and Aaskov 1989, Kay et al. 1987a, Marshall and Miles 1984, Ryan et al. 1997, Spradbrow 1973, Whitehead 1969). Additionally, recent research suggests fecund vertebrates, such as mice, may contribute to RRV transmission (Carver et al. 2008, Glass 2005). It is unknown if viremia makes hosts more attractive to questing vectors.

Transmission of RRV without detectable viremia has been observed in horses and flying foxes (Kay et al. 1987a, Ryan et al. 1997), which may be nonviremic or nonpropagative. Persistence of symptoms and IgM antibodies for up to 8 years, and persistence of nucleic acid in synovial fluid, have been recorded in humans (Kapeleris et al. 1996, Soden et al. 2000), but long-term infection or recurrent viremia have not.

Cross-Protective Immunity and Antibody-Dependent Enhancement

In a virally induced acquired immune response, a host produces antibodies that can confer cross-protective immunity (Table 1) to other strains of that virus or antigenically related viruses (Kuno and Chang 2005). For example, antibodies confer cross protection for Sindbis and Semliki viruses in mice (Carballal et al. 1987). The degree of cross-protective immunity among hosts varies between viruses, the order in which hosts are exposed to multiple viruses and, most likely, host species. For example, Lassa virus protected 70% of mice against Mozambique virus with 45% of mice protected in reverse order of exposure (Barkor and Lukashevich 1989). Furthermore, immunization of bonnet macaques with Japanese encephalitis virus protects against West Nile virus, but not in the reverse (Goverdhan et al. 1992). By extrapolating these results, cross-protective immunity may influence viral transmission where arboviruses cocirculate.

Antibody-dependent enhancement (Table 1) contrasts with cross-protective immunity, as some viruses utilize antibody presence to facilitate their uptake into cells, promoting infection. Hawkes (1964) demonstrated antibody-dependent enhancement following MVEV and West Nile virus infection, but could not offer an explanation. Halstead and coworkers found antibody-dependent enhancement also occurred between DENV serotypes (Halstead et al. 1973, Halstead and O'Rourke 1977). Antibody-dependent enhancement has been found in Japanese encephalitis (Gould and Buckley 1989, Peiris and Porterfield 1979), West Nile (Peiris and Porterfield 1979), yellow fever (Gould and Buckley 1989, Gould et al. 1987), Potiskum (Fagbami et al. 1987), and tick-borne encephalitis (Phillpotts et al. 1985) viruses. Modeling suggests that such enhanced disease transmission and mortality of hosts should maintain coexistence of distinct viral serotypes or antigenically related species (Adams et al. 2006, Gubler and Kuno 1997, Kawaguchi et al. 2003). Therefore, antibody-dependent enhancement could potentially be a mechanism of arboviral mutualism, whereby multiple re-

lated serotypes or antigenically similar species avoid competition for susceptible hosts (unlike cross-protective immunity) and cocirculate. For example, Fagbami et al. (1988) demonstrated coexistence of multiple flavivirus antibodies (DENV-2, yellow fever and West Nile virus) in human sera from Nigeria and that these antibodies enhanced infection of one another.

DENV

There are large genetic and immunological distances between the four DENV serotypes and little or no cross-protective immunity (Halstead et al. 1973, Kuno 1995). However, some modeling has suggested persistent phases of epidemics between serotypes in Bangkok may result from moderate cross-protective immunity (Adams et al. 2006, Wearing and Rohani 2006). Primary infection with a DENV serotype induces a monotypic antibody response (Kuno 1995). Subsequent infection with a different serotype leads to a massive anamnestic response, with high antibody titers that cross-react with other serotypes and flaviviruses (Fagbami et al. 1988, Hawkes 1964, Kliks et al. 1988, Kuno 1995). Dengue hemorrhagic fever is thought to be predominantly due to antibody-dependent enhancement (Kuno 1995, Monath 1986). Maternal transfer of IgG antibodies via the placenta influences the susceptibility of newborns and children to antibody-dependent enhancement and hemorrhagic fever (Deparis et al. 1998a,b, Kliks et al. 1988, Qui et al. 1993).

Multiple DENV serotypes have been introduced to Australia (Russell 1995, Russell and Dwyer 2000). Potential exists for the occurrence of antibody-dependent enhancement in areas where DENV has previously been active. Indeed, in 2004 a fatal case of dengue hemorrhagic fever occurred on Thursday Island in the Torres Strait (Hanna et al. 2001). Potential exists for DENV activity to be influenced by the activity of other flaviviruses in Australia, such as infection of hosts previously exposed to MVEV or Kunjin, but the significance of risk has not been assessed.

MVEV

Antibody-dependent enhancement is observed for MVEV in mice previously exposed to subneutralizing concentrations of heterologous Japanese encephalitis antiserum and, in reverse, occurs for Japanese encephalitis when mice are immunized with killed MVEV (Lobigs et al. 2003, Wallace et al. 2003). In both cases, enhanced viremia and mortality of mice were observed. If increased viremia occurs in nature and in other host species, antibody-dependent enhancement could potentially affect transmission of MVEV in Australia. This could occur where Japanese encephalitis periodically occurs or where other enzootic or introduced flaviviruses, such as Kunjin or DENV, cocirculate (Johansen et al. 2003, Mackenzie et al. 1998). Conversely, Williams et al. (2001) observed that pigs primarily exposed to MVEV or Kunjin virus did not exhibit antibody-dependent enhancement when challenged with Japanese encephalitis virus, probably due to cross-protecting antibodies. Lobigs et al. (2003) also found that a vaccine composed of MVEV structural proteins could induce cross-protective immunity to Japanese encephalitis virus. Research on the potential and incidence of antibody-dependent enhancement and cross-protective immunity on MVEV activity in Australia is warranted. It is possible antibody-dependent enhancement may partially account for cocirculation of MVEV and other similar arboviruses, such as Kunjin virus, but this hypothesis has not been examined.

RRV

Spradbrow (1973) demonstrated pig RRV antibodies cross-neutralized with Getah virus, but neither pig nor sheep RRV antibodies cross-neutralized with Sindbis virus. However, there is no known role of cross-protective immunity or antibody-dependent enhancement for RRV in nature. Cocirculation of RRV with other alphaviruses occurs in Australia. For example, RRV and Barmah Forest virus circulate in southwest Western Australia (Lindsay et al. 1995a, 1995b, Lindsay et al. 2005). Cross-protective immunity may influence RRV activity where other alphaviruses cocirculate, but research is required to more widely establish cross-protective immunity between RRV and other alphaviruses,and its occurrence in nature. Antibody-dependent enhancement has not been documented in alphaviruses.

Host Abundance

Vector contact rates with hosts are generally a function of host abundance (2001) found that transmission of Buggy Creek virus was related to the size of cliff swallow colonies, and Shaman (2007) used modeling to demonstrate that clustering of hosts positively influenced transmission of arboviruses, such as West Nile virus. Seasonal forcing (Table 1) is arguably the most pervasive influence of nonhuman host abundance (Altizer et al. 2006, White et al. 1996). For example, seasonal breeding of herons in Japan influences transmission of Japanese encephalitis virus by introducing pulses of susceptible hosts to feeding mosquitoes (Scherer et al. 1959). Small hosts have high birth and death rates, exhibit short life cycles, and respond quickly to seasonal forcing, whereas large-bodied, long-lived hosts have lower birth and death rates and longer cycles arising from seasonal forcing (Altizer et al. 2006, Carver et al. 2008, Glass 2005). Reviews also suggest seasonal forcing may influence immune function and pathogen transmission (Dowell et al. 2003, Nelson et al. 2002). For example, seasonal shortages in resources may incite stress and compromise a host's ability to immunologically respond against a pathogen. While this is an accepted theory, published evidence in arboviral transmission is lacking.

Transmission can be driven by host density or frequency of contact between pathogen and hosts (Dobson 2004). Density-dependent transmission occurs when transmission rates increase with increasing density of infected hosts. This assumes mixing and contact of hosts, vectors, and pathogens are essentially random. Frequency-dependent transmission occurs when transmission rates increase with the total proportion of the population that is infected (Dobson 2004). Typically this is where transmission is likely to be a saturating function of host density, due to an inability to transmit beyond a certain rate (Dobson et al. 2006). Naturally all transmission systems are likely to have frequency-dependent properties, but comparisons of systems, under this theoretical construct, are likely to produce a type of continuum between density-dependent and frequency-dependent transmission. Arboviruses tend to display frequency-dependent transmission, because transmission is tied to vector repro-

duction (Dobson 2004, Dobson et al. 2006). For example, vectors obtain blood meals to provide protein for egg production and host seeking is limited by the reproductive cycle of the vector. Beyond a threshold density, vectors will only contact a host at the rate of their reproductive cycle.

DENV

Human abundance (urbanization) is a key factor attributed to increases in DENV activity (Gubler 1998, Kuno 1995). Human population density is thought to be critical to enable sufficient contact with vectors for dengue to persist (Morlan and Hays 1958, Muir and Kay 1998, Wolfinsohn and Galun 1953). The critical urban population size for ongoing DENV transmission is believed to be between 150,000 and 1,000,000 people (Kuno 1995, Wearing and Rohani 2006). In regional centers of Australia where *Ae. aegypti* and DENV activity occur, such as Townsville and Cairns, current populations are fewer than 150,000 and DENV transmission does not persist (Hanna et al. 2006). These populations are possibly insufficient to support DENV becoming endemic, although (justifiably) current vector and health intervention programs prevent this hypothesis from being evaluated. Future population growth in northern Queensland is predicted and may influence persistence of DENV in Australia. It should also be noted that another DENV vector (*Ae. albopictus*) has recently been detected on islands in the Torres Strait, and if this species establishes on mainland Australia it may influence the threshold population abundance required for persistent DENV transmission (Ritchie et al. 2006).

Compared to other arboviruses, DENV transmission is relatively density dependent. This is because *Ae. aegypti* has a partial feeding behavior, due to dependence on humans for both carbohydrates and protein (Harrington et al. 2001, Kuno 1995). Hence, multiple hosts can be exposed to DENV by the same vector in relatively short succession (density dependence) and the threshold density of hosts is likely to be relatively high before contact rates saturate.

MVEV

The abundance of many vertebrates in Australia fluctuates, particularly in association with seasonality. However, the role of host abundance on the transmission of MVEV is not well understood. It is likely that colonial nesting of avian hosts contributes to MVEV transmission (Anderson 1953, Liehne et al. 1976, Scherer et al. 1959, Whitehead et al. 1968). For example, a surge in ciconiiform breeding in the Murray Valley basin occurred just prior to an epidemic of MVE in 1974–1975 (Braithwaite and Clayton 1976, Marshall 1988). Most MVEV activity is recorded between December and June, the northern wet season (Gard et al. 1976, Kay et al. 1987b, Russell 1995). Seasonal forcing, particularly rainfall and drought, is associated with reproduction of waterbirds (and MVEV activity) (Braithwaite and Clayton 1976, Broom et al. 2003, Marshall et al. 1982a). Additionally, some mammals, such as rabbits and kangaroos, may act as amplifiers in spring (Kay et al. 1985c).

Transmission of MVEV is likely to depend on vector reproduction rates, because *Cx. annulirostris* seeks hosts primarily for protein (frequency-dependent transmission). This may have implications for the rate of transmission.

RRV

Macropods are widely abundant (Caughley et al. 1987) and their abundance is likely to play a significant role in amplification (Table 1) and epizootic activity of RRV before epidemics occur. However, it is important to acknowledge RRV transmission may also be linked to abundance of other mammal species. For example, urban RRV transmission is associated with humans, brushtail possums and horses in Brisbane (Boyd et al. 2001, Boyd and Kay 2001, Kay et al. 2007), and mice in northwest Victoria (Carver et al. 2008). Infection studies of a greater range of potential host species are required to establish which species are reservoir hosts of RRV. Furthermore, surveys of host abundance and contact rates with vectors are currently lacking.

Macropods and other potential RRV host populations respond to seasonality (Arnold et al. 1991, Carver et al. 2008, Caughley et al. 1987, Menkhorst and Knight 2001, Singleton 1989). In southern Australia, human RRV notifications are seasonal and may be related, at least partially, to seasonal forcing of host population dynamics (Gard et al. 1973, Lindsay et al. 1996, Lindsay et al. 1993a, Lindsay et al. 2005, McManus and Marshall 1986, Mudge et al. 1981, Russell and Cloonan 1989, Russell et al. 1991). For example, gray kangaroos, a hypothesized RRV reservoir, reproduce seasonally (Arnold et al. 1991, Caughley et al. 1987). In tropical Australia, seasonality is less pronounced and host population dynamics may fluctuate less. Accordingly, seasonal transmission of RRV is also less pronounced (Aaskov et al. 1981c, Harley et al. 2001, Russell 1998, 2002). The comparison of southern and northern Australia provides circumstantial support that seasonal forcing may influence hosts and RRV transmission, but empirical research on host population dynamics and associated RRV activity is needed.

Like MVEV, transmission of RRV is likely to be more frequency dependent, because the main vectors across Australia seek hosts to acquire protein for reproduction.

Host Diversity

The effect of host species diversity on pathogen transmission has received recent and insightful review. Keesing et al. (2006) determined the effect of host diversity on disease dynamics in a focal host (Table 1) is likely to depend on properties of that species relative to the community. However, the general conclusion from theoretical and empirical studies is that high diversity of hosts decreases overall disease prevalence because proportionally fewer hosts are competent (Ezenwa et al. 2006, Keesing et al. 2006). Exceptions to these generalizations are where mosquitoes predominantly feed on a single host species (i.e., DENV and yellow fever).

Manipulation of the abundance of key hosts, addition of less competent hosts, habitat modification, or other measures that alter encounter rates and the relative contribution of competent hosts is also known as the dilution effect: the net effect of species diversity reducing disease risk (Keesing et al. 2006). For example, diversity appears to have a dilution effect on the prevalence of Lyme disease in northeastern United States (LoGiudice et al. 2003) and West Nile virus (Ezenwa et al. 2006, 2007). Diverse communities of hosts tend to have proportionally more incompetent hosts than less di-

verse (Keesing et al. 2006, Ostfeld and LoGiudice 2003). Thus, proportionally more bites from vectors are occupied by inefficient reservoirs. Coupling preservation of diverse host communities with dead end hosts may therefore provide an effective mechanism for disease reduction. Dead end hosts (cattle), e.g., may explain reduced Japanese encephalitis infections in Burma and Thailand (Gould et al. 1974, Thein et al. 1988). However, it is important to keep in mind many vectors are not obligate generalists, having preferences for particular host species (Apperson et al. 2004). For example, the malaria vector *Anopheles arabiensis* prefers humans even when agricultural animals are abundant (Tirados et al. 2006), and *Ae. albopictus* prefers dogs, cats, and humans in California (Richards et al. 2006, Sardelis et al. 2002, Turell et al. 2001). Accordingly, mosquito blood meal analyses reflect: the relative density of host species to one another in the host community, mosquito feeding preferences, and the relative availability of preferred host species to feeding mosquitoes. Vector feeding preferences may enhance or reduce the dilution effect if vectors feed on incompetent or competent hosts, respectively.

While host diversity may dilute arboviral prevalence, the supply of supplementary host species may also enhance transmission if these species provide a source of infection and reinfection of vectors (Altizer et al. 2006, Keesing et al. 2006). For example, Japanese encephalitis virus and Rift Valley fever virus can be amplified in hosts in rural and urban settings (Bouloy 2001, Endy and Nisalak 2002). The effect of host diversity on vector-borne disease will partially be a consequence of whether additional hosts have equal or greater competence and/or contribute to the breeding success of vectors (by providing additional blood meal sources) (Dobson 2004, Keesing et al. 2006).

DENV

Host diversity is not known to influence transmission of DENV, because humans are the only host species and *Ae. aegypti* is anthropophilic (Kuno and Chang 2005). However, *Ae. aegypti* does feed on dogs when humans are less accessible, and cats in the laboratory (Gomes et al. 2001, Suwonkerd et al. 2006). *Aedes albopictus* is also anthropophilic, with 24% of blood meals derived from humans in North Carolina (Richards et al. 2006). Only *Ae. aegypti* currently occurs on mainland Australia (Ritchie et al. 2006). Specialization of *Ae. aegypti* for humans makes the effects of species diversity negligible.

MVEV

Culex annulirostris has a wide host range, but preferentially feeds on placental mammals and marsupials when available (Kay et al. 1985a, van den Hurk et al. 2003). This is in contrast to the reservoir status of waterbirds. Further, interspecific host competence is variable (see Host immunity), suggesting host diversity may influence MVEV transmission. During the dry season in northern Australia, when vector abundance and waterbird migration are limited, it is thought that host-vector contacts (and MVEV transmission) tend to cluster among relatively few host species (Marshall 1988, Russell 1995). During the wet season, diverse hosts come into contact with MVEV (Marshall 1988). For example, humans, birds, and cattle are frequently exposed to MVEV around the Ord river (Liehne et al. 1976). Susceptible domestic and wild mammals and birds may amplify MVEV, whereas agricultural animals, such as cattle, are likely to have a dilution effect. To establish if host diversity influences MVEV activity, studies examining arboviral activity and host diversity, in a number of endemic and epidemic areas, are required. Additionally, vector feeding preferences could be better defined by field studies combining surveys of vector blood meals, during the wet and dry season, and host community composition.

RRV

Vectors of RRV feed widely upon mammals and birds (Kay et al. 1979, 1985a, 2007, Lindsay et al. 1998) and hosts vary in their competencies (see Host immunity), suggesting host diversity may be influential over RRV transmission. For example, domestic and agricultural animals are often dead end hosts, whereas macropods appear to be reservoirs. Additionally, the switch from enzootic to epizootic and epidemic RRV activity may relate to changes in the frequency vectors feed on host species in the community. For example, increased reproduction of macropods may cause an increase in encounter rates with mosquitoes and reduction in encounters between mosquitoes and other dilution hosts. Alternatively, amplification of RRV might be observed, such as the introduction of a susceptible host population. Humans congregating in towns during summer near RRV zoonotic foci (e.g., Mandurah in Western Australia) may enable amplification (Choi et al. 2002, Lindsay et al. 1996, Lindsay et al. 1992). Research examining temporal patterns in host-vector encounter rates, community composition of hosts, vector feeding preferences, and enzootic, epizootic, and epidemic patterns of RRV is likely to yield insights on the influence of species diversity to transmission.

Pathogen Spillover and Dispersal

Dispersal of arboviruses is often attributed to mobile vectors. However, mobile hosts, such as migratory species, may have an appreciably greater influence (Gubler 2001). Spillover (Table 1) is frequently associated with pathogen dispersal (Broom et al. 2003, Endy and Nisalak 2002, Jourdain et al. 2007, Marshall et al. 1982c, Scherer et al. 1959), and for this reason arboviral dispersal and spillover are discussed together (although dispersal is not an absolute requirement for spillover). For example, Scherer et al. (1959) concluded that Japanese encephalitis was disseminated by viremic ciconiiforms from rookeries to other locations in Japan, because arrival of birds coincided with initiation of human disease incidence. Humans can facilitate the dispersal of pathogens by hosts (Gubler 2001, Kuno 1995), enabling viruses to establish in new geographic locations where susceptible hosts and vectors provide permissive conditions for epidemics.

Spillover occurs when epidemics in a host population are driven by transmission from a zoonotic or other heterospecific reservoir population (Power and Mitchell 2004). For example, West Nile virus spills over from avian hosts to humans (Turell et al. 2002). Spillover can also lead to secondary amplification (Table 1). For example, Japanese encephalitis

virus can spillover from avian reservoirs to porcine and poultry farms, and undergo secondary amplification plus further spillover to humans (Endy and Nisalak 2002).

Dispersal may also influence the transmissibility (Table 1) of arboviruses, due to pathogen contact with a greater frequency of susceptible hosts (referred to as infectivity by Boots and Mealor 2007). Virulence (defined as death rate due to infection) may also be influenced by dispersal (Boots et al. 2004, Boots and Sasaki 1999, Haraguchi and Sasaki 2000, Rand et al. 1995), but DENV, MVEV, and RRV are rarely fatal to their hosts (but see Kuno 1995, Mackenzie et al. 1993, Seay et al. 1981). The underlying theory of dispersal and transmissibility suggests that when pathogen contacts with hosts are local, pathogens with a high transmission probability will rapidly raise host population immunity and consequently become locally extinct (Boots et al. 2004, Boots and Mealor 2007). As such, local interactions promote pathogen adaptations toward reduced transmission probability, reducing the risk for local extinction. Widespread movement promotes the reverse, because a highly dispersed pathogen is likely to contact fewer hosts and accordingly a low transmissibility would increase the probability of extinction. This theory has not been tested for arboviruses, but is plausible.

DENV

Spillover of human DENV serotypes is not known to occur, and as such, spillover will not be discussed further (but see evolution/spillover of sylvatic DENV to humans: Kawaguchi et al. 2003, Moncayo et al. 2004, Wang et al. 2000, Weaver 2006, Wolfe et al. 2007). DENV is a poignant example of host-mediated dispersal. Enhanced travel, combined with duration of latency and viremia, have facilitated movement of DENV between countries (Halstead 1992, Weaver 2006). Prior to 1970, nine countries had experienced dengue hemorrhagic fever outbreaks; by 1995, this increased fourfold (Rogers et al. 2006, WHO 2002). In Australia, multiple outbreaks of DENV-1, -2, and -3 have occurred and emergence of DENV is attributed to infected travelers entering Queensland (Hanna et al. 1998, 2001, 2006, Ritchie et al. 2004, Russell and Dwyer 2000, Russell and Kay 2004). Dispersal of DENV can also take place over smaller scales. For example, movement of viremic people between residences, workplaces, and schools in Townsville and Cairns facilitated dispersal of DENV-2 in 2003–2004 (Hanna et al. 2006).

Human travel and DENV dispersal have led to the rise of DENV subtypes with greater transmissibility and epidemic potential (Twiddy et al. 2003, Wang et al. 2000). Dengue-2 and -3 appear to have the greatest epidemic potential (Gubler et al. 1978, Lanciotti et al. 1994, Messer et al. 2003, Rico-Hesse et al. 1997, Rosen 1997). Additionally, within serotypes, some strains have a greater transmission probability than others (Armstrong and Rico-Hesse 2003), which may be due to dispersal. For example, the Southeast Asian strain of DENV-2 has a greater ability to infect *Ae. aegypti* than the American strain and appears to be displacing the latter strain in America (Armstrong and Rico-Hesse 2003). Research is needed to establish if more widely dispersed dengue strains have a greater transmission probability than less dispersed strains, and if strains become more infectious when subject to increased dispersal.

MVEV

Epidemics of MVE are hypothesized to result from dispersal of ciconiiforms and spillover to humans, other birds, and mammals (Marshall et al. 1982a). For example, in 1993 an epidemic of MVE in northern Australia was hypothesized to be associated with local influxes of dispersing ciconiiforms (Broom et al. 2002, 2003, Burrow et al. 1998), and in 2000, following heavy rainfall, MVEV seroconversions in sentinel chickens spread sequentially southward, most likely due to waterbird dispersal, ultimately into southeastern Australia (Smith 2003). The durations of latency and viremia (1–2 and 3–5 days, respectively) probably assist with host dispersal of MVEV (Boyle et al. 1983a). Research examining the migratory pathways of MVEV hosts is needed to provide further support to dispersal hypotheses. Molecular evidence indicates Australian MVEV reflects frequent circulation from a constrained enzootic focus in northern Australia and is not known to result from human dispersal (Johansen et al. 2007, Lobigs et al. 1986, 1988, Mackenzie et al. 1996).

Movement and spillover data on MVEV are sparse and accordingly knowledge to what extent spillover (and possibly secondary amplification) influences MVEV activity is limited (Marshall 1988, Marshall et al. 1982a,b,c). Future research examining contact rates and contact patterns between vectors and hosts in enzootic, epizootic, and epidemic areas is a priority. A better understanding of vector-host contacts will enable predictions of how MVEV moves between waterbirds and other host species, such as humans and domesticated animals. It is possible host movement may influence the transmissibility of MVEV. Seasonally dry periods which limit dispersal of hosts and vectors (promoting local contacts between hosts and vectors) may encourage adaptations within MVEV toward reduced transmissibility. It may be feasible to measure how host movement influences MVEV transmissibility by following the temporal patterns and spatial movements of MVEV (from enzootic to epizootic or epidemic areas), trapping infectious vectors, and testing the transmissibility of isolates.

RRV

Spillover of RRV is considered likely because vectors seek blood meals from a variety of mammalian, and some avian, hosts and seroprevalence studies demonstrate that wildlife, agricultural, domestic, and human hosts are exposed to RRV (see Host immunity and Host diversity). Secondary amplification may also occur in host species, such as susceptible juvenile sheep during the lambing season (Spradbrow 1973). Furthermore, epizootic activity is likely to initiate human RRV incidence (Aaskov et al. 1981b, Lindsay et al. 1996). Lindsay et al. (2005) speculated that human–mosquito–human transmission predominates during epidemics. This is supported by observations of RRV epidemics, followed by apparent local extinction, in Perth city and Fiji, where reservoir hosts are notably absent (Aaskov et al. 1981b, Lindsay et al. 1996).

Local dispersal of RRV by macropod hosts is likely to be limited due to relatively small and fixed home ranges (Caughley et al. 1987, Priddel et al. 1988). Bats are implicated as dispersal hosts for other arboviruses, such as Japanese encephalitis virus (Ito and Saito 1952, Kuno 2001, La Motte 1958, Miura 1968), and may contribute to the dispersal of

RRV (Lindsay et al. 1993b, Mackenzie et al. 1998, Menkhorst and Knight 2001, Ryan et al. 1997). Humans are also implicated in RRV dispersal. For example, transmission of RRV in metropolitan Perth following epidemic activity farther south in Western Australia (Lindsay et al. 2005).

Across Australia, RRV strains are similar with some geographical overlaps among strains, and it is thought that incursions and overlaps among strains are due to viral dispersal (Lindsay et al. 1993b, Sammels et al. 1995). Dispersal may be mediated by air travel of viremic hosts (primarily humans, but possibly livestock, domesticated animals, and migrating bats as well) (Lindsay et al. 1993b, Mackenzie et al. 1996, Ryan et al. 1997). A supporting example of dispersal took place in 1979–1980, when RRV epidemics occurred in Fiji, American Samoa, Cook Islands, and Wallis Islands (Aaskov et al. 1981b, Faragher et al. 1985). These isolated islands were previously considered to be free of the virus until this time.

Host movement and transmissibility of RRV have not been studied. Mackenzie et al. (1996) have suggested that movement of RRV genotypes may influence the size of epidemics. Dispersal of RRV may promote adaptations that enhance transmissibility. However, some genotypes that historically were geographically isolated may simply have a greater ability to infect hosts and vectors than others (Lindsay et al. 1993b, Mackenzie et al. 1996, Sammels et al. 1995). There is evidence to suggest intrastrain variability exists in transmissibility of RRV to mice and *Ae. aegypti* (Gard et al. 1973, Taylor and Marshall 1975a,b).Whether this variation in transmissibility results from movement of RRV by hosts is unknown. Research to support or refute this idea may potentially be measured, as described for MVEV.

Recommendations for Future Research

Disease transmission is inherently an ecological process involving a network of species (Keesing et al. 2006). It is unsurprising that a rich array of mechanisms exists by which hosts may influence arboviral transmission. Much has been learned about which hosts are involved in transmission. However, knowledge of the mechanisms that govern host effects is splintered among diverse subdisciplines and understudied. Our intention therein has been to provide an interdisciplinary review of hosts and to highlight promising avenues for future research.

The mechanisms by which hosts influence DENV, MVEV, and RRV transmission in Australia warrant further investigation. This is critically important to effectively evaluate and predict patterns in disease activity and to determine optimal management and intervention. Russell and Dwyer (2000) concluded that ecology and seasonal activity of the major vectors are relatively well known in Australia, but natural arboviral cycles are more complex, requiring deeper understanding. Currently there is little public health prospect of human arboviral cases improving. Research projects examining the ecology of hosts on transmission of DENV, MVEV, and RRV are exciting challenges with promising prospects for arbovirology in Australia.

Most management practices that attempt control of arboviral transmission are aimed at vector intervention. Does this achieve the most effective outcome for reducing disease incidence? The answer to this question is likely to depend upon the individual arbovirus. Management of arboviruses through management of vertebrate hosts additionally has potential to be socially and ethically contentious, particularly when hosts may be human, large animals, native animals, and/or threatened. However, objective scientific assessments of disease management should not be abandoned for fear of igniting debate. It should be acknowledged that arboviral management may be complementary with environmental restoration and conservation (Ezenwa et al. 2006, 2007, LoGiudice et al. 2003, Ostfeld and Keesing 2000).

A challenging aspect of arbovirology is identifying and disentangling important mechanisms that influence the current state of transmission. Mechanisms described in this paper may have influences on epizootic/epidemic activity. Of equal importance, some of these mechanisms may underlie current arboviral transmission at equilibrium or low prevalence, providing conditions from which epizootic/epidemic activity can occur. We suggest the following four points may provide a useful framework (where it is not already in place) for research targeting hosts and arboviral transmission, and ultimately management: (1) identification of potential mechanisms whereby hosts influence observed patterns of viral activity; (2) modeling of identified mechanisms, and simulations of perturbations to those, to attribute their relative importance in transmission; (3) analysis of previous research and/or collection of empirical data to evaluate hypotheses from 1 and 2; and (4) where feasible, manipulation of host contributions to transmission and monitoring to determine if observed changes meet predictions.

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