Review Articles

The epidemiology of dengue infection: Harnessing past experience and current knowledge to support implementation of future control strategies

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ABSTRACT

Dengue is the most important mosquito-borne viral infection of humans. Although outbreaks of disease which are now recognized as clinically consistent with dengue have been reported for centuries, it was not until half a century ago that laboratory identification of dengue viruses as the etiological agent of febrile illness was achieved. This debilitating and sometimes fatal disease is widely distributed in >125 countries in tropical and subtropical zones of the world. Asia, South America and the Pacific Islands are hyper-epidemic regions while currently there is less prevalence in Europe, North America and Australia. The estimated global incidence ranges between 200 and 400 million clinical cases per year. While some areas of past epidemics are now considered to be under control, recent decades have witnessed an epidemic rise in dengue worldwide. Major factors facilitating expansion include climate change and increase in urbanization and international travel. Concurrently, the non-availability of an efficacious antiviral drug or vaccine and a lack of effective vector control strategies collectively make dengue a serious public health concern. Thus, it is of paramount importance to analyze the history of the spread of infection and to gain a deeper understanding of patterns of transmission in order to anticipate epidemiological trends more accurately, thereby enabling better preparedness for future outbreaks.

Key words  Aedes; control; dengue; epidemiology; transmission

INTRODUCTION

Dengue is a mosquito-transmitted viral disease. More than 2.5 billion people in the tropics and subtropics are at risk of infection\(^1\) and an estimated 390 million dengue infections occur annually in around 125 countries worldwide\(^2\) (Fig. 1). In the last 50 yr the incidence of dengue has increased almost 30 fold (Fig. 2). The etiological agent of disease is dengue virus (DENV), a member of the family Flaviviridae. Although, a large number of potential vectors have been identified, Aedes aegypti and Ae. albopictus are responsible for the majority of dengue transmission. These mosquito species are distributed throughout tropical regions of Asia, Africa, Australia, South Pacific, the Americas and some parts of the Middle East\(^3\). The World Health Organization (WHO) and Special Programme for Research and Training in Tropical Diseases (TDR) have recently revised the guidelines for dengue case classification. It categorizes clinical infection as either: Mild self-limiting illness; dengue with a wide range of warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy and increasing haematocrit with decreasing platelets); or severe dengue (dengue with severe plasma leakage, severe bleeding, or organ failure)\(^4\). Prior to this revision, infection was widely classified as dengue fever (DF), dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS)\(^5\). The unavailability of effective antiviral drugs and licensed vaccines until now,

![Fig. 1: Global distribution of dengue (World Health Organization 2014).](image)
despite decades of intensive research, makes dengue a major global public health priority. This review provides a detailed history of dengue, highlights the current epidemiological situation, and predicts future trends in transmission of infection and measures for its control.

Dengue viruses

Dengue is one of the major human pathogens of the family Flaviviridae, which also includes viruses that cause yellow fever, Japanese encephalitis and West Nile encephalitis. Four serotypes (DENV-1 to 4) have been known for years. Recently, a mooted fifth serotype has been reported\(^6\), although its recognition remains to be ratified. This was discovered during screening of virus samples which were collected during an outbreak that occurred in Malaysia in 2007\(^6\). The established four dengue viruses are similar, showing around 65% genome homology\(^7\), while the ostensible fifth serotype appears phylogenetically distinct\(^6\).

DENV is single-stranded positive sense RNA virus of approximately 50 nm in diam\(^8\). Structurally, its genome is surrounded by a capsid (C) and again by an outer glycoprotein shell and inner lipid bilayer. The similar nature of the lipid layer to the host cell membrane suggests that it is derived from the later. Surface projections in the lipid membrane consist of envelope (E) and membrane (prM/M) glycoproteins. The genome is about 11 kb in size and encodes three structural genes (C, prM and E) and seven non-structural (NS) genes (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5). The proteins coded by the NS genes play roles in viral replication and assembly\(^8\).

Dengue history: Past and present

Dengue is a historically important disease which has been known for centuries. Symptoms recorded in a Chinese medical encyclopaedia in 992 AD are compatible with recognised clinical manifestations of dengue\(^9\). This may be the first documented information relating to dengue. Several archived manuscripts reported Africa to be the origin of DENV, which as late as the 18th century was distributed to many parts of the world, due in large part to the transatlantic and African-Middle East-Asian slave trade\(^10\)-\(^12\). The principal vector, \textit{Ae. aegypti}, is also thought to have arisen in Africa\(^13\). However, its origin has been debated to be from either Africa or Asia\(^14\)-\(^15\). A strong rationale to suggest the evolution of the virus in Asia from a progenitor of African origin is the maintenance of all the serotypes in enzootic forest cycles in Africa\(^16\). Moreover, it is believed that the DENV may have originated from a forest cycle involving lower primates and canopy-dwelling mosquitoes in the Malay Peninsula\(^17\). Later, humans and/or monkeys exposed to viruses in the forest acted as carriers for its introduction to village settings where further propagation took place through transmission by peri-domestic \textit{Anopheles} mosquitoes. Finally, villagers introduced the infection to urban areas\(^18\). There are still multiple opinions relating to the origin of DENV in humans, discussion of all of which is beyond the scope of this review.

It is possible that different DENV serotypes evolved in taxonomically related mosquito species in different geographical regions. The first four recognised DENV serotypes have been documented to exist in a forest cycle in Asia, while only one (DENV-2) has been reported in Africa\(^19\), suggesting that DENV probably had an Asian origin. Moreover, serological surveys conducted in rural communities of Malaysia in the early 1950s also support the concept of Asian origin\(^12\). Regardless, by the start of the 19th century, dengue was globally widespread in tropical coastal zones as a consequence of the inadvertent transportation of both infectious mosquitoes and humans in shipping vessels to ports around the world\(^15\),\(^20\). Later, the incidence of dengue flared during World War II when troops deployed within and between countries were convoyed by sea\(^14\). Although, dengue emerged as a major public health concern only in the second half of the 20th century in many tropical and sub-tropical regions of the world, its evolutionary history shows that the time to the most recent common ancestor of all of the dengue serotypes and the time of the split of the DENV-4 lineage were during or prior to the 4th century AD\(^21\).
Global distribution

Dengue in Asia: Disruption of ecosystems, increased troop movement and rapid urbanization after World War II facilitated the spread of DENV in Asia. Discarded water storage containers for domestic purposes, surplus war equipment and other mechanised debris all served as ideal breeding habitats for *Ae. aegypti*. By 1945, Cambodia, Philippines, Thailand and Vietnam; countries that were already endemic for dengue, became hyperendemic. Isolation of all serotypes in the 1940s and 1950s in these areas led to an assumption of their earlier existence. DHF emerged in Manila, Philippines, in 1954, then in Thailand in 1958 and in Malaysia, Cambodia, Singapore and Vietnam in the 1960s. In India, the first virologically proven epidemic occurred in Kolkata and the East Coast in 1963-64. By 1988, DHF was starting to simmer in various parts of India. Cases of DHF were also reported in Karachi, Pakistan, in 1994. It has been estimated that Asia bears 70% of the global dengue burden, a figure to which India alone is calculated to contribute 34%. As India is the largest trading hub in South Asia, it is likely to be the major disseminating source of infection for neighbouring countries like Bangladesh, Bhutan, Maldives, Nepal, and Pakistan. In Bangladesh, DF was documented from the mid-1960s to the mid-1990s, but an outbreak of DHF was reported in 2000. Bhutan and Nepal reported epidemics only as recently as 2004.

Approximately, two thirds of the global population that is exposed to dengue resides in the Asia-Pacific region. Of these, around 1.3 billion people live in ten dengue-endemic countries of Southeast Asia where dengue is one of the most common causes of hospitalisation and fatalities in children. The rate of severe dengue in the region is 18 times higher than that in the Americas. A total of 1,87,333 dengue cases from the region were reported to WHO in 2010. According to WHO, dengue-risk territories are Bangladesh, Bhutan, Brunei, Cambodia, Hong Kong, India, Indonesia, Laos, Macau, Malaysia, Myanmar, Nepal, Pakistan, Philippines, Singapore, Sri Lanka, Taiwan, Thailand, and Vietnam. It is apparent that 11 countries in the WHO Southeast Asia region (Bangladesh, Bhutan, India, Indonesia, Maldives, Myanmar, Nepal, North Korea, Sri Lanka, Thailand and East Timor) have become hyper-endemic, with regular reporting of dengue cases since 2000 with the exception of North Korea. The highest ever combined totals of clinical cases (3,55,525) and deaths (1982) were recorded in 2010.

Several countries in Southeast Asia have recently reported large increase in dengue fever cases for October 2015, when compared to the same time in 2014. Notably, increases in cases were seen in Malaysia (19.4% increase), the Philippines (31.9%) and Vietnam (21.1%) when compared to the same time in 2014. A decreasing number of cases were reported for China and Cambodia. Using mathematical modelling, Cummings et al predicted that DENV in Thailand spreads at an average speed of 148 km per month, and suggested that similar rates of range increase may be expected elsewhere. Despite a major outbreak in western Japan between 1942 and 1945, it was thought that Japan was subsequently a dengue risk-free country. However, according to the national case-based surveillance system of Japan, the reported DENV incidence was 200 in 2010, four times greater than that in 2006. While these cases were, in fact, associated with travelers, the combined effect of the persistence of *Ae. albopictus* and globalization has always posed a threat of possible outbreaks in Japan.

Dengue in Australia: Dengue appeared in Australia in 1873 with the importation of eight cases from Mauritius. Subsequent outbreaks occurred in what is now Queensland, in Townsville (1879) and Rockhampton (1885). The first death caused by dengue was recorded in Charters Towers in 1885. Since then there have been at least 13 major dengue outbreaks in Queensland. Dengue reached Brisbane in 1905. Cases were also reported in northern New South Wales (1898) and Western Australia (1909-10). In 1925-26, the epidemic extended as far south as Newcastle, New South Wales. No cases have been reported in Western Australia since the 1940s. The last epidemic in the Northern Territory (Darwin) occurred in 1955.

The widely distributed vector of dengue in Australia is *Ae. aegypti*, which may have been introduced inadvertently in the early or mid-19th century with the settlement of the tropics and subtropics. By the end of the 19th century, this mosquito dispersed extensively in northeast coastal areas. Later, due to the successful implementation of vector control interventions, the *Ae. aegypti* population as well as the disease it transmits declined from northern New South Wales and Western Australia. In contrast, Darwin in the Northern Territory and Cairns and Townsville in the tropical north of Queensland have always remained at risk of dengue outbreak. A multi-sectoral approach has led to the progressive decline of *Ae. aegypti* from Australia. This strategy includes the conversion of urban water supplies from household rainwater tanks to a reticulated supply, the change from steam to diesel locomotives, the use of domestic insecticides, the advent of the motor mower, and greater awareness by local environmental health officers promoting improved...
education of the general public\textsuperscript{39, 42}. Although \textit{Ae. albopictus} is not the principal vector of dengue in Australia, it is widespread in the northern Torres Strait Islands. This mosquito is thought to have been introduced into the Australasian region by widespread illegal fishing activity originating from Indonesia\textsuperscript{43}.

Following a quarter of a century without incidence, dengue re-emerged in northern Queensland in 1981–82. Unlike a previous epidemic in the same region and in neighbouring Northern Territory in 1955, which was caused by DENV-3\textsuperscript{44}, this outbreak was due to DENV-1\textsuperscript{45–46}. Cairns, Townsville and Thursday Island were affected by this epidemic. Further to this, DENV-1 and -2 cases were reported sporadically during 1990–93\textsuperscript{39}. In the most recent Queensland epidemic of 1993, 238 serologically positive cases of DF and one case of DHF were identified while outbreaks of DENV-2 centred on Townsville and in Charters Towers with 1,850 clinically suspected and laboratory confirmed cases were reported among around 2,00,000 inhabitants of these regional towns\textsuperscript{47–49}.

Dengue is a major cause of illness for overseas travellers returning to Australia. The majority of cases identified in Australia were related to a travel history to Indonesia (Bali), Thailand, East Timor and Papua New Guinea\textsuperscript{50}. The main concern arising from such imported cases is the infected person potentially providing a focus for local transmission. The number of overseas-acquired cases of dengue, almost 10 times higher than locally acquired, continues to increase each year: 350 in 2007–08; 593 in 2009–10; 1133 in 2010–11; 1390 in 2011–12\textsuperscript{51}.

A 14-yr retrospective study (1999–2012) showed that over half of all cases with a known country of acquisition originated in Indonesia\textsuperscript{52}. For Western Australia, in 2010–11, >80\% of cases from Indonesia were acquired in the popular holiday destination of Bali, a trend which continued in 2012\textsuperscript{53}. During 2000–11 the relative risk of travellers returning to Australia with dengue from Indonesia compared to all other destinations was 8.3\textsuperscript{52}.

\textbf{Dengue in the Pacific Islands:} Dengue epidemics were first reported in the Pacific Islands during the second half of the 19th century\textsuperscript{54}. There has been a recent increase in dengue cases in many Pacific Islands including the Cook Islands, French Polynesia, Fiji, New Caledonia, Samoa, Tonga and Vanuatu\textsuperscript{54}. With reference to current data (April 2015), there is an ongoing DENV-2 outbreak in Macuata Province, Fiji. In French Polynesia and Tonga, incidences of DENV-1 and DENV-3 have been notified, respectively\textsuperscript{55}. There were frequent outbreaks reported from French Polynesia and Tahiti in 1996–7\textsuperscript{56}, and from French Polynesia and the Solomon Islands in 2013\textsuperscript{57}. Unlike for inhabitants of Southeast Asian countries, it is rare for more than one serotype to circulate in Pacific Islanders. However, to date, all four established serotypes have been identified within the population. The pattern of single serotype circulation was DENV-3 (1989–96), DENV-2 (1996–2000), DENV-1 (2001–09), and DENV-4 (2008–09)\textsuperscript{56}. The main reason for outbreaks of dengue in these geographically isolated islands is international and inter-island travel\textsuperscript{56}. Post World War II was the most prevalent period for occurrence of dengue in countries of this region.

\textbf{Dengue in Africa:} As far back as the 19th and early 20th centuries, dengue was recorded in a number of geographically widespread African countries: Zanzibar (1823, 1870); Egypt (1887, 1927); Burkina Faso (1925); South Africa (1926–27); and Senegal (1927–28). These dengue cases were confirmed by neutralizing antibody tests performed in the mid 1950s\textsuperscript{58–59}. Since 1960, 20 laboratory-confirmed outbreaks of dengue have been reported in 15 African nations, with most occurring in East Africa. Nearly 300,000 cases were reported in the five largest epidemics in the Seychelles (1977–7900), Réunion Island (1977–78), Djibouti (1992–93), Comoros (1992–93) and Cape Verde (2009)\textsuperscript{59–60}. Five countries in North Africa (Algeria, Libya, Morocco, Tunisia and Western Sahara), from which the vectors have yet to be clearly identified, are considered to be at low risk for dengue\textsuperscript{61}.

The first laboratory isolated dengue virus in Africa was from Nigeria in 1964\textsuperscript{62}. All four established DENV serotypes have been isolated, with DENV-2 reported to cause most epidemics\textsuperscript{61}. These serotypes are maintained in enzootic cycles, most likely between non-human primates and arboreal mosquitoes\textsuperscript{8, 63}. Outbreaks in Pemba, Mozambique during 1984–85 were due to DENV-3. This was also detected in Somalia and the area around the Persian Gulf in 1993. Although occurring infrequently, DENV-4 was isolated from Senegal in the 1980s. Other than \textit{Ae. aegypti} and \textit{Ae. albopictus}, common vectors in Africa are \textit{Ae. africanus} and \textit{Ae. luteocephalus}\textsuperscript{61}. There are 34 countries across all regions of Africa that are endemic for dengue. The remaining 12 nations have identified dengue cases among travelers returned from endemic zones\textsuperscript{64}. In the last few years, infection with DENV-3 has been reported in travellers returning to Europe from several West African countries (Benin, Burkina Faso, Ivory Coast, Mali, and Senegal)\textsuperscript{65}.

Although, the enzootic forms of DENV may be becoming less infective in Africa, there is still a potential for endemic forms of the virus to emerge from sylvatic
cycles between mosquitoes and non-human primates. It is acknowledged that poor diagnostic facilities may have prevented the exact prevalence of dengue in African countries from being revealed.

**Dengue in Europe:** Europe is a continent with relatively less or no prevalence for dengue infection. In general, cases reported in Europe are usually associated with return travel from another region. According to the European Centre for Disease Prevention and Control (ECDC), Europe has not experienced sustained transmission of DF since outbreaks in Athens in the late 1920s, with the exception of a large outbreak of DENV-1 infection in 2012 which occurred on the Portuguese autonomous region of the Madeira Islands in the Atlantic Ocean, to the east of Morocco, from October 2012 to March 2013, resulting in over 2100 cases. This outbreak resulted in 78 active dengue fever cases being introduced into 13 other European countries via travelers departing Madeira. A total of 42 cases imported from this Madeira outbreak were reported in the UK and Germany alone. Due to recent changes in climate and temperatures, the environment across Europe has become increasingly favourable for mosquito breeding; hence, the distribution of Ae. aegypti has increased. This provides the potential for future dengue outbreaks in Europe. Although, Ae. aegypti is the predominant vector, Ae. albopictus has also become established in Europe. Several domestic incidences of dengue due to Ae. albopictus transmission have been noted in France and Croatia. The occurrence of this mosquito was reported initially in Albania in 1979, then in Italy in 1990. At present, this mosquito is established in southeastern France (including Corsica), the eastern coast of Spain, most of Italy (including Sardinia and Sicily), southern Switzerland, Slovenia, Malta, San Marino, Vatican City, Croatia, Bosnia and Herzegovina, Montenegro and Albania. Serbia, the western coast of Greece, southeastern Bulgaria and western Turkey. It has also been detected, in imported used tyres in Belgium and the Netherlands and in green houses in the Netherlands.

**Dengue in North America:** Dengue is an emerging infection in North America. Travel-associated dengue infections have been reported in each of the 48 contiguous states of USA. Since, the vector Ae. aegypti is abundant all year around in Puerto Rico, the US Virgin Islands, American Samoa and Guam, these territories are endemic for DENV. This has presented a particular challenge in Puerto Rico, where outbreaks have been recorded for one hundred years, and for which since the late 1960s large island-wide epidemics have been documented. The virus, DENV-3 serotype, was first isolated from Puerto Rico during a large outbreak in 1963–64. The first case of DHF was documented in 1975, with notifications more frequent after 1986. Prior to this time, dengue transmission had been significantly interrupted during the 1960s and early 1970s following an Ae. aegypti eradication campaign in the Americas. However, re-infestation of mosquitoes and periodic outbreaks of dengue occurred in the Caribbean, Mexico and Central America because of poor vector surveillance and control measures. By 2005, locally acquired outbreaks had been described in Hawaii, US Virgin Islands, along the Texas-Mexico border, and in the western part of Florida.

**Dengue in South and Central America:** Reports of dengue have come from most countries in South and Central America. Argentina, Brazil, Colombia, Dominican Republic, El Salvador, Guatemala, French Guyana, Mexico, Peru, Puerto Rico and Venezuela are nations in which infections of all four established DENV serotypes have been recorded. Chile and Uruguay are the only countries in Latin America without indigenous transmission of any serotype. There was partial interruption of dengue during the 1960s and early 1970s as a consequence of the Ae. aegypti mosquito eradication campaign designed to prevent yellow fever. However, poor vector surveillance and control measures enabled mosquito re-infestations and hence reintroduction of dengue, notably DENV-2, in these regions. In the late-70s and early-80s, DENV-1 and DENV-4 were introduced into some Latin American and Caribbean countries, causing devastating epidemics. Since then, the region has reported the highest incidence of cases globally (68% of all notifications worldwide during 2000-06), with periodic outbreaks every 3–5 yr. The first large epidemic of DHF in the region occurred in Cuba in 1981, with 24,000 cases of DHF, 10,000 cases of DSS and 158 deaths reported during a three month period. In 1986–87, massive dengue outbreaks were reported in Brazil. In 1990, nearly a quarter of the 3,00,000 inhabitants of Iquitos, Peru, acquired DF, and in the same year, 3108 cases of DHF with 78 deaths were reported in Venezuela. To date, the largest epidemic occurred in 2002, with <1 million reported cases. From 2000-07 the average annual number of case reports was 71.5 per 100,000 people, an increase on the period from 1990–99. The average incidence rate of DHF was 1.7 per 1,00,000 during 2000–07, with a total of 1391 dengue-related deaths. Over the last decade the Southern Cone countries (Argentina, Brazil, Chile, Paraguay and Uruguay) have reported the majority of dengue incidence. During 2001–07, 64.6% (2,798,601) of all dengue cases (DEN-1, -2 and -3) in the Americas were reported from this region, of which 6733
were DHF with a total of 500 deaths. Brazil accounted for the vast majority (98.5%) of these fatalities.

**Future perspectives**

There is considerable evidence to support the proposal that public health problems relating to dengue are set to become increasingly severe. Vaccination and vector control treatment are the major strategies for combating dengue although at present there are no effective strategies. Vaccines are still in clinical trial, and to date there are no effective antiviral drugs. Therefore, a magnified focus should be directed towards disease prevention and mosquito control. Despite the launch of many awareness programmes, various challenges remain to be handled effectively. Rapid urbanization, lack of basic sanitation, and increased intra- and inter-migratory activities have compounded the problem in most regions. In this context, it is also worth considering potential factors that drive dengue activity, such as virus evolutionary changes (viral genotype switching), climate diversity, industrialization, urbanization and the trade cycle, and the potential for spread from urban to rural foci.

**Viral genotype switching**

On the basis of the nature of transmission and severity of clinical infection in humans, DENV serotypes have been categorized as making a low, medium or high epidemiological impact. Viruses that are maintained within sylvatic cycles and among non-human primate populations are rarely transmitted to humans, while other genotypes cause mild to severe disease in humans. For DENV-2 and DENV-3, genotypes found more commonly in the Americas are comparatively less virulent than Asian genotypes. By analysis of modifications to the virus envelope protein postulated to correlate with endemic and/or epidemic emergence, it was shown that domain III of the E protein may play a role in viral adaptation to hosts, whether mosquito or human. Moreover, phylogenetic and epidemiological analyses suggest that genotypes with greater virulence are driving out virus strains of lesser epidemiological impact.

**Climate diversity**

As a result of increased global warming, mean air temperatures are predicted to rise. In 2000, it was estimated that average global temperatures would rise by 1–3.5°C by 2011. This has a direct impact on the survival and migration of mosquitoes. Any adverse climate conditions influence the vector to choose a more favourable environment for settlement. This will ultimately make suitable habitats of previously non-endemic geographical regions. Proliferation of *Aedes* mosquitoes is climate-dependent; hence, meteorological factors can potentially provide useful information on predictive models of dengue incidence. This presents a challenge to tropical and subtropical regions that are currently non-endemic for dengue but which share similar climatic conditions to endemic areas. Evidence suggests that both *Ae. aegypti* and *Ae. albopictus* could become established or re-established in the near future in presently un-colonised areas. A rise in global temperatures observed over the last four decades may correlate with increased risk of dengue outbreaks. Climate changes – elevated average global temperature and humidity – increase the epidemic potential of dengue. It has been estimated that half of the world’s population may be living in areas at risk of dengue transmission by the year 2085. In contrast, only 35% of people would be at risk if anticipated changes in climate did not eventuate.

**Urbanization, trade and travel**

As a consequence of the predilection of *Aedes* for citified settings, dengue is unusual for a mosquito-borne disease in having a greater prevalence in urban areas than in rural villages. Urban and suburban development may also provide plentiful ready-made breeding sites, for instance artificial containers often used for urban water collection. The increased density of both mosquito and human populations in the same location as a result of urbanization promotes man-vector contact and thus transmission of dengue.

An effect of globalization is increased travel and trade, which are major factors for heightened dengue transmission. Growth of commerce such as exportation and importation of goods, and movement of students both within and between countries for educational purposes are probable reasons for the expanded epidemiology of dengue. Developed nations such as Australia, Canada, Germany, Denmark, Norway, Sweden, UK and USA are the focus of migration for residency, work and education. Hence, there is always a risk of introducing travel-associated dengue into these countries.

Travel and tourism are key issues in the context of dengue transmission as the movement of dengue-infected persons is thought to be a main driver for global expansion of the disease. Fast track transportation has facilitated rapid expansion of dengue from endemic areas into geographically distant non-endemic areas. Routes by which importation of dengue is an increased risk have been established through passenger air travels. In particular, routes between Latin America and the USA, and between Asia and Europe, were identified as risky...
for dengue dissemination\textsuperscript{100}.

International transportation of cargo and freight, especially via commercial sea shipment, also facilitates the export and import of dengue vectors\textsuperscript{101}. Used motor vehicle tyres may carry both adult and larval mosquitoes. The capacity of \textit{Aedes} to hatch, breed and survive sea travel has contributed to a major public health threat in recent decades\textsuperscript{102}. The inevitable escalation of private car ownership in future will lead to a vast number of tyres to be discarded; if they collect rain water, each will serve as an ideal breeding site for mosquitoes.

\textbf{Rural areas: A potential future locus of dengue infection}

Previous underestimation of the importance of rural locations for dengue transmission may have contributed to providing vector-suitable breeding sites similar to those in urban areas. With increasing ease of transportation, interconnectivity between rural and urban areas has grown commensurately. People from the countryside now travel daily to towns and cities for the purposes of employment, education, health and for trading livestock, crops, fruits and vegetables. In contrast, many people visit rural regions for recreation and to enjoy the peaceful environment. The extended construction of trunk roads, especially in developing countries, has effectively narrowed the travel time, if not actual distance, between rural and urban areas, and has thereby acted as a silent conduit of dengue transmission\textsuperscript{103}. In addition to environmental and climatic factors, human practices have performed a significant part in creating a situation that is conducive to the global spread of dengue\textsuperscript{40}.

\textbf{Discovery of a new dengue serotype: DENV-5}

The recently claimed discovery of a new serotype, DENV-5, provides a further challenge to dengue control\textsuperscript{6}. As this has yet to be confirmed by publication in the peer-reviewed scientific literature an unequivocal demonstration of this serotype awaits the attaining of an isolate, which should be characterized definitively to confirm, or conversely to refute, its novelty. It appears that the four previously discovered serotypes originated from monkeys conversely to refute, its novelty. It appears that the four previously discovered serotypes originated from monkeys and transferred to humans either in Africa or Asia a few hundred years ago\textsuperscript{104}. However, the first recorded isolation of DENV-1 to DENV-4, respectively, were in 1943 in Japan, 1944 in Papua New Guinea, and 1953 in Philippines and Thailand\textsuperscript{105}. Interestingly, these four serotypes have human cycles, while the fifth one belongs to a sylvatic cycle\textsuperscript{6–7}. Although much further research is needed to determine the extent of its current existence, its past epidemiology and its future potential epidemic strength, it should be assumed that DENV-5 poses a threat to human beings. Following this finding it may be said that dengue is not limited to only five serotypes; it is quite possible that there are others, as yet undetected, which also circulate in sylvatic cycles. In itself, the discovery of DENV-5 complicates both dengue diagnosis and vaccine development.

\textbf{Public knowledge, attitude and practice}

The existing level of knowledge of the general public, their attitude and behaviour all play major roles in determining the outcome of programmes that are implemented to limit dengue. Although, many people might have heard of dengue, most of them are unaware of the symptoms of disease and possess inadequate knowledge of preventive methods or vector control. While this may be anticipated for poorer nations, ignorance regarding dengue also applies to the residents of countries like Australia\textsuperscript{106}, which is economically developed and has a literacy rate of almost 99%. Hence, not prioritizing the fitting of domestic door and window screens, careless discarding of domestic waste, inattentive maintenance of external household containers (\textit{e.g.} disposed tyres, broken bowls and cups, flower pots) in which water may collect and thereby provide breeding sites for mosquitoes, all contribute to vector proliferation and dispersal.

\textbf{Future options for dengue control}

\textbf{Integrated vector management:} WHO is advocating integrated vector management (IVM) as a further method of combating \textit{Aedes} transmission of dengue\textsuperscript{107}. IVM is defined as “a rational decision-making process for the optimal use of resources for vector control”. The premise behind IVM is an integrated collaborative initiative among different contributing sectors for support, social mobilization and legislation\textsuperscript{108}. The fundamentals of dengue control under this multidisciplinary strategy are to implement evidence-based selection and delivery of different interventions (or combinations of interventions) that are informed by, and thereby tailored to, local settings.

\textbf{Biological control:} A new vector control tool for \textit{Ae. aegypti} population suppression and replacement is currently under investigation. This is the ‘release of insects carrying a dominant lethal’ (RIDL) system for mass rearing of male mosquitoes with the introduction of a lethal genetic mutation\textsuperscript{109}. The principle of this technique is to micro-inject a lethal gene into the eggs of \textit{Ae. aegypti}. Subsequently, the gene integrates into the genome of the mosquito and regulates the production of toxic metabolites in the larval stage, killing the newly
hatched larva. Antibiotics such as tetracycline, which inhibit expression of the lethal gene, are used in the laboratory to enable the larva to develop into an adult mosquito\textsuperscript{110}. It is intended that under controlled environmental conditions, RIDL males will be released to mate with wild type females. Fertilized females should produce RIDL gene-containing eggs that hatch into larvae. All those carrying the gene will die at late larval or early pupal stage. This project is being conducted by the Malaysia Institute for Medical Research in three phases: (1) establishment of the transgenic Malaysian strain of \textit{Ae. aegypti}; (2) simulated release trial inside a field house; and (3) field release in a suitable experimental field site\textsuperscript{111}. Currently, phase three is underway.

Another development for biological control of the vector is to introduce strains of a naturally occurring intracellular endosymbiotic bacterium called \textit{Wolbachia} into \textit{Ae. aegypti}. In trials, the effects observed in mosquitoes depend on the strain of \textit{Wolbachia} that is used\textsuperscript{112–113}. The introduced bacterial strains should be effective for vector control by both direct blocking of virus transmission and, indirectly, by reducing the expected lifespan of the mosquitoes. Only older mosquitoes transmit DEN\textsubscript{V}, so this is predicted to reduce transmission. An additional benefit of using \textit{Wolbachia} is that while it can spread actively in insect populations it is non-infectious to humans. It is transmitted between generations inside the eggs of the mosquito. It also inhibits reproduction of females that do not themselves carry \textit{Wolbachia}, when mated with infected males, by a phenomenon known as cytoplasmic incompatibility\textsuperscript{114}.

\textbf{Vaccines:} For several years, despite major challenges dengue vaccine development has been an area of active research. Although, clinical testing of attenuated vaccine candidates began in the 1980s, a vaccine licensed for commercial use is not yet available\textsuperscript{115}. With the increased incidence and continued geographical spread of dengue, there is a pressing need for a new and highly effective vaccine that is safe and affordable. Several vaccine candidates are showing promise in current clinical trials\textsuperscript{116}. The preparation of a tetravalent formulation, which aims to be active against all of the four established serotypes, DEN\textsubscript{V} 1–4, is a technically challenging task. However, recombinant DNA approaches have provided significant advances and a number of products are in different clinical phases\textsuperscript{115–116}. Sanofi Pasteur has completed the active phase of two pivotal Ib/III efficacy studies for ChimeriVax, a DEN\textsubscript{V} 1–4 vaccine, which were carried out in Asia and Latin America\textsuperscript{117}. The ChimeriVax technology is based on four recombinant viruses containing the prM and E genes from each of DEN\textsubscript{V} 1–4 inserted into the Yellow Fever virus 17D vaccine strain backbone\textsuperscript{118–119}. Following completion of these clinical trials a number of questions have been raised that pertain to either serotype-specific efficacy, anti-dengue baseline immunity or surrogate markers of prior exposure. However, these aspects should be on the manufacturer’s list of priorities to be addressed. A more detailed description of current approaches and future directions for dengue vaccine strategies is provided elsewhere\textsuperscript{116, 120}.

\textbf{CONCLUSION}

Although, dengue was considered initially as a neglected tropical disease, it has recently been prioritized via the multi-sectoral approaches of the WHO’s Global Strategy for Dengue Prevention and Control\textsuperscript{31}. This strategy aims to reduce the burden of dengue through applied research, field-based training and capacity building between relevant public health stakeholders at regional and national levels. The strengthening of capacity development is recognized to require advocacy, partnership, coordination and collaboration. Sustainable vector control is one technical element of the Global Strategy for Dengue Prevention and Control, 2012–20. In light of limited therapeutic strategies and the current lack of a vaccine, effective mosquito control methods are an essential component of the drive to reduce dengue mortality and morbidity by 2020. The IVM is the strategic approach promoted to dengue-endemic countries by the WHO as a rational, cost-effective and optimal decision-making process for vector control programmes\textsuperscript{31}.

In spite of many and varied efforts to target both the dengue virus and its mosquito vector, with strategies initiated and programs practiced in many endemic regions, to date the outcome has been disappointing. Over the past fifty years, the global incidence of dengue has risen by a factor of 30 (Fig. 2)\textsuperscript{31}, which is a matter of serious global public health concern. With a regular pattern of dengue epidemics every 3–5 yr, an increase in clinical cases has been reported for all countries of South East Asia during the last decade. Nearly 75% of the worldwide incidence of dengue occurs in the Asia-Pacific region\textsuperscript{31}. The situation is almost as alarming in the Americas, where in the last 30 yr the number of dengue cases has increased more than eight-fold\textsuperscript{30}. While the trend for expansion is not repeated in Africa, it is possible that there is under-reporting in this continent due to inadequate provision of diagnostic resources. Australia has implemented successful vector control interventions that eradicated the \textit{Ae. aegypti} population and eliminated cases of dengue from New South Wales and Western Australia, states which
experienced outbreaks of dengue a couple of decades earlier. However, the number of overseas-acquired cases reported in Australia continues to increase each year, which poses an ongoing threat for local transmission of dengue in north and central Queensland, where *Ae. aegypti*, still persists. For all countries in which there is local transmission of dengue, it is an imperative to effectuate a range of technical factors that promote anti-dengue activity, as well as to promulgate the strategic direction that is required in order to achieve the WHO goal of IVM on a global scale.

Conflict of interest
The authors declare no conflicts of interest.

Disclaimer
Richard Bradbury is co-authoring this manuscript in his personal capacity and as an adjunct academic at Central Queensland University.

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