8 Dengue along the Silk Road

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Abstract

Dengue is a mosquito-borne viral disease that has rapidly spread in all regions of the world in recent years, including the BRI countries. Dengue virus (DENV) is a mosquito-borne virus belonging to the Flaviviridae family. There are DENV-1, DENV-2, DEN-3 and DENV-4 four antigenically different serotypes DENV. Aedes mosquitoes act as vector of DENVs. Dengue is found in tropical and sub-tropical climates worldwide, 70% of the actual burden is in Asia, high number of cases were reported in Bangladesh, Malaysia, Philippines, Vietnam etc. Dengue poses a significant health and economic burden in the BRI Asia Region. DENV is frequently transported from one place to another by infected travelers. Mosquito vector spread is also important risk factor. Imported dengue cases are thought to be an important source for transmission in China. DENV infection results in a wide spectrum of clinical symptoms, including dengue hemorrhagic fever (DHF). Dengue infection diagnosis include clinical and laboratory diagnosis. Dengue control measures includes patient treatment and mosquito control. Therefor, it is important to to cooperate in in dengue control among the BRI counties.

Keywords

Dengue fever · Dengue virus · Aedes · The Silk Road

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8.1 Dengue Virus, Vectors, and Epidemiology

Dengue virus circulates in many parts of the world, impacting most tropical and subtropical countries. Millions of people are affected each year and global dengue incidence has dramatically increased in recent decades.

First proposed in 2013 and hailed by Xi Jinping as the "project of the century," China's Belt and Road Initiative (BRI) promises a win–win partnership with China offering loans and investment and host countries supplying new markets in the process of "inclusive globalization" (Liu et al. 2016; Zhang et al. 2018). Among 146 BRI countries, dengue is endemic or reported in more than 86 BRI countries, some of which have severe dengue epidemics.

8.1.1 Dengue Virus

Dengue is a mosquito-borne viral disease that has rapidly spread in all regions of WHO in recent years. The incidence of dengue has grown dramatically worldwide in recent decades. The virus is transmitted by female mosquitoes mainly of the species *Ae. aegypti* and, to a lesser extent, *Ae. albopictus*.

Dengue virus (DENV) is a mosquito-borne virus belonging to the Flaviviridae family. DENV is a 50-nm virus particle surrounded by a lipid membrane. The genomic RNA of about 11.000 nucleotides of length contains a single open reading frame which encodes a large polyprotein that is co- and post-translationally processed into three structural proteins (capsid (C), precursor membrane (prM), and envelope (E)) and seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5). There are four DENV serotypes, four phylogenetically and antigenically distinct dengue virus (DENV1–4) (Messina et al. 2014). Although infection with one type confers long-term immunity, it is to that type only and not to the other three type. While many DENV infections produce only mild illness, DENV can cause an acute flu-like illness. Occasionally, this develops into a potentially lethal complication, called severe dengue. Severe dengue is a leading cause of serious illness and death in some Asian and Latin American countries. It requires management by medical professionals.

8.1.2 Dengue Vectors

Aedes mosquitoes act as a vector of DENVs. *Aedes aegypti* is considered the major vector of DENV in most of the BRT countries. It could breed in both natural containers and man-made containers. Natural contains involve such as tree holes and bromeliads, and man-made containers include discarded containers, buckets, pots, and used tires. Nowadays, in urban areas, artificial containers are the main breeding grounds for *Ae. aegypti*. *Ae. aegypti* take blood meal during daytime. There are a peak biting periods in the early morning and in the evening before sunset, respectively. Female *Ae. aegypti* may take blood meal several times between each egg-laying period, thus leading to multiple infected individuals. *Aedes* mosquito eggs can remain viable for several months after being laid under dry conditions, and they will hatch when they come into contact with water.

Aedes albopictus is the secondary dengue vector in most dengue epidemic countries. *Ae. albopictus* also take blood meal during daytime, and it is considered the primary vector of DENV in the areas with a limited number of outbreaks, where *Ae. aegypti* is either not present or present in low numbers; for example, it is the main vector in most areas of mainland China.

Ae. albopictus is native to Asia and the South Pacific and has recently been introduced into North and South America and European Region, mainly due to the international trade in used tires (*Aedes* mosquito breeding habitat) and others (lucky bamboo, etc.). The favorable breeding sites of *Ae. albopictus* seem close to dense vegetation, including plantations that is linked to increased risk of exposure for rural workers such as those in palm oil and rubber plantation; in urban areas, abundant breeding sites also have been found.

8.1.3 Dengue Epidemiology

8.1.3.1 Dengue Distribution

Dengue is found in tropical and subtropical climates worldwide, mostly in urban and semi-urban areas. Since the 1960s, the dengue virus has spread from less than 10 known countries where the disease was endemic and a few thousand cases reported each year to 128 endemic countries, an estimated 400 million infections and 100 million symptomatic cases annually. The number of dengue cases reported to WHO increased more than eightfold over the past two decades, and dengue is the only communicable disease that has increased exponentially with rapid urbanization and environmental changes. The vast majority of cases are asymptomatic or mild and self-managed; hence, the actual numbers of dengue cases are under-reported. Currently, around 100 countries and territories in WHO's Americas, South-east Asia, and Western Pacific regions report dengue cases regularly. Despite a risk of infection existing in 129 countries, 70% of the actual burden is in Asia. A high number of cases were reported in Bangladesh (101,000), Malaysia (131,000), the Philippines (420,000), and Vietnam (320,000) in Asia.

In Asia, BRI countries including Singapore, Timor-Leste, Malaysia, Myanmar, Cambodia, Viet Nam, Pakistan, Sri Lanka, Bangladesh, Nepal, Maldives, Saudi Arabia, Afghanistan, Thailand, Indonesia, the Philippines, Yemen, Lao, and China have dengue epidemic or dengue case reports. There have been no dengue reports by the National Disease Surveillance and Response System (NDSR) in Afghanistan before 2019. For the first time, locally acquired DENV cases have been detected in Afghanistan by the national surveillance and response system, mostly in provinces bordering Pakistan in 2019 (Sahak 2020). As a dengue nonendemic country, China has experienced several dengue outbreaks in recent years.

Among the 49 BRI countries in Africa, dengue has been reported, including dengue reported only in travelers, and the presence of *Ae. aegypti* mosquitoes in

31 countries. Dengue has not been reported in 9 countries (Sierra Leone, Guinea, Mauritania, Chad, Congo, Zimbabwe, Congo, Botswana, and Central Africa) but where *Ae. aegypti* mosquitoes are present (Were 2012). Before 2013, there had been no records of the dengue virus in Ethiopia (Mohan et al. 2021), but the virus has since spread to multiple regions. Dengue outbreaks were recorded in Ethiopia in 2017, 2019, and 2021, according to epidemiological evidence. Dengue fever can be transmitted all year; however, the danger is greatest during and immediately after the rainy season, which runs from June to August.

Dengue epidemics or cases have been reported in all BRI countries in North (12 BRI countries) and South America (9 BRI countries). In Europe, 4 BRI countries have reported dengue cases, including only imported cases. In the Oceania area, dengue epidemics or cases have been reported in BRI countries other than New Zealand. The threat of a possible outbreak of dengue now exists in Europe; local transmission was reported for the first time in the BRI country Croatia in 2010. Although there have been no case reports in Turkey due to DF, there is sero-epidemiological evidence indicating the presence of dengue virus (DENV) in Turkey (Uyar et al. 2013).

8.1.3.2 Dengue Transmission

Dengue is caused by a virus of the Flaviviridae family, and there are four distinct, but closely related, serotypes of the virus (DENV-1, DENV-2, DENV-3, and DENV-4) that cause dengue. DENVs are spread mainly through mosquito bites and in some cases through maternal transmission or other means.

8.1.3.2.1 Transmission through the Bite Mosquito of *Aedes* Mosquito

DENV is transmitted from human to humans through the bites of DENV-infected female *Aedes* mosquitoes, mainly the *Ae. aegypti* mosquito. Other species such as *Ae. albopictus* can also act as secondary vectors.

When mosquitoes bite on people who are viremic with DENV, they can become infected. This can be someone who has a asymptomatic, pre-symptomatic, and symptomatic dengue infection. Human-to-mosquito transmission can occur up to 2 days before the patient develops symptoms and up to 2 days after the fever subsides.

After taking an DENV-infected blood meal, the virus replicates first in the mosquito midgut and finally disseminates to the salivary glands. The extrinsic incubation period (EIP) is the time from ingesting the virus to actual transmission to a new host. When the ambient temperature is 25–28 °C, the EIP need takes about 8–12 days. The variation of external latency is not only affected by ambient temperature and also by a number of factors such as the initial viral concentration, the virus genotype, the symbiotic bacteria, and range of daily temperature fluctuations. Once infectious, the *Aedes* mosquito is capable of transmitting the virus for the rest of its life.

The risk of mosquito infection is positively associated with high viremia and high fever in the patient; conversely, high levels of DENV-specific antibodies are associated with a decreased risk of mosquito infection.

8.1.3.2.2 Maternal Transmission

The primary mode of transmission of DENV between humans involves mosquito vectors. There is the possibility of maternal transmission (from a pregnant mother to her baby). Vertical transmission rates appear low, with the risk of vertical transmission seemingly linked to the timing of the dengue infection during the pregnancy. When a mother does have a DENV infection when she is pregnant, babies may suffer from pre-term birth, low birthweight, and fetal distress.

8.1.3.2.3 Other Transmission Modes of Dengue

Rare cases of transmission via blood products, transfusions, and organ donation have been recorded. Similarly, transovarial transmission of the virus within mosquitoes has also been recorded.

8.2 Dengue Disease Burden

Dengue virus is a mosquito-borne infection that has become a health threat globally. It has been estimated to cause a substantial health and economic burden in epidemic countries. Within the Global Burden of Disease study 2013, it was estimated that dengue was responsible for 1.14 million disability-adjusted life years (DALYs) globally, and it is estimated that it is responsible for 39,884 disability-adjusted life years (DALYs) annually, representing an economic burden of US$94.87 million per year (in 2016 price) (Hung et al. 2018).

Dengue poses a significant health and economic burden in the BRI Asia Region. In Thailand, Dengue illness often leads to school and work absenteeism, medical and nonmedical expenditures, and foregone income. A research about household costs of hospitalized dengue illness in semi-rural Thailand demonstrated that hospitalized dengue illness costs approximately 19–23% of the monthly household income, although 74% of the households reported that the patient received free medical care (Tozan et al. 2017). Dengue also contributes significantly to socioeconomic burden in Nepal, and the risk of dengue infection and outbreak in Nepal is increasing year by year at different spatial scales.

In 2020, dengue affected several countries, with reports of increases in the numbers of cases in Bangladesh, Brazil, Cook Islands, Ecuador, India, Indonesia, Maldives, Mauritania, Mayotte (Fr), Nepal, Singapore, Sri Lanka, Sudan, Thailand, Timor-Leste, and Yemen. Dengue continues to affect Brazil, India, Vietnam, the Philippines, the Cook Islands, Colombia, Fiji, Kenya, Paraguay, Peru, and the Reunion islands in 2021.

Imported dengue cases are thought to be important sources for transmission of autochthonous dengue in Europe (Ahmed et al. 2020). A number of cases were imported to Norway, Sweden, Finland, Russia, Turkey, Israel, Romania, Poland, Spain, Portugal, Italy, Switzerland, Czech Republic, Denmark, the United Kingdom, the Netherlands, Belgium, Germany, and France.

8.3 Influence Factors of Dengue Epidemic

Dengue is widespread throughout the tropics, and local spatial variation in dengue virus transmission is strongly influenced by rainfall, temperature, urbanization, and distribution of the principal mosquito vector *Aedes aegypti*. The spread of secondary vector *Ae. albopictus* also contributes to the dengue epidemic.

8.3.1 Risk Due to Climate Changing

Climatic changes, landscape management, and massive human, animal, and commodity transportation represent important factors that contribute to the spread of dengue.

8.3.2 Risk Due to Travel

DENV is frequently transported from one place to another by infected travelers; when susceptible vectors are present in these new areas, there is the potential for local transmission to be established. Travel-acquired dengue cases have been increasing as the overall global dengue burden has expanded. Globalization has led to an increased incidence of the virus both in foreign travelers returning home and local outbreaks in traditionally nonendemic areas, such as southern Europe. The rise in global travel and trade has posed Europe with an increased risk of introduction and expansion of exotic arthropod vectors and autochthonous transmission of arboviruses, like dengue and chikungunya viruses, following new introductions from endemic areas. Europe is already partially colonized by another DENV vector, *Ae. albopictus.*

In Korea, imported dengue cases have been reported since 2000 when it first became a notifiable disease.

Every year in South Korea, it is reported that a few hundred people are infected during travel to dengue-endemic countries. However, there have been no domestic infections reported so far. With a gradual change toward a subtropical climate owing to global warming, Korea could face a spread of domestic dengue in the near future.

8.3.3 Risk Due to Mosquito Vector Spread

Among the invasive mosquitoes registered all over the world, *Aedes* species are particularly frequent and important. *Ae. albopictus* is highly adaptive. Its geographical spread is largely due to its tolerance of colder conditions as an egg and adult. In Europe, *Ae. albopictus* first arrived in 1979 in Albania and in 1990 in Italy. Currently, the species is established in more than 20 countries, and it has been responsible for outbreaks of dengue in Croatia, France, and Italy. Public health concerns have spurred research on the suitability of the European continent to the establishment of *Ae. albopictus.*

8.3.4 Risk Due to Other Infectious Diseases

The COVID-19 pandemic is placing immense pressure on health care and management systems worldwide. Recently, as COVID-19 has spread around the globe and more adults have been exposed to it, there have been more reports of coinfections with other infectious diseases. WHO has emphasized the importance of sustaining efforts to prevent, detect, and treat vector-borne diseases during this pandemic such as dengue and other arboviral diseases, as case numbers increase in several countries and place urban populations at the highest risk for both diseases. The combined impact of the COVID-19 and dengue epidemics could have devastating consequences on the populations at risk.

In August 2020, during the coronavirus disease (COVID-19) pandemic, five locally acquired cases of dengue virus type 1 were detected in a family cluster in Vicenza Province, North-East Italy, where *Aedes albopictus* mosquitoes are endemic. The primary case was an importation from West Sumatra, Indonesia. This is the first outbreak of autochthonous dengue reported in Italy. During the COVID-19 pandemic, screening of febrile travelers from endemic countries is crucial in areas where competent vectors are present.

In Bangladesh, an alarming situation is a devastating dengue outbreak amid the COVID-19 pandemic. As the COVID-19 outbreak wreaks havoc, the following rise in dengue illnesses has been a source of considerable concern. As health care has been stretched thin in these dangerous times, the vulnerable population has been left at the mercy of these two viral infections.

In Africa BRI countries, for example, Ethiopia has been facing a serious public health problem regarding the dengue outbreak amid the COVID-19 pandemic.

Under the current pandemic, when health officials are mainly focused on containing the virus, every other infectious disease outbreak could obstruct COVID-19-fighting efforts and pose diagnostic challenges for medical personnel.

8.4 Disease Characteristics (Signs and Symptoms)

DENV infection results in a wide spectrum of clinical symptoms, ranging from mild fever to dengue hemorrhagic fever (DHF), the latter of which can progress to dengue shock syndrome (DSS) and death. There are around 90 million symptomatic cases of dengue each year, with severe disease in around 1% of cases, including life-threatening hemorrhage or shock syndrome.

Symptoms of DENV infection typically appear 3–14 days after inoculation by the *Aedes* mosquito and most commonly manifests as a self-limiting febrile illness. However, in severe dengue, plasma leakage may be profound and result in hemorrhage, disseminated intravascular coagulation, and circulatory collapse. The dengue virus may also cause organ dysfunction. Cases of myocarditis, myocardial dysfunction, and arrhythmias, including atrioventricular block, have been reported. The World Health Organization classifies dengue into two major categories: dengue (with/without warning signs) and severe dengue.

8.4.1 Dengue Fever

Most DENV infections are asymptomatic or present a mild illness. It can manifest as a severe, flu-like illness that affects infants, young children, and adults but seldom causes death. Symptoms usually last for 2–7 days, after an incubation period of 4–10 days after the bite from an infected mosquito. These symptoms are known as dengue fever (DF), which is an acute, self-limited, febrile illness. Symptoms usually last for 2–7 days, after an incubation period of 4–10 days after the bite from an infected mosquito.

Recovery from infection is believed to provide lifelong immunity against that serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections (secondary infection) by other serotypes increase the risk of developing severe dengue.

8.4.2 Severe Dengue

Severe dengue is a severe form of dengue fever with clinical manifestations of severe bleeding, shock, and severe organ damage. It was first recognized in the Philippines and Thailand in the 1950s during dengue epidemics. Nowadays, severe dengue has become a leading cause of hospitalization and death among children and adults in most Asian and Latin American regions. Severe dengue fever is a potentially fatal complication caused by severe bleeding, plasma leaking, respiratory distress, fluid accumulation, and organ impairment.

Some dengue patients develop dengue hemorrhagic fever (DHF), which is a severe syndrome, and patients may present hematomas with marked thrombocytopenia or extremely low platelet counts. DHF symptoms include increased vascular fragility, raised plasma leakage/heme concentration coagulation abnormalities, and loss of fluid. DHF appeared in Singapore in the 1960s and quickly became a major cause of childhood death (Ooi et al. 2006). DHF is probably caused by viral antigens and host immune responses, virus-specific antibodies, or other factors. If dengue patients develop dengue shock syndrome (DSS), more severe clinical symptoms occur. Symptoms of DSS are similar to DHF, and it may develop into hypovolemic shock and have the risk of multiple organ failure.

Genetic differences among DENV genotypes are associated with differential viral virulence that may contribute to the development of the severe diseases, such as DHF and DSS.

8.5 Diagnostics

Dengue infection diagnosis includes clinical and laboratory diagnosis. Dengue infection has a wide clinical spectrum that includes both severe and mild manifestations.

In the 2009 WHO guidelines, dengue is defined as fever plus two or more of the following: nausea/vomiting, rash, aches and pains, positive tourniquet test, leukopenia, or any warning sign (outlined in the guidelines).

In China's 2018 guidelines for case surveillance of dengue fever, the diagnosis of dengue fever is based on the epidemiological history, clinical manifestations, and laboratory results.

Several laboratory methods can be used for the diagnosis of DENV infection. Depending on the time of patient presentation, the application of different diagnostic methods may be more or less appropriate. Patient samples collected during the first week of illness should be tested by laboratory methods.

8.5.1 Virus Isolation Methods

The virus may be isolated from the blood during the first few days of infection. Isolation of dengue virus from the serum, cerebrospinal fluid, blood cells, or tissues of patients in the acute phase can confirm the diagnosis.

8.5.2 RT-PCR or Real-Time Fluorescence Quantitative PCR Technique

The gene sequence of the dengue virus was detected by RT-PCR or real-time fluorescence quantitative PCR can help confirm the diagnosis. Various reverse transcriptase–polymerase chain reaction (RT-PCR) methods are available and are considered the gold standard. However, they require specialized equipment and training for staff to perform these tests.

8.5.3 Serological Methods

8.5.3.1 Detection of Dengue Virus NS1 Antigen

The virus may also be detected by testing for a virus-produced protein, NS1. In China, a clinically diagnosed case with a positive result of dengue virus NS1 antigen detection can be confirmed. There are commercially produced rapid diagnostic tests available for this, and it takes only ~20 mins to determine the result, and the test does not require specialized laboratory techniques or equipment.

8.5.3.2 Detection of Anti-Dengue Virus Antibodies

Enzyme-linked immunosorbent assays (ELISA) is one of the commonly used antibody detection methods. The detection of anti-dengue antibodies may confirm the presence of a recent or past infection. IgM antibodies are detectable ~1 week after infection and remain detectable for about 3 months. The presence of IgM is indicative of a recent DENV infection. IgG antibody levels take longer to develop and remain in the body for years. The presence of IgG is indicative of a past infection. A clinically diagnosed case with the titer of serum specific antibody in the convalescent period increased more than four times than that in the acute period should be laboratory confirmed. A number of preventive strategies have been proposed particularly on reduction of the mosquito vector by using mechanical, chemical, and biological approaches.

8.6 Prevention and Control

Dengue virus is a mosquito-borne infection that has become a health threat globally. A large number of dengue cases are reported during monsoon seasons due to the high prevalence of vectors each year, and many of the dengue cases are not reported or classified. Dengue control measures include isolation and treatment of existing patients and medical observation of close contacts, active epidemic surveillance, mosquito control, community engagement, and vaccine prevention. Given an optimal temperature for vector breeding and a lack of a safe, effective dengue vaccine and urban transmission cycle of dengue virus (human-mosquito-human), dengue preventive measures are emphasized in endemic areas such as Southeast Asia.

8.6.1 Dengue Patient Treatment

There is no specific treatment for dengue fever. Currently, treatments for dengue infection are only symptomatic, as no antiviral agents nor vaccines are available to combat this virus. Patients should rest, stay hydrated, and seek medical advice. Depending on the clinical manifestations and other circumstances, patients may be sent home, be referred for in-hospital management, or require emergency treatment and urgent referral.

Supportive care such as fever reducers and painkillers can be taken to control the symptoms of muscle aches and pains and fever. The best options to treat these symptoms are acetaminophen or paracetamol.

NSAIDs (non-steroidal anti-inflammatory drugs), such as ibuprofen and aspirin, should be avoided. These anti-inflammatory drugs act by thinning the blood, and in a disease with a risk of hemorrhage, blood thinners may exacerbate the prognosis.

For severe dengue, medical care by physicians and nurses experienced with the effects and progression of the disease can save lives, decreasing mortality rates to less than 1% in the majority of the countries.

Dengue patients in China displayed distinct clinical characteristics compared to patients in endemic countries. To standardize the diagnosis and treatment of dengue fever, the experts of the Society of Infectious Diseases, the Society of Tropical Medicine and Parasitology of Chinese Medical Association, the Chinese Society of Emergency Medicine, and the Association of Chinese Medicine have reached this guideline based on guidelines for diagnosis, treatment, prevention, and control of dengue; guidelines for diagnosis and treatment of dengue; health industry standard of the People's Republic of China "diagnosis for dengue fever (WS216–2018)"; and systemic reports on dengue. The guideline includes eight aspects: introduction, terminology, epidemiology and prevention, etiology and pathogenesis, clinical features, diagnosis, treatment, and problems to be solved.

The dengue virus may circulate in the blood during the first week of illness. So if people have been infected with dengue, he/she should avoid getting further mosquito bites during the time; if not, the infected person may transmit the virus to new uninfected mosquitoes, who may in turn infect other people.

8.6.2 Vaccination against Dengue

Vaccines are a principal preventive approach for combating infectious diseases. Vaccination in the human population is one of the key strategies to prevent the risk of dengue virus transmission from a human host to a mosquito vector (Bos et al. 2018).

Because DENV has four different serotypes, a practical dengue vaccine should provide long-term protection for infections of homotypic and heterotypic serotypes. Multiple strategies have been exploited for vaccine development. There are live attenuated dengue vaccines, live chimeric dengue vaccines, inactivated dengue vaccines, and recombinant protein, DNA, and subunit dengue vaccines.

Live attenuated vaccines, which contain attenuated pathogenic microorganisms, are capable of producing a broad range of immune responses. The scientists of Mahidol University in Thailand developed a tetravalent attenuated dengue vaccine (LAV), which was generated by serial passaging of four DENV serotypes in a cell culture. Three dengue serotype viruses (DENV1, 2, and 4) were attenuated in primary dog kidney cells, whereas DENV3 was serially passaged to reduce its virulence in primary African green monkey kidney cells. The candidate vaccine was used in phase I and II clinical trials in Thai adults and children. Not all of the volunteers developed antibodies for all four dengue serotypes, and some experienced unacceptable reactogenicity and further clinical testing was terminated.

The first dengue vaccine, Dengvaxia® (CYD-TDV) developed by Sanofi Pasteur, was licensed in December 2015 and has now been approved by regulatory authorities in ~20 countries. The Dengvaxia vaccine is a tetravalent chimeric vaccine. For each of the four dengue serotypes, the prM and E genes from virulent DENV strains are substituted into the backbone of the yellow fever virus 17D vaccine strain.

Except the licensed Dengvaxia vaccine, several dengue vaccine candidates are in clinical trials or under preclinical evaluation, and multiple strategies have been exploited for vaccine development.

Although many vaccines that target either the DENV virions or the viral structural proteins have been licensed or under clinical trials, significant safety concerns remain unresolved (Liu et al. 2016).

Vaccination should be considered as part of an integrated dengue prevention and control strategy. There is an ongoing need to adhere to other disease preventive measures such as well-executed and sustained vector control. Individuals, whether vaccinated or not, should seek prompt medical care if dengue-like symptoms occur.

8.6.3 *Aedes* Mosquito Vector Control

The rise of dengue cases can be prevented by controlling vector spread. Due to the lack of an effective vaccine and drug to cure these diseases, mosquito control is the only method available to reduce disease risk. At present, the main method to control or prevent the transmission of dengue virus is to combat the mosquito vectors.

Reduction of the mosquito vector is achieved using environmental management and chemical, mechanical, and biological approaches. The integration of vector management approaches is encouraged by WHO to achieve sustainable, effective, locally adapted vector control interventions.

8.6.3.1 Environmental Management

The proximity of mosquito vector breeding sites to human habitation is a significant risk factor for dengue, preventing mosquitoes from accessing egg-laying habitats by environmental management and modification;

Prevention of mosquito breeding is performed by disposing of solid waste properly and removing artificial man-made habitats that can hold water; covering, emptying, and cleaning of domestic water storage containers on a weekly basis; reducing the breeding sites for *Aedes* mosquitoes that transmit vector-borne dengue by enhancing access to piped water, constructing houses with built-in screens to block mosquito entry; clearing waste; and improving drainage and keeping the environment clean.

8.6.3.2 Mechanical Approaches

Mechanical approaches such as mosquito traps, electric mosquito swatters, and mosquito nets are used.

8.6.3.3 Chemical Control

Insecticides are among the most effective ways to control mosquito populations, but the majority of them have negative impacts on health and environment and some are no longer effective due to the emergence of insecticide-resistant mosquitoes. Most of the available preventive and control measures involve an application of chemical-based products. The inappropriate use of chemicals causes insecticide resistance and environmental contamination.

8.6.3.4 Biological Control

As there are few effective sustainable tools available to combat *Aedes*-borne diseases, all new tools that demonstrate public health value against dengue and similar viruses will be a welcome addition to the vector control arsenal. A number of novel approaches have been employed to control mosquito populations. Biological control using bacterial infections such as *Wolbachia* results in the reduction of vector. Over the past two decades, various innovative strategies to reduce the transmission of dengue have been developed. Some strategies aim to reduce mosquito populations, which are known as population suppression; the strategies that aim to make wild mosquitoes unable to transmit infectious diseases by spreading genetic modifications or bacterial infections through natural populations are known as population replacement. Both population suppression and population replacement have developed in some BRT countries, like China, Singapore, Malaysia, Indonesia, and Thailand.

8.6.3.4.1 Population Replacement

Wolbachia are intercellular natural symbiotic bacteria in insects that are known to reduce the capacity of *Ae. aegypti* and *Ae. albopictus* to transmit dengue virus and related viruses under laboratory conditions. However, epidemiological evidence has been awaited to demonstrate the large-scale deployment of *Wolbachia*-infected *Ae. aegypti* in reducing the overall frequency of the transmission of the dengue virus within a population; the results of the study from Indonesia are therefore of great interest.

A three-year trial in Indonesia has produced encouraging results that show a significant reduction in the number of dengue cases. The trial conducted by the World Mosquito Program in close collaboration with the Tahija Foundation and the Gadjah Mada University in Indonesia tested *Ae. aegypti* mosquitoes carrying *Wolbachia* for their capacity to inhibit the transmission of the dengue virus.

It involved the release *Wolbachia*-infected *Ae. aegypti* mosquitoes in and around the dengue-endemic city of Yogyakarta.

The study found that in the city and surrounding areas where the infected mosquitoes were released the number of cases of dengue decreased significantly compared with parts of the city where they were not. *Ae. aegypti* mosquitoes infected with the wMel strain of *Wolbachia pipientis* are less susceptible than wild-type *Ae. aegypti* to dengue virus infection. Introgression of wMel into *Ae. aegypti* populations was effective in reducing the incidence of symptomatic dengue and resulted in fewer hospitalizations for dengue among the participants (Utarini et al. 2019).

In Malaysia, releases of *Ae. aegypti* mosquitoes carrying wAlbB were carried out in six diverse sites in greater Kuala Lumpur, with high endemic dengue transmission (Nazni et al. 2019). The strain was successfully established and maintained at very high population frequency at some sites or persisted with additional releases following fluctuations at other sites. In the release sites, reduced human dengue incidence was observed when compared to control sites based on passive case monitoring. *Wolbachia* provides a promising option as a tool for dengue control.

8.6.3.4.2 Population Suppression

Population suppression strategies currently being developed in BRT countries include sterile insect technique (SIT), incompatible insect technique (IIT), and combination of IIT with SIT (IIT-SIT). All these strategies reduce mosquito density by continuously releasing sterilized males.

In SIT, artificially-reared radiation-sterilized males are released into the field to mate with wild females. SIT has been used with great success against other insect pests; for example, the New World screwworm, *Cochliomyia hominivorax*, has been eradicated from Northern and Central America; the tsetse fly, *Glossina austeni*, from Unguja Island, Zanzibar, since 1997; and the Mediterranean fruit fly, *Ceratitis capitata*, from Mexico. The program is still ongoing to contain its reinvasion from Guatemala, and the codling moth, *Cydia pomonella*, has been suppressed using SIT in British Columbia, Canada, for more than 25 years.

SIT is an innovative nuclear technique that sterilizes mosquitoes to be tested in countries to control dengue, Zika, and chikungunya. It is an environmentally friendly control method. The SIT against mosquitoes is still under development in BRT countries. SIT is not a stand-alone technique, but rather meant to complement existing vector control measures within area-wide integrated control strategies for mosquito control.

The development of SIT against mosquitoes has progressed rapidly in recent years with significant advances made with the development of genetic sexing strains, mass-rearing, sex separation, handling, radiation, quality control, and release technologies.

Recent progress in the development of the SIT package against mosquitoes allows envisaging its larger-scale deployment. Four phases are presented, that is, from preparatory activities to operational deployment, with some milestones highlighted that include go/no-go criteria.

Phase 0 is a pre-intervention phase in which stakeholder commitment is secured; eight BRT countries are at phase 0: Brunei Darussalam, Myanmar, Pakistan, Cambodia, Fiji, Lao P.D.R., Nepal, and Viet Nam.

Phase I includes the collection of all relevant baseline data that are required to develop an appropriate intervention strategy against target mosquito populations. The Philippines and Bangladesh are at phase 1.

Phase II includes all necessary activities for a successful small-scale field trial; China, Indonesia, Malaysia, Sri Lanka, and Thailand are at phase 2.

Phase III includes the necessary activities to upscale the intervention; only Singapore is at phase 3.

Phase IV corresponds to the area-wide deployment of the intervention (including the release of sterile mosquitoes) that is guided by an adaptive management approach and the evaluation of the SIT program. No BRI countries are at this phase.

IIT and IIT-SIT.

Incompatible insect technique (IIT) uses cytoplasmic incompatibility (CI) caused by the maternally inherited endosymbiotic bacteria *Wolbachia* to sterilize field females when they mate with released males infected with a different *Wolbachia* strain. *Wolbachia*-based sterilization used by IIT has little or no impact on male fitness and mating competitiveness. The successful field trial in Guangzhou, China, demonstrates the feasibility of the area-wide application of IIT/SIT for mosquito vector control. Combined IIT/SIT nearly eliminated two field populations of *A. albopictus* over a two-year period (Zhang et al. 2018).

In Singapore, a three-year trial demonstrated that *Wolbachia*-based IIT dramatically reduces both wild-type *Ae. aegypti* populations [reductions of 92.7% (95% CI: 84.7%–95.8%) and 98.3% (97.7%–99.8%)] and dengue incidence [reductions of 71% (43%–87%) to 88% (57%–99%)] in ten targeted areas. Releases of male *Wolbachia*-infected *Ae. aegypti* suppress dengue mosquitoes and reduce dengue incidence in high-rise urban areas in Singapore (Liew et al. 2021).

In Thailand (Kittayapong et al. 2019), the first proof of-concept to suppress *Aedes aegypti* vector populations by using IIT-SIT in semi-rural settings was conducted. Whether open field release of sterile males, produced from combining the sterile insect technique using radiation with the insect incompatible technique through *Wolbachia*-induced incompatibility (SIT/IIT), could suppress natural populations of *Ae. aegypti* in semi-rural village settings was explored. The pilot trial involved the release of 100–200 sterile males per household in a treated area over a 6-month period. High efficacy of this approach was evidenced by a significant reduction in the numbers of wild *Ae. aegypti* females and an increase in sterility by reduction in the egg hatch rate of wild *Ae. aegypti* females in the treated area.

However, IIT may be undermined by the accidental release of females infected with the same *Wolbachia* strain as released males. Accidental release of fertile females might cause population replacement, whereby individuals infected with the same *Wolbachia* strain as released males replace the wild-type field population, preventing population suppression (as mating between released males and field females are no longer incompatible). While combining IIT and SIT, low-dose irradiation sterilizes residual females not removed from released males without affecting the latter's fitness or mating performance. Irradiation provides protection against accidental female release, especially compared to manual checking, as wPip-positive larvae did not increase despite more (>ten-fold) mosquitoes being released. In addition, irradiated HC males also induce HC female sterility and further reduce the risk of population replacement.

8.6.4 Personal Protection to Avoid Mosquito Bites

Some personal household protection measures can be used for avoiding mosquito biting, such as repellents, coils, vaporizers, window screens, etc. Because the *Aedes* mosquito vectors bite throughout the day, these measures must be observed during the day both inside and outside of the home or at work/school. When going outside, it is recommended to wear clothing that minimizes skin contact with mosquitoes.

8.6.5 Community Engagement

Some unsuccessful mosquito control strategies have often been associated with the lack of local community involvement and the inability to scale-up local, small-scale success to mega-cities and large geographical areas.

The following approaches have been implemented to achieve mosquito control: educating the community on the risks of mosquito-borne diseases; engaging with the community to improve participation and mobilization for sustained vector control; and mosquito vector control programs working jointly with city planners, environmentalists, engineers, and sectors that manage water and sanitation.

8.6.6 Active Mosquito Monitoring

Vector abundance and species composition should be actively monitored to determine the effectiveness of control measures.

Monitoring the prevalence of the virus in the *Aedes* mosquito population was performed by an active screening of sentinel mosquito collections prospectively. The monitoring of mosquito vectors can also be combined with environment and clinical surveillance. In addition, many international collaboration groups conduct research to find new tools and innovative strategies that can contribute to global efforts to interrupt dengue transmission. In Singapore, types of urban housing influence indoor breeding and dengue cases. The strategic plan of Urban Redevelopment Authority of Singapore focuses on affording public housing in high-rise buildings as a solution for the growing population.

References

Ahmed AM, Mohammed AT, Vu TT et al (2020) Prevalence and burden of dengue infection in Europe: a systematic review and meta-analysis. Rev Med Virol 30(2):e2093. https://doi.org/10.1002/rmv.2093. Epub 2019 Dec 13

Bos S, Gadea G, Despres P (2018) Dengue: a growing threat requiring vaccine development for disease prevention. Pathog Glob Health 112(6):294–305. https://doi.org/10.1080/20477724.2018.1514136

Hung TM, Clapham HE, Bettis AA et al (2018) The estimates of the health and economic burden of dengue in Vietnam. Trends Parasitol 34(10):904–918. https://doi.org/10.1016/j.pt.2018.07.007. Epub 2018 Aug 9

Kittayapong P, Ninphanomchai S, Limohpasmanee W et al (2019) Combined sterile insect technique and incompatible insect technique: the first proof-of-concept to suppress Aedes aegypti vector populations in semi-rural settings in Thailand. PLoS Negl Trop Dis 13(10):e0007771. https://doi.org/10.1371/journal.pntd.0007771

Liew C, Soh LT, Chen I, Ng LC (2021) Public sentiments towards the use of Wolbachia-Aedes technology in Singapore. BMC Public Health 21(1):1417. https://doi.org/10.1186/s12889-021-11380-w

Liu Y, Liu J, Cheng G (2016) Vaccines and immunization strategies for dengue prevention. Emerg. Microbes Infect 5(7):e77. https://doi.org/10.1038/emi.2016.74

Messina JP, Brady OJ, Scott TW, Zou C, Pigott DM, Duda KA, Bhatt S, Katzelnick L, Howes RE, Battle KE, Simmons CP, Hay SI (2014) Global spread of dengue virus types: mapping the 70 year history. Trends Microbiol 22(3):138–146. https://doi.org/10.1016/j.tim.2013.12.011. Epub 2014 Jan 24. PMCID: PMC3946041

Mohan A, Fakhor H, Nimavat N et al (2021) 2021 dengue and COVID-19: a risk of coepidemic in Ethiopia. J Med Virol 93(10):5680–5681. https://doi.org/10.1002/jmv.27116. Epub 2021 Jun 9

Nazni WA, Hoffmann AA, NoorAfizah A et al (2019) Establishment of Wolbachia strain wAlbB in Malaysian populations of Aedes aegypti for dengue control. Curr Biol 29(24):4241–4248.e5. https://doi.org/10.1016/j.cub.2019.11.007

Ooi EE, Goh KT, Gubler DJ (2006) Dengue prevention and 35 years of vector control in Singapore. Emerg Infect Dis 12(6):887–893. https://doi.org/10.3201/10.3201/eid1206.051210

Sahak MN (2020) Dengue fever as an emerging disease in Afghanistan: epidemiology of the first reported cases. Int J Infect Dis 99:23–27. https://doi.org/10.1016/j.ijid.2020.07.033

Tozan Y, Ratanawong P, Sewe MO et al (2017) Household costs of hospitalized dengue illness in semi-rural Thailand. PLoS Negl Trop Dis 11(9):e0005961. https://doi.org/10.1371/journal.pntd.0005961

Uyar Y, Aktaş E, Yağcı Çağlayık D et al (2013) An imported dengue fever case in Turkey and review of the literature. Mikrobiyol Bul 47(1):173–180. Turkish. https://doi.org/10.5578/mb.4564

Were F (2012) The dengue situation in Africa. Paediatr Int Child Health 32(S1):18–21. https://doi.org/10.1179/2046904712Z.0000000004

Zhang FC, He JF, Peng J et al (2018) Guidelines for diagnosis and treatment of dengue in China. Zhonghua Nei Ke Za Zhi 57(9):642–648. Chinese. https://doi.org/10.3760/cma.j.issn.0578-1426.2018.09.005