

Dengue Fever: An Update

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Abstract

Dengue is a mosquito-borne viral infection. The infection causes flu-like illness, which occasionally develops into a potentially lethal complication called severe dengue. The global incidence of dengue has grown dramatically in recent decades. About half of the world's population is now at risk. Dengue is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas. Severe dengue is a leading cause of serious illness and death among children in some Asian and Latin American countries. There is no specific treatment for dengue/ severe dengue, but early detection and access to proper medical care lowers fatality rates below one percent. Dengue prevention and control depends on effective vector control measures. A dengue vaccine has been licensed by several National Regulatory Authorities for use in people 9-45 years of age living in endemic settings.

Keywords: Dengue; Viral Infection; Severe; Flu-Like; Fatal.

Introduction

Dengue fever is a mosquito-borne viral disease that has rapidly spread in all regions of the world in recent years. It is caused by the dengue virus. Mild dengue fever causes high fever, rash, muscle and joint pain. A severe form of dengue fever, also called dengue hemorrhagic fever, can cause severe bleeding, a sudden shock and death [1]. Symptoms typically begin 3 to 14 days after infection [2]. This may include a high fever, headache, vomiting, muscle, joint pains, and a characteristic skin rash [1,2]. Recovery generally takes less than 2 to 7 days [1]. In a small proportion of cases, the disease develops into the life-threatening dengue hemorrhagic fever, resulting in bleeding, low levels of blood platelets, blood

plasma leakage, or into dengue shock syndrome, where dangerously low blood pressure occurs [2]. As we have come to understand this illness, fluid therapy has become the most important aspect in the management of dengue. In 2009, WHO new guidelines for management of dengue were published [3]. In 2012 the revised comprehensive guidelines were published by WHO [4].

History

The first record of a case of probable dengue fever is in a Chinese medical encyclopedia from the Jin Dynasty (265–420 AD) which referred to a "water poison" associated with flying insects [5]. The primary vector, *Aedes aegypti*, spread out of Africa in the 15th to 19th centuries due in part to increased globalization secondary to the slave trade [6]. There have been descriptions of epidemics in the 17th century, but the most plausible early reports of dengue epidemics are from 1779 and 1780, when an epidemic swept across Asia, Africa and North America [7]. From that time until 1940, epidemics were infrequent [7]. In 1906, transmission by the *Aedes* mosquitoes was confirmed, and in 1907 dengue was the second disease (after yellow fever) that was shown to be caused by a virus. Further investigations by John Burton Cleland and Joseph Franklin Siler completed the basic understanding of dengue transmission [8].

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The marked spread of dengue during and after the Second World War has been attributed to ecologic disruption. The same trends also led to the spread of different serotypes of the disease to new areas, causing the emergence of dengue hemorrhagic fever. This severe form of the disease was first reported in the Philippines in 1953; by the 1970s, it had become a major cause of child mortality [7]. Dengue hemorrhagic fever and dengue shock syndrome were first noted in Central and South America in 1981, as DENV-2 (one of the five strains) was contracted by people who had previously been infected with DENV-1 (one of the five strains) several years earlier [9]. The origins of the Spanish word “dengue” are not certain, but possibly is derived from “dinga” in the Swahili phrase “Ka-dingea pepo”, which describes the disease as being caused by an evil spirit [5]. Slaves in the West Indies having contracted dengue were said to have the posture and gait of a dandy, thus the disease was known as “dandy fever” [10,11]. The term “break-bone fever” was applied by physician and United States Founding Father Benjamin Rush, in a 1789 report of the 1780 epidemic in Philadelphia. In the report, he uses the more formal term “bilious remitting fever” [12]. The term dengue fever came into general use only after eighteen hundred and twenty eight. Other historical terms include “breakheart fever” and “la dengue”. Terms for severe disease include “infectious thrombocytopenic purpura” and “Philippine”, “Thai”, or “Singapore hemorrhagic fever” [11].

Epidemiology

Dengue is common in more than 110 countries. The high risk regions for catching dengue fever are Central America, South America, the Caribbean and tropical Asia; more specifically - northern Argentina, northern Australia, Bangladesh, Barbados, Bolivia, Brazil, Cambodia, Costa Rica, Dominican Republic, Guatemala, Guyana, Honduras, India, Indonesia, Jamaica, Laos, Malaysia, Mexico, Micronesia, Pakistan, Panama, Paraguay, Philippines, Puerto Rico, Samoa, Singapore, Sri Lanka, Suriname, Taiwan, Thailand, Trinidad, Venezuela and Vietnam, and increasingly in southern China [3].

In many parts of the tropics and subtropics, dengue is endemic; usually during a season when *Aedes* mosquito populations are high, often when rainfall is optimal for breeding. These areas are at periodic risk for epidemic dengue, when large numbers of people get infected during a short period. Dengue epidemics require a coincidence of large numbers of vector mosquitoes, large numbers of people with no immunity to one of the four virus types

(DENV 1, DENV 2, DENV 3, DENV 4), and the opportunity for contact between the two. It infects 50 to 528 million people worldwide a year, leading to half a million hospitalizations [13], and approximately 20,000 deaths [14]. In 2015, 2.35 million cases of dengue were reported in the Americas alone, of which 10 200 cases were diagnosed as severe dengue causing 1181 deaths. The number of cases reported increased from 2.2 million in 2010 to 3.2 million in two thousand and fifteen [1]. The year 2015 was characterized by large dengue outbreaks worldwide, with the Philippines reporting more than 169 000 cases and Malaysia exceeding 111 000 suspected cases of dengue, representing a 59.5% and 16% increase in case numbers than the previous year, respectively. Brazil alone reported over 1.5 million cases in 2015, approximately 3 times higher than in two thousand and fourteen. Also in 2015, Delhi, India, recorded its worst outbreak since 2006 with over 15 000 cases [16,17,18].

Infections are most commonly acquired in the urban environment [19]. In recent decades, the expansion of villages, towns and cities in the areas in which it is common, and the increased mobility of people have increased the number of epidemics and circulating viruses [20]. Rates of dengue increased 30 fold between 1960 and two thousand ten [21]. This increase is believed to be due to a combination of urbanization, population growth, increased international travel, and global warming [13]. An infection with dengue is second only to malaria as a diagnosed cause of fever among travelers returning from the developing world [22]. It is the most common viral disease transmitted by arthropods [23], and has a disease burden estimated at 1,600 disability-adjusted life year per million population [24]. The World Health Organization counts dengue as one of seventeen neglected tropical diseases [25].

Like most arboviruses, dengue virus is maintained in nature in cycles that involve preferred blood-sucking vectors and vertebrate hosts [15]. The viruses are maintained in the forests of Southeast Asia and Africa by transmission from female *Aedes* mosquitoes – of species other than *A. aegypti* – to their offspring and to lower primates [19]. In towns and cities, the virus is primarily transmitted by the highly domesticated *A. aegypti*. In rural settings the virus is transmitted to humans by *A. aegypti* and other species of *Aedes* such as *A. albopictus* [19]. Both these species had expanding ranges in the second half of the 20th century [26]. In all settings the infected lower primates or humans greatly increase the number of circulating dengue viruses, in a process called amplification [19].

Etiology

There are four dengue viruses (DEN-V) that cause dengue fever, all of which are spread by a species of mosquito known as the *Aedes aegypti* mosquito, more rarely by the *Aedes albopictus* mosquito. Infection with one serotype does not protect against the others, and sequential infections put people at greater risk for dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Dengue fever virus (DENV) is an RNA virus of the family Flaviviridae; genus *Flavivirus*. Other members of the same genus include yellow fever virus, West Nile virus, St. Louis encephalitis virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kyasanur forest disease virus, and Omsk hemorrhagic fever virus. Most are transmitted by arthropods (mosquitoes or ticks), referred to as arboviruses (arthropod-borne viruses) [27].

The dengue virus genome contains about 11,000 nucleotide bases, which code for the three different types of protein molecules (C, prM and E) that form the virus particle and seven other types of protein molecules (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) that are found in infected host cells only which are required for replication of the virus [23,28]. There are five [29] strains of the virus, called serotypes, of which the first four are referred to as DENV-1, DENV-2, DENV-3 and DENV-4 [30]. The fifth type was announced in two thousand thirteen [29]. The distinctions between the serotypes are based on their antigenicity [27]. The genetic variation in dengue viruses is region specific; suggesting that establishment into new territories is relatively infrequent, despite dengue emerging in new regions in recent decades [26].

Transmission

Dengue is transmitted between people by the several species of mosquito of the *Aedes* type, principally *Aedes aegypti* and *Aedes albopictus*. In rare cases, dengue can be transmitted in organ transplants or blood transfusions from infected donors; there is evidence of transmission from an infected pregnant mother to her fetus [31]. Other person-to-person modes of transmission have also been reported, but are very unusual [22]. But in the vast majority of infections, a mosquito bite is responsible [1]. These mosquitoes usually live between the latitudes of 35° North and 35° South below an elevation of 1,000 meters [30]. They typically bite during the early morning and in the evening [32], but they may bite and thus spread infection at any time of day [33].

Humans are the primary host of the virus [27], but it also circulates in nonhuman primates [34]. An infection can be acquired via a single bite [35]. A female mosquito that takes a blood meal from a person infected with dengue fever, during the initial 2- to 10-day febrile period, becomes itself infected with the virus in the cells lining its gut [36]. About 8–10 days later, the virus spreads to other tissues including the mosquito's salivary glands is subsequently released into its saliva. The virus seems to have no detrimental effect on the mosquito, which remains infected for life. *Aedes aegypti* is particularly involved, as it prefers to lay its eggs in artificial water containers, to live in close proximity to humans, and to feed on people rather than other vertebrates [19].

Symptoms of infection usually begin 4–7 days after the mosquito bite and typically last 3–10 days. In order for transmission to occur the mosquito must feed on a person during a 5-day period when large amounts of virus are in the blood; this period usually begins a little before the person become symptomatic. Some people never have significant symptoms but can still infect mosquitoes. After entering the mosquito in the blood meal, the virus will require an additional 8–12 days incubation before it can then be transmitted to another human. The mosquito remains infected for the remainder of its life, which might be days or a few weeks. The virus causing Dengue is spread by five different types [37]; infection with one type usually gives lifelong immunity to that type, but only short-term immunity to the others. Subsequent infection with a different type increases the risk of severe complications [1]. A number of tests are available to confirm the diagnosis including detecting antibodies to the virus or its RNA [2].

Pathogenesis

When a mosquito carrying dengue virus bites a person, it enters the skin together with the mosquito's saliva. It binds to and enters white blood cells; reproduces inside the cells while they move throughout the body. The white blood cells respond by producing a number of signaling proteins, such as cytokines and interferons, which are responsible for many of the symptoms. In severe infection, the virus production inside the body is greatly increased, affecting different organs (such as the liver and the bone marrow). Fluid from the bloodstream leaks through the wall of small blood vessels into body cavities due to capillary permeability. As a result, less blood circulates in the blood vessels, and the blood pressure becomes so low that it cannot supply sufficient blood to vital organs. Furthermore, dysfunction of the bone marrow due to infection of

the stromal cells leads to reduced numbers of platelets, which are necessary for effective blood clotting; this increases the risk of bleeding, the other major complication of dengue fever [38].

Once inside the skin, dengue virus binds to Langerhans cells [38]. The virus enters the cells through binding between viral proteins and membrane protein on the Langerhans cell, specifically the C-type lectins [23,24]. The dendritic cell moves to the nearest lymph node. Meanwhile, the virus genome is translated in membrane-bound vesicles on the cell's endoplasmic reticulum, where the cell's protein synthesis apparatus produces new viral proteins that replicate the viral RNA and begin to form viral particles. Immature virus particles are transported to the golgi apparatus. The now mature new viruses are released by exocytosis. They are then able to enter other white blood cells, such as monocytes and macrophages [23].

The initial reaction of infected cells is to produce interferon that raises a number of defenses against viral infection through the innate immune system by augmenting the production of a large group of proteins. Some serotypes of dengue virus appear to have mechanisms to slow down this process. Interferon also activates the adaptive immune system, which leads to the generation of antibodies against the virus as well as T cells that directly attack any cell infected with the virus. Various antibodies are generated; some bind closely to the viral proteins and target them for phagocytosis but some bind the virus less well and appear instead to deliver the virus into a part of the phagocytes where it is not destroyed but is able to replicate further [23].

Predisposition/Risk Factors

Severe disease is more common in young children but in contrast to many other infections, it is more common in children who are relatively well nourished [39]. Other risk factors for severe disease include female sex, high body mass index, and viral load [40]. While each serotype can cause the full spectrum of disease [23], virus strain is a risk factor [40]. Infection with one serotype is thought to produce lifelong immunity to that type, but only short-term protection against the other three [30]. The risk of severe disease from secondary infection increases if someone previously exposed to serotype DENV-1 contracts serotype DENV-2 or DENV-3, or if someone previously exposed to DENV-3 acquires DENV-2. Dengue can be life-threatening in people with chronic diseases such as diabetes and asthma [28].

Polymorphisms in particular genes have been linked with an increased risk of severe dengue complications [13].

Clinical Features

As there are different severities of dengue fever, the symptoms can vary. Typically; people infected with dengue virus are asymptomatic (80%) or have only mild symptoms such as an uncomplicated fever [13,30]. Others have more severe illness (5%), and in a small proportion it is life-threatening [20]. The incubation period ranges from 3 to 14 days, but most often it is 4 to 7 days [19]. Therefore, travelers returning from endemic areas are unlikely to have dengue if fever or other symptoms start more than 14 days after arriving home [39]. Children often experience symptoms similar to those of the common cold and gastroenteritis have a greater risk of severe complications [39,40]. The characteristic symptoms of dengue are sudden-onset fever, headache (typically located behind the eyes), muscle and joint pains, and a rash. The course of infection is divided into three phases: febrile, critical, and recovery. The febrile phase involves high fever, potentially over 40 °C (104 °F), and is associated with generalized pain and a headache; this usually lasts two to seven days [22]. Nausea and vomiting may also occur [40]. A rash occurs in 50–80% of those with symptoms [22,41] in the first or second day, 4 of symptoms as flushed skin, or later in the course of illness (days 4–7), as a measles-like rash [41]. A rash described as “islands of white in a sea of red” has also been observed [27]. Some petechiae that do not disappear when the skin is pressed can appear at this point, as may some mild bleeding from the mucous membranes of the mouth or nose [22,39]. The fever itself is classically biphasic or saddleback in nature, breaking and then returning for one or two days [9,27].

In some people, the disease proceeds to a critical phase as fever resolves [6]. During this period, there is leakage of plasma from the blood vessels, typically lasting one to two days [42]. This may result in fluid accumulation in the chest and abdominal cavity as well as depletion of fluid from the circulation and organs. There may also be organ dysfunction with severe bleeding, typically from the gastrointestinal tract [39,42]. Shock (dengue shock syndrome) and hemorrhage (dengue hemorrhagic fever) occur in less than 5% of all cases of dengue, however those who have previously been infected with other serotypes of dengue virus (“secondary infection”) are at an increased risk [23,39]. This critical phase, while rare, occurs relatively more commonly in children and young adults [6].

The recovery phase occurs next, with resorption of the leaked fluid into the bloodstream [42]. This usually lasts two to three days [39]. The improvement is often striking; can be accompanied by severe itching with a slow heart rate [39,42]. Another rash may occur with either a maculopapular or a vasculitic appearance, which is followed by peeling of the skin [6]. During this stage, a fluid overload state may occur; if it affects the brain, it may cause a reduced level of consciousness or seizures [39]. A feeling of fatigue may last for weeks in adults [6].

Severe Disease

It is not entirely clear why secondary infection with a different strain of dengue virus places people at risk of dengue hemorrhagic fever and dengue shock syndrome. The most widely accepted hypothesis is that of antibody-dependant enhancement (ADE). The exact mechanism behind ADE is unclear. It may be caused by poor binding of non-neutralizing antibodies and delivery into the wrong compartment of white blood cells that have ingested the virus for destruction [23,28]. There is a suspicion that ADE is not the only mechanism underlying severe dengue-related complications [43], also various lines of research have implied a role for T cells and soluble factors such as cytokines and the complement system [38].

Severe disease is marked by the problems of capillary permeability with disordered blood clotting [6]. These changes appear associated with a disordered state of the endothelial glycocalyx, which acts as a molecular filter of blood components. Leaky capillaries are thought to be caused by an immune system response [6]. Other processes of interest include infected cells that become necrotic – which affect both coagulation, fibrinolysis and low platelets in the blood [38].

Complications

Dengue can occasionally affect several other body systems [42], either in isolation or along with the classic dengue symptoms. A decreased level of consciousness occurs in 0.5–6% of severe cases, which is attributable either to inflammation of the brain by the virus or indirectly as a result of impairment of vital organs, for example, the liver [27].

Other neurological disorders have been reported in the context of dengue, such as transverse myelitis and Guillain-Barre syndrome [44]. Infection of the heart and acute liver failure are among the rarer complications [39,42].

A pregnant woman who develops dengue may be at a higher risk of miscarriage as well as low birth weight and premature birth [45].

Prognosis

Most people with dengue recover without any ongoing problems. The fatality rate is 1–5% [39], and less than 1% with adequate treatment [46]; however those who develop significantly low blood pressure may have a fatality rate of up to 26% [39].

Diagnosis

The diagnosis of dengue is typically made clinically, on the basis of reported symptoms, physical examination especially in endemic areas [43]. However, early disease can be difficult to differentiate from other viral infections [39]. A probable diagnosis is based on the findings of fever plus two of the following: nausea and vomiting, rash, generalized pains, low white blood cell count, positive tourniquet test, or any warning sign in someone who lives in an endemic area [46]. Warning signs typically occur before the onset of severe dengue [42]. The tourniquet test involves the application of a blood pressure cuff at between the diastolic and systolic pressure for five minutes, followed by the counting of any petechial hemorrhages; a higher number makes a diagnosis of dengue more likely with the cut off being more than 10 to 20 per 1 inch [2,42].

The diagnosis should be considered in anyone who develops a fever within two weeks of being in the tropics or subtropics [26]. It can be difficult to distinguish dengue fever and chikungunya, a similar viral infection that shares many symptoms and occurs in similar parts of the world to dengue [22]. Often, investigations are performed to exclude other conditions that cause similar symptoms, such as malaria, leptospirosis, viral hemorrhagic fever, typhoid fever, meningococcal disease, measles, and influenza [39,47]. Zika fever also has similar symptoms as dengue [48].

The earliest change detectable on laboratory investigations is a low white blood cell count, which may then be followed by low platelets and metabolic acidosis [39]. A moderately elevated level of aminotransferase (AST and ALT) from the liver is commonly associated with low platelets and white blood cells [26]. In severe disease, plasma leakage results in hemoconcentration (as indicated by a rising hematocrit) with hypoalbuminemia. Pleural effusions or ascites can be detected by physical examination when large, but the demonstration of

fluid on ultrasound may assist in the early identification of dengue shock syndrome [39]. Dengue shock syndrome is present if pulse pressure drops to ≤ 20 mm Hg along with peripheral vascular collapse [26]. Peripheral vascular collapse is determined in children via delayed capillary refill, rapid heart rate, or cold extremities [42]. While warning signs are an important aspect for early detection of potential serious disease, the evidence for any specific clinical or laboratory marker is weak [49].

Laboratory Tests

The diagnosis of dengue fever may be confirmed by microbiological laboratory testing [46]. This can be done by virus isolation in cell cultures, nucleic acid detection by PCR, viral antigen detection (such as for NS1) or specific antibodies (serology) [24,47]. Virus isolation and nucleic acid detection are more accurate than antigen detection, but these tests are not widely available due to their greater cost [47]. Detection of NS1 during the febrile phase of a primary infection may be greater than 90% sensitive however is only 60–80% in subsequent infections [6]. All tests may be negative in the early stages of the disease [28,39]. PCR and viral antigen detection are more accurate in the first seven days [6]. In 2012 a PCR test was introduced that can run on equipment used to diagnose influenza; this is likely to improve access to PCR-based diagnosis [50].

These laboratory tests are only of diagnostic value during the acute phase of the illness with the exception of serology. Tests for dengue virus-specific antibodies, types IgG and IgM, can be useful in confirming a diagnosis in the later stages of the infection. Both IgG and IgM are produced after 5–7 days. The highest levels (titers) of IgM are detected following a primary infection, but IgM is also produced in reinfection. IgM becomes undetectable 30–90 days after a primary infection, but earlier following re-infections. IgG, by contrast, remains detectable for over 60 years and, in the absence of symptoms, is a useful indicator of past infection. After a primary infection, IgG reaches peak levels in the blood after 14–21 days. In subsequent re-infections, levels peak earlier and the titers are usually higher. Both IgG, IgM provide protective immunity to the infecting serotype of the virus [19,22,24]. In testing for IgG, IgM antibodies there may be cross-reactivity with other flaviviruses which may result in a false positive after recent infections or vaccinations with yellow fever virus or Japanese encephalitis [6]. The detection of IgG alone is not considered diagnostic unless blood samples are collected 14 days apart with a greater than fourfold increase in levels of specific

IgG is detected. In a person with symptoms, the detection of IgM is considered diagnostic [19].

Management

There are no specific antiviral drugs for dengue; however maintaining proper fluid balance is important [6]. Addressing the plasma leakage and complications of it has become the mainstay of treatment of dengue. Treatment depends on the symptoms [51]. WHO in their 2012 handbook on management of dengue, have described stepwise approach to the management of dengue, where only isotonic solutions have been advised, followed by serial monitoring of clinical status, fluid balance and hematocrit. Judicious fluid resuscitation was advised to maintain effective circulation during the leak period. Those who are able to drink, are passing urine, have no “warning signs” and are otherwise healthy can be managed at home with daily follow up and oral rehydration therapy [51]. Those who have other health problems have “warning signs”, or who cannot manage regular follow-up should be cared for in hospital [39,51]. In those with severe dengue care should be provided in an area where there is access to an intensive care unit [51].

Fluid must be administered orally as much as possible. Intravenous supplementation is necessary when the patient is not able to take fluids orally (severe vomiting, prostration) or is in shock. The rationale in fluid management is to keep enough fluid in the vascular system during the leakage phase to avoid hypovolemia and while also avoiding overloading the patient with too much fluid. Intravenous hydration, if required, is typically only needed for one or two days [51]. Two main types of volume expander are used to replace lost fluid in the management of dengue fever: crystalloids and colloids. The recommended first-line intravenous fluid is crystalloids (0.9% saline). Colloids (eg, dextran) are recommended as second-line therapy when hypotension is not responsive to boluses of intravenous crystalloids (with reference to local or World Health Organization guidance). The rate of intravenous fluid administration should be at stepwise increments or decrements with at least 4–6-hourly hematocrit monitoring during the critical phase. However, in situations of shock, immediate resuscitation with 20 mL/kg boluses is recommended until blood pressure is recordable [52]. The rate of fluid administration is then titrated to a urinary output of 0.5–1 mL/kg/h, stable vital signs and normalization of hematocrit [39]. The smallest amount of fluid required to achieve this is recommended. Administration of fluids should be

guided by frequent monitoring and assessment of intravascular volume status during the critical stage, and fluids should never be administered at a constant rate without monitoring [51].

Invasive medical procedures such as naso-gastric intubation, intramuscular injections, arterial punctures are avoided, in view of the bleeding risk [39]. Paracetamol (acetaminophen) is used for fever or discomfort while NSAIDs such as ibuprofen, aspirin are avoided as they might aggravate the risk of bleeding [51]. Blood transfusion is initiated early in people presenting with unstable vital signs in the face of a decreasing hematocrit, rather than waiting for the hemoglobin concentration to decrease to some predetermined "transfusion trigger" level. Packed red cells or whole blood is recommended, while platelets and fresh frozen plasma are usually not [53]. A rise in hematocrit indicates further hemoconcentration due to leakage, and hence a need for more fluids. However a drop in hematocrit may be due to either convalescence (reabsorption of extravasated fluid) or internal bleeding. If the patient is still ill and in critical phase with low platelet counts, always suspect bleeding. Sometimes there may not be any overt external manifestations of bleeding. In cases of suspected bleeding, the management strategy is transfusion of fresh whole blood [51,52,53].

There is not enough evidence to determine if steroids have a positive or negative effect in dengue fever [54].

During the recovery phase intravenous fluids are discontinued to prevent a state of fluid overload [39]. If fluid overload occurs and vital signs are stable, stopping further fluid may be all that is needed. If a person is outside of the critical phase, a loop diuretic such as furosemide may be used to eliminate excess fluid from the circulation [53].

Prevention

The best method of prevention is to avoid being bitten by mosquitoes. Prevention depends on control of and protection from the bites of the mosquito that transmits it [32,55]. The World Health Organization recommends an Integrated Vector Control program consisting of five elements [32]:

- Advocacy, social mobilization and legislation to ensure that public health bodies and communities are strengthened;
- Collaboration between the health and other sectors (public and private);

- An integrated approach to disease control to maximize use of resources;
- Evidence-based decision making to ensure any interventions are targeted appropriately; and
- Capacity-building to ensure an adequate response to the local situation.

The primary method of controlling *A. aegypti* is by eliminating its habitats. This is done by getting rid of open sources of water, or if this is not possible, by adding insecticides or biological control agents to these areas [32]. Generalized spraying with organophosphate or pyrethroid insecticides, while sometimes done, is not thought to be effective [20]. Reducing open collections of water through environmental modification is the preferred method of control, given the concerns of negative health effects from insecticides and greater logistical difficulties with control agents [32]. People can prevent mosquito bites by wearing clothing that fully covers the skin, using mosquito netting while resting, and/or the application of insect repellent (DEET being the most effective) [35]. However, these methods appear not to be sufficiently effective, as the frequency of outbreaks appears to be increasing in some areas, probably due to urbanization increasing the habitat of *A. aegypti*. The range of the disease appears to be expanding possibly due to climate change [37].

Vaccine

There are ongoing programs working on a dengue vaccine to cover all four serotypes [55]. Now that there is a fifth serotype this will need to be factored in [29]. One of the concerns is that a vaccine could increase the risk of severe disease through antibody-dependent enhancement (ADE). The ideal vaccine is safe, effective after one or two injections, covers all serotypes, does not contribute to ADE, is easily transported and stored, and is both affordable and cost-effective [56].

Six dengue fever vaccines are in development, but not yet available. The vaccine that's furthest in development is a three-dose vaccine for children. The results of a phase III trial were published in July 2014. This study showed that the vaccine appears to be safe, and it prevented dengue infections slightly more than half the time.

As of December 2015, there was no commercially available vaccine for dengue fever [49]. One that is partially effective is now available in Mexico, the Philippines, and Brazil from 2016 [57,58]. It received approval in December 2015 [58]. The vaccine is produced by Sanofi and goes by the brand name

Dengvaxia [59]. It is based on a weakened combination of the yellow fever virus and each of the four dengue serotypes [60,61]. Two studies of a vaccine found it was 60% effective and prevented more than 80 to 90% of severe cases [62,63].

Research

Research efforts to prevent and treat dengue include various means of vector control [64], vaccine development, and antiviral drugs [55]. With regards to vector control, a number of novel methods have been used to reduce mosquito numbers with some success including the placement of the copepods in standing water to eat the mosquito larvae [64]. There are also trials with genetically modified male *A. aegypti* that after release into the wild mate with females, and render their offspring unable to fly [64]. Attempts are ongoing to infect the mosquito population with bacteria of the *Wolbachia* genus, which makes the mosquitoes partially resistant to dengue virus [6]. While artificially induced infections with *Wolbachia* are effective, it is unclear if naturally acquired infections are protective. Working is still ongoing as of 2015 to determine the best type of *Wolbachia* to use [66].

Apart from attempts to control the spread of the *Aedes* mosquito there are ongoing efforts to develop antiviral drugs that would be used to treat attacks of dengue fever and prevent severe complications. Discovery of the structure of the viral proteins may aid the development of effective drugs [67]. There are several plausible targets. The first approach is inhibition of the viral RNA-dependent RNA polymerase (coded by NS5), which copies the viral genetic material, with nucleoside analogs. Secondly, it may be possible to develop specific inhibitors of the viral protease (coded by NS3), which splices viral proteins [68]. Finally, it may be possible to develop entry inhibitors, which stop the virus entering cells, or inhibitors of the 5' capping process, which is required for viral replication [69].

Campaign: Anti-Dengue day

International Anti-Dengue Day is observed every year on June 15 [70]. The idea was first agreed upon in 2010 with the first event held in Jakarta, Indonesia in 2011. Further events were held in 2012 in Yangon, Myanmar and in 2013 in Vietnam [70]. Goals are to increase public awareness about dengue, mobilize resources for its prevention and control and, to demonstrate the Asian region's commitment in tackling the disease [71].

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