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Chapter

Asymptomatic Dengue and Silent Transmission

Pavithra Dilakshini Dayananda and B.G.D. Nissanka K. de Silva

Abstract

With over 90% of infected proportions being asymptomatic to dengue, their possible contribution to silent transmission has generated much attention in epidemic and non-epidemic settings. The challenges in identifying the true asymptomatic representation, owing to no clinical symptoms, have limited scientific knowledge of the asymptomatic dengue, its viral kinetics, immune mechanisms and underlying protective mechanisms in action. The chapter gives an overview of dengue, and its asymptomatic counterparts. It elaborates on the current knowledge in immunity, and immunopathology in symptomatic cases and provides postulations on possible protective mechanisms responsible for the asymptomatic nature of individuals. The chapter further discusses the importance of identifying the asymptomatic proportion in a community and the challenges in diagnosis. It highlights the major role, that asymptomatic carriers play in silent transmission, and its implications and further discuss the possible measures to minimize the transmission risk.

Keywords: dengue, dengue without symptoms, asymptomatic, dengue transmission, silent transmission, transmission risk

1. Introduction

Dengue is considered the most prevalent arthropod-borne viral disease in the world, causing more than 90 million cases and approximately 40,000 deaths per year [1, 2]. Causative agent- Dengue virus (DENV) is a single-stranded RNA virus of the Genus Flavivirus, which is comprised of 4 closely related, antigenically discrete serotypes, DENV1, DENV2, DENV3 and DENV4. However, in 2013 a 5th DENV serotype (DENV5) also has been reported [3]. DENV is transmitted by *Aedes* mosquitoes, mainly *Aedes aegypti* and *Aedes albopictus*. The virus and its vectors are widespread in over 100 countries worldwide, both tropical and subtropical [4]. Since there is no specific medication other than clinical management, the prevention of the disease relies mainly on vector control, and vaccine development is urgently required. Currently, a live attenuated vaccine, chimeric yellow fever 17D—tetravalent dengue vaccine (CYD-TDV), has been licensed for clinical use in some countries, and many candidate vaccines; including live attenuated vaccines, inactivated vaccines, recombinant subunit vaccines, viral vectored vaccines, and DNA vaccines are still under research and development [5].

Many factors have contributed to the expansion of dengue spread such as population growth, urbanization, inadequate water management, poor waste management, lack of effective mosquito control and increased global travel. Changes in global climatic patterns are believed to have expanded the vector habitat range and resulting increased epidemic activity may have caused an increase in the rate of viral genetic change and the emergence of strains or genotypes with greater epidemic potential [6–8].

Dengue has a wide spectrum of clinical outcomes ranging from asymptomatic to symptomatic; resulting in asymptomatic infections, undifferentiated fevers, Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) [1, 9]; alternatively, they can be classified as dengue with warning signs (DWS), Dengue without warning signs (DWOS) and severe dengue (SD) as suggested by WHO [10]. Each year, 390 million DENV infections occur globally and an estimated 300 million result in asymptomatic/mildly symptomatic [11–14].

Primary Dengue infections are often observed to be asymptomatic and are known to generate immunity to the homologous DENV strain. However, 90% of DWS are known to reportedly occur following a second exposure to a heterologous strain of DENV [15]. It has been observed that sequential or secondary DENV infections are more likely to produce severe diseases [16, 17]. Cross-protection from previous infections and the neutralizing antibody levels also seem to play a major role in determining the level of severity of the disease [18, 19].

2. DWOS; asymptomatic infections

The incidence of dengue infection has been rising over the last five decades [20] and the majority of infected individuals are known to have no or insufficient symptoms to result in clinical presentation [12, 14]. Mildly symptomatic or subclinical infections are mostly referred to as DENV infections without major symptoms requiring medical attention, while the patients who have virologically or serologically confirmed dengue with no reported or detected symptoms are named dengue 'asymptomatic' patients [12].

Although asymptomatic infections are considered more frequent than symptomatic, the relative number of cases is observed to be vary according to the year of infection, geographical area, the epidemiological context, the immunological status of individuals, and the circulating serotypes and viral strains [21]. The ratios of asymptomatic to symptomatic cases have been shown to vary from 2.1:1 to 13:1 around the world [22] making this change in the proportion of symptomatic to asymptomatic infections, one of the main contributors to the rise in the dengue incidence.

A study carried out in Thailand during 1980–1981 reported a ratio of asymptomatic to symptomatic cases as 6.1:1, while this ratio was refined as 5.5:1 for DENV 1 cases, 4.5:1 for DENV 2 cases and for entirely asymptomatic for DENV4 cases [16]. During the period of 1998–2000, a similar survey in Northern Thailand reported a ratio of 1.1:1 [23]. A study carried out in Central America reported a ratio of 13:1 during the period of 2001–2003 when DENV2 was dominant and a ratio of 6.1 when DENV1 was frequent [24]. It has been reported that the Health authorities in Singapore assumed ratios between 2:1 and 10:1 during the period of 2006–2007 [25]. Studies from Sri Lanka have shown that the asymptomatic to symptomatic ratio was 3.4:8.4 between 2008 and 2010 [22]. In a pediatric dengue cohort study in Nicaragua, a wide variation from 16.5:1 in 2006–2007 [26] to 1.2:1 in 2009–2010 [27] has been shown. All these studies reveal the extensive variation of asymptomatic to

symptomatic ratios, where the differences might be attributed to the extrinsic and intrinsic factors of the host and the circulating virus types [24, 28].

Clinically apparent dengue is frequently studied with various research objectives. However, the science behind asymptomatic dengue is inadequately investigated mainly due to the challenges in diagnosing asymptomatic cases on time. Thus, understanding the host factors such as the role of immunity on the lack of clinical symptoms and or the other protective mechanisms for being symptomless has mainly been based on careful investigation of symptomatic cases.

2.1 Dengue; immunity

Once an immune-susceptible host meets with the infection, an acute, self-limiting febrile systematic syndrome is known to develop usually within initial 4–7 days. This is known to be associated with strong innate and adaptive immune responses [29].

2.1.1 Innate immune response

At the site of the mosquito bite, Langerhans cells, dermal cells and interstitial dendritic cells of the innate immune system become the initial targets for DENV [29]. The three cell types, monocytes, macrophages, and dendritic cells which are tolerable for DENV infection act as the main phagocytic cells of the innate immune system, responsible for detecting and removing hostile pathogens. These three major phagocytic cells also function as antigen-presenting cells critical for the initiation, expansion, and polarization of adaptive cellular immunity [30]. All these innate immunity mechanisms are triggered immediately upon pathogen invasion and play a significant role in managing pathogenic infection. The killing of target cells is associated with inflammatory cytokine and or chemokine responses [30]. However, DENV has evolved successfully to suppress innate immunity and to infect the host productively using passive and active evasive strategies, which have a negative effect on the subsequent production of antigen-specific adaptive immunity to these viruses [31].

2.1.2 Adaptive immune response (cell-mediated immune response)

Many studies have shown that the adaptive immune response to DENV has protective as well as detrimental aspects [32]. Dengue-induced immune enhancement plays a major role in the clinical manifestations of dengue disease. The imbalanced and deregulated, cell-mediated immunity is considered as a major component in severe dengue conditions [29]. It is hypothesized that DENV infection of monocytes and macrophages increases T cell activation, leading to the release of cytokines and chemical mediators such as Tumor Necrosis Factors (TNF), Interleukins (IL), Platelet Activating Factors (PAF), complement components and histamines causing increased vascular permeability, plasma leakage, shock and malfunction of the coagulatory system resulting in hemorrhage and shock [33, 34]. In this phenomenon, DENV infection of dendritic cells strongly activates CD4+ and CD8+ T cells which produce a surplus of cytokines, which recruit numerous other cytokines and chemical mediators that further increase the vascular permeability of the host [34, 35].

2.1.3 Adaptive immune response (humoral response)

Individuals infected with DENV generate serum antibody titers that provide long-term protection against future homotypic infections with the same serotype [32].

Infection with DENV also builds a degree of cross-protective immunity against the other three DENV serotypes by means of heterotypic (cross-reactive) IgG antibodies which usually persist for a duration of several months to a few years [36]. The produced heterotypic antibody titers are known to reduce over long time periods of approximately 4 to 20 years [37]. However, conversely, the homotypic IgG antibody titers are known to increase over time which could be due to the preferential survival of long-lived memory B cells producing homotypic antibodies [37].

2.2 Dengue; immunopathogenesis

The postulated hypotheses on dengue immunopathogenesis include the antibody enhancement theory, cross-reactive memory T cells activation and the original antigenic sin where all in a way cause either an overproduction or a skewed profile of cytokine release [38, 39].

Antibody-dependent enhancement (ADE); The leading hypothesis is that DHF occurs via ADE of a DENV infection [40–43]. Preexisting heterologous, cross-reactive antibodies from a previous infection (or maternal antibodies in infants) recognize and bind to heterologous DENV in a secondary or tertiary infection (primary infection in infants), are unable to neutralize this virus, either because they are non-neutralizing, or due to inadequate avidity or occupancy [41, 44–46]. These non-neutralizing antibody–virus complexes are known to increase the infection of monocytes via their Fc receptors, dramatically increasing viral replication and load, thereby causing DHF. Weak and non-neutralizing cross-reactive antibodies induced from immunodominant B cell epitopes are known to comprise the majority of the humoral immune response to DENV infection [38, 47, 48].

Cross-reactive memory T cells activation and Original antigenic sin; the second hypothesis indicates that there is a highly skewed cellular response to heterologous DENV infection motivated by low affinity, cross-reactive memory CD4+ and CD8+ T cells [49–51]. Cross-reactive T cell epitopes have been identified across the DENV proteome, however, immunodominant CD8+ T cell epitopes in dengue non-structural protein NS3 have been found strongly associated with DHF [15, 52, 53]. The common theme throughout DENV immune enhancement is the concept of "original antigenic sin," which describes the shift in the hierarchy of immunodominance that occurs when previous exposure to cross-reactive antigens alters and inhibits the subsequent immune response to related antigens, either as a new infection or by vaccination [49]. Both humoral and cellular responses are known to be plagued by such misdirected or inappropriate heterotypic immunity [54].

All these mechanisms are known to increase the activation of immune cells, resulting in impaired immune responses or cytokine storms that cause endothelium dysfunction and increase vascular permeability. However, multiple host and viral factors seem to be influencing the determination of the disease severity of DENV infections via favorable and unfavorable interactions thus have triggered much research interest [55].

2.3 DWOS; asymptomatic infections - protective mechanisms

Fundamental immunological differences in the immune responses associated with symptomatic and asymptomatic infections have been studied [56, 57]. The kinetics of asymptomatic infections are known to differ from the symptomatic infections in the magnitude of the viremia and the rate of clearance [58]. The protective mechanisms that contribute to the lack of clinical manifestations in individuals, that remain asymptomatic

or inapparent compared to symptomatic dengue cases have been found interesting and are still being investigated. Epidemiological risk factors such as age, duration between consecutive dengue infections, DENV serotypes of previous infections, concentrations of pre-existing heterotypic neutralizing antibodies, interactions between viral genotype within the serotype and resulting immune responses are known to be associated with these subclinical outcomes after the dengue infection [12, 23, 59–61].

In general, it is regarded that secondary infections are associated with more severe disease due to the phenomenon of ADE and/or cross-reactive T cells [62]. However, post-secondary infections are known to induce different immune responsiveness in susceptible hosts and have also been found to impact upon inapparent rates [63]. Thus, the role of previous infection in perhaps decreasing or increasing the risk of infection causing it inapparent needs to be further investigated [12, 64]. Alexander et al. (2020) have studied the impact of frequent immune boosting; that occurs as a result of frequent disease exposure in dengue-endemic areas, on the fluctuating symptomatic and asymptomatic ratios [28]. It has been reported that antibodies play a greater role than immune cells in heterologous DENV infections [65]. Neutralizing antibodies seem to play a major role in this and it is evident that, the individuals who are previously exposed to DENV, manifest clinical symptoms differently due to the presence of pre-existing neutralizing antibodies resulting in asymptomatic or inapparent dengue status on many occasions. Furthermore, high concentrations of neutralizing antibodies against DENV infection have been frequently observed in asymptomatic individuals [61, 66–68].

Variations in immune reactions to the virus have been reported in dengue asymptomatic and symptomatic patients. In a study carried out by Simon-Loriere et al. (2017), the inflammatory pathways and innate immune responses were found similar in asymptomatic and symptomatic diseases. However, the expression of proteins related to antigen presentation and subsequent T and B cell activation pathways were found differently regulated, independent of the viral load or previous DENV infections. Asymptomatic individuals have been found to have increased T cell responses with feedback regulation compared to symptomatic counterparts [57]. According to his findings, asymptomatic infections seem to be determined by increased activation of the adaptive immune response and properly controlled mechanisms leading to the removal of viral infection without excessive immune activations [57].

Furthermore, apart from immune status, host genetic factors are considered to have an impact on the protective mechanisms in asymptomatic diseases [56], which involves a complex network of genes that are expressed differentially in the asymptomatic or inapparent individuals. A polymorphism in Fc gamma receptors (FcgRIIA) has been found to be associated with inapparent infections compared to symptomatic infections with DF or DHF in the Cuban population [56]. Moreover, according to the studies of [67] a broad down-regulation of host defense response (innate, adaptive, cytokines and matrix metalloprotease) genes in asymptomatic individuals against symptomatic patients. A selective up-regulation of distinct genes which are associated with protection has been observed [66]. However, these observations warrant further investigations in order to correlate their expression with conferring protection against clinical dengue infections.

2.4 DWOS; asymptomatic infections- detection

Detection of DWOS or asymptomatic infections is known to be challenging. The symptomatic dengue can be clinically suspected based on the symptoms and

a confirmatory laboratory diagnosis will provide a definite diagnosis. Detection of asymptomatic cases happens only based on laboratory diagnosis, since there are insufficient or no clinical cues for infection [68].

Direct diagnostic methods such as molecular and antigen-detecting methods are not usually considered convenient to detect asymptomatic infections owing to the shorter period of viremia after the infection. Serological tests such as HAI, ELISA and PRNT have been accepted as suitable methods to detect DWOS and have been frequently applied in detecting asymptomatic dengue cases than the direct diagnostic methods [68]. However, direct methods to detect acute infection and indirect methods; mostly the serological methods and further, mosquito inoculation techniques have also been incorporated in many studies for detecting asymptomatic infection in high-risk cohorts (**Figure 1**) [69–71].

Surveillance studies for DWOS or asymptomatic infections are carried out in the general population over a long period of time with frequent blood sampling and testing [16, 23] and by screening the dengue high-risk groups [71].

2.5 Dengue transmission

Transmission of DENV among human hosts occurs through horizontal and vertical transmission pathways. In horizontal transmission, viruses are transmitted among individuals of the same generation. Human-to-mosquito transmission is known as the most common mode of horizontal transmission, while transmission through blood transfusion [25, 70, 72–76] and organ transplants [25, 77] have also been infrequently reported. In addition to these transmission modes, a few cases of nosocomial transmission through needle stick injury and mucocutaneous exposure have also been reported [78, 79]. The difficulties in differentiating non-vector transmission from vector or mosquito transmission in dengue-endemic areas could be the result of the observed infrequency of records of these cases [80].

Studies have been carried out to investigate the possible sexual transmission of DENV. So far, cases of DENV in semen [81, 82], and vaginal secretions [83] have been

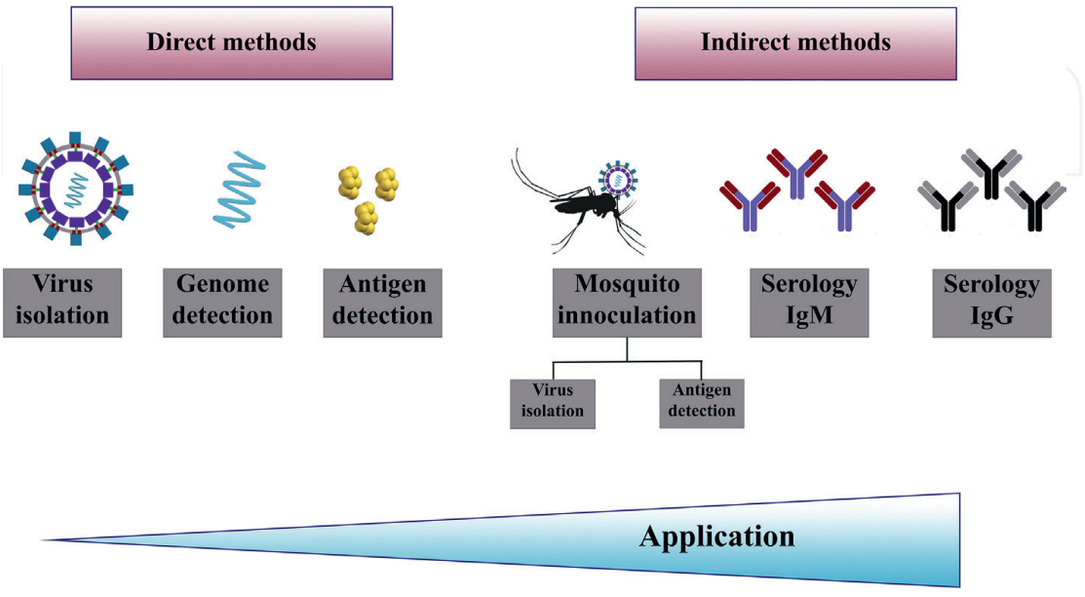

Figure 1.
Schematic diagram illustrating the application of diagnostic tests for the detection of asymptomatic dengue.

rarely recorded. However, in 2019, two cases of possible sexual transmission were reported in Spain and South Korea [84, 85]. Thus, though plausible, sexual transmission of dengue is considered extremely rare and uncommon in endemic communities [86].

Vertical transmission occurs when the virus is transmitted from mothers to their offspring, through intrapartum transmission [87–89] or transmission at the onset of delivery [80, 87]. Although DENV virus particles have been found in breast milk, the studies are insufficient to conclude the transmission of DENV via breast milk [90], however considering the benefits and immunological protection from breast milk to infants, breastfeeding in DENV-infected mothers are encouraged in dengue -endemic regions [91, 92].

2.5.1 Human to mosquito transmission of DENV

A susceptible female *Aedes* mosquito acquires a DENV infection after it consumes a blood meal from a dengue viremic person. When viremic blood reaches the mosquito midgut, the extracellular virus binds to undefined receptors on the cellular surface of the midgut epithelium. Once the virus is capable of successfully infecting and replicating in midgut epithelial cells, a new progeny of viruses is shed into the hemocoel, where it can, later on, disseminate and infect secondary tissues, legs, brain and salivary glands [93]. The duration of the viral incubation between the time of ingestion and reaching the salivary glands, where mosquitoes become infectious is known as the extrinsic incubation period (EIP), which is generally considered as 8–12 days [94]. Upon adequate viral replication in the salivary glands, the mosquito becomes a potential vector to transmit DENV to a new host during the next probing or feeding event [93].

The factors influencing the transmission of DENV from humans to mosquitoes include viral, host, vector and environmental aspects. In terms of host factors, viral titer in the human plasma and duration of human infectiousness are considered. The amount of viral titer circulating in the blood of an infected human influences the possibility of a mosquito becoming infected after a blood meal. Mosquito infectious dose, or the viremia in humans that is required to infect 50% of mosquitoes differs between viral serotypes [95]. A dose-response relationship is generally observed with an increasing number of DENV RNA copies [96]. The period between infection and the onset of infectiousness in a human is called the Intrinsic Incubation Period (IIP). The intrinsic incubation period of a human varies, and it is typically considered as 4–7 days [94]. It is estimated that onward transmission results from mosquitoes biting during the pre-symptomatic phase of DENV infections in most cases than, during the post-symptomatic period [14]. Further, it is also reflected that, patients with a high early viremia have a greater probability of having an extended duration of DENV infectiousness. Furthermore, host immune factors [96] and host stimuli for mosquito attraction such as body temperature, body odor, blood type [87, 97], etc. are also known to contribute as host factors for dengue transmission.

As for vectors, diurnal and crepuscular biting behavior of both *Aedes* mosquito species [98], anthrophonic nature, considerable flying span, and highly domesticated nature, especially of the primary vector, *Ae. aegypti* mosquitoes [99] have made them excellent vectors in disease transmission. Mosquito susceptibility to infection and vector competence (VC), which elaborates on mosquito infection, dissemination and onward transmission of the virus, plays a major role in transmission. Relative vector competence of two major vectors *Ae. aegypti* and *Ae. albopictus* have been extensively studied. *Ae. albopictus* are known, more susceptible to midgut infection than *Ae. aegypti*, but the ability to disseminate the virus of *Ae. aegypti* has been found greater

suggesting a greater potential for transmission in nature [100]. The susceptibility for DENV in mosquitoes of different geographical strains has been reported [101, 102] and population-specific differences in the susceptibility with each serotype, have revealed consistent patterns of high and low infection [103]. Further, differential susceptibility by different viral isolates of genotypes within the same serotype in a single geographical population has also been reported [101, 104, 105].

Dengue virus is also known to manipulate the biology and behaviors of the infected host to facilitate virus transmission [93, 106]. Studies on the blood-feeding behavior of DENV-infected mosquitoes have investigated the time duration of probing and feeding [107], transmission efficiency during probing [108], and motivation and avidity to feed [106, 109] and revealed the relationships of such in disease spread.

Environmental factors have been known to play a major role in dengue transmission via mosquito vectors [110]. The temperature has been known to have implications in altering mosquito VC to transmit viruses. The lower temperatures are known to induce slow virus replication and high temperatures are known to induce increased virus replication resulting in reduced EIPs [100, 111]. Changes in the humidity levels are also known to intervene with the vector competency of vector mosquitoes, which affect DENV transmission [110]. Research interest in the factors contributing to DENV mosquito transmission is ongoing and in-depth studies are warranted [93].

2.6 Silent transmission; vector and non-vector transmission

Studies on vector transmission of DENV from asymptomatic patients are rare and the level of mosquito infectiousness has not been adequately investigated [69]. It was long assumed that people with inapparent and asymptomatic infections fail to infect mosquitoes and have low viremia levels. Many studies have reported lower viremia in asymptomatic infections than those of symptomatic infections but also in detectable levels [58, 69, 112–115].

It has been shown that people with asymptomatic infections have had 100-fold lower infectious doses of viruses to mosquitoes that eventually have resulted in larger viral loads in infected mosquitoes [116]. This was also evident to us in a study carried out in Sri Lanka, where silent transmission from asymptomatic individuals (with no detectable viremia or sometimes no detectable antigen levels), to vector mosquitos (with detectable antigen levels) was observed [71]. A recent study has reported a slower viral decay rate in asymptomatic subjects compared to symptomatic individuals, enabling the asymptomatic cases more available for silent transmission [58]. Furthermore, studies to evaluate mosquito infectivity of asymptomatic subjects have shown a significant increase in mosquito infectiousness among asymptomatic cases than the symptomatic cases (**Figure 2**) [18, 69], postulating that strong immunological response and high cytokine levels during symptomatic illness reduce human infectiousness to mosquitoes in symptomatic dengue cases [69].

Non-vector transmission of DENV via atypical routes such as blood transfusion, organ transplant and intrapartum transmission has been confirmed in many studies, and the possibility of these transmission routes originating from asymptomatic, pre-symptomatic or subclinical cases has also been discussed [12, 73, 117–120]. Furthermore, vertically transmitted dengue in a neonate born to a mother with asymptomatic dengue infection has been reported in a recent case study from Sri Lanka, and instances, where such cases are misdiagnosed owing to no maternal history in asymptomatic mothers have been discussed [121].

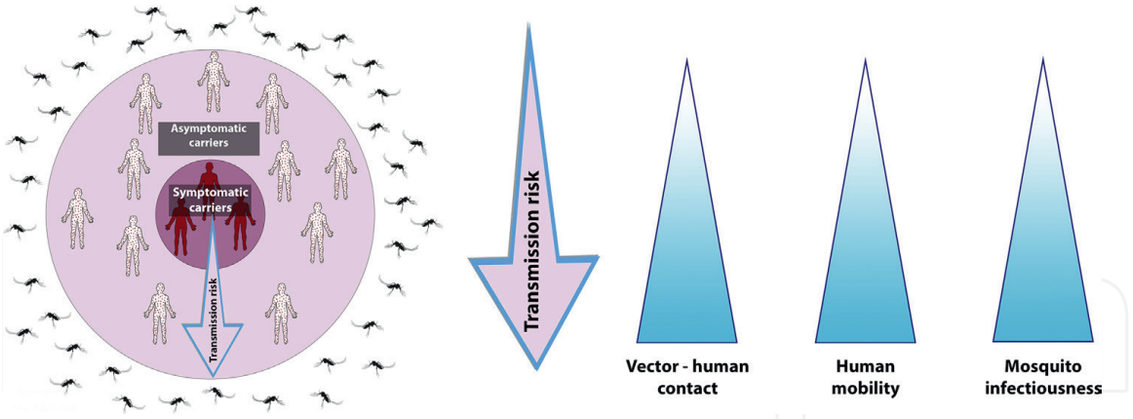

Figure 2.
Schematic diagram illustrating the increasing transmission risk towards the asymptomatic proportion of an infected community.

According to the modeling analysis of Bosh et al., (2018), it has been suggested that inapparent infections contribute appreciably to DENV transmission and its disease burden [14]. Further, their finding that approximately one-quarter of an individual's infectiousness occurs prior to symptom onset, supports the hypothesis that a large proportion of human to-mosquito transmission is silent [14]. Collectively, these evidences show that asymptomatic cases play a major role in silent transmission, having a high transmission risk compared to symptomatic cases (**Figure 2**). Furthermore, the fact that the vector- host contact is considerably high in asymptomatic carriers through their daily routines compared to symptomatic cases, who will be hospitalized or less accessible should also be accounted with great concern. In addition, human mobility is also known to play a key role in the spread [122, 123], thus silent transmission of dengue via undisrupted daily routings of these asymptomatic or mildly symptomatic carriers can be identified as a key factor contributing to the dengue spread than the symptomatic cases [69, 100] (**Figure 2**).

2.7 Seroprevalence and risk of antibody-dependent enhancement

Relatively high dengue seroprevalence among the dengue endemic communities around the world has been reported [13, 24, 124–129]. Comparative to the number of confirmed dengue cases, an increased level of dengue infection suggested by high IgG seropositivity in endemic areas, has revealed a vast majority of DENV infections [128]. Attributing to the fact that the majority of dengue infections in these communities are either asymptomatic or inapparent [11, 14, 16, 23, 65].

As a consequence of this, a considerable proportion of the population who are immune to a circulating dengue serotype/strain after an epidemic will be created. Co-circulation of several dengue serotypes in dengue-endemic areas has been reported [129, 130]. Worsening the situation, the prolonged seroprevalence in symptomatic and asymptomatic individuals has also been observed in studies [13]. Thus, this proportion would be at risk of developing ADE or severe dengue in a subsequent epidemic of a differing dengue serotype with non-neutralizing antibodies or neutralizing antibodies at sub-neutralizing levels (**Figure 3**).

Furthermore, the transmission of heterogeneous anti-dengue antibodies from symptomatic or asymptomatic cases through blood transfusion or organ transplant, and transmission of maternal antibodies to infants has also been suggested to enhance

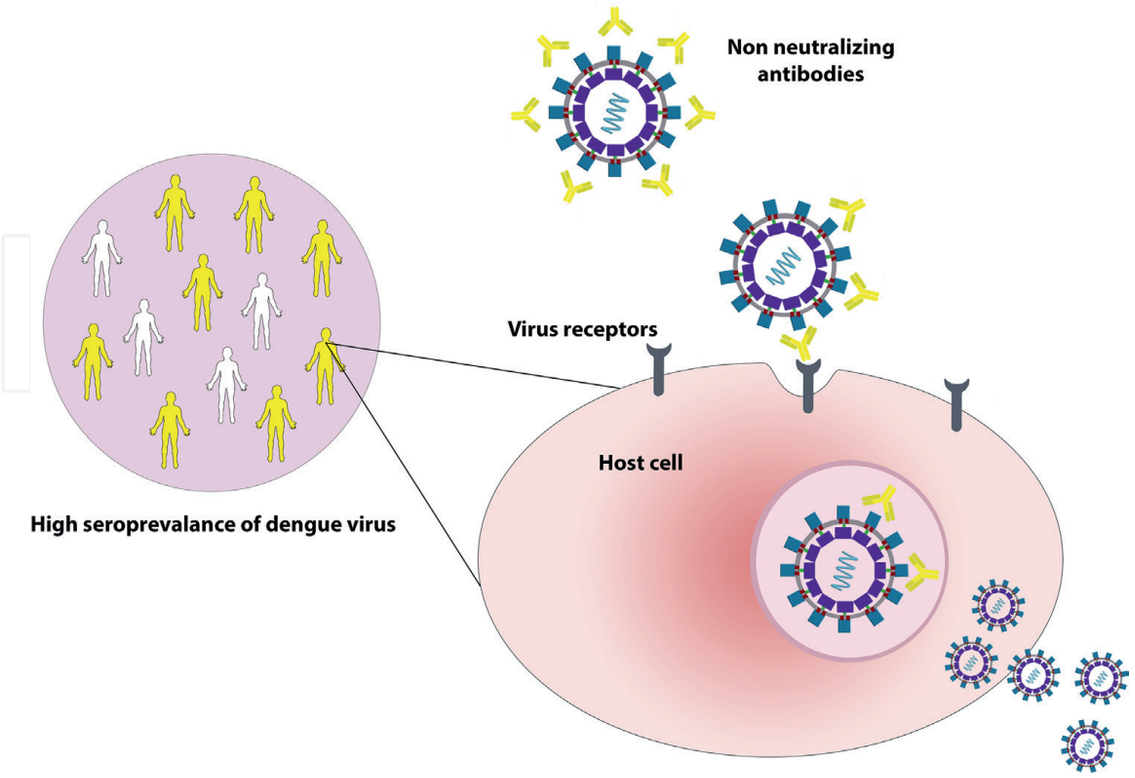

Figure 3.
Schematic diagram depicting the high seroprevalence of dengue virus in dengue-endemic communities and the risk of developing antibody-dependent enhancement during subsequent infections.

the viral infectivity and virulence in recipients who will later be exposed to a heterotypic DENV infection [131].

The global incidence of DHF/DSS has increased more than 500-fold in recent years [11]. And the risk of dengue virus or its antibodies which can be transmitted through such different passive modes of transmission has been identified as a major counterpart.

2.8 Prevention; a way forward

Prevention from silent transmission through mosquito vectors can only be achieved by vector control, in a setting where asymptomatic carriers can only be identified by certain laboratory identification techniques. However, the routing fogging and insecticide spraying practices just after a case report (peri-domestic space spraying) can be taken as an initial step to reduce the risk of transmission from asymptomatic carriers. Although many studies have suggested the importance of screening the populations for DENV, and dengue seroprevalence, no available efficient measures and or diagnostic services for such events prevail in many dengue-endemic countries [75].

However, there is a need to incorporate integrated approaches including increasing awareness among the community, establishing routine diagnostic methods for screening asymptomatic carriers and incorporating preventive measures to reduce the exposure, which will eventually help in reducing the dengue burden [75].

Many endemic countries have identified the risk of transfusion-associated transmission from asymptomatic donors, and have adopted policies where they recommend screening of blood products. The positive blood donors will be deferred for periods depending on the endemicity of the region. Similarly, transplant guidelines in

some countries have recommended dengue screening prior to transplantation and a specific deferral period before taking up for transplant surgery if the donor or recipient is found positive for dengue.

Vaccines and herd immunity; though seems like the only promising solution, limited knowledge of immune responses against dengue infection, lack of human or animal model of disease, and suboptimal assay strategies to detect immune responses after infection or vaccination, which are some barriers to the vaccine and drug development. Furthermore, in addition to the protection against symptomatic infection, it is also important to assess protection against asymptomatic infection.

3. Conclusion

Asymptomatic or inapparent dengue infections provide a fundamental link in the chain of disease transmission in dengue-endemic communities. The knowledge gap in understanding the viral kinetics of asymptomatic individuals along with their immunorespnoses must be urgently fulfilled and investigative studies on such should be encouraged. Understanding the presence and the prevalence of asymptomatic to symptomatic proportion of a community enables a glimpse of the targeted population and helps in introducing disease management strategies. The chapter highlights the increased transmission risk towards the asymptomatic carriers of the community, attributed to the increased vector-human contact, human mobility and mosquito infectiousness. All precautions must be taken to reduce dengue transmission in a community via vector and non-vector routes. Furthermore, the seroprevalence of a community must be routinely monitored and the vaccine efficacy in such settings depending on the endemicity, should be closely evaluated.

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Conflict of interest

The authors declare no conflict of interest.

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