COMMENTARY

Why Are Children Highly Vulnerable to Dengue Infection?

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ABSTRACT

The prevalence of dengue infection poses a great public health concern among people living in tropical and subtropical countries like the Philippines. Just recently in 2019, the Philippines had a dengue virus (DENV) outbreak where nearly half of the mortalities were children between 5 and 9 years of age, and around 73% of confirmed DENV cases were under the age of 19. Children are disproportionately affected and are considered to be highly vulnerable to severe dengue infection compared to adults due to several factors. These include: immunological differences--poorly developed immune systems, making them more susceptible to the virus; smaller body sizes and weight means that they are more likely to experience severe symptoms; and their tendency to play outdoors, make them more exposed to mosquito bites. Hence, this article provides an overview of the current understanding for the vulnerability of children to severe dengue infection compared to adults.

Keywords: *dengue virus; dengue infection, dengue shock syndrome, plasma leakage*

Introduction

Dengue is a viral illness spread to people by the bite of an infected female Aedes mosquito. Although mostly of dengue infections are unremarkable and self-limiting, a small number of cases will develop into life-threatening complications, such as systemic vascular leakage, hemoconcentration, thrombocytopenia, and hemostatic derangements that favor bleeding. Usually, this vascular leak condition reverses spontaneously, but in some cases plasma losses can be substantial, particularly in infants and children. This can potentially lead to hypovolemic shock, or dengue shock syndrome (DSS), and occasional death [1-5]. Early diagnosis/intervention, meticulous fluid replacement, and better clinical management with balance nursing care can significantly improve outcomes for children with dengue fever [4,6]. Delayed diagnosis of severe dengue is associated with a high mortality rate of up to 40% [7].

A recent report by the Save the Children Fund disclosed that in the first 7 months of a 2019 DENV outbreak in the Philippines, there were 170,000 confirmed cases, with 720 deaths. Three hundred, or 42% of those deaths were children between the ages of 5 and 9 years old and around 73% of recorded DENV cases under the age of 19 [8]. Likewise, a 3-year retrospective report in Pakistan found that almost 90% of all dengue infections recorded were of children below 18 years of age [9]. Moreover, according to a recent Epidemiological Update Report from Pan American Health Organization (PAHO) and the World Health Organization (WHO), the highest incidence rates of DENV in 2019 were among children less than 15 years old (546.3 cases per 100,000 population) [10]. National surveillance data from Asian countries demonstrates that infants and children ages 4-9 are consistently at risk for severe dengue disease, with the vast majority of dengue cases found in children less than 15 years of age [11].

Understanding why children are more prone to develop severe dengue is important to parents to provide some level of comfort, reassurance, better comprehension, and awareness so that they can take preventive measures and seek medical attention in a timely manner. It will also help clinicians and hospital practitioners finds better insights, beneficial preventive strategies, and effective treatment options to manage dengue infection in children.

Why are children exceptionally vulnerable to dengue infection?

Children are more susceptible to contract severe dengue because their immune systems are not fully developed making them more vulnerable to DENV. Children tend to

play outdoors wearing shorts, making them less protected and more exposed to mosquito bites. Parks and schools in endemic regions can be hotspots for dengue because of the population density, unscreened windows or doors, and the lack of mosquito repellents in these areas [8].

Moreover, because children have smaller body sizes and lower blood volumes, they are more prone to rapid and severe dehydration, a common complication of severe dengue. In addition, children also have lower body weight, which means that the same amount of viral loads may have a more significant impact on their body's immune responses compared to adults.

The most severe and dangerous complication of dengue is vascular permeability, also known as plasma leakage (PL). Plasma leakage is the distinctive feature of DHF from dengue fever, and in severe dengue can cause circulatory insufficiency, shock, organ failure, and occasional death.

The exact mechanisms underlying PL in dengue are not fully understood. Studies demonstrated that reactive oxygen species, enzymes, and inflammatory mediators (cytokines) produced during the immune response may breakdown the endothelial glycocalyx layer (the layer that regulates vascular permeability) allowing plasma to leak out of the blood vessels. The changes to the glycocalyx layer are transient, so the leakage often resolves spontaneously [12]. However, severe PL in adults occurs less frequently than in children and may reflect the maturity of the homeostatic mechanisms that help to prevent cardiovascular decompensation in the face of volume depletion. It must be noted, however, that PL may still occur in adults with DHF and lead to severe complications. Moreover, PL may also reflect higher intrinsic permeability of pediatric micro vessels [2,3,13]. The high microvascular permeability in young children results from the greater density and greater surface area of growing micro vessels in skeletal muscles. Immature growing capillaries are more permeable to water and plasma proteins than when mature [2,3]. The higher permeability characteristic in children may explain, in part, why they readily develop acute PL or hypovolemic shock.

Children, particularly infants, are at a higher risk of developing severe dengue compared to adults due to the immaturity of their physiological functions. This includes immature hemodynamic function, underdeveloped immune systems, immature homeostatic mechanisms, intrinsic permeability of growing micro vessels, and the inherent incapability to compensate for vascular leakage and other systemic organ dysfunctions [3,4,11-14]. This can lead to increased PL and resultant complications such as dengue hemorrhagic fever (DHF) or DSS. Thus, infants with DHF can be difficult to manage as they may rapidly develop complications, such as bleeding and/or shock, which can be life-threatening if not treated effectively and immediately. DHF in infants most often represent a primary DENV infection compared to DHF in children and adults where they are associated with secondary DENV infection due to heterotypic DENV [4,15].

However, seniors or elderly individuals who live in regions where the local epidemiology favors symptomatic dengue are at greater risk for developing severe dengue. This is probably due to the complex interplay of factors such as vascular aging, immune senescence, and the presence of chronic diseases and comorbidities [16]. While vascular aging can increase capillary permeability or PL, immune senescence and/or comorbidities can weaken or impair immune function leading to a more severe course of the disease. It appears that children and seniors can manifest the same clinical symptoms related to vascular permeability and reduced immune response. The underlying mechanisms, however, for these symptoms are somewhat different. In children, it can be the result of immaturity in immune response, whereas in seniors, it can be due to senescence or the aging process. Understanding both the similarities and differences in clinical symptoms between seniors and children is useful in developing effective treatments and preventive measures for both age groups.

What other factors contribute to DENV infection?

Apart from the above, many other factors contribute to the elevated levels of transmission, incidence, and severity of DENV. These include viral loads, co-infection/dual infection, socio-economic conditions, nutritional status, and climate change [1,4,17]. High viral loads due to secondary heterotypic infection may increase the production of inflammatory cytokines and vasodilatory molecules that promote vascular permeability, the hallmark of severe dengue. Co-infection or dual infection occurs when two or more different vectors (infected mosquitoes) carrying either the same or different viral strains bite the same prey consecutively within a day. This will double the viral infectious dose, resulting in “super infection.” High viral load early in the course of infection has been linked to severe dengue with increased PL. Simply put, because of the increased double load, the immune system must work twice as hard to fight off the disease. Otherwise, the body will be overwhelmed by the side effects of viremia, *e.g.*, increased PL

and multiple organ impairments that can have catastrophic impacts. Likewise, infants are vulnerable to severe dengue because of the relatively high viral load and the inherent poor capacity to compensate for vascular leakage.

Socioeconomic factors, typified by dwelling characteristics such as household income and size, availability of closed air-conditioning, window screens, and basic sanitation, can strongly affect the levels of dengue transmission and incidence. People of higher socioeconomic status, with access to resources that make their dwellings resistant to mosquito presence, have lower incidences of dengue cases than those in lower income backgrounds. In other words, the unequal distribution of dengue infections can be partly attributed to wealth and social status. Nutritional status like undernutrition (malnourishment) is associated with weakened immunity while overnutrition (obesity) increases risk of severe dengue infection due to the activation of inflammatory pathway. The heightened production of inflammatory mediators leads to an increase in capillary permeability and PL [18].

Climate change has also broadly affected the rate of dengue transmission. The most important climatic factors include temperature, rainfall, and relative humidity. Temperature change plays a vital role in vector survival, viral replication, infectivity, transmission, and migration. In higher temperature climates, DENV grows and spreads in mosquitoes' salivary glands at a faster rate than at lower and fluctuating temperatures. Higher temperatures and relative humidity can significantly energize mosquitoes to fly further and bite more frequently. These climatic conditions also increase rates of larval development and virus replication. Moreover, climate change raises the epidemic potential of dengue. Heavy rainfall and damage to environmental hygiene can lead to an expansion and proliferation in dengue mosquito breeding grounds. However, in extremely hot and cold temperatures, DENV grows at a slower rate, may not even spread to salivary glands, and/or they may succumb to the climate.

In summary, children, especially infants, are more vulnerable to severe dengue infections compared to adults due to a variety of factors. These include their less-developed immune systems, greater exposure to the virus, smaller size, relatively high viral loads, and immaturity in microvascular formation and functions, as well as homeostatic mechanisms that can cause increased PL and other systemic organ impairments. The increased PL compounded by the inherent inability to compensate for the leakage can cause severe DHF and DSS, which can be fatal if not treated immediately.

It is important for parents to take steps to protect children from mosquito bites and to seek medical attention immediately if they show symptoms of dengue fever. Early recognition, greater awareness, prompt supportive treatment, and close monitoring for complications with heedful clinical and balanced nursing care can significantly reduce dengue fever complications and mortality in children.

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