Invited Commentary: Dengue Lessons from Cuba

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An 18-year interval between a dengue virus type 1 outbreak in 1977–1979 and a dengue virus type 2 outbreak in 1997 in Santiago de Cuba, Cuba, provided a unique opportunity to evaluate risk factors for dengue disease. All patients with symptomatic dengue, including 205 cases of dengue hemorrhagic fever and 12 deaths, were adults born before the dengue virus type 1 epidemic, and nearly all (98%) experienced secondary dengue virus infections. In contrast, almost all of those who seroconverted without illness (97%) experienced primary dengue virus infection. This provides epidemiologic support for the immune enhancement theory of dengue pathogenesis. The Cuban experience suggests that immune enhancement can be seen even 20 years after the primary dengue virus infection. It also supports the contention that primary infections with dengue virus type 2 (and dengue virus type 4) are largely subclinical. These observations have implications for dengue vaccine development based on live-attenuated viruses. Am J Epidemiol 2000;152:800–3.

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Dengue is an emerging infectious disease of great public health importance. The ever-increasing range of distribution for both the four dengue virus serotypes (dengue virus type 1 (DEN-1), dengue virus type 2 (DEN-2), dengue virus type 3 (DEN-3), and dengue virus type 4 (DEN-4)) and the primary vector mosquito, Aedes aegypti, has led to a dramatic increase in disease incidence and severity since World War II (1). In this issue of the American Journal of Epidemiology, Guzmán et al. report their findings after a DEN-2 epidemic in Santiago de Cuba (2). A well-documented hiatus in dengue virus transmission between a DEN-1 epidemic in 1977–1979 (and a DEN-2 epidemic in 1981) and the described DEN-2 epidemic in 1997 set the stage for important epidemiologic observations. Their data shed needed light on several questions central to our understanding of dengue, including the role of preexisting cross-reactive antidengue virus antibody, age as a risk factor for dengue hemorrhagic fever (DHF), and the possible natural attenuation of certain dengue virus serotypes in flavivirus-naïve hosts.

In an epidemic described by the authors as “small,” there were an adjusted 5,208 laboratory-confirmed DEN-2 illnesses in Santiago de Cuba in 1997, including 205 patients with DHF and 12 deaths (2–5). Among both dengue fever and DHF cases, more than 98 percent of the patients had serologic evidence for a secondary dengue virus infection. This means that the patients had previously been infected with another serotype of dengue virus (or possibly a non-dengue flavivirus). Long-term surveillance data strongly suggested the DEN-1 outbreak of the late 1970s as the preceding dengue virus exposure. The lack of dengue disease among anyone younger than age 18 years and the lack of antidengue virus antibody other than to DEN-2 among children supported this contention. In the same way that the vast majority of patients with clinically apparent disease exhibited a secondary antibody response pattern, a serosurvey conducted at the end of the epidemic suggested that the vast majority of people with serologic evidence for a primary DEN-2 infection did not experience an illness consistent with dengue fever (97 percent of an estimated 13,116 persons). These observations solidly suggest that for this particular strain of DEN-2 (Southeast Asian genotype (2, 6)), prior dengue virus exposure was the key risk factor for disease. At least for DEN-2, these observations lend further credence to the immune enhancement theory of dengue pathogenesis proposed by Dr. Halstead and his colleagues (7). Briefly, the antibody-dependent enhancement theory states that cross-reactive, yet nonneutralizing, antibody from a previous flavivirus infection enhances infections in Fc receptor-bearing cells such as monocytes and macrophages and possibly dendritic cells (8). Increased virus replication and antigen presentation lead to an exaggerated immune response and increased disease manifestations (9). The Cuban outbreak suggests that this effect can be seen even 20 years after the primary dengue virus infection. Other reports suggest that immune enhancement may also be important to make DEN-4 infections clinically apparent (10). While elevating the relative importance of immune enhancement as a risk factor for severe disease, these findings do not reduce the importance of other potential risk factors, such as virus virulence (11). The epidemiologic observations of dengue in...
Peru during the 1990s (no DHF cases with a DEN-2 epidemic of the American DEN-2 genotype after a DEN-1 epidemic) suggest that some genotypes may enhance more easily or to a greater degree than others (6, 12). Other suggested risk factors include age (discussed below), sex (13, 14), nutritional status (15), and population genetics (16, 17). This outbreak documented White race as a risk factor for severe disease, as was also seen in the 1981 Cuban epidemic (5, 18).

Age as a risk factor for severe dengue disease must be reevaluated on two counts. First, among adult patients in the Santiago de Cuba epidemic, the full range of dengue disease severity, including 12 deaths, was documented. The dogma has been that adults are less likely to experience DHF. Since children born after the DEN-1 epidemic in the late 1970s were not immunologically “primed,” it was not possible to compare disease severity between children and adults. The DEN-2 outbreak in 1981 identified childhood age as a risk factor for severe disease. In that study, it was possible to compare adults with children since the DEN-1 epidemic had occurred just 2–4 years before. Other studies have also identified childhood as a risk factor (19–22), although the increased risk in hyperendemic areas can be largely attributed to immunity among the adult population. DHF can occur in adults (23–29). While the outbreaks in Santiago de Cuba and elsewhere demonstrate clearly that adults are at risk for DHF, the risk may be less than that for infants and school-aged children in hyperendemic areas. This increased risk among symptomatic, school-aged children (peak age commonly around 8 years (10, 30, 31)) is largely due to their exposure to sequential dengue virus infections (subclinical or mild infection as young children with enhanced disease with subsequent infections). However, this increased risk for severe disease may also reflect peculiarities of the age-dependent maturation of the immune system (32, 33). More research is needed.

A second aspect relative to age is that nearly all primary DEN-2 transmission was silent in this outbreak. While clinically silent virus transmission is routine in children (31, 34) and subclinical infection among adults has been suspected for some time (35–38), there have been few reports of such large numbers of silent dengue virus infections among adults (39). The dogma has been that while adults are less likely to experience DHF, they are more likely than children to become symptomatic after infection with a dengue virus. This was based on early reports of clinical attack rates of 75–100 percent among adults (40–42). Other outbreaks with lower attack rates were attributed to partially immune populations. However, for most epidemics with high clinical attack rates, either the infecting serotype was not known or the identified serotype was DEN-1 (as discussed below). Of course, it is difficult to document subclinical transmission without a prospective study or careful serologic surveillance. There is evidence that DEN-2 circulated in all age groups in Caribbean Basin countries from 1946 to 1963, even though there was no record of epidemic dengue virus transmission (1, 43–45).

This brings us to the question about whether DEN-2 and DEN-4 are naturally attenuated in flavivirus naive hosts (10). A literature review identified few DEN-2 outbreaks in which the majority of patients were thought to have experienced primary DEN-2 infections, and some of these outbreaks were characterized by extremely mild disease (39, 46–48). No reports of primary DEN-4 outbreaks could be identified. Care must be taken to interpret dengue serology as indicating a primary versus a secondary antibody response pattern. A validated assay and convalescent serum at least 7 days after the onset of illness are required. A low titer early in the infection may be misinterpreted as evidence for a primary infection. To summarize, a literature review suggests that for flavivirus-naive individuals some dengue virus infections may be more likely than others to result in clinically apparent disease at any age—DEN-1 and DEN-3 much more so than DEN-2, which may be more likely than DEN-4. In fact, the data presented by Guzmán et al. (2) suggest that DEN-2 may be less likely to even infect naive individuals. The DEN-2 infection rate in DEN-1-immune individuals was 3.8 times higher than that in nonimmune individuals (18). A lower than expected seroconversion rate was also seen among flavivirus-naive volunteers in the Rayong, Thailand, study in 1980 (31).

Low numbers of symptomatic cases among those with a primary DEN-2 and DEN-4 infection may have significant implications for vaccine development. It brings into question the safety of live-attenuated DEN-2 and DEN-4 vaccine candidates until extensive testing is performed in volunteers who are partially immune to dengue. Will putatively attenuated dengue viruses cause (perhaps severe) disease when given to hosts with preexisting antidengue virus antibody? This concern includes vaccines classically attenuated through serial passage in cell culture viruses (49–53) or through site-directed mutagenesis and perhaps chimeric viruses based on DEN-2 or DEN-4 backbones or expressing DEN-2 or DEN-4 structural genes (54–56). Good safety profiles in flavivirus-naive adult volunteers may be misleading if subclinical infections for DEN-2 and DEN-4 are common. Risk may be reduced if all four viruses are given simultaneously as a tetravalent formulation.

Dengue epidemiology is complex. There are four known serotypes and multiple genotypes. Individual exposure histories must consider the sequence of dengue virus infection and the interval between infections. Serotype-specific diagnoses are rare, and serology can be difficult to interpret. Exposure to other nondengue flaviviruses may also influence infection outcome for better or for worse, although current evidence suggests that dengue virus infections are most important in effecting outcome (57, 58). Current efforts to model disease incidence and severity based on the circulation of multiple serotypes may lead to an increased ability to predict severe outbreaks (59). This will allow directed attempts at vector control until such time as effective vaccines are available.

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