Enhanced severity of secondary dengue-2 infections: death rates in 1981 and 1997 Cuban outbreaks

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ABSTRACT

Objective. *To understand the possible effect that length of time has on disease severity with sequential dengue infections.*

Methods. *Death and hospitalization rates for dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) per 10 000 secondary dengue-2 infections were compared in the same age group for two dengue-2 (DEN-2) epidemics in Cuba. The first DEN-2 epidemic affected all of Cuba in 1981; the second one, in 1997, impacted only the city of Santiago de Cuba. The sensitizing infection for DHF/DSS for each of the DEN-2 epidemics was dengue-1 (DEN-1) serotype virus, which was transmitted in 1977–1979, that is, 4 years and 20 years before the two DEN-2 epidemics. Using published seroepidemiological data from the cities of Havana and Santiago de Cuba, we estimated the rates at which persons aged 15–39 years old and those 40 years and older were hospitalized or died of DHF/DSS in Havana and in all of Cuba in 1981 and in just Santiago de Cuba in 1997.*

Results. *Among adults 15–39 years old the death rate per 10 000 secondary DEN-2 infections was 38.5 times as high in Santiago de Cuba in 1997 as in Havana in 1981. As a further indication of the increased severity coming with a longer period between the initial DEN-1 infection and the secondary DEN-2 infection, the case fatality rate for that same age group was 4.7 times as high in Santiago in 1997 as it was in Havana in 1981.*

Conclusion. *We found a marked increase in severity with the longer of the two intervals (20 years) between an initial DEN-1 infection and a secondary DEN-2 infection. Such a difference may be due to subtle shifts in causative dengue strains or to changes with the passage of time in the circulating population of human dengue antibodies. These observations have important implications for dengue control, pathogenic mechanisms, and vaccine development.*

Keywords Dengue, Cuba.

Since the 1960s, more than 4 000 000 persons from Southeast Asia, the Western Pacific region, and the Americas have been hospitalized with dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). Most of these persons have been children, and more than 65 000 of them have died (1). As evidenced by all the published prospective studies on DHF/DSS (2–8) and by the experience with a DHF/DSS epidemic in Cuba in 1981 (9), in both children and adults DHF/DSS is associated with secondary dengue infections, that is, with these persons suffering a second dengue infection with a different viral serotype.

A mathematical model that used data from early epidemiological studies on dengue predicted that DHF/DSS would occur only if the primary and secondary infections occurred within an interval of 5 years (10). An unexpected opportunity to study this hypothesis occurred in 1997, when a focal dengue epidemic in Cuba produced 205 classic DHF/DSS cases, with 12 deaths in persons 18 years and

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older in Santiago de Cuba, the vast majority with a secondary type of antibody response (11, 12). No fatalities were observed among those under 18 years of age. Located in the eastern part of Cuba, Santiago de Cuba is the country's second-largest city. Because of Cuba's vigorous nationwide mosquito control program and intensive disease surveillance during the period of 1981–1997, it is clear there were no other dengue viral introductions and that the DHF/DSS cases in 1997 occurred in persons infected initially with dengue-1 (DEN-1) serotype in 1977–1979 (13). During the 1997 outbreak, cases were ascertained prospectively and dengue infections studied retrospectively, permitting the calculation of age-specific DHF/DSS hospitalization and death rates per 10 000 secondary dengue-2 (DEN-2) infections (14).

Comparable age- and infection-specific clinical hospitalization and death rates are available from the 1981 epidemic for all of Cuba and also for just Havana, which is Cuba's capital and largest city (9, 15). These data have made possible a comparison of DHF/DSS and death rates and case fatality rates among individuals who experienced a secondary DEN-2 infection at an interval of either 4 or 20 years after a DEN-1 infection. In the sections that follow we report on much higher death and DHF/DSS hospitalization rates with secondary DEN-2 infections that occurred following the longer, 20-year interval of time since the primary dengue infection.

MATERIALS AND METHODS

1981 and 1997 epidemics

In the 1981 Cuban epidemic, DHF/DSS was recognized in the city of Havana in late May, just prior to an explosive extension to the rest of the country (13). By October a total of 344 203 cases had been reported, with approximately 10 000 of them being classified as severely ill (grade II, III, or IV on the four-level DHF/DSS grading system of the World Health Organization). There were 158 deaths, including 96 among persons less than 15 years old. Several strains of dengue virus type 2 isolated from this 1981 epidemic have been sequenced and identified as belonging to a Southeast Asian genotype closely related to DEN-2 New Guinea C (16, 17). The 1981 epidemic was preceded by a major episode of DEN-1 transmission in Cuba that began in 1977 and continued in a few areas until 1979. More than a half million cases were reported in 1977, with a much higher percentage of the population infected (44.5%) (13). In 1981 a nationwide campaign to eradicate the *Aedes aegypti* mosquito was launched. As a result, from 1982 to 1996, no instance of indigenous dengue transmission was identified (11, 12) although carefully monitored by active case detection. The vector was re-established in eastern Cuba in 1992. At the end of 1996, relatively high vector densities were reported. In January 1997, DEN-2 was recovered from febrile cases in Santiago de Cuba. The ensuing epidemic resulted in 5 208 clinically documented febrile dengue infections and 205 DHF/DSS cases, with 12 deaths, all adults (11, 12, 14).

Seroepidemiological studies

During 1983 a retrospective seroepidemiological study of the 1981 epidemic was conducted in the Cerro district of the city of Havana, which is located in the western part of Cuba (9). The prevalence of plaque reduction neutralizing (PRNT) antibodies to DEN-1 and DEN-2 viruses was measured in sera obtained from an age-stratified random cohort of 1 945 residents.

After the 1997 epidemic in Santiago de Cuba, DEN-1 and DEN-2 neutralizing antibodies were measured in age-stratified random cluster samples of 1 151 residents of Santiago de Cuba (14) and 264 residents of nearby Palma Soriano (MG Guzmán, et al., unpublished, 1998). Information obtained from both retrospective seroepidemiological studies was analyzed, making it possible to estimate the age-specific DHF/DSS and death rates per 10 000 secondary DEN-2 infections for both the 1981 and the 1997 epidemics. These data have been published previously (9, 14, 15).

Statistical studies

Data were analyzed using *z* scores to assess the differences between proportions.

RESULTS

Table 1 shows the DHF/DSS attack (hospitalization) rate and death rate by age group in persons experiencing a secondary DEN-2 infection in Havana and in all of Cuba (including Havana) in 1981 and in just Santiago de Cuba in 1997. The age distribution of DHF/DSS cases and deaths is based on two sources: 1) published hospital reports from a major pediatric facility, William Soler Hospital, a 400-bed pediatric teaching hospital that provided approximately 30% of all the pediatric beds in the city of Havana in 1981 (15, 18) and 2) a complete death registry—containing the name, age, sex, address, date of hospitalization, and date of death of all patients with a diagnosis of dengue—maintained at the Pedro Kouri Institute, which is Cuba's national reference center for the study of tropical and infectious diseases (15). Also analyzed, for adults, were additional published data and medical postgraduate theses (15, 19–24). Death reports provide the "strongest" (clearest) measure for comparing disease severity. Because of the small number of deaths, two comparison groups were selected, persons 15–39 years old and persons 40 years and older. All individuals in the younger age group had been exposed to dengue infections only in 1977, 1981, and 1997. There is serological evidence that some persons in the older group had been exposed to DEN-2 around the time of World War II (9, 15). The size of each older age group (persons 40 years and older) at risk from secondary DEN-2

TABLE 1. Comparative attack and death rates for dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) per 10 000 secondary dengue-2 (DEN-2) infections in two age groups of adults, separately and then combined, at intervals of 4 and 20 years after dengue-1 (DEN-1) infection, for DHF/DSS outbreaks in Cuba in 1981 and 1997[a]

Age group (years)	Site and year of DHF/DSS outbreak[b]	Interval between DEN-1 and DEN-2 infs.	Hospitalized DHF/DSS cases (no.)	DHF/DSS deaths (no.)	DHF/DSS case fatality rate (%)	Secondary DEN-2 infs. (no.)	DHF/DSS attack rate (per 10 000 sec. DEN-2 infs.)[c]	DHF/DSS death rate (per 10 000 sec. DEN-2 infs.)
15–39	Havana/1981	4 yr	1 005	6	0.6	147 543	68.1	0.4
15–39	All of Cuba/1981[b]	4 yr	2 967	36	1.2	400 526	74.1	0.9
15–39	Santiago/1997	20 yr	143	4	2.8	2 552	560.3	15.7
40–65+	Havana/1981	4 yr	324	15	4.6	94 527	34.3	1.6
40–65+	All of Cuba/1981[b]	4 yr	958	26	2.7	210 838	45.4	1.2
40–65+	Santiago/1997	20 yr	59	7	11.9	2 258	261.3	31.0
All adults	Havana/1981	4 yr	1 329	21	1.6	242 070	54.9	0.9
All adults	All of Cuba/1981[b]	4 yr	3 925	62	1.6	611 364	64.2	1.0
All adults	Santiago/1997	20 yr	202[d]	11[d]	5.4	4 810	419.9	22.9

[a] Some of these data have been published elsewhere (14, 15).
[b] Data for all of Cuba 1981 include the Havana data.
[c] The "DHF/DSS attack rate" column shows the rates of DHF/DSS hospitalizations per 10 000 secondary DEN-2 infections.
[d] Out of the 205 DHF/DSS cases observed during the 1997 Santiago de Cuba outbreak, 202 suffered a secondary infection; out of the 12 DHF/DSS fatal cases, 11 of them suffered a secondary infection.

infections in 1981 was adjusted to account for this earlier infection experience (15). Analyzing these data made it possible to calculate age-specific DHF/DSS hospitalization and death rates among estimated secondary DEN-2 infections (15). Age data for adult cases of DHF/DSS in 1981 were obtained from hospital records, and total cases were estimated from death records (15).

In both comparison age groups, the rates of DHF/DSS hospitalizations and deaths accompanying secondary DEN-2 infections were significantly higher in Santiago in 1997 than they had been in Havana and in all of Cuba in 1981 (Table 1). Clinical and seroepidemiological data were more thoroughly documented in Havana than in the rest of Cuba in 1981. For this reason we have handled data from each of these areas separately. Further, deaths are a "harder" clinical outcome than the number of DHF/DSS cases, especially since the disease was not well diagnosed during the 1981 epidemic. Comparing Santiago in 1997 with Havana in 1981, death rates for those with secondary DEN-2 infections were 19.5 times as high among persons 40 years and older and 38.5 times as high among those 15–39 years old. The case fatality rate among those 15–39 years old in Santiago in 1997 was 4.7 times as high as the comparable rate in Havana in 1981. All the DHF/DSS hospitalization (attack) rates and death rates in the comparison groups differed significantly (Table 2).

DISCUSSION

The much greater severity found in the 1997 outbreak in Santiago de Cuba is not likely to be due to clinical management or case detection. The Cuban health care system is well-known for being accessible to all strata of the population. Competent supportive treatment was given to DHF/DSS cases throughout Cuba in 1981, as reflected in the remarkably low case fatality rate nationwide (13). This prior experience, plus the assignment in 1997 of experienced DHF/DSS consultants from Havana to Santiago de Cuba, assured that similar high-quality care was provided during that later outbreak. The strongest evidence for severity differences between outbreaks are deaths, events that were accurately reported. An extraordinarily high percentage of fatal cases from both epidemics were autopsied, 100% in 1997 and 62% in 1981 (24–26). Dengue etiology was established for each of the 12 fatal cases in Santiago de Cuba in 1997 (26).

An earlier mathematical model (10) that was designed to fit infection rates and age-specific hospitalization rates predicted that DHF/DSS would be limited to those second dengue infections that occurred within 5 years of a first dengue infection. This hypothesis, now definitively disproved, had been developed in an epidemiological setting in which all adults were solidly dengue-immune but assumed to be not at risk of DHF/DSS. A recent reanalysis of the 1981 Cuban data has shown that DHF/DSS, while intrinsically more common in children, does occur in adults (15). And adults clearly acquired DHF/DSS with second infections in 1997 in Santiago de Cuba (14).

There would appear to be no time limit to the sensitization that follows a first dengue infection. But, what could be the explanation for the increase in severity of secondary dengue with the passage of time between the first and successive dengue infections, as seen in our data from Cuba? The variation in clinical expression might be caused by the different DEN-2 strains transmitted in the country in 1981 and 1997. Envelope and partial NS-1 gene sequences place the Cuba 1981 DEN-2 strain with Southeast Asian strains (16, 17). Two

TABLE 2. Statistical comparisons of the attack (hospitalization) rate and death rate for dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) in two age groups of adults, separately and then combined, at intervals of 4 and 20 years after DEN-1 infection, for DHF/DSS outbreaks in Cuba in 1981 and 1997

Age group	Comparison	DHF/DSS attack rate[a]	DHF/DSS death rate[b]
15–39 years	Havana/1981 and Santiago/1997	$z = 28.3$, $P < 10^{-6}$	$z = 9.1$, $P < 10^{-4}$
15–39 years	All Cuba/1981 and Santiago/1997	$z = 27.9$, $P < 10^{-6}$	$z = 7.1$, $P < 10^{-4}$
40–65+ years	Havana/1981 and Santiago/1997	$z = 17.0$, $P < 10^{-5}$	$z = 9.2$, $P < 10^{-5}$
40–65+ years	All Cuba/1981 and Santiago/1997	$z = 14.8$, $P < 10^{-6}$	$z = 11.5$, $P < 10^{-4}$
All adults	Havana/1981 and Santiago/1997	$z = 31.9$, $P < 10^{-8}$	$z = 13.2$, $P < 10^{-7}$
All adults	All Cuba/1981 and Santiago/1997	$z = 30.1$, $P < 10^{-7}$	$z = 14.0$, $P < 10^{-6}$

[a] The "attack rate" column shows *z* scores and *P* values comparing the rates of DHF/DSS hospitalizations per 10 000 secondary DEN-2 infections.
[b] The "death rate" column shows *z* scores and *P* values comparing the rates of DHF/DSS deaths per 10 000 secondary DEN-2 infections.

strains from the 1997 epidemic in Santiago de Cuba have been fully sequenced, and they were found to be very similar to DEN-2 Jamaica 82 (MG Guzmán, R Rico-Hesse, unpublished data, 1999). That viral strain is of Southeast Asian origin, but it has frequently been recovered from DHF/DSS cases in the tropics in the Americas since the early 1980s (27). The most recent DEN-2 phylograms place strains from Thailand and strains recovered from fatal Cuban cases in 1981 and in 1997 in different branches of the same genotype (16, 17, 27). It is not known whether the nucleotide and amino acid differences observed between the 1981 and the 1997 DEN-2 strains lead to variation in the pathogenic consequences.

A second explanation might be that changes in the avidity of viral antibody over time are related to the severity of secondary DEN-2 infections. There is strong evidence that antibody regulates dengue infection severity. This is most explicitly demonstrated with infants who are born to dengue-immune women and who develop DHF/DSS during a first dengue infection (28). Infants are at risk to DHF/DSS when protective maternal antibodies have waned, permitting more abundant infection-enhancing antibodies to be expressed. From human volunteer studies it is known that a single DEN-1 infection protects against DEN-2 challenge for a period of 3 months (29). This phenomenon is likely to be an outcome of heterotypic DEN-2 neutralizing antibodies observed following DEN-1 infection (30). Heterotypic neutralizing antibodies could serve to down-regulate secondary dengue infections and thus prevent severe disease. It is well-known that the avidity of viral antibody increases progressively after infection (31, 32). A corollary and testable hypothesis is that increasing avidity to homotypic critical sites is accompanied by decreasing neutralizing activity directed against heterotypic neutralizing sites. When critical sites on a second infecting dengue virus are not covered, antibody-dependent enhancement of infection may occur. A fuller understanding of mechanisms underlying severity differences during DHF/DSS epidemics should contribute to a needed ability to identify markers of safety and protection in dengue, a phenomenon of importance to dengue vaccine development.

The observations reported in this paper suggest that once an individual is infected with the DEN-1 serotype, that person could be susceptible to developing DHF/DSS for at least 20 years. Three key implications of these observations are worthy of note. First is the importance of firm dengue control in order to avoid having a huge mass of individuals who are susceptible to DHF/DSS on a long-term basis. Second is the need to carefully study the role of time for homotypic and heterotypic neutralizing antibodies and their avidity characteristics. Third is the need for a dengue vaccine to elicit extended protection for the four serotypes in order to avoid vaccine sensitization to DHF/DSS.

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RESUMEN

Aumento de la gravedad de las infecciones secundarias por dengue-2: tasas de mortalidad en los brotes cubanos de 1981 y 1997

Objetivos. Investigar el posible efecto del tiempo sobre la gravedad de la enfermedad en sucesivas infecciones por dengue.

Métodos. Se compararon las tasas de mortalidad y hospitalización por dengue hemorrágico/síndrome de choque por dengue (DH/SCD) de las infecciones secundarias por dengue-2 (DEN-2) en el mismo grupo de edad en dos epidemias de DEN-2 ocurridas en Cuba. La primera afectó a todo el país en 1981, mientras que la segunda, de 1997, solo afectó a la ciudad de Santiago de Cuba. La infección sensibilizante para el DH/SCD en cada una de las dos epidemias fue el virus del dengue del serotipo 1 (DEN-1), que se transmitió entre 1977 y 1979, o sea, 4 años y 20 años antes de la primera y la segunda epidemias de DEN-2, respectivamente. Utilizando datos seroepidemiológicos publicados referidos a las ciudades de La Habana y Santiago, se estimaron las tasas de mortalidad y de hospitalización por DH/SCD en personas de 15–39 años y en mayores de 40 años de La Habana y de toda Cuba en 1981, y solo de Santiago en 1997.

Resultados. En los adultos de 15 a 39 años, la tasa de mortalidad por 10 000 habitantes correspondiente a las infecciones secundarias por DEN-2 fue 38,5 veces mayor en Santiago en 1997 que en La Habana en 1981. Otro indicio del aumento de la sensibilidad a medida que aumenta el tiempo transcurrido entre la infección inicial por DEN-1 y la infección secundaria por DEN-2 fue el hecho de que la tasa de letalidad del mismo grupo de edad fuera 4,7 veces mayor en Santiago en 1997 que en La Habana en 1981.

Conclusiones. Observamos un marcado aumento de la gravedad con el mayor intervalo (20 años) entre la infección inicial por DEN-1 y la infección secundaria por DEN-2. Esta diferencia puede deberse a pequeñas diferencias entre las cepas causales del virus del dengue o a cambios de los anticuerpos humanos anti-dengue circulantes en la población a medida que pasa el tiempo. Estas observaciones tienen importantes implicaciones en el control del dengue, en los mecanismos patógenos de la enfermedad y en el desarrollo de vacunas.