Reemergence of Dengue in Cuba: A 1997 Epidemic in Santiago de Cuba

After 15 years of absence, dengue reemerged in the municipality of Santiago de Cuba because of increasing migration to the area by people from disease-endemic regions, a high level of vector infestation, and the breakdown of eradication measures. The 1997 epidemic was detected early through an active surveillance system. Of 2,946 laboratory-confirmed cases, 205 were dengue hemorrhagic fever, and 12 were fatal. No deaths were reported in persons under 16 years of age. Now the epidemic is fully controlled.

Cuba had its first dengue epidemic of modern times in 1977; transmission continued probably until 1981, and more than 500,000 mild cases were reported. A 1978 serologic survey for flavivirus antibody indicated that 44.6% of the Cuban population had been infected with dengue-1 virus, whereas before 1977 only 2.6% had antibodies (1,2).

A second dengue epidemic in 1981, caused by dengue-2 virus (2), was unusually severe and widespread. Of 344,203 cases, 10,312 were clinically classified as dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), and 158 persons (101 children and 57 adults) died (3). Before 1981, only 60 suspected or confirmed DHF sporadic cases had been reported in the region (4). Dengue-2 virus isolated during the 1981 epidemic was classified in the same genotype as New Guinea 1944 (5). Not previously known to circulate in the Americas, this genotype was not isolated again in the region until 1994 in Venezuela and in 1995 in Mexico (6). Retrospective studies show that although the 1981 epidemic was detected in May, the first cases occurred in December 1980. After the epidemic ended on October 10, 1981, a campaign to improve mosquito control and eradicate *Aedes aegypti* was immediately launched. Eradication was not achieved, but most of the 169 Cuban municipalities were free of the vector.

Passive Surveillance—1981

A passive dengue surveillance system was established at the end of the 1981 epidemic. Of 9,543 paired sera (acute- and convalescent-phase) from all suspected dengue patients, only 14 showed seroconversion to immunoglobulin G (IgG) by enzyme-linked immunosorbent assay (ELISA) (7); none developed IgM antibodies to dengue virus by capture IgM ELISA (8). Dengue virus infection was excluded on the basis of clinical and epidemiologic investigation. No *Ae. aegypti* mosquitoes were found in the residence localities of these patients. The surveillance system detected cases, imported from other Latin American countries, that had no evidence of indigenous transmission. Since 1987, 4,983 samples received through the surveillance system for measles and rubella, as well as paired sera of patients with rash, were studied for dengue antibodies [María Guzmán, World Health Organization (WHO)/Pan American Health Organization (PAHO) Collaborating Center for the Study of Viral Diseases, unpub. info.]. No dengue cases were identified. The low *Ae. aegypti* premise indexes and the results of the passive surveillance system indicate no dengue transmission in Cuba between 1981 and the end of 1996. However, reinfestation has occurred in some areas; the municipality of Santiago de Cuba was reinfested in 1992 by *Ae. aegypti* transported in imported tires (9).

Active Surveillance—1997

In January 1997, the Institute of Tropical Medicine "Pedro Kourí" of the Cuban Ministry of Health (a WHO/PAHO Collaborating Center for the Study of Viral Diseases) established an active surveillance system for dengue in Santiago de Cuba municipality. The municipality is located in Santiago de Cuba province, in the eastern part of the country, and has several risk factors for the reemergence of dengue: limited water supply, inadequate eradication efforts, high vector infestation, and increasing migration of people from Latin American and Caribbean disease-endemic countries to the municipality. Following the Guidelines for the Prevention and Control of Dengue and Dengue Hemorrhagic Fever in the Americas (4), this surveillance system actively

searched for febrile patients in the primary health-care subsystem whose clinical picture was compatible with dengue fever and whose sera collected 5 to 6 days after onset of the disease contained dengue IgM antibodies. As a result of this system, dengue cases were detected on January 28, 1997, in one area of the municipality. In three of the first seven cases, dengue-2 virus was detected by polymerase chain reaction (10) and was confirmed by viral isolation and identification using C6/36 cell line and monoclonal antibodies to the four dengue serotypes.

Although retrospective seroepidemiologic studies indicated that the initial transmission occurred during the second half of December 1996, it is highly probable that the cases detected on January 28 were the first. Of 60,000 cases reported from the emergency rooms of Santiago de Cuba hospitals from November 1 to January 28, 592 were clinically compatible with dengue fever. Home interviews of these 592 patients reduced the figure to 154. Blood samples from 143 of 154 patients were examined for IgM antibodies, but no positive cases were detected.

The breakdown of the vector control campaign in this municipality interfered with our efforts to abort the epidemic, despite the early detection of the first dengue cases; however, the partial vector control measures implemented once the outbreak was detected prevented its extension to the other 30 Cuban municipalities infested with the *Ae. aegypti* mosquito.

Active surveillance continued from January to July 1997. Serologic confirmation of cases was carried out by IgM capture ELISA, confirming recent infection. The serologic diagnosis was decentralized to the Provincial Laboratory in Santiago de Cuba, which used an ultramicro-ELISA for dengue IgM detection (11). The Institute of Tropical Medicine served as the national reference laboratory for serology, viral isolation, and strain identification and characterization.

During the epidemic, 17,114 febrile patients were initially considered to have dengue, but serologic testing of 10,024 of these patients confirmed dengue in only 2,946; 46 dengue-2 isolates from 160 serum samples were obtained. The nucleotide sequence of the E\NS1 gene junction of the first isolated strain (12) indicated that it belonged to the Jamaica genotype, which during recent years is being transmitted extensively throughout Latin American and Caribbean countries and is associated with DHF/DSS in some countries (6,13).

Epidemiology

After the end of the 1981 Cuban DHF epidemic, seroepidemiologic studies in Palmira, Cienfuegos, and Cerro municipalities examined dengue-1 and dengue-2 seroprevalence in these populations (14,15). Taking into consideration these data and the total population of the Santiago de Cuba municipality, we estimated the prevalence of dengue-1 and dengue-2 antibodies. The estimated total population at risk for dengue-2 infection was 301,986 adults and children susceptible to a primary infection by any dengue virus serotype (63.5% of the population) and 88,108 adults with antibodies to dengue-1 virus acquired during the epidemic of 1977 to 1980, now susceptible to a secondary infection with dengue-2 and at increased risk for DHF/DSS (18.5% of the population).

The earlier Cuban experience (3) confirms other reports of secondary infection (dengue-1 and dengue-2) as the main risk factor for DHF/DSS. During the 1997 dengue outbreak, secondary infection was again confirmed as a risk factor for DHF/DSS. Of the 2,946 confirmed cases, 205 (including 12 fatal adult cases) were classified as DHF/DSS cases according to the criteria established by PAHO (4). DHF/DSS was observed mostly in adults, the only age group in whom secondary infection was possible. DHF/DSS-compatible symptoms were seen only in one child with primary infection. Preliminary studies indicated that secondary infection was present in 100 (98%) of 102 DHF/DSS cases. In fatal cases, secondary infection could be documented in 11 (92%) of 12 cases. In Thailand the greatest risk appeared when the secondary infection occurred 6 months to 5 years after the primary one (16). For that reason, an epidemic of DHF/DSS was not expected in Santiago de Cuba, perhaps only sporadic cases. However, DHF/DSS in adults who contracted a secondary infection at least 16 years after the primary infection was not previously reported.

Because in Cuba dengue-1 circulated from 1977 to 1980-81, the youngest patients expected to contract secondary infection should be older than 16 years of age; the youngest DHF/DSS patient with confirmed secondary infection was a 17-year-old, which indicates that the "enhancing" antibodies can circulate and be effective for at least 16 years and maybe for life.

A significant number of febrile patients with suspected dengue had respiratory signs and symptoms; therefore, simultaneous circulation of

respiratory or other pathogens was considered. Serologic screening for respiratory viruses using hemagglutination-inhibition and ELISA confirmed that 29.3% of 41 nonconfirmed dengue cases were influenza A, influenza B, or adenovirus infections. Additionally, some children had fever and rash clinically compatible with herpangina, and some had diarrheal disease with fever, as is common in Cuba during the summer. These febrile syndromes contributed to the high number of patients whose infections were provisionally considered suspect dengue cases. Suspect dengue cases were broadly defined to maximize sensitivity of detection and retain all possible dengue cases. This active surveillance excluded other febrile syndromes but recorded them as suspected cases. In practice, the risk perception by the population was very high, especially when the epidemic was officially declared and deaths were noted. Both the patients and the health providers appeared to think of dengue as the first diagnostic possibility. For this reason, the figure of 17,114 cases was considered the magnitude of the epidemic from the clinical management perspective. Since most cases were tested serologically, the incidence of clinical cases was probably close to the 2,946 serologically or virologically confirmed cases. Because asymptomatic and subclinical dengue cases are frequent, especially in children, the true rate of infection may be higher. In a separate and limited study on asymptomatic contacts of dengue cases, for every clinical case, 13.9 asymptomatic or subclinical cases were produced. Serologic studies of contacts in Santiago de Cuba are planned for a more in-depth study of this question.

Clinical Management

The health authorities established a liberal policy of hospitalization that varied with the availability of beds. Hospitalization permitted vector control of the human reservoir, more precise case classification, and close clinical surveillance.

When beds were available, all patients with suspected cases were hospitalized. When the numbers of patients surpassed the availability of beds, patients were treated at home under the supervision of the family doctor. The family doctor transferred the patient to the hospital if any medical complication appeared. Wards with specialized personnel were established where the patients were protected from vectors, and observation wards were organized for patients with complications. Intensive and intermediate care units, as well as an emergency subsystem for the transfer of patients from one unit to another, were available. As in 1981, some patients rapidly developed hypovolemic shock and died within hours of admission to the hospital (17).

An ad hoc task force followed the case definitions for dengue and DHF/DSS established by PAHO (4) for classifying the cases at the closure of the medical record. The accumulated experience of the Cuban scientists and doctors and the increased international knowledge about dengue and DHF/DSS in the last 15 years permitted a much deeper and more comprehensive study of this outbreak with more accurate classification and management of cases than in 1981. Nevertheless, the case-fatality rate was three times higher, mainly because of a much better classification of DHF/DSS cases. Other countries in the region with a very accurate case classification, such as Puerto Rico (13), also have a high case-fatality rate.

Vector Control

The campaign to control the vector started before the beginning of the 1997 dengue outbreak and is well established. Although the campaign required the mobilization of scarce financial resources and experts from all over the country, early intervention prevented spread of the outbreak to other potentially vulnerable municipalities. Of 169 municipalities in Cuba, 30 had *Ae. aegypti* mosquitoes. The epidemic was limited to the municipality of Santiago de Cuba; no autochthonous transmission to other municipalities of the province or country was detected.

An active search for cases detected transmission very early, before "fever alert" signaled an outbreak. In the Provincial Center for Hygiene, Epidemiology, and Microbiology of Santiago de Cuba, a special Unit for Analysis and Trends maintains a permanent fever alert system. For several years, this system has provided a weekly tabulation of febrile patients for every population. The tabulation allows us to evaluate fever alert (4) as applied to an active surveillance system. Because the fever alert did not appear in the epidemic area until May 1997, after the epidemic was already occurring, we consider fever alert an indicator with low sensitivity for the early and timely detection of dengue transmission, at least under the conditions of this study.

As a result of the 1997 epidemic, an epidemiologic alert was established, and antivector intervention, as well as active seroepidemiologic surveillance, was reinforced in the entire country. The epidemiologic characterization of the outbreak (now fully controlled) is in the final phase. Although mosquitoes persisted at a low level after the 1981 DHF/DSS epidemic, the campaign was successful in eradicating dengue from Cuba for more than 15 years, precisely when the disease was reemerging in nearly all the other tropical regions of the Americas. According to PAHO, 250,707 cases of dengue fever and 4,440 cases of DHF/DSS were reported in 1996 alone; 29 countries reported dengue in 1996, and 10 of these reported DHF/DSS. Overall, from 1981 to 1996, 25 countries reported 41,000 cases of DHF/DSS (F. Pinheiro, pers. comm.).

The 1997 Cuban dengue outbreak demonstrated once again that dengue reappears where *Ae. aegypti* control is relaxed. Taking into account these facts, Cuba maintains its policy of vector eradication and recommends an exerted effort in the American region to prevent a recurrence of dengue similar to the one in Southeast Asia, where DHF/DSS is the leading cause of hospitalization and death among children (18).

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References

1. Cantelar N, Fernández A, Albert L, Pérez E. Circulación de dengue en Cuba 1978-1979. Rev Cubana Med Trop 1981;33:72-8.
2. Kourí G, Mas P, Guzmán MG, Soler M, Goyenechea A, Morier L. Dengue hemorrhagic fever in Cuba, 1981: rapid diagnosis of the etiologic agent. Bull Pan Am Health Org 1983;17:126-32.
3. Kourí G, Guzmán MG, Bravo J, Triana C. Dengue hemorrhagic fever/dengue shock syndrome: lessons from the Cuban epidemic. Bull World Health Organ 1989;67:375-80.
4. Dengue and dengue hemorraghic fever in the Americas: guidelines for prevention and control. Washington: Pan American Health Organization; 1994. Scientific publication No. 548.
5. Guzmán MG, Deubel V, Pelegrino JL, Rosario D, Sariol C, Kourí G. Partial nucleotide and amino-acid sequences of the envelope and the envelope/nonstructural protein-1 gene junction of four dengue 2 virus strains isolated during the 1981 Cuban epidemic. Am J Trop Med Hyg 1995:52:241-6.
6. Ricco-Hesse R, Harrison LM, Salas RA, Tovar D, Nisalak A, Ramos C, et al. Origins of dengue type 2 viruses associated with increased pathogenicity in the Americas. Virology 1997;230:244-51.
7. Fernández R, Vázquez S. Serological diagnosis of dengue by an ELISA inhibition method (EIM). Mem Inst Oswaldo Cruz 1990;85:347-51.
8. Vázquez S, Saenz E, Huelva G, González A, Kourí G, Guzmán MG. Detección de IgM contra el virus del dengue en sangre entera absorbida en papel de filtro. Rev Panamericana de Salud Pública. In press 1998.
9. Ministerio de Salud Pública de Cuba. Dengue en Cuba. Julio 1997. Boletín Epidemiológico Organización Panamericana de la Salud 1997;18:7.
10. Lanciotti RS, Calisher CH, Gubler DG, Chang G, Vordam V. Rapid detection and typing of dengue viruses from clinical samples by using reverse transcriptase-polymerase chain reaction. J Clin Microbiol 1992;30:545-51.
11. Laferte J, Pelegrino JL, Guzmán MG, González G, Vázquez S, Hermida C. Rapid diagnosis of dengue virus infection using a novel 10µl IgM antibody capture ultramicroELISA assay (MAC UMELISA Dengue). Advances in Modern Biotechnology 1992;1:19.4.
12. Rico-Hesse R. Molecular evolution and distribution of dengue viruses type 1 and 2 in nature. Virology 1990;174:479-93.
13. División de Prevención y Control de Enfermedades, Programa de Enfermedades, Programa de Enfermedades Transmisibles, HCP/HCT, OPS. Resurgimiento del dengue en las Américas. Boletín Epidemiológico. Organización Panamericana de la Salud 1997;18:1-6.
14. Guzmán MG, Kourí G, Bravo J, Hoz de la F, Soler M, Hernández B. Encuesta seroepidemiológica retrospectiva a virus dengue en los municipios Cienfuegos y Palmira. Rev Cubana Med Trop 1989;41:321-32.
15. Guzmán MG, Kourí G, Bravo J, Soler M, Vázquez S, Morier L. Dengue hemorrhagic fever in Cuba, 1981: a retrospective seroepidemiologic study. Am J Trop Med Hyg 1990;42:179-84.
16. Halstead SB. Observations related to pathogenesis of dengue hemorrhagic fever. Yale J Biol Med 1970;42:350-60.
17. Díaz A, Kourí G, Guzmán MG, Lobaina L, Bravo J, Ruiz A, et al. Description of the clinical picture of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) in adults. Bull Pan Am Health Organ 1988;22:133-44.
18. Gubler DJ, Clark GG. Dengue/dengue hemorrhagic fever: the emergence of a global health problem. Emerg Infect Dis 1995;1:55-7.