Thirty Years after the Cuban Hemorrhagic Dengue Epidemic of 1981

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ABSTRACT

In 1981, Cuba reported the first hemorrhagic dengue epidemic in the Americas, with 344,203 cases, including 10,312 severe and very severe cases, resulting in 158 deaths. In the 30 years following the epidemic, surveillance, control and research have kept Cuba dengue free; although isolated, interrupted epidemics and transmissions have been reported. In this article, we summarize issues of interest regarding the 1981 epidemic, as well as laboratory surveillance data and various related research results.

KEYWORDS dengue, hemorrhagic dengue, Cuba, 1981 epidemic

INTRODUCTION

Dengue in the Americas and Cuba before 1981 Dengue is an acute febrile disease caused by any of four dengue virus serotypes (Den 1, 2, 3, 4) transmitted to humans by the *Aedes aegypti* mosquito. It has been recognized in the Americas since the 18th century, although epidemics of a dengue-type disease were reported as early as 1699 in Panama. In 1780, dengue was first described during an epidemic in Philadelphia. Information for the period between 1780 and 1800 is scarce. During the 19th century and first half of the 20th century, publications refer to epidemics occurring mainly in the Caribbean and southern United States.[1,2]

In the early 1950s, dengue virus (Den 2) was isolated for the first time in the Americas, in nonepidemic conditions in Trinidad and Tobago. From 1960 to 1980, the region experienced three large epidemics: Den 3 in 1963–1964, Den 2 and Den 3 in 1968–1969 and Den 1 in 1977–1978. These epidemics, characterized by the benign form of the disease (dengue fever, DF) mainly affected countries in the Caribbean, Central America and some countries in South America.[2,3] This was a period of low endemicity with isolated cases of dengue hemorrhagic fever (DHF), the severe form of the disease.[1]

After 1945, the year Havana experienced a dengue outbreak, there were no cases of suspected dengue reported until introduction of Den 1 virus during the 1977 pandemic.[4,5] Serologic studies during the early 1970s confirmed absence of circulating dengue virus in Cuba at the time.[6] During the Den 1 epidemic in 1977, more than 400,000 cases were reported, all of the benign form.[5,7] Later serologic studies demonstrated that 44.46% of the Cuban population was infected by this virus serotype and at risk of secondary infection if another dengue virus serotype were to enter the country.[6]

THE 1981 CUBAN HEMORRHAGIC DENGUE EPIDEMIC

Background At the end of 1980, there was low circulation of Den 2 virus in the Americas region. On the other hand, almost half the Cuban population was at risk of a second infection by another dengue serotype. Finally, at the beginning of 1981 the first introduction of Den 4 virus in the region was reported (in Dominica), as well as the first epidemic of DHF, the latter in Cuba.[1,3,8]

Data on the epidemic The epidemic was recognized as such in late May 1981. Retrospective epidemiologic studies found it had begun at the end of 1980 in three municipalities located in eastern, central and western Cuba. Cases were reported during the same epidemiologic week in persons with no history of travel outside the country or their localities. A total of 344,203 cases were registered, including 10,312 severe and very severe cases, resulting in 158 deaths (101 of them children) (Table 1).

Table 1: General data on the Cuban hemorrhagic dengue epidemic of 1981

Detection	Late May 1981
Etiologic agent	Den 2 virus, Asian genotype
Total cases reported	344,203, with 10,312 serious (9203 severe and 1109 very severe) and 158 deaths
Case fatality	0.49/1000 patients
Mortality	1.58/100,000 population
Duration	Four months
Date last case reported	October 10, 1981
Months with most case reports	June, July, August
Date with most case reports	July 6 (11,400 cases)
Hospitalizations over four months	116,151

Clinical presentation DHF was seen both in children and adults.[8,9] In the former, clinical presentation was similar to that reported in Southeast Asia.[9–11] In adults, this was the first report of an epidemic of this nature.[12] Shock was more frequent in children but more severe in adults. Serologic studies showed that DHF was seen in cases of Den 1/Den 2 secondary infection, with a frequency of 1 in every 23 secondary infections in children and 1 in every 79 in adults.[13] Studies of these cases permitted identification of DHF clinical warning signs for the first time.[9]

Management, control and elimination of the epidemic This process included establishment of clinical guidelines for diagnosis and case management, in which early hospitalization and appropriate hydration were crucial for adequate recovery. For better patient care and surveillance, schools were converted into hospitals, with a network for immediate transport of patients requiring hospitalization. Medical personnel were also redistributed according to patient needs and expert groups were created to rapidly train both medical and paramedical personnel. Medical students played an essential role in clinical surveillance of hospitalized patients, carrying out followup of clinical findings and monitoring for DHF warning signs.

An intensive vector eradication campaign was mounted, in which community participation was fundamental.[7,14] The measures

taken made it possible to end the epidemic in four months, the last case reported on October 10, 1981.

Etiologic agent diagnosis and laboratory surveillance Studies of sera collected during the first days of fever onset in patients with clinically suspected dengue enabled detection of elevated levels of flavivirus antibodies. These results, together with clinical signs and symptoms typical of the disease and population epidemiologic status, led to a presumptive dengue diagnosis and communication to health authorities that a DHF epidemic was under way. Viral isolation studies from samples collected during the acute disease phase enabled isolation and identification of Den 2 as the etiologic agent in the earliest days of the epidemic.[15–17]

For better followup and characterization of the epidemic, serologic surveillance was established in three stages:

1. The first, until July 24, was aimed at identifying the epidemic's etiologic agent and confirming transmission throughout the country's provinces. During this stage, 4000 single serum samples from patients were processed.
2. During the second stage, clinical cases were confirmed by studying paired sera to determine diagnostic efficacy. In this stage, 2017 paired sera were studied.
3. In the third and final stage, 100% of suspected dengue cases were studied in order to certify elimination of the epidemic. During the entire epidemic period, virologic surveillance was maintained, allowing virus isolation in samples from 22 cases of DF and DHF, some of the latter fatal.[15,17]

Research during the epidemic The first studies carried out during and after the epidemic's elimination enabled: a) characterization of DHF clinical presentation in both children and adults with confirmed Den 2 infection; b) clinical, virologic and pathologic characterization of manifestations in 13 children who died of DHF; c) identification of DHF risk factors in several groups of patients with confirmed infection; d) characterization of the etiologic agent; e) establishment of primary and secondary infection serologic criteria in the Cuban setting; and f) introduction of new diagnostic technology.[9–12,15–23]

1982–2011 PERIOD

In the 30 years since the 1981 DHF epidemic, increases in dengue and DHF have been observed worldwide, with increases in cases and epidemics reported, as well as geographical extension of vector and dengue transmission. Today, an estimated one third of the world population lives in areas at risk for infection. The disease is reported in Southeast Asia, the Western Pacific, the Americas, Africa and the Eastern Mediterranean. All four viral serotypes have been identified in each of these regions.[24,25]

In the Americas, reports of dengue have increased sixfold, and of DHF 12-fold. In 2010, 1,663,276 cases were reported; 48,954 were DHF and there were 1194 deaths. Thirty countries report co-circulation of two or more serotypes. Epidemics have become more frequent and the cycles between them shorter (See http://new.paho.org/hq/index.php?option=com_content&task=view&id=4497&Itemid=3526&limit=1&limitstart=3).[26]).

In this complex context, Cuba has worked throughout these years to keep the country transmission-free. These efforts rely on a strong laboratory-supported clinical epidemiologic surveillance program that, together with the vector control and eradication program, has kept dengue from becoming endemic, even within a very complex regional context. Decisive to this achievement are political will, community participation and intersectoral action.

Diagnosis and surveillance Over the last 30 years, apart from strengthening diagnostic, surveillance and reference activities, dengue studies have been carried out in different disciplines. They have supported the country's surveillance and control programs and have also provided new evidence and insights for Cuba and the world. Cuba is acknowledged today as the only country to succeed in remaining free from endemic dengue, eliminating transmissions when these have occurred. It is also considered a center of excellence for training personnel and, through international collaboration and reference activities, has assisted many countries in the region in their efforts to confront and control dengue.

The country is working on improving comprehensive surveillance (environmental, entomologic, epidemiologic, clinical and laboratory) with participation by all levels of the health system. Laboratory surveillance is mainly aimed at early identification and confirmation of transmission, followup and characterization of epidemics and their etiologic agent, and at certification of transmission elimination. In 1997, active surveillance was established to search for cases and confirm diagnosis. Critical to this pursuit have been: the primary health care subsystem; the network of provincial laboratories capable of serologic diagnosis with Cuban technology (UMELISA Dengue IgM developed by the Immunoassay Center); national reference center activities (responsibility of the Pedro Kourí Tropical Medicine Institute's National Reference Laboratories); and active integration of all levels of the system to ensure dynamic analysis of epidemiologic situations.

Within this comprehensive strategy, vector surveillance plays a decisive role, in order to identify increases in vector presence and breeding grounds, enabling prompt action to decrease risk and in order to measure insecticide resistance. These activities rely on a network of entomology laboratories throughout the country, as well as the Pedro Kourí Tropical Medicine Institute's National Entomology Reference Laboratory and the National Vector Surveillance and Control Division.

Clinical epidemiologic surveillance at all levels of the national health system is another essential part of the comprehensive strategy, enabling early risk identification, timely notification of cases and study of their temporal-spatial distribution, as well as design and evaluation of elimination strategies. These actions are inserted in the Cuban program for international sanitary control.

RESULTS OF VARIOUS STUDIES CARRIED OUT DURING THE PERIOD

Unlike the experience in Southeast Asia and most countries of the Americas, epidemics in Cuba have been eliminated when they have occurred. Subsequent to the 1981 epidemic, others have been reported: one in 1997 (Den 2) in Santiago de Cuba and one in 2001–2002 (Den 3), mainly affecting the capital city.[27–31] After 2004, transmissions of imported cases have been reported, which have been controlled and eliminated. In 2006, another epidemic was reported, which was also eliminated (http://www.paho.org/spanish/ad/dpc/cd/eid-eer-2006-oct-24.htm). In this epidemiologic context, research has provided new knowledge in the field of dengue. Several of the main results are summarized below:

1. Virologic, immunologic and clinical epidemiologic studies have enabled characterization of the 1981, 1997 and 2001–2002 epidemics, providing important data for early diagnosis and followup of outbreaks and understanding of decisive factors in their control and elimination, as well as contributing better knowledge of dengue.
2. Secondary infection by a different serotype than the primary infection has been confirmed as the main risk factor for DHF. Greater risk for DHF has been associated with certain viral sequences (Den 1/Den 2; Den 1/Den 3), and more production of IL-10 has been observed in these patients. Research showed higher DHF rates with secondary infection in children than in adults, and identified DHF cases during tertiary infections. Finally, seroepidemiologic studies have made it possible to determine dengue and DHF case rates according to type of infection and serotype in the Cuban setting. [13,20,30–35]
3. For the first time, it was demonstrated that higher DHF risk was associated with longer interval between infections. It was also shown that humoral response specificity increased with time, with decreasing heterologous neutralizing antibodies and memory T-cell cross-reactivity persisting even 20 years after primary infection.[36–38]
4. DHF risk factors identified were: white skin color, bronchial asthma, diabetes mellitus and sickle cell disease.[20,23]
5. Higher association with DHF was found for persons of European descent, with stronger memory T-cell response and cross-reactivity in white compared with black dengue-immune persons and with higher IFN alpha production in white persons.[39–43]
6. Increased and different expression levels of chemokines and cytokines (CCL2, CCL3, TNFα, IFNγ, IL–10 and TGFβ) were demonstrated in persons with different dengue immunity histories, suggesting that previous immunity to a serotype strongly influences early immune response to reinfection. [34,35,44]
7. Immune response genes associated with disease severity (HLA class I A*31, B*15, Fc g RIIa HH131, MICA*008 and MICB*008) or protection (HLA class II DRB1*04, DRB1*07, Fc g RIIa RR31) have been identified.[41,45]
8. Virus role in severity of Cuban epidemics was demonstrated, with identification of strains and genotypes capable of producing DHF. An evolving pattern was demonstrated in non-structural proteins in strains isolated at different points in the epidemic.[46–52]
9. Increase in epidemic severity was associated with longer duration, with possible selection of more virulent virus variants, whether by neutralization escape (hypothesis of escape mutants) or viral evolution.[20,23,49,53]
10. A comprehensive hypothesis was put forward, explaining the development of DHF epidemics, in which host and virus characteristics and epidemiologic conditions play a fundamental role.[8,23,54]
11. Research aimed at better clinical understanding of the disease has enabled its characterization, greater comprehension of its complications, detection and validation of clinical warning signs and demonstration of dengue infection clinical sequelae even a year after infection, as well as its possible relation to an autoimmune phenomenon.[9,21,55–61]
12. Studies to develop and implement diagnostic methods, characterize humoral immune response in patients with primary or secondary infection, and to determine diagnostic usefulness of different clinical specimens have been important in laboratory surveillance (serologic, virologic and molecular) and in deepening understanding of the disease.[62–73]
13. Production of biologic reagents such as monoclonal antibodies, diagnostic kits for dengue IgM antibody determination by an ultramicroanalytic system (SUMA), among others, has contributed to serologic diagnosis and better understanding of this agent.[74–76]
14. It has been shown that efforts to control *Aedes aegypti* are only sustainable through conscious, systematic, proactive and preventive actions carried out by persons and groups—what in the Cuban context we term "autofocal," referring to a "set of measures directed towards detection and elimination of possible mosquito breeding places. It hinges on weekly self-directed inspection by families and workers in their homes and workplaces."
15. During this period, research has been carried out to improve comprehensive, integrated surveillance, institutionalizing community strategies against dengue and evaluating community interventions, as well studying new control methods.[77–82]
16. Among the main studies undertaken are those aimed at estimating key epidemiologic parameters during outbreaks and seasonality of *Ae. aegypti* and *Ae. albopictus* populations; determining the entomologic burden for dengue transmission; developing methods to predict dengue severity; designing models to analyze social conditions favoring transmission and of models for measuring *Ae. aegypti* infestation. [78,79,83–89]
17. Research on dengue's economic impact has identified costs during and outside of transmission periods; costs of prevention programs, clinical case control and direct and indirect costs to families; cost-effectiveness of community participation strategies; and cost-effectiveness of vector control measures for *Ae. aegypti*.[90–93]
18. Development of a Cuban vaccine candidate for dengue control is one of the principal lines of research in the country. In this context, a model for obtaining attenuated vaccines was designed; humoral and cellular immune responses induced by membrane proteins and their precursor were characterized; a monkey model was established for dengue vaccine candidate evaluation; and the immunogenic and protective capacity of Den 4 virus envelope protein expressed in *Pichia pastoris* was assessed. Currently, two vaccine candidates based on a recombinant strategy (domain III of the dengue virus envelope protein and capsid/domain III) have shown satisfactory results in preclinical studies.[74,94–121]

INTERNATIONAL COLLABORATION

During the past 30 years, the country has maintained strong collaboration with countries in our own and other geographic regions, as well as with international organizations involved in dengue study (PAHO; WHO; Special Programme for Research and Training in Tropical Diseases, TDR; Dengue Vaccine Initiative, DVI; and others). Several approaches enable Cuba to share its knowledge and capacities for better dengue control with other nations, and also to keep current on the global situation, benefiting from dengue control strategies and research by other countries and international organizations. These approaches are: participation in diagnosis, clinical management of patients and outbreak response and control; evaluation of control programs in countries of the Americas; coordination of quality control tests; introduction of diagnostic methodologies; evaluation of insec-

ticide resistance; personnel training in several dengue-related disciplines; introduction and evaluation of the new dengue clinical classification; implementation in the region of the Integrated Management Strategy for Dengue Prevention and Control (IMS) promoted by PAHO; participation in international expert groups (PAHO, WHO, TDR, DVI, among others); participation in multicenter research projects; and collaboration with high-level national and international scientific institutions.

CONCLUSIONS

During these 30 years, unlike most countries of the region, Cuba has been able to keep dengue from becoming endemic. Epidemics and transmissions that have occurred have been interrupted. The country has followed the five basic principles recommended by WHO–PAHO for dengue response, political will being the fundamental pillar and promoter of success. Nevertheless, the increasing complexity of dengue's epidemiologic situation in the region and the high and growing volume of travel between Cuba and endemic regions enhance risk. In this context, the country is working to strengthen and improve its programs. Application of scientific results and continuous and increasing international collaboration must play a key role in a more effective response to dengue.

DEDICATION

This paper is dedicated to the memory of Professor Gustavo Kourí Flores, who through his work, dedication and teaching was a tireless warrior in the battle against dengue. He worked intensively to develop Cuban science, as a fundamental contribution to addressing infectious and tropical diseases.

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