Dengue haemorrhagic fever/dengue shock syndrome: lessons from the Cuban epidemic, 1981*

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Dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) is one of the principal causes of hospitalization and death among children in several south-east Asian countries. Also, in the Region of the Americas, there has been an increase in the frequency of dengue fever epidemics and in the number of cases of DHF/DSS. In 1981 an epidemic of dengue haemorrhagic fever occurred in Cuba and this suggests that there is a high risk that such epidemics could recur in the region. The article summarizes the main clinical, virological, and epidemiological data obtained during the outbreak, some of which are reported for the first time.

Introduction

Although circulation of dengue virus has been widely documented in the Region of the Americas, reports of dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) have been sporadic—in contrast to the situation in the South-East Asia and Western Pacific Regions of WHO, where four dengue serotypes are endemic and have been major causes of hospitalization and death, particularly among children since the 1950s (*1*).

In 1981 a major epidemic of DHF/DSS occurred in Cuba that affected the whole country and produced a large number of cases and fatalities (*2*). The epidemic, the first to be documented in Cuba, and probably the world's largest epidemic hitherto reported, opened a new chapter in the study of the disease.

Here, we briefly review the main findings on the epidemic. The results are based on follow-up studies of 124 cases of DHF/DSS among children and 104 cases among adults, as well as on a detailed analysis of the clinical data and autopsy protocols for 57 children and 26 adults who died.

In the Region of the Americas the increasing number of dengue epidemics and of DHF/DSS cases being reported, the continuous and simultaneous circulation of at least three serotypes of dengue virus, the almost complete breakdown in *Aedes aegypti* control in many countries, and the recent introduction of *A. albopictus* are reminiscent of the situation in south-east Asia in the 1950s (*3*).

Background

A small, limited outbreak of dengue-like illness was reported in Cuba in 1945. Subsequently, until the late 1970s the disease was not identified clinically in the country, and in 1975 a nationwide serological survey (randomly selected and age-stratified) of dengue virus demonstrated that, based on the results of the haemagglutination inhibition test, only 2.6% of the urban Cuban population had antibodies against group B arboviruses. A total of 2000 sera were studied.

In 1977, however, a major epidemic of dengue fever, caused by dengue virus type 1 occurred in Cuba (*4*); in this outbreak more than 0.5 million cases were reported. A serological survey carried out in 1978 showed that 44.5% of the urban Cuban population had been infected by dengue virus type 1 and was consequently at risk of a secondary infection if a different serotype were introduced into the country. This event occurred in 1981 (*2*).

The 1981 outbreak

General information

The epidemic was recognized in late May 1981, after the beginning of the rainy season. Cases were reported simultaneously in three municipalities in the eastern, central, and western part of Cuba. The epidemic extended explosively to the rest of the country in a few days. A total of 344 203 cases were reported; 10 312 were classified as severely ill (WHO grades II–IV) and 158 persons died (101 children and 57 adults). The highest daily incidence during the epidemic occurred on 6 July 1981, when 11 400 cases were reported. Dengue virus of serotype 2 was iso-

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lated from the sera of affected individuals as well as from *A. aegypti* mosquitos using newborn mice and LLC-MK2 cell cultures. The virus was identified using immunofluorescence (IF) and plaque reduction neutralization tests (PRNT) (*5*).

Criteria were established for the diagnosis and classification of patients, based on their need for hospitalization and different kinds of treatment. Early hospitalization and early use of rehydration therapy were favoured. In order to carry out the therapeutic measures selected, boarding schools in all the provinces were used as hospitals, and a transportation network for the transfer of patients was established. Also, medical personnel were redistributed, close supervision of activities was maintained, and the necessary organizational and operational adjustments were made as the epidemic evolved. A total of 116 143 patients were hospitalized and a low case-fatality rate was recorded (0.46 per 1000 dengue fever cases).

An intensive campaign to eradicate the *A. aegypti* vector was launched immediately after the epidemic was recognized and the necessary human and financial resources needed for this were allocated. Initially, a vertical campaign was established and managed by the Cuban civil defence, but later the responsibility for this was transferred to the Ministry of Public Health.

The epidemic was completely controlled in about 4 months, the last case being reported on 10 October 1981. Since then, close surveillance of the disease has been maintained, and no new cases have been documented (*2*).

As a result of the campaign the *A. aegypti* vector has been eradicated in 13 of the 14 provinces in Cuba. Approximately 10 000 health workers are still permanently engaged with the eradication programme, and all the necessary supplies are guaranteed.

Cost and economic impact

The economic impact of the epidemic was about US$ 103 million—the cost of the control measures and medical services during the months that it lasted. This figure is based on: the cost of medical care—hospitalization, emergency rooms, outpatient clinics, and intensive care units—determined using indices supplied by the Ministry of Public Health (US$ 41 million); salaries paid to adult patients under the social security regulations (US$ 5 million); the cost of lost production calculated from indices supplied by the Central Planning Ministry and the Ministry of Finances (US$ 14 million); and the direct initial cost of the *A. aegypti* control campaign (US$ 43 million, unpublished data, Ministry of Public Health). The cost was greater than that of the DHF/DSS epidemic in Thailand in 1980 (US$ 6.8 million for hospitalization and mosquito control) or the epidemic of dengue fever due to dengue virus type 2 and type 3 in Puerto Rico in 1977 (US$ 6 million to US$ 16 million for medical costs, lost work, and control measures) (*6*, *7*).

Clinical picture

Studies of children

The clinical picture observed for children (*8*) did not differ greatly from that described previously for outbreaks in south-east Asia. The predominant signs were fever, gastrointestinal and haemorrhagic manifestations, while petechiae and upper gastrointestinal bleeding were also frequently observed. Abdominal pain, enlargement of the liver, and presence of ascites were usually associated with the more severe cases of the disease.

Shock frequently occurred after the sudden onset of fever and vomiting, usually on the fourth or fifth day of the disease. In numerous cases it was preceded by abdominal pain and petechiae. In most cases the shock syndrome in children was not fatal, so long as rapid and appropriate treatment was given.

In children, the haemorrhagic manifestations among fatal cases and those who exhibited the severe form of the disease but who survived, were similar, although among those who died the severity of the disease and the frequency of gastrointestinal severe bleeding were higher. Thrombocytopenia and haemoconcentration occurred in 78% and 97%, respectively, of the 57 children who died and in 83% and 96%, respectively, of the 124 children who suffered the severe disease but who survived (*8*).

The modal age of patients with DHF/DSS who were hospitalized was 4 years. There was no significant difference in the hospitalization rate between the sexes, and a significant ($P < 0.01$) proportion of children with grade III–IV DHF/DSS and of those who died were White. It must be pointed out that 122 out of 124 children (98%) with grade III–IV DHF/DSS exhibited a secondary serological response in the PRNT (*8*). No hospital cases or fatalities occurred among 1- or 2-year-olds. It should be noted that such children were born after the dengue-1 epidemic (*2*) and were, therefore, exposed only to dengue-2 virus.

During the epidemic four fatal cases were registered among newborns, in whom maternal antibodies could have played the role of the primary infection (*8*).

Studies of adults

In endemic areas the clinical picture of dengue haemorrhagic fever in adults has not previously been

described because children are generally infected several times with dengue viruses and then develop immunity. However, the occurrence of a large number of cases gave us the opportunity to describe, for the first time, the clinical picture of DHF/DSS in adults (*9*).

Among adults, DHF/DSS was characterized by fever (100%), constitutional manifestations (100%), gastrointestinal symptoms (90%), purpura (66%), and upper gastrointestinal bleeding (40%). Hepatomegaly (35%), abdominal pain (58%), and haematemesis (35%) were frequently recorded in fatal cases; these can be considered to be signs of a poor clinical prognosis. Shock was documented in all fatal adult cases studied (26 out of 57 adult fatalities) and was particularly severe, indicating a poor clinical outcome. Thrombocytopenia and haemoconcentration were frequently observed (71% and 92%, respectively) particularly among those who died. No particular age group was significantly represented among hospitalized patients; however, a high proportion of those who died (62%) were women. A significantly greater proportion of those who developed DHF/DSS were White ($P < 0.01$). However, the proportion of Whites who died was not significant and is probably related to the small sample size and particularly to the presence of sickle cell anaemia, a known risk factor, in two of the Blacks who died. A total of 98% (102/104) of all the cases examined using PRNT exhibited a serological pattern that was consistent with a secondary infection.

Risk factors

Individual risk factors

Individual risk factors determine the appearance of DHF/DSS in a particular person or group in a given population.

In the Cuban epidemic the following individual risk factors were identified, in both severe and fatal cases (*10*):

—pre-existence of antibodies to dengue virus;
—age (high frequency among children);
—sex (high frequency among adult females);
—race[a] (high frequency among Whites); and
—chronic diseases: asthma, sickle cell anaemia and diabetes mellitus were frequently recorded as personal or familial antecedents in those who developed severe clinical pictures.

Below are discussed only those factors that according to our results are particularly interesting (*1*, *4*, *5*).

[a] As defined by the Cuban population census, 1981.

Pre-existence of antibodies to dengue virus. The pre-existence of antibodies to dengue virus, which is reported by Halstead to be the most important risk factor for DHF/DSS, was repeatedly found in the Cuban outbreak (*8–10*). As mentioned above, samples of sera from 98% of children (122/124) and adults (102/104) who were screened by PRNT exhibited a secondary serological response. Additionally, there were no fatal or severe cases among 1–2-year olds—precisely those children who had experienced only a primary infection, since they were not born until after the first epidemic of dengue fever caused by dengue-1 virus in Cuba in 1977–78.

It should be noted that in a retrospective, cross-sectional seroepidemiological study carried out in El Cerro, a populous urban municipality in Havana City, we found five clinically and serologically confirmed DHF/DSS cases (three children and two adults), all of whom exhibited a secondary serological response. The ratio of DHF/DSS hospitalizations to secondary infections in El Cerro was 1:23 among children compared with 1:79.5 among adults (M.G. Guzmán, personal communication, 1988). These results provide further evidence for the importance of sequential infection as a risk factor for DHF/DSS and also indicate that children are at higher risk than adults of developing the severe form of the disease.

Race. Of 123 children with DHF/DSS (grades III–IV), 86% were Whites and only 6% Blacks. Also, of 104 adults with DHF/DSS, 81% were Whites and 6% Blacks. Racially the Cuban population consists of 66% Whites, 12% Blacks, and 22% mulattos. Comparison of the proportions of individuals with DHF/DSS with this ethnic distribution indicates that the frequency of DHF/DSS both among children and adults was significantly higher among Whites ($P < 0.01$) (*10*).

During the epidemic it was popularly held that DHF/DSS was "not a negro's disease" because it was observed that the majority of the severe and fatal cases were Whites (*10*).

Chronic diseases. It has previously been suggested that chronic diseases are possible risk factors for DHF/DSS in south-east Asia (*11*). In Cuba, we identified bronchial asthma, sickle cell anaemia, and, possibly, diabetes mellitus as individual risk factors for the occurrence of the severe clinical form of the disease (*10*). According to the 1983 national survey on the prevalence of bronchial asthma, the proportion of fatal cases of DHF/DSS among children and adults with bronchial asthma was double that of the Cuban population as a whole (*12*). The number of non-fatal cases of DHF/DSS among children with bronchial asthma was also double that reported for

the Cuban child population as a whole. These differences were statistically significant ($P < 0.01$). Non-fatal adult cases of DHF developed a mild clinical form of the disease, and there was no difference between the proportion of bronchial asthma in this group and that in the general population.

Sickle cell anaemia was frequently observed in patients with DHF/DSS and the proportion of fatal cases among adults was significantly higher ($P < 0.01$) than that for the Cuban population as a whole (Martinez-Antuña, personal communication, 1987). No cases of sickle cell anaemia were identified in children with DSS or among adults whose clinical evolution was favourable. The clinical and pathological pictures presented by fatal cases with sickle cell anaemia were typical of DHF/DSS and did not exhibit the "haemolytic crisis" usually observed in patients with sickle cell anaemia; we therefore ascribed the deaths of such patients directly to DHF/DSS.

One of 23 (4%) fatal adult cases of DHF/DSS suffered from diabetes mellitus, while only 2 of 104 (2%) adults with DHF/DSS who recovered satisfactorily exhibited diabetes mellitus. The prevalence of diabetes in the Cuban population as a whole has been reported to be 1% (*13*); the distribution of diabetes among cases of DHF/DSS that had a favourable outcome was therefore double this level and increased to four times among adult fatal cases. These proportions, however, are not statistically significant, probably because of the small sample sizes involved. Among children, no personal antecedent of diabetes mellitus was reported in severe or fatal cases of DHF/DSS.

The identification of risk groups for DHF/DSS is of utmost importance for delineating future vaccination strategies and for planning protective measures to prevent, as much as possible, individuals who are likely to develop the severe form of the disease from being bitten by mosquitos during outbreaks. Clearly, such factors must be validated through well-designed epidemiological studies and, in this respect, some of our results are relevant.

Epidemiological factors

Antibodies to dengue viruses were almost absent from the Cuban population prior to 1977 (the year in which dengue-1 virus was introduced), while most other countries in the Region of the Americas have suffered successive outbreaks of dengue fever due to dengue-2 and dengue-3 virus at irregular intervals over the last 25 years.

During the outbreak the density of *A. aegypti* mosquitos in all urban areas of Cuba was high. Sequential infection occurred in Cuba over a 3-year period. In contrast, in the rest of the Caribbean the interval between the introduction of dengue-2 virus and dengue-3 virus was 10 years, while 13 years elapsed between the introduction of dengue-3 virus and dengue-1 virus. The sequence of infection in Cuba was dengue-1 virus followed by dengue-2 virus. A positive relationship has been reported between the emergence of DHF/DSS epidemics and this particular infection sequence, although other sequences have been involved in major epidemics in south-east Asia.

In the rest of the Caribbean, the introduction of different serotypes of dengue virus has not favoured the occurrence of secondary infections with a sequence ending in dengue-2 virus, since this virus was already established before the other serotypes were introduced into the region.

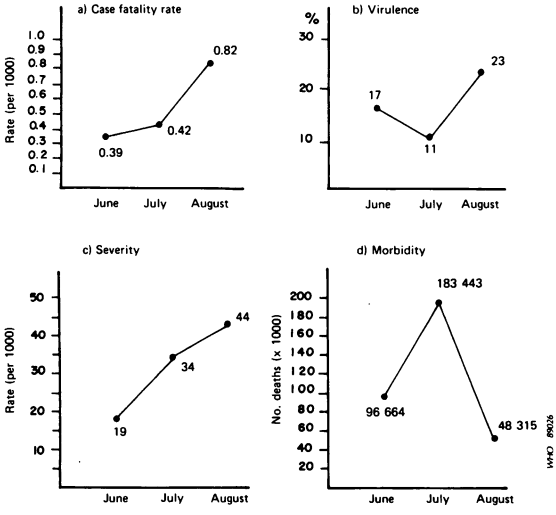
Viral factors

The strain of dengue-2 virus that was circulating in Cuba appears to have become more virulent with successive passages through the human host, and, although our data are not conclusive, this may have resulted in the increase in the case fatality rate observed towards the end of the epidemic (*14*). Since neither Cuba nor other Caribbean countries have had any previous experience in managing DHF/DSS patients, an initially high case-fatality rate that decreased towards the end of the outbreak would have been expected as health personnel gained experience in the complex care needed. In practice, however, this was not observed.

The case fatality rate, expressed as the ratio of the number of fatalities to the total number of cases of dengue fever reported during the epidemic, increased to reach a peak in August 1981 (*14*), although at that stage medical care was much better than at the beginning of the outbreak (Fig. 1a). If, however, the case fatality rate is expressed as the ratio of the number of fatal cases to that of DSS cases (termed here the "virulence" index) during the 3 months of the epidemic, the curve shown in Fig. 1b is obtained. The drop in this index in July 1981 could have been associated with improved case management, due mainly to the measures taken by the Ministry of Public Health and the experience acquired by doctors; nevertheless, in August 1981, probably after a second passage of the virus through the human host, an increase in the "virulence" index occurred, reaching levels that were even higher than those observed at the beginning of the outbreak.

During the epidemic, severe cases (WHO grades II–IV) were reported daily to the Ministry of Health. From these data we calculated the "severity" index (the ratio of the number of severe cases reported to the total number of cases over a given period of time). This index increased steadily as the epidemic

Fig. 1. **Plots showing: a) the case fatality rate ((number of fatal cases ÷ number of dengue fever cases) x 1000); b) the virulence ((number of fatal cases ÷ number of cases of dengue shock syndrome) x 100); c) the severity ((number of cases of dengue haemorrhagic fever/dengue shock syndrome) ÷ (number of cases of dengue fever) x 1000); and d) the morbidity from dengue haemorrhagic fever/dengue shock syndrome, Cuba, 1981.**



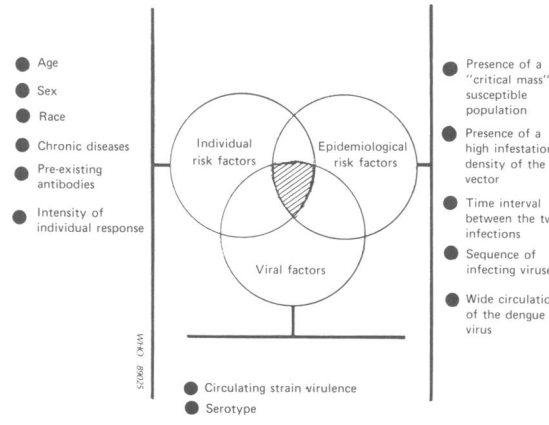
proceeded (Fig. 1c). The virulence of viruses increases with successive passages through a competent host and this may explain the epidemiological findings we observed. Not all strains of dengue virus have the same virulence and our results indicate that the virulence of the circulating strain must be taken into consideration when an epidemic of DHF/DSS is studied. Any increased virulence of the dengue virus could be associated with a higher efficiency of the strain to produce immunological enhancement in the presence of adequate host conditions (e.g., risk factors and intensive immunological response) leading to a greater number of DHF/DSS cases. This epidemiological finding supports previous reports of increases in the virulence of dengue viruses that have been circulating in south-east Asia for long periods (*15*).

Analysis of risk factors in the epidemic

Fig. 2 shows diagrammatically the interaction between the factors that have a bearing on the appearance of DHF/DSS in epidemic or endemic form.

At the intersection (shaded area) of the three groups of factors (epidemiological, individual, and viral) DHF/DSS can be expected in epidemic form. In contrast, sporadic cases and endemic situations

Fig. 2. **Diagram showing the interactions between the various factors that have a bearing on the appearance of dengue haemorrhagic fever/dengue shock syndrome in epidemic or endemic form.**



arise with the simultaneous occurrence of factors that are conducive to the appearance of the syndrome in a given individual or group (*14*).

This analysis is able to account for a variety of epidemiological situations and also facilitates assessment of the risk for a population group or individual of developing DHF/DSS.

Control of the epidemic

The epidemic was brought under control in a little over 4 months, essentially for the reasons outlined below.

- Rapid diagnosis. Once the epidemic was reported, health authorities were given a presumptive diagnosis within 24 hours and a definitive diagnosis within 4 days.
- Patients with suspected complications were hospitalized early and given appropriate treatment.
- As soon as the incidence fell to a level that matched the availability of hospital beds, all patients were hospitalized. Certain health-care facilities were kept free of the *A. aegypti* vector and patients were also admitted there.
- One of the most important actions in bringing the epidemic under control was the national campaign to eradicate *A. aegypti*. This began as soon as the epidemic was recognized and succeeded in bringing the vector infestation rates down to levels sufficiently low to break the chain of transmission. In order to prevent new cases from arising, the first stage concentrated on spraying adult mosquitos with malathion (ultra low volume). At the same time, temephos was used in an intensive campaign against mosquito

larvae in water tanks and a large-scale environmental sanitation campaign was begun, with community participation, to eliminate existing and potential vector breeding sites.

• The decision to bring the epidemic under control and to eradicate the *A. aegypti* vector, together with the participation of the Ministry of Public Health, all health workers and the community, were factors of vital importance in bringing the outbreak under control.

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Résumé

Dengue hémorragique/dengue avec syndrome de choc: les leçons de l'épidémie cubaine de 1981

L'épidémie de dengue hémorragique/dengue avec syndrome de choc DHF/DSS des anglo-saxons qui s'est déclarée à Cuba en 1981 a été la première épidémie de dengue signalée dans la Région des Amériques. Cette flambée a permis de recueillir des données cliniques, épidémiologiques et virologiques dans une population des Caraïbes constituée de races et de groupes ethniques autres que ceux jusqu'ici touchés par cette maladie. L'épidémie a débuté à la fin mai 1981, après le début de la saison des pluies, et le dernier cas a été signalé le 10 octobre 1981. On a enregistré au total 344 203 cas, dont 116 146 ont nécessité une hospitalisation, avec plus de 10 000 cas classés comme sévères et 158 décès. On a relevé des infections secondaires chez 98% des sujets atteints de DHF/DSS étudiés. Il s'est produit un cas de DHF/DSS pour 23 infections secondaires chez les enfants et un cas pour 183 infections secondaires chez les adultes. Les maladies chroniques comme l'asthme bronchique, la drépanocytose et le diabète sucré ont constitué les facteurs de risque possibles d'une évolution grave de la maladie, qui s'est produite chez une proportion significativement plus élevée de Blancs que de Noirs. Chez les enfants, le tableau clinique n'a pas été différent de celui observé auparavant en Asie du Sud-Est; toutefois, pour les adultes, ce tableau, décrit pour la première fois, a présenté certaines différences par rapport à celui des enfants. Le coût de cette épidémie a été estimé à US$ 103 millions.

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