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THE REAPPEARANCE OF DENGUE-3 AND A SUBSEQUENT DENGUE-4 AND DENGUE-1 EPIDEMIC IN PUERTO RICO IN 1998

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Abstract. In January 1998, dengue-3 (DEN)-3 (group III genotype) was detected in Puerto Rico after an absence of 20 years. Public health officials intensified education efforts to promote community participation in dengue control. Virologic surveillance revealed an unexpected paradox: DEN-4 and DEN-1 produced a large epidemic overlaying the DEN-3 epidemic. In 1998 there were 17,000 reported cases of dengue (4.8/1,000 persons), and among all virus isolations (n = 960), DEN-4 (419, 43.6%), DEN-1 (337, 35.1%), and DEN-2 (143, 14.9%) were detected much more frequently than DEN-3 (61, 6%). Age group-specific attack rates were highest for persons 10–19 years old, followed by infants less than a year of age. Nineteen fatal cases (median = 37 years old, range = 8 months to 90 years) had a positive laboratory diagnosis of dengue. Among DEN-3 cases no fatalities were documented, 50 were hospitalized, and 10 of 48 (21%) fulfilled the criteria for dengue hemorrhagic fever (four had primary infections and six had secondary infections). During 1999, DEN-3 became the predominant serotype isolated (182 of 310 isolations, 59%). The reappearance of DEN-3 and its subsequent circulation from 1999 to 2001 produced no changes in dengue incidence that could have been detected in the absence of virologic surveillance.

INTRODUCTION

Dengue is an acute viral disease caused by any of four dengue virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). The principal vector is the *Aedes aegypti* mosquito, which is present in tropical and many semitropical areas of the world. All four serotypes produce a similar illness (characterized by fever, intense headache, myalgias, arthralgias, rash, nausea, and vomiting), and induce life-long immunity that is specific to the infecting serotype.[1,2] A small proportion of infected persons may develop the severe form of disease, dengue hemorrhagic fever (DHF), and excessive capillary permeability that may lead to shock (dengue shock syndrome [DSS]) and death.[2,3] Fatality rates among persons with DSS can be more than 10%.[4]

In Puerto Rico, dengue is endemic with a seasonal pattern of minimal occurrence from March to June and a transmission peak from September to November. During the 1977 dengue epidemic in Puerto Rico, DEN-3 was the most frequently isolated serotype, but it then disappeared from the island.[5] Beginning in 1985, three dengue serotypes (DEN-1, -2, and -4) circulated in Puerto Rico, producing local epidemics annually, and 2–3-year cycles in the prevailing serotype. In 1994–1995, DEN-2 produced a large epidemic, but in 1996 and 1997, DEN-4 dominated by a small margin among the three serotypes isolated.[6,7] Following the 1977 epidemic in Puerto Rico, DEN-3 was not detected anywhere in the Americas, until the near simultaneous detection in Nicaragua and Panama in 1994.[8–10] In the following three years, it was found in all Central American countries.[11,12] In 1998, DEN-3 isolates were obtained from patients in the Caribbean islands of Puerto Rico, Jamaica, Barbados, and St. Kitts and Nevis.[13] This report describes the reappearance of DEN-3 in Puerto Rico in 1998; the intensified surveillance and control efforts in anticipation of an expected large epidemic (given that the population less than 21 years old in 1998 had little or no immunity to DEN-3); the epidemic that followed, caused by serotypes DEN-4 and DEN-1; and the continued transmission and expansion of DEN-3 to become the dominant (almost exclusive) circulating dengue serotype.

METHODS

Surveillance. The surveillance system maintained by the Puerto Rico Department of Health (PRDH) and the Dengue Branch, Centers for Disease Control and Prevention (CDC) in San Juan, receives blood specimens from clinics, hospitals, laboratories, and physicians' offices throughout Puerto Rico. These specimens are sent directly or collected locally by personnel of the PRDH and delivered to the Dengue Branch. The goals of the surveillance system are to provide early and precise information on dengue activity (including virus serotype and disease severity) to predict transmission and guide implementation of control measures. For this reason, the reintroduction of DEN-3 was a possibility that had been contemplated during the last 15 years, and discussions of joint contingency plans (CDC-PRDH) had been held periodically.[14] To increase the probability of detecting DEN-3 infections after the first case was documented, surveillance in early 1998 was intensified by increasing the number of samples processed weekly for virus isolation, attempting isolations from all early acute samples submitted from the San Juan metropolitan area, doubling the frequency of visits to hospitals by PRDH couriers, and establishing two sentinel locations (San Juan City Hospital and Ponce University Hospital, in the largest cities on the northern and southern coasts, respectively) for dengue diagnosis among children with undifferentiated febrile illnesses.

Surveillance information is presented by date of onset of symptoms and municipality of residence of the patient. Population data are from the 1990 United States census for Puerto Rico. Significantly increased reporting (epidemic threshold) was defined, for the island and for each municipality, as a number of case reports greater than the mean plus two standard deviations in five non-epidemic years.[15] Comprehensive vector surveillance is not routinely conducted in Puerto Rico. For inspections of case homes and neighborhoods, the Breteau index (number of containers with larvae per 100 houses inspected), the house index (number of houses with containers with larvae per 100 houses), and ovitraps were used to monitor mosquito infestation levels.[16]

To evaluate the clinical severity of reported cases, the form that accompanies samples seeks information on whether the patient had any hemorrhagic manifestations or was hospitalized. Infection control nurses (ICN) at hospitals throughout the island (i.e., the Puerto Rico Association of Epidemiologists) voluntarily provide more extensive clinical information on hospitalized patients with suspected dengue, and the Demographic Registry of Puerto Rico provides copies of all death certificates that mention dengue as a cause of death. In addition, the severity of DEN-3 infections was investigated in 1998 through calls to attending physicians and a review of patients' hospitalization records.

A case of DHF was defined according to the World Health and Pan American Health Organizations' (WHO/PAHO) guidelines, fulfilling all of the following criteria: fever (or recent history of acute fever), any hemorrhagic manifestation, thrombocytopenia (platelet count $\leq$ 100,000/mm^3), and objective evidence of increased capillary permeability. The latter was documented by hemoconcentration (hematocrit increased by $\geq$ 20% or decreased an equivalent amount after intravenous fluid therapy), pleural or abdominal effusion (by radiography or other imaging method), or hypoalbuminemia or hypoproteinemia. Cases of DSS met all these criteria and showed hypotension or narrow pulse pressure ($\leq$ 20 mm of Hg), or frank shock.[3]

Laboratory diagnosis. Serum specimens collected less than six days after the onset of illness were either processed for virus isolation in C6/36 mosquito cell cultures or inoculated into *Toxorhynchites amboinensis* mosquitoes. Dengue viruses were detected by the use of a direct fluorescent antibody test using pooled human serum and subsequently identified to serotype using specific monoclonal antibodies in an indirect fluorescent antibody test on virus–infected cell cultures.[17,18] For virus genotype identification, the E gene of DEN-3 viruses was amplified by the polymerase chain reaction. Both strands of the amplified DNA were sequenced using primers that produced overlapping sequences and the Dye Terminator Cycle sequencing kit (Applied Biosystems, Foster City, CA) according to the manufacturer's protocol.[19] Phylogenetic relationships were determined using the maximum parsimony program of the PHYLIP software (version 3.5, J. Felsenstein) for sequence analysis.

Serum specimens collected six or more days after onset of symptoms were tested for anti-dengue IgM by the IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA).[20] Tests for IgG antibody were made using an IgG ELISA.[21] Because the measurement of IgM antibody may fail to diagnose approximately 5% of secondary dengue infections,[22] specimens with borderline results by the MAC-ELISA were tested by an IgG ELISA in an attempt to confirm the diagnosis by detection of an anamnestic anti-dengue antibody response. Specimens from which a dengue virus was isolated were also evaluated with an IgG ELISA to determine whether the patient's infection was primary (first dengue infection) or secondary (a subsequent infection), based on the presence of IgG antibody in the acute-phase sample or high IgG titers in the convalescent-phase serum specimen, as specified in this report.

A reported case of dengue was defined as a person with any illness diagnosed as dengue by a health care professional, and who submitted a sample for dengue diagnosis. Laboratory confirmation of a current dengue infection was based on one of the following criteria: 1) dengue virus isolation from serum or autopsy tissue samples; 2) seroconversion from negative to positive or a four-fold or greater change in anti-dengue antibody titers in paired serum samples; or 3) demonstration of dengue virus antigen in autopsy tissue samples by immunofluorescence or immunohistochemical analysis (IHC).[1,23] Probable dengue cases were those individuals from whom a single serum sample was submitted, and which was IgM positive or had an antibody titer by the IgG ELISA $\geq$ 163,840. These cases were considered only probable because the persons might have had dengue in the past three months (IgM may be detectable for 90 days or longer), and the symptoms at the time of blood collection might have been due to an illness other than dengue.[22] Unless otherwise stated, probable and confirmed cases are considered together in this publication as laboratory-diagnosed or laboratory-positive cases. In specimens collected six or more days after onset of symptoms, the absence of IgM antibodies ruled out the diagnosis of dengue, and the case was considered negative. From July 23 to December 31, 1998, the number of samples received far exceeded the laboratory's capacity to process them. Priority was given to samples from fatalities, severely ill patients, from municipalities where an increase in incidence had not been previously detected, and from the two sentinel hospitals. Samples not processed because of the criteria for testing applied during the epidemic, and single acute-phase specimens negative for virus and for IgM were considered non-diagnostic, and the case was categorized as indeterminate.

RESULTS

Reappearance of dengue-3. On January 6, 1998, a previously healthy 83-year-old man, a resident of San Juan, developed fever, general malaise, joint pains, back pain, and severe pain radiating to the right shoulder. He was hospitalized on January 9, and DEN-3 was subsequently isolated from a serum sample collected that day. Clinically, he fulfilled the criteria for DHF with spontaneous bleeding; he was treated with intravenous fluids, and was discharged on January 17. On January 25, a 66-year-old woman, a resident of Toa Baja (10 km west of San Juan, and part of the metropolitan area), in good health but with aortic and mitral valve prostheses and a permanent cardiac pacemaker, developed fever, lower back and leg pain, headache, and a cough. She was admitted to the hospital the next day and DEN-3 was isolated from a serum sample obtained January 27. While hospitalized, she showed a platelet count nadir of 33,000/mm^3 and hemoconcentration of 22%, without evidence of hemorrhagic manifestations or low blood pressure. She was treated with intravenous fluids and discharged on February 3. These patients were not acquainted with each other, denied any travel outside of Puerto Rico for at least five weeks prior to onset of illness, and had no relatives, friends or colleagues who had traveled to Asia or Central America in the six weeks before onset of illness. Therefore, these DEN-3 infections were acquired in Puerto Rico, indicating that transmission was occurring on the island. Analysis of the nucleotide sequence of the glycoprotein gene of these two DEN-3 isolates showed that they were genetically distinct from the DEN-3 that occurred in the Americas up to 1977. They belonged to the genotype (group III) that caused DHF epidemics in Sri Lanka and India in 1989 and

1990 and later circulated in Central America starting in 1994 and 1995.

The low herd immunity to DEN-3 on the island, and the demonstrated epidemic potential of this virus strain suggested that there was a high risk for a dengue epidemic in subsequent months. Despite intensified virologic surveillance, this virus serotype was not detected after the January cases until April (in a 22-year-man in Vega Alta, west of Toa Baja). Subsequently, the virus was isolated in May (two cases: a 30-year-old man and a 17-year-old man), June (five cases: a nine-year-old boy, a 17-year-old man, a 64-year-old man, a six-year-old girl and a 15-year-old girl), and almost weekly in July and thereafter (Figures 1 and 2). All the DEN-3 cases that were identified from January through June 1998 resided in the northern half of the island, and the range of the virus was approximately 100 km west (San Juan to Moca). None of the patients reported from April to June showed hemoconcentration or low blood pressure, and only two had hemorrhagic manifestations (petechiae). They were not acquainted with each other, and denied travel outside of Puerto Rico for at least five weeks prior to illness. The sentinel clinic at the Ponce University Hospital identified an additional DEN-3 importation in a 14-year-old boy who became ill on July 26, 1998 in El Salvador and visited the hospital in Ponce on July 29, but no other DEN-3 infections were documented in that city in 1998 or 1999.

Epidemic. The incidence of reported dengue in Puerto Rico from late February through April 1998 was unusual in that the number of suspected cases, though decreasing as expected from seasonal trends, did not go below the epidemic threshold (Figure 3). Reports increased markedly after mid-June, and peaked on week 35 (August 30–September 5), when the number of cases was 6.3 times greater than expected and 70 (90%) of the 78 municipalities on the island had a statistically significant increase in reports. On September 21, 1998, Hurricane Georges passed over the entire length of Puerto Rico, causing extensive property damage. Dengue reporting was briefly interrupted for one week and returned to above average historic levels through November (weeks

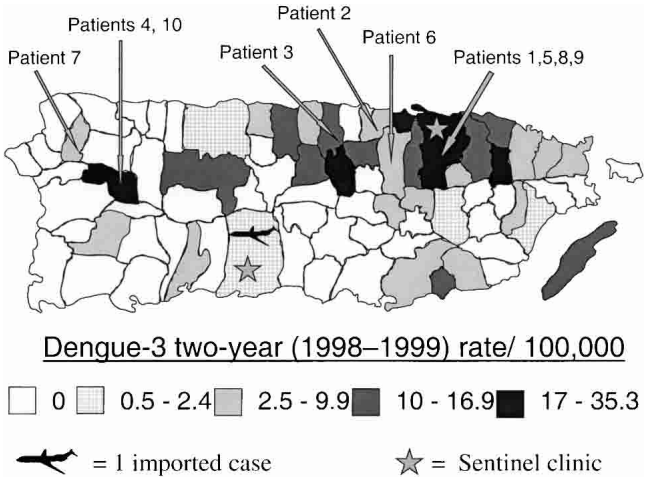

FIGURE 1. Dengue-3 rates by municipality in Puerto Rico, 1998–1999. Patient numbers refer to the residence of the first 10 dengue-3 cases diagnosed in 1998; the sentinel clinics were in the pediatric emergency rooms of teaching hospitals in San Juan (north) and Ponce (south).

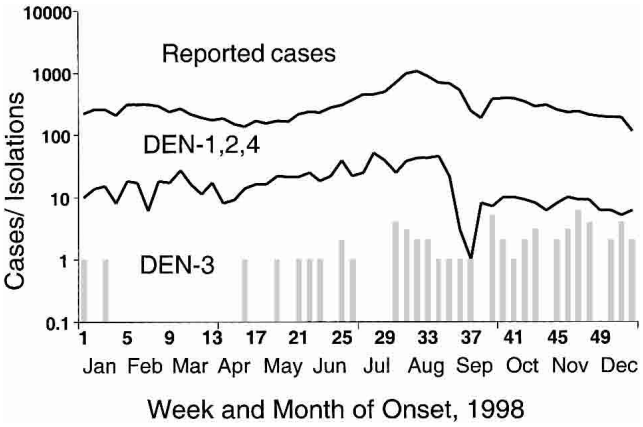

FIGURE 2. Reported dengue (DEN) cases and virus isolations by week of onset of symptoms in Puerto Rico, 1998.

43–47), with no upsurge in cases following the hurricane. There were a total of 17,000 reported cases of dengue with onset of symptoms in 1998 (incidence rate = 4.8/ 1,000 persons), of which 5,188 (30.5%) were laboratory-positive, 1,004 (5.9%) were negative, and 10,808 (63.6%) were indeterminate. This high proportion of indeterminate diagnoses reflects the application of laboratory priorities for testing, as defined earlier. Among all (n = 960) virus isolations in 1998, DEN-4 (419, 43.6%), DEN-1 (337, 35.1%), and DEN-2 (143, 14.9%) were isolated much more frequently than DEN-3 (61, or 6%) (Figure 2). Disease incidence (reported and laboratory-positive) was highest in the municipalities of the central and western regions (Figure 4). In both reported and laboratory-positive cases, the male:female ratio was 1:1, and ages ranged from six days to 98 years (median = 22 years). Age group-specific attack rates were highest for persons 10–19 years old, followed by infants less than a year of age whether considering reported (6.6 and 5.6/1,000, respectively) or laboratory-positive disease (3.6 and 3.1/1,000, respectively). An estimated 4,607 (27.1%) patients were hospitalized (based on review of a 5% random sample of reports), and 4,693 (27.6%) had some hemorrhagic manifestation. There were 19 deaths (12 males) with a confirmed or probable dengue diagnosis (one DEN-1, one DEN-2, three DEN-4, and 14 with positive IgM results), with ages ranging from eight months to 90 years (median = 37 years). Four of the 14 IgM-positive individuals had a documented diagnosis of other severe infections: leptospirosis (2) by immunohistochemistry (IHC), a positive antigen test result for *Neisseria meningitidis*, and *Staphylococcus aureus* in blood culture. It is not possible to determine precisely if the anti-dengue IgM titers in these four cases were due to concurrent infection or to a prior dengue infection occurring several weeks before the time of death. Most laboratory-positive deaths occurred at the peak of the epidemic (August-September) (Figure 5). An additional 37 suspected dengue deaths were recorded in 1998, of which six were negative by dengue laboratory analyses, 24 were indeterminate following laboratory testing, and seven were identified only by the review of death certificates and lacked a diagnostic specimen. Of these 37 cases, one negative case and two indeterminate cases were positive for *Leptospira* by IHC. Three indeterminate cases had laboratory or autopsy evidence of *N. meningitides* infection, endocarditis, or brain tumor as the cause of death.

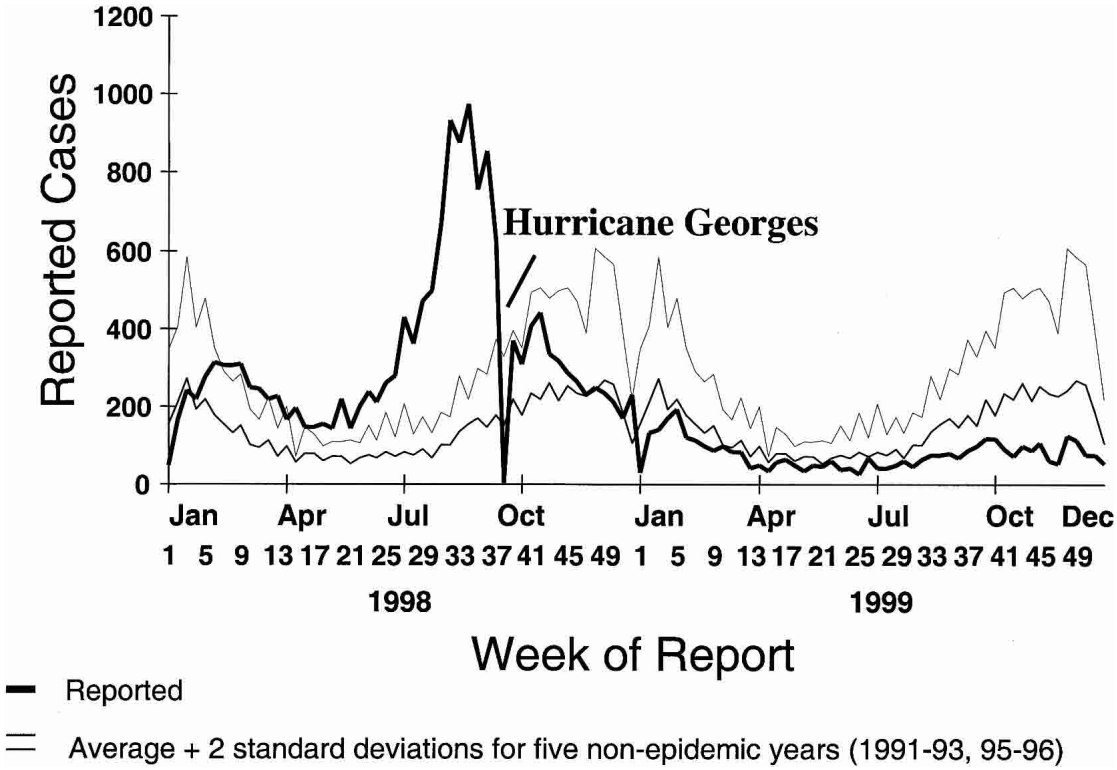

FIGURE 3. Reported dengue cases by week of report to the surveillance system in Puerto Rico, 1998–1999. The calculation of maximum expected reports is based on the weekly average, plus two standard deviations, of five non-epidemic years (1991, 1992, 1993, 1995, and 1996).

Dengue reporting is mandated by law in Puerto Rico, but DHF is not. Only one laboratory-positive fatality was reported with sufficient information to meet the case definition for DHF. The ICNs reported 1,580 hospitalized cases in the alternative surveillance system for obtaining more clinical detail. Of those, 174 (11.0%) were classified as DHF, and of 70 DHF-classified cases with available samples, 59 (84.3%) were laboratory-positive. The highest rate of DHF (7.8 per 100,000 population) occurred in persons 55–59 years old. In contrast, the highest rates of laboratory-positive DHF were seen in infants and persons 20–24 years old (3.1 per 100,000) and in persons 55–59 years old (2.1 per 100,000).

The first two years of DEN-3 transmission in Puerto Rico (1998 and 1999) produced a low number of identified cases. Dengue-3 accounted for only 61 (6% of 960) virus isolations in 1998, and 182 (59% of 310) in 1999, when it became the predominant serotype isolated (Figures 2 and 6). Fifty DEN-3 cases were hospitalized in 1998, and all but two hospitalization records were available for review. Ten (20.8%) of the 48 fulfilled the criteria for DHF (four had primary infections and six had secondary infections), and no fatalities were documented. Comparison with infections due to other serotypes was not possible because the detailed follow-up was applied only to DEN-3 cases. Dengue activity for all serotypes in 1999 was relatively low, and no laboratory-positive deaths were reported (Figures 5 and 6). Nevertheless, ICNs reported 431 hospitalizations for suspected dengue in 1999, of which 55 (12.8%) fulfilled the criteria for DHF (three of those had

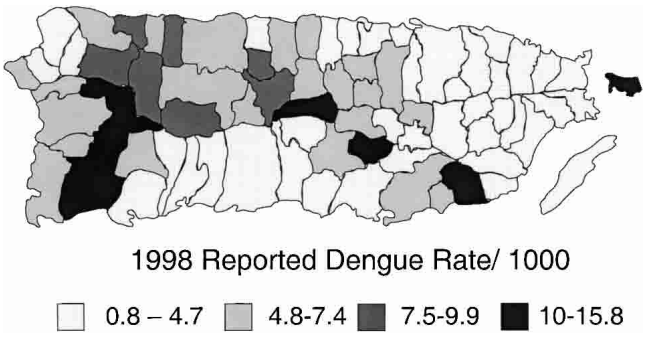

FIGURE 4. Reported dengue rates by municipality in Puerto Rico, 1998.

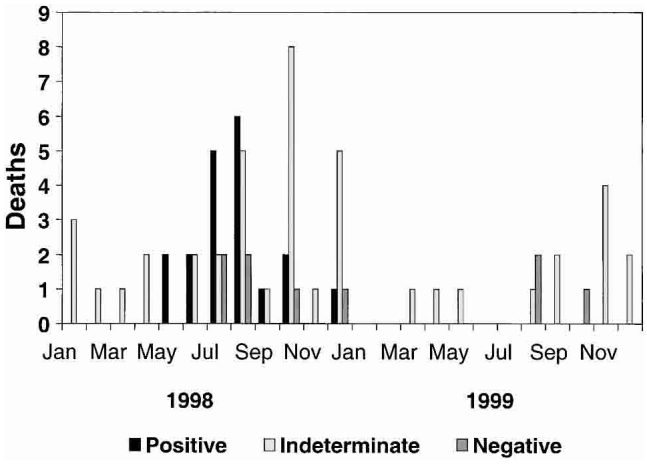

FIGURE 5. Deaths suspected to be due to dengue, by month and laboratory diagnosis, in Puerto Rico, 1998–1999.

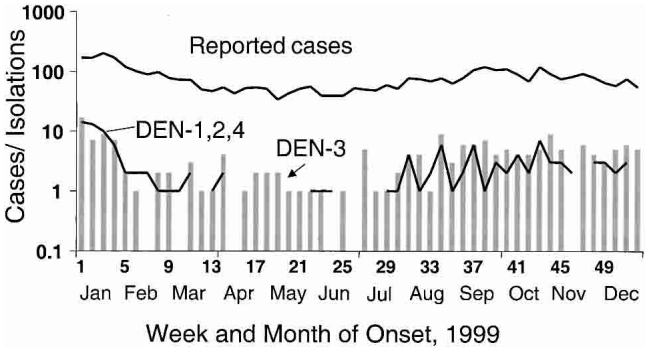

FIGURE 6. Reported dengue (DEN) cases and virus isolations by week of onset of symptoms, in Puerto Rico, 1999.

DSS), and 30 (54.6%) of the 55 were laboratory-positive. Of the 243 DEN-3 patients reported in 1998 and 1999, 140 (57.6%) were males (slightly higher than the other serotypes, range = 47.2–53.2%), 94 (38.7%) were reported as hospitalized, and 54 (22.2%) had some hemorrhagic manifestation. DEN-3 cases were identified throughout the island (Figure 1) in 36 (46%) of the 78 municipalities, but the highest ratio (2.5) of the incidence, in contrast to all reports of dengue (Figures 1 and 4), was observed in the northeastern quadrant of Puerto Rico, especially the San Juan metropolitan area. Cases of DEN-3 cases ranged in age from three months to 83 years (median = 17 years). All serotypes produced a higher incidence of infection in the younger population (< 20 years old) than in persons ≥ 20 years old, but DEN-3 showed the highest ratio of the incidence in persons ≤ 19 years old compared with persons ≥ 20 years old (2.5 versus 20 years old for DEN-1, 1.4 for DEN-2, and 1.2 for DEN-4). Immune response, which was determined for cases with positive virus isolation, showed that the number of secondary infections for every primary infection detected in 1998 (when DEN-4 and DEN-1 predominated) was 2.4, lower than in the epidemic year of 1994 (4.6, when DEN–2 predominated). These differences may be explained by the predominant serotypes each year. For the years 1998 and 1999 combined, the ratio of secondary infections detected by serotype for each primary infection increased as follows: DEN-1 (0.9), DEN-3 (1.5), DEN-4 (5.6), and DEN-2 (9.8).

Response. In response to each of the first two DEN-3 isolates, the PRDH quickly issued statements in print and broadcast media to alert the public to take immediate action to empty, eliminate, or clean all containers that hold water (i.e., potential mosquito breeding sites) and to continue doing this on a weekly basis to interrupt the mosquito life cycle. Entomologic investigation of the homes of the first 10 DEN-3 cases indicated the presence of adult mosquitoes in all locations by ovitraps positive for *Ae. aegypti* eggs, or water-holding containers with *Ae. aegypti* larvae or pupae. From January 1998 to May 1999, 38 DEN-3 case premises were inspected by PRDH staff in San Juan and the adjacent city of Bayamón after patients had recovered from the illness. Of these, 22 (House index = 58%) still had one or more containers positive for *Ae. aegypti*. Large water-storage containers (cisterns, 55-gallon drums) were the most common breeding sites observed (9 of 27, 33%). A survey of 45 premises around the residence of the second DEN-3 patient at the time of her diagnosis showed that 27 (House index = 60%) had one or more containers positive for *Ae. aegypti* larvae or pupae, with a Breteau index of 133. A qualitative assessment of knowledge, attitudes, and practices (KAP) showed that high *Ae. aegypti* indices persisted in spite of the high level of knowledge demonstrated by community residents about *Ae. aegypti* larval habitats, dengue as an illness, and how it is transmitted. In these and other interviews, many people expressed the opinion that the responsibility to control the mosquito belonged to the government (including agencies such as the PRDH), not to the individuals or the families. After weekly reporting increased markedly in mid-June 1998, the PRDH warned the public that a dengue epidemic was in its initial stages. The PRDH and individual municipalities also decided to include ultra-low volume malathion spraying among their control efforts. The PRDH and CDC coordinated a public education campaign addressing the results of KAP studies and emphasizing the presence of DEN-3 on the island. The CDC Dengue Branch and the PRDH defined the focus of an educational campaign, based on the slogan *Te toca a tí* (It's up to you or It's your turn now) to promote personal responsibility, and made sure that all messages to the public emphasized what the PRDH was doing to fulfill its duties. The PRDH and the Dengue Branch conducted an island-wide teleconference for mayors and leaders of civic groups, presenting information on dengue transmission and the organization and function of local dengue control committees. The Puerto Rico Department of Education and the Corporation for Public Broadcasting, television and radio stations, health insurance and pharmaceutical companies, health care professionals' associations, and community organizations participated in carrying out this campaign. An evaluation of the education efforts, scheduled for September, was cancelled in the aftermath of Hurricane Georges. The physical and social disruption caused by the hurricane made it virtually impossible to conduct entomologic and KAP surveys to evaluate the impact of the campaign on the population.

DISCUSSION

The reappearance of DEN-3 in Puerto Rico allowed us to examine the impact of a virus introduction into a susceptible population. DEN-3 cases occurred as anticipated (widespread geographic distribution and higher attack rates among those less than 20 years of age), and technically, DEN-3 caused an epidemic (the low number of cases was still higher than expected for the specific population, place, and time). Nevertheless, the circulation of this DEN-3 genotype (virulent by previous accounts) would have gone unnoticed for months or years in the absence of a well-established surveillance program and extensive virologic testing. Virologic surveillance revealed an unexpected paradox: the activity of other dengue serotypes (predominantly DEN-4 and DEN-1) resulted in a large epidemic overlaying the DEN-3 epidemic. Mathematical models suggest that a dengue virus introduction in a completely susceptible human population with high mosquito densities would quickly (within the year) produce a large epidemic.[24,25] In contrast, an extended lag time may result from the characteristics of the introduced virus strain, the competition of other serotypes (high concurrent endemicity), herd immunity in the population affected (a large number of immune individuals from previous infections with the introduced serotype) and the environment in which transmis-

sion is occurring.[26,27] For example, the arrival of DEN-4 (1981) and DEN-2 (1985) in Puerto Rico also failed to immediately produce an explosive increase in the incidence of those serotypes. Dengue-2, the co-predominant serotype of the epidemic of 1977, disappeared in 1978, and was next detected in 1984 (one case) and 1985.[28,29] It was expected that this serotype would quickly produce an epidemic, since it was the new Asian (Jamaican) serotype. There was an epidemic in 1986, but the predominant serotypes, as in 1998, were DEN-4 and DEN-1, and it was another eight years before DEN-2 produced an island-wide epidemic.[29–31] These virus introductions may be an instructive scenario for an even more feared event, the introduction of yellow fever into dengue-endemic urban areas. If specific diagnostic services are not readily available, only an outbreak with high lethality may signal the arrival of yellow fever in a population where dengue is endemic because yellow fever infections characterized by only fever and constitutional symptoms are common.[32]

We were able to identify only a small proportion of DEN-3 infections in Puerto Rico during 1998 and 1999 because our surveillance for DEN-3 was limited to the results of virus isolation in reported cases. We obtained virus isolation in 18.5% of all laboratory-positive cases (960 of 5,188), but our detection ratio for DEN-3 infections might be reduced by 10- or even 100-fold, given that for asymptomatic infections no samples were submitted, and primary infections were relatively difficult to detect. The distribution of immune responses in our findings is similar to the observations in the epidemics of 1986 in Puerto Rico, and 1997 in Santiago de Cuba, with dengue types 2 and 4 most often isolated from secondary infections.[29,33] To improve the detection of dengue infections, sentinel centers, as exemplified here, must be used carefully. The Ponce University Hospital was able to identify an imported case of DEN-3 on the southern coast and yielded many isolations of other dengue serotypes among febrile patients with undifferentiated illness, but no additional case of DEN-3. In contrast, no case of DEN-3 was identified through the San Juan City Hospital sentinel clinic, while other cases of DEN-3 were found through its routine diagnostic mechanisms. Well-placed sentinels may give early information of the occurrence of a rare event, but the selection of special methods and locations has disadvantages. Sentinels are not representative of the epidemiologic situation, as is population-based surveillance, and require considerable effort to maintain an effective network.

In contrast to the 1994 epidemic in Puerto Rico, the early announcement of a dengue epidemic (the reappearance of DEN-3 and the increase in dengue incidence in the summer of 1998) allowed the implementation of a massive community education effort, including activities for the medical community.[34] Governmental and private agencies mobilized quickly, even though disbelief was an unexpected consequence of the early warning (before clinics and hospitals were crowded with patients). The design and wording of announcements were considered carefully to address concerns and false impressions that communities revealed in KAP surveys and informal consultations. The surveys and case premise inspections carried out in 1998 and 1999 agree with the findings of a larger evaluation carried out in Puerto Rico in 1995, which concluded that levels of awareness regarding dengue and the *Ae. aegypti* mosquito are very high, but the entire population is not yet taking action to control this vector. The principal barriers to action, as shown by recent studies, are lack of knowledge about how to locate and eliminate containers that could serve as larval habitats, the absence of external motivators to prompt the behavior, and the lack of positive feedback and other factors to encourage the public to carry out the necessary actions (Winch PJ, Leontsini E, unpublished data).

It is possible that the early announcement of increased dengue activity and vector control and clinical efforts produced the epidemic's unusually early peak (the usual seasonal peak is in October or November), but there was no apparent impact on the epidemic's lethality or duration. Although no deaths due to DEN-3 were documented, the 1998 epidemic produced a record number (n = 19) of laboratory–positive deaths associated with dengue in Puerto Rico. This increased mortality is a reflection of the general phenomenon of increased dengue incidence and severity in Puerto Rico. In the 1970s, low dengue years meant an incidence rate of less than 0.5 cases per 1,000 population, and no DHF. In the 1980s, low years had rates between 0.5 and 1 per 1,000, and rare cases of DHF (except for the 1986 epidemic). The number of reported cases during the last five nonepidemic years (1992, 1993, 1995–1997) ranged from 4,645 to 11,078 (an average rate of 2.0 cases per 1,000 population). In 1994, 23,693 cases were reported (6.7 per 1,000), while in 1998 they totaled 17,000 (4.8 per 1,000).[6,7] From 1990 to 1994, the average proportion of hospitalized cases fulfilling the DHF criteria was 5% (range = 3–8%), but from 1995 to 1999 it was 13% (range = 10–17%) (CDC, unpublished data).

The duration of the 1998 epidemic (six months of higher than expected incidence, from June through November) was consistent with the duration of epidemics in Puerto Rico in the previous 35 years (from month of first increase to month of resumption of normal incidence, inclusive): 6–7 months, except for the 10 months of the 1994 epidemic.[5–7,29,35] Other well–described epidemics, distant from each other in time and location, had similar duration (mean = 6.4 months, range = 4–9, standard deviation = 1.6; Athens, 1928; Bangkok, 1958 and 1960; Calcutta, 1963; Koh Samui, Thailand, 1966; Bantul, Indonesia, 1976, Cuba, 1981 and 1997; French Polynesia, 1988 and 1996; Thailand, 1987 and 1990; Venezuela, 1989; and Townsville, Australia, 1992).[36–47] Although short dengue epidemics are less likely to be represented in the scientific literature, the consistency of epidemic duration in spite of the differences of year, place, and control methods indicates that there is an urgent need to critically evaluate the different approaches recommended for arresting dengue epidemics, and that health officials must consider these epidemics as a long-lasting phenomenon, currently without any available radical cure. In the absence of effective primary prevention methods, secondary prevention must be ensured. Therefore, the adequacy of medical care systems (medical education, sufficient resources, guaranteed rapid availability of appropriate treatment locations) must be established promptly, concurrently with any vector control efforts, to minimize mortality.

In spite of the different weather conditions in tropical and subtropical areas of the globe, dengue had a banner year throughout the world in 1998.[48,49] As in 1996, the passing of a hurricane did not affect the shape and height of the dengue epidemic curve in Puerto Rico, except for a brief interruption in reporting in the week following Hurricane Georges.[7]

Weeks later, the same phenomenon was observed in Central America with the passing of Hurricane Mitch. No significant increases in dengue incidence were registered in the post-hurricane period.[50] In Puerto Rico, the years 1999–2001 resulted in low to average dengue activity and DEN-3 as the predominant (at times the only) circulating serotype, leaving an uncertain forecast for dengue activity in the immediate future. There is the possibility of an explosive DEN-3 epidemic due to the large number of susceptible individuals, but there may also be a slow, surreptitious diffusion of the serotype, eventually infecting a large proportion of the susceptible individuals.

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