INTRODUCTION

Dengue or dengue-like illnesses have been recorded in the Caribbean region as far back as the 17th century.1–3 Yet, it is only within the past few decades that this mosquito-borne flaviviral disease has gained public health significance throughout the archipelago.4,5 More than a million dengue cases have been recorded for the region since the beginning of the 1960s, involving several thousand episodes of severe dengue hemorrhagic fever (DHF) and hundreds of deaths.2,6 It is noticeable that dengue epidemics have recurred at narrowing intervals since the beginning of the 1980s, whereas outbreaks involving severe DHF have become regular phenomena for several of the larger island-states, such as Puerto Rico, the Dominican Republic, and Trinidad.1,11 The manifestation of epidemic DHF on these islands has coincided with the establishment of serotype co-circulation, thus resembling observations made in the larger island-states, such as Puerto Rico, the Dominican Republic, and Trinidad.1,11–13 The mechanisms of dengue pathogenesis attributable to viral factors or immunologic host responses are not fully described.12,14 In addition, the actual population threshold for continued hyperendemic transmission remains uncertain, as this is governed by a complex set of host, viral, and vector-dependent factors.16,18

Studies of dengue activity in the Caribbean have for the most part been carried out on the larger islands of Puerto Rico, Cuba, and Trinidad where effective surveillance systems and dedicated research groups have been established for several years. These studies have provided insight on the epidemiology and clinical manifestations, as well as genetic determinants of dengue infections in the sizeable insular populations (range 1.1–11.2 million).19–26 However, of the 24 additional island-states or territories in the Caribbean, only the Dominican Republic, Haiti, and Jamaica hold populations greater than one million.27 The population base for the remaining Caribbean islands ranges from less than 10,000 to just over 400,000 people (average 143,000), while occupying no more than 10% of the total landmass of the archipelago.27,28 Available dengue data from the smaller islands are very limited but do indicate a general pattern of single serotype outbreaks followed by periods of low or undetected transmission in populations of less than 200,000.4,10,29 Given inadequate surveillance and restricted sampling for most of the smaller islands it is difficult, however, to discern the true extent of serotype transmission. Likewise, there have been few studies assessing the epidemiology or clinical profile of dengue transmission within the smaller Caribbean populations. Hence, it remains uncertain whether the small-island setting of the Caribbean fall below the required population threshold for maintaining hyperendemic activity and to what extent this might affect the manifestation of disease severity at the population level.

The aim of this study was to explore the level of viral activity, seroprevalence, and general epidemiology of dengue transmission in the small-island setting of the Caribbean using Grenada as an example. The prospective 18-month study involved the introduction of active, laboratory-based surveillance in an attempt to attain the highest possible detection rate for the clinical cases at all primary health care facilities on the island.

MATERIALS AND METHODS

Study area. Grenada is the main island of the tri-island state of Grenada, Carriacou, and Petit Martinique. It is the most southerly (12.1°N, 61.4°W) of the Windward Islands within the Caribbean archipelago, with the nearest mainland country of Venezuela located 160 km to the south. The 310 km² island is of volcanic origin with relatively narrow coastal plains and a mountainous interior. The tropical climate is tempered by the northeast trade winds, which carry a yearly average precipitation of more than 350 cm on the windward side of the island, and less than 150 cm on the lower coastal plains. Rainfall and humidity levels are highest between June and November, whereas average day temperatures remain constant throughout the year at 29°C (26–32°C).30 Grenada holds a total population of 96,551 of which more than a third (N = 37,057) reside in the capital town of St. George’s and the immediate suburbs (The 2001 Population and Housing Census. St. George’s Grenada: Central Statistical Office, Ministry of Finance). The capital is located on the southeast coast within the parish of St. George. Five additional and sparser populated

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parishes each hold minor townships and villages, the majority of which are located along the coastline of the island.

**Surveillance program.** An active surveillance and diagnostic program was established from January 2001 through June 2002. The surveillance approach was adapted from the *Guidelines for Prevention and Control of Dengue and Dengue Hemorrhagic Fever*, published by the Pan American Health Organization (PAHO). All public and private primary health care units (HCUs), i.e., medical offices, health clinics, medical stations, and hospitals, were invited to participate in the program via the Division of Epidemiology, Ministry of Health, and the Environment (MOH). Reminders of the program were issued regularly to all HCUs by the Public Health and Surveillance Nurse, who held the overall responsibility of actively identifying and studying all probable dengue cases on the island. The HCUs were requested to submit 5 mL venous blood and a standardized investigation form for all patients fitting the World Health Organization (WHO) criteria for probable dengue virus infection (i.e., acute febrile illness with two or more symptoms including, headache, retro-orbital pain, myalgia, arthralgia, rash, and hemorrhagic manifestations). All patients with suspected dengue were included in the study regardless of age, sex, place of residence, and nationality.

**Laboratory support.** The diagnostic analyses were conducted at the laboratory of the Windward Islands Research and Education Foundation (WINDREF) located at St. George’s University in Grenada. The Laboratory of Microbiology at the General Hospital in St. George’s acted as the formal collection point for all blood samples referred to the WINDREF laboratory. To the extent possible, samples were also collected directly from the individual HCUs or delivered to the WINDREF laboratory by HCU staff. All HCUs were requested to notify the WINDREF laboratory immediately on blood draw to facilitate sample receipt and tracking. The requirement for rapid sample transfer and cold-chain delivery was emphasized throughout. Test results were reported directly to the referring HCU and to the Division of Epidemiology (MOH).

**Detection of dengue virus.** Acute phase serum (blood draw < 6 days after symptom onset) was tested for the presence of dengue virus using a semi-nested reverse transcription-polymerase chain reaction (RT-PCR) assay modified from Lanciotti and others. A second convalescent phase sample (> 14 days post onset) was requested for all RT-PCR negative cases to confirm the result by paired serology (see later). The RT-PCR negative cases were reported as “indeterminate” if the second sample was unattainable.

**Detection of anti-dengue IgM antibodies.** Convalescent serum (blood draw ≥ 6 days after symptom onset) were tested for the presence of anti-dengue IgM antibodies using either of two commercially available assays: INDX Dip-S-Ticks kit (PanBio INDX Inc., Baltimore, MD) or Dengue Duo IgM and IgG Rapid Strip Test (PanBio, Windsor, Australia). Both assays were completed according to the instructions of the manufacturer. Samples positive for anti-dengue IgM antibodies were recorded as evidence of presumptive acute dengue virus infection (i.e., infection within the past 3 months). A second late-convalescent phase sample (blood draw > 14 days after symptom onset) was requested for paired serology (see later), if an early convalescent phase sample (blood draw 6–10 days post onset) tested IgM negative. These cases were reported as “indeterminate” if a second sample was unattainable.

**Detection of anti-dengue IgG antibodies.** An IgG capture enzyme-linked immunosorbent assay (ELISA), modified from Chungue and others and Kuno and others was used for paired acute and convalescent phase samples to confirm dengue virus infection by seroconversion (minimum 4-fold increase of anti-dengue IgG-ELISA titers between paired samples). Single acute phase samples with positive virology were also tested to differentiate between primary and secondary infections, as described by Miagostovich and others.

**Phylogenetic analysis.** A 600 nucleotide region in the Envelope gene was sequenced using the Taq DyeDeoxy Terminator Cycle Sequencing kit and an ABI PRISM 377 DNA sequencer (Applied Biosystems, Foster City, CA). Sequence assembly and alignment were completed with Lasergene software (DNASTar, Madison, WI), whereas phylogenetic trees were generated using PHYLIP. All sequencing and phylogenetic procedures were kindly conducted by the Centers for Disease Control and Prevention (CDC) Dengue Branch in Puerto Rico.

**Ethical approval.** Formal ethical clearance and research approval of the study were granted by the Grenada MOH, as well as the Internal Review Boards at WINDREF and St. George’s University, Grenada.

**Data analyses.** Data management and statistical analyses (odds ratio [OR], with 95% confidence intervals [CIs]) were completed using Excel 2000 (Microsoft Office XP, Microsoft Corp., Redman, WA).

**RESULTS**

**Temporal distribution of recorded cases.** The active dengue surveillance program recorded 545 cases of suspected dengue from January 2001 through June 2002 (Figure 1). The distribution of cases was highly skewed with only 38 referred patients during the initial 9 months of the study against 507 cases during the latter 9 months. A short transition period characterized by a shift in reported age and increased frequency of suspected cases (monthly average of 14) occurred between October (Week 42) and December 2001 (Week 51). This pre-epidemic phase was followed by the onset of full epidemic momentum with continuous weekly reporting of suspected cases lasting ~25 weeks and peaking with 139 cases during the month of March 2002.

**Laboratory confirmation.** The WINDREF laboratories received a total of 577 blood samples during the surveillance period of which 427 (74%) were obtained from the patients in the acute phase (average of 2.3 days after symptom onset). Another 116 samples (20%) were obtained from the patients 6 days or more after symptom onset (average of 11.6 days) while a total of 34 samples had no record of status because of incomplete investigation forms. Of the 545 patients with suspected dengue, 223 were laboratory confirmed as either acute (N = 150) or presumptive acute (N = 73) dengue virus infections. Thirty suspected cases tested negative while 289 cases were categorized as “indeterminate,” and three were lost to testing. The causative serotype was identified by RT-PCR for 139 of the acute infections (3 DENV-2 and 136 DENV-3), whereas the infecting serotypes were unknown in 11 cases confirmed by seroconversion.

**Age-specific disease rates.** More than 71% (5/7) of the cases that were confirmed during the period of low endemic transmission (January–September 2001) occurred in children less than 15 years of age—as opposed to 18% (35/194) of the
cases during the pre-epidemic and epidemic period (October 2001–June 2002). The median age for confirmed cases shifted from 9 years (range 3–27 years) to 27 years (range 1 month–78 years) between the periods of low and high transmission.

**Symptoms, age, and immune status.** Classic dengue fever (DF) was reported for 94% (198/211) of confirmed cases with recorded symptoms. Less than 6% (12/211) of the cases had DF with hemorrhagic manifestations such as ecchymosis, epitaxis, or hematuria, whereas a single patient was diagnosed with DHF, Grade II. Disease manifestations in children of verbal age (4–14 years) appeared somewhat milder than for adults, as these children were less likely to report symptoms such as headache, myalgia, and arthralgia (Table 1). Hemorrhagic manifestations were not recorded for any child (<15 years of age) with confirmed or suspected dengue.

The immune status was assessed for 140 confirmed cases, of which 113 (81%) were identified as secondary infections. Stratification by age, for Grenadian nationals, showed previous infection in 83% (10/12) of children (<15 years of age) compared with 95% (60/63) of adults. Of the 12 DF patients with hemorrhagic manifestations, five suffered secondary infections, whereas the status for the remaining seven is unknown. The single case of DHF occurred in a 30-year-old male with secondary infection. A sub-analysis comparing the symptoms of primary and secondary cases did not reveal any significant difference at the given sample size, except for a higher occurrence of rash (OR = 3.2, 95% CI = 1.4–7.6) and lower occurrence of joint pain in primary infections (OR = 0.4, 95% CI = 0.1–0.9).

**Spatial and temporal disease distribution.** The first laboratory-confirmed DENV-3 infection, defined as the index case, occurred in November 2001. The parish of St. George was noted as the epicenter of the DENV-3 outbreak (December 2001–June 2002) hosting the index case and nearly 70% (117/171) of all confirmed cases with stated residence. The index case was a 48-year-old male residing ~5 km southeast of the town of St. George’s. He had no history of traveling before disease onset, but his unique profession as a boat surveyor and service provider to the yachting community would have involved daily interaction with sailors having arrived recently from other dengue endemic Caribbean islands or the South American continent.

The highest number of confirmed cases during the DENV-3 epidemic was observed within the capital town of St. George’s and the immediate suburbs and bordering peri-urban communities. The confirmed disease rate for the entire parish of St. George (32:10,000) was twice that of neighboring St. David (16:10,000) presenting the second highest transmission level. St. Patrick located furthest to the North of the Capital parish, recorded the lowest rate of detected cases for the entire island (3:10,000) (Figure 2). A lag period of 2 or more weeks was observed between the epidemic onset in St. George’s (Week 52, 2001) and the occurrence of confirmed cases in the remaining parishes. The main activity in these areas took place between Week 5 and Week 19 (2002), with less than four weekly cases reported from each parish.

**Identification of circulating strains.** Phylogenetic inference by comparison to reference and regional strains grouped a DENV-2 isolate from Grenada within the America/Asian

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**Table 1** Reported signs and symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>4–14 years</th>
<th>≥15 years</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>35 (100%)</td>
<td>156 (96%)</td>
<td>NA–NA</td>
</tr>
<tr>
<td>Headache</td>
<td>27 (77%)</td>
<td>149 (92%)</td>
<td>0.3 0.1–0.8</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>19 (54%)</td>
<td>115 (71%)</td>
<td>0.5 0.2–1.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>22 (63%)</td>
<td>143 (88%)</td>
<td>0.2 0.1–0.5</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13 (37%)</td>
<td>132 (81%)</td>
<td>0.1 0.1–0.3</td>
</tr>
<tr>
<td>Rash</td>
<td>7 (20%)</td>
<td>26 (16%)</td>
<td>1.3 0.5–3.5</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>13 (37%)</td>
<td>80 (49%)</td>
<td>0.6 0.3–1.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (6%)</td>
<td>34 (21%)</td>
<td>0.2 0.1–1.0</td>
</tr>
<tr>
<td>Chills</td>
<td>16 (46%)</td>
<td>129 (80%)</td>
<td>0.2 0.1–0.5</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (20%)</td>
<td>44 (27%)</td>
<td>0.7 0.3–1.7</td>
</tr>
<tr>
<td>Sore throat</td>
<td>6 (17%)</td>
<td>42 (26%)</td>
<td>0.6 0.2–1.6</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>7 (20%)</td>
<td>31 (19%)</td>
<td>1.1 0.4–2.8</td>
</tr>
<tr>
<td>Petechia</td>
<td>0 – 4 (2)</td>
<td>0.0 NA–NA</td>
<td></td>
</tr>
<tr>
<td>Purpura/ecchymosis</td>
<td>0 – 3 (2)</td>
<td>0.0 NA–NA</td>
<td></td>
</tr>
<tr>
<td>Haematemesis</td>
<td>0 – 4 (2)</td>
<td>0.0 NA–NA</td>
<td></td>
</tr>
<tr>
<td>Melaena</td>
<td>0 – 4 (2)</td>
<td>0.0 NA–NA</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0 – 4 (2)</td>
<td>0.0 NA–NA</td>
<td></td>
</tr>
<tr>
<td>Bleeding gums</td>
<td>0 – 3 (2)</td>
<td>0.0 NA–NA</td>
<td></td>
</tr>
<tr>
<td>Haematuria</td>
<td>0 – 3 (2)</td>
<td>0.0 NA–NA</td>
<td></td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>0 – 0 – NA</td>
<td>0 NA–NA</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>0 – 2 (1)</td>
<td>0.0 NA–NA</td>
<td></td>
</tr>
<tr>
<td>Total cases</td>
<td>35 162</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*General manifestations reported for children of verbal age (4–14 years) and adult patients with confirmed dengue infection.

*OR = Odds ratio.

†Confidence interval.
genotype, whereas isolates of DENV-3 were shown to belong to Genotype Group III.

**Reported travel activity and temporary immigration.**

Seven patients with confirmed infections reported regional or international traveling within 14 days from symptom onset. Serotype DENV-3 was reported before or during this particular period from each of the regional countries stated as the site of travel (Brazil, Dominica, Guyana, and Martinique). None of the specific cases could be linked, however, to the origin of the Grenadian outbreak, as each case occurred after the epidemic onset.

The number of monthly visitors arriving in Grenada from countries with confirmed DENV-3 activity was compared with the number of dengue cases detected on the island during the pre-epidemic and epidemic period (October 2001–June 2002) marked according to reported area of residence. Number of cases detected and the disease rate per 10,000 people stated for each parish of the island (in brackets).

**Limitations of surveillance system.** Underreporting of clinical cases cannot be excluded, yet the study recorded as many as 546 cases of suspected dengue in just 18 months as compared with 220 cases during the previous 7 years (1994–1999) of mandatory but passive surveillance. The introduction of active surveillance and rapid diagnostic feedback was widely credited for enhancing the index of suspicion and the report compliance among health care professionals on the island.

**Limitations of diagnostic assay.** The large number of “indeterminate” acute phase cases ($N = 289$) suggest inadequate performance by the RT-PCR assay in use. This was confirmed by comparison of the assay to paired serology (IgG ELISA) based on 30 available paired samples. The comparison revealed an overall RT-PCR specificity of 100% (12/12), but a sensitivity of merely 50% (9/18). Optimization of the RT-PCR assay was not attempted. However, it is noted that the DENV-3 specific primers was set at a lower concentration than specified in the original protocol, which may have prevented sufficient amplification in specimens with limited viral numbers as assumed for secondary infections with high IgG titers. Furthermore, a comparison of the Grenadian DENV-3 sequence and that of the DENV-3 specific primer (TS3: based on prototype H87) revealed two nucleotide substitutions at the 5′-end of the primer, flanking a “weak” motif of double Adenine bases. The inadequate sequence homology may have caused incomplete primer annealing, exacerbating the negative impact of low primer concentration.

**Disease transmission patterns and viral activity.** Over the course of 18 months, we observed three distinct dengue transmission patterns in Grenada, in the form of low endemic, pre-epidemic, and acute epidemic activity. The period of low endemicity involved a monthly average of just four suspected cases mainly within the pediatric population and with confirmed infections ($N = 7$) occurring up to 12 weeks apart. Unfortunately, the causative serotype(s) was not identified for any of these cases. However, DENV-2 (American Asian genotype) was strongly suspected given confirmed activity in the years leading up to this study (1997–2000) and in addition to three cases identified during the epidemic period. The pre-epidemic phase was characterized by an increase in suspected cases to a monthly average of 14, with confirmed cases ($N = 12$) occurring no more than 2 weeks apart. The phase also carried a noticeable shift toward the adult demographic, while including the first laboratory-confirmed DENV-3 infection in Grenada (index case). The overall changes in transmission dynamics and the shift in the age span of confirmed cases, as observed during the pre-epidemic phase, suggested a loss of age-dependant herd immunity with the replacement of DENV-2 by DENV-3—effectively predicting an oncoming epidemic. The DENV-3 epidemic was the largest dengue outbreak yet to be recorded on the island.

**Age, disease manifestations, and immune status.** The highest levels of DENV-3 activity were recorded for ages 15 to 44 years, which could reflect increased exposure among the more active age groups of the population. Yet, presentation bias resulting from milder manifestations in children cannot be excluded (see later). It is also probable that DENV-3 was transmitted on the island as part of a regional epidemic in 1963–1965. Hence, DENV-3 immunity acquired during the...
1960s could be a contributing factor to the lower disease rates observed for Grenadians over 40 years of age.

The vast majority of patients in this study reported symptoms of DF, whereas more than 90% of the Grenadian patients were shown to suffer a secondary infection. Unfortunately, the Tourniquet test and platelet counts were not performed systematically for all patients. This may explain the lower rates of observed hemorrhagic phenomena and leakage, as compared with other reports from the region. However, it is remarkable that hemorrhagic phenomena were reported exclusively for adults during the epidemic period, and with no significant association to the immune status of these patients. Importantly, there were no reports of hemorrhagic manifestations among children experiencing secondary infections—in fact, pre-exposed children, of verbal age, reported generally milder manifestations than did adults. Although based on relatively few cases, the lower incidence of severe manifestation in the pediatric population seems to fit a general pattern in South America and the Caribbean. At the global scale, however, children with secondary infections continue to suffer the brunt of morbidity and mortality due to DHF and dengue shock syndrome. 

Spatial and temporal disease distribution. Patients with laboratory-confirmed dengue and stated area of residence (N = 178) were clearly concentrated in the urban south—an area broadly defined by the political boundaries of St. George and St. David. These parishes hold 50% (48,543/96,551) of the island population, but accounted for 79% (140/178) of all confirmed cases with reported residence during the surveillance period. A systematic assessment of spatial or temporal vector indices and climate parameters was not included in this study. Yet, provisional entomologic data indicated high infestation levels of Aedes aegypti throughout the study period for small villages, townships, and urban areas alike, with average House and Breteau indices at 14% and 23%, respectively (Vector Control Division, MOH, unpublished data). This would imply that most Grenadians were at high risk of vector exposure, irrespective of location or time of year. In fact, it is noted that the epidemic occurred during the dry season.

Possible disease surveillance biases caused by geographic differences in patient presentation and report compliance by the different HCUs cannot be excluded for this study. Yet, the spatial distribution and apparent delay in viral progression into the sparser populated, rural communities fit the general understanding that dengue virus transmission is favored by urban conditions, such as high densities of susceptible hosts and possibly higher activity levels of urban Ae. aegypti to that of its rural counterpart. A shift toward increased rural transmission has, however, been noted in several dengue endemic countries and could also take place in Grenada. As tourism replaces the agricultural-based economy, employment opportunities are shifting from the rural areas to the tourism centers in and around St. George’s. The resulting boost in rural–urban commuting could increase the possibilities for viral spread into the rural communities.

Possible transmission clusters. Infection within private households was suggested in at least 20 cases. Yet, the true extent of household transmission remains uncertain, as does the level of transmission at other typical sites of host aggregation. Notably, four medical doctors working at the General Hospital (GH) in St. George’s had confirmed dengue infection. Three of the doctors reported symptom onset during the first month of acute epidemic transmission (January 2001). The observation suggests that the 240-bed, unscreened hospital building may have acted as a focal point of transmission. Indeed, the presence of Ae. aegypti was confirmed on the hospital compound at the time of the study (Vector Control Division, MOH, unpublished data). Unfortunately, it was not possible to determine the overall incidence of dengue infections among hospital personnel, or to determine whether infections occurred in patients who were hospitalized because of unrelated disease. Furthermore, available data do not reveal the actual distribution between hospitalized as opposed to ambulant dengue patients referred from the GH. It is notable however that the Accident and Emergency ward was credited for the majority of suspected (98/139) cases reported from this particular HCU.

St. George’s University located about 4 km to the south of the capital town was recognized as another cluster of activity, as the university clinic referred more than 8% (18/223) of all confirmed infections. These data align with a previous study showing an annual infection rate of 5% within the predominantly foreign student body of ~2,000 people (Pulim S, unpublished data). Non-nationals, many of which were temporary visitors from non-endemic areas, represented an additional 25 confirmed infections (11.3%). The relatively high rate of student and other non-national cases could well reflect differences in the health care seeking behavior to that of Grenadians. However, with an influx of 261,392 stay-over visitors during the study period, non-nationals should be recognized as a potential source of susceptible hosts capable of extending endemic transmission and intensifying epidemic activity (Annual Statistical Reports 2001 and 2002. St. George’s, Grenada: Research and Planning Department, Grenada Board of Tourism).

Possible viral entry and spread of dengue viruses. All DENV-3 strains isolated from Grenadian patients were shown to belong to Group III, the only genotype of DENV-3 known to circulate in the region at the time of the study. The genotype was introduced into Central America from South Asia in 1994, possibly via Africa. Its presence in the Caribbean Basin was confirmed in 1998, with concurrent reports from Jamaica, St. Kitts and Nevis, Barbados and Aruba. By the end of year 2000, DENV-3 had been isolated from all of the larger and almost half of the smaller Caribbean islands. The 2001 appearance of DENV-3 in Grenada followed a continuation of regional epidemics in 2000 and 2001 including, for the latter year, 13,000 reported cases in Cuba; 4,471 in Martinique; 1,043 in Barbados; 292 in St. Lucia; and 2,244 in Trinidad and Tobago. Nearby Venezuela reported 83,180 dengue cases while Brazil reached a toll of more than 400,000. Apart from the smaller island of St. Lucia (population = 153,000), all outbreaks were associated with at least two serotypes, even as the main epidemic activity was attributed to DENV-3. Noticeably, DHF cases were reported from all outbreaks except for St. Lucia.

Grenada is a popular tourist destination where most visitors arrive by regional or international flights at the Point Salines airport while staying in the Grand Anse area immediately to the south of the capital of St. George’s. Compilation of data regarding the travel history of confirmed cases showed several episodes of visitors and Grenadians harboring infections acquired abroad. Seasonal trends in travel activity suggested increased risk of viral introduction during the carnival month of August, as the influx of visitors from regional
DENV-3 endemic countries, doubled from the monthly average. The combined increase in potential DENV-3 carriers and the assembly of large volumes of carnival revelers (locals and visitors) would seem to provide favorable conditions for viral introduction and subsequent proliferation.

**General epidemiology.** This study identified the fourth serotype to be confirmed in Grenada, within a 20-year span. Data recorded before this study are extremely limited but do suggest that the introduction of each serotype has been followed by epidemic transmission possibly quelled by increasing herd-immunity and/or replacement by a novel serotype.\(^{19,20}\) Whereas the 2002 DENV-3 epidemic affected all age groups (age range of confirmed cases: 1 month to 78 years), future dengue outbreaks may be limited to the age cohorts born after the last introduction or epidemic manifestation of each serotype (i.e., DENV-4: 1981, DENV-1: 1995, DENV-2: 1999, DENV-3: 2002).\(^{3,8,46}\) Restricted by fewer numbers of susceptible hosts, prospective epidemics may be of shorter duration but not necessarily of less severe character, given an increased risk of immunopathogenesis caused by heterotypic re-infection. Apparently, the Grenadian population may be too small to sustain hyperendemic transmission and thereby local escalation of strain virulence leading to severe outbreaks. However, there is a continuous risk that virulent strains may be imported from the larger, neighboring populations that suffer hyperendemic activity with frequent outbreaks (e.g., in Venezuela and Trinidad). Available data indicate that most of the small-island states in the Caribbean may have similar transmission and disease patterns as those observed in Grenada. Together, these islands offer an intriguing setting for the study of outbreak severity and the possible interactions between population size, generation of virulence, and immunopathogenesis.

There is no immediate prospect of dengue eradication, given the lack of available vaccines or sustainable methods for vector elimination. As such, current efforts are focused on limiting dengue morbidity and mortality by curbing and possibly preventing epidemic transmission through vector control.\(^{11}\) This study indicates that active laboratory-based surveillance may identify pre-epidemic transmission in the small-island setting by early detection of novel serotypes, intensified disease activity and/or a shift in affected age groups. The predictive capability of the active surveillance system should enable activation of timely and targeted prevention efforts. However, it is obvious that such efforts must be tailored to the noted transmission dynamics and risk factors of viral introduction and spread within the insular population. For Grenada, this includes a deliberate focus on the high-risk areas and population groups in the urban South with specific vigilance around periods of increased visitor influx from other dengue endemic areas.

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