TITLE PAGE

Epidemiology of clinical hantavirus infections in Barbados, 2008-2016

Epidemiology of hantavirus infections in Barbados

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Summary

Analysis of the demographic, temporal and seasonal distribution of hantavirus infections in Barbados was conducted using national surveillance data for 861 laboratory confirmed cases during 2008-2016. The crude incidence rate of hantavirus infections varied from 5.05 to 100.16 per 100,000 persons per year. One major hantavirus epidemic occurred in Barbados during 2010. Hantavirus cases occurred throughout the year with low level transmission during the dry season (December to June) with increased transmission during rainy season (July to November) and a seasonal peak in August. Hantavirus incidence rates were significantly higher in females than males every year during the study period. More than 50% of hantavirus cases were 30 years of age or less. The highest incidence rate (63.36 cases per 100,000 population) was observed among patients 0–4 years of age. This represents the first epidemiological data for hantavirus disease among an entire population in the English-speaking Caribbean.

Article summary line

The first epidemiological study of hantavirus infections in the Caribbean showed varied observations including significantly higher incidence in females than males, a 2010 epidemic, and year-round transmission with a seasonal peak in August.

Introduction

Hantaviruses are single stranded (SS) negative-sense RNA viruses approximately 120-160 nm in diameter from the Bunyaviridae virus family (1, 2). Hantaviruses can be separated into two groups, Old World (SEO, DOB, THAI and HTN) and New World (PUU, Prospect Hill, Sin Nombre etc) based on the M segment (nucleotides 1987-2315) (1, 2).

Hantavirus infection is an emerging disease in the world as well as in the Americas. It is estimated that there are 150,000 to 200,000 annual hantavirus cases globally, however this may be a gross underestimate due to the lack of proper diagnostic testing and even awareness and or proper diagnostic testing (3).

Most clinical hantavirus infections occur through direct or indirect contact with infected rodents. Hantavirus epidemics are influenced by environmental and behavioural factors including rainfall, topography, vegetation, occupational factors (4, 5).

Hantavirus infection can cause three main clinical diseases namely haemorrhagic fever with renal syndrome (HFRS), nephropathia epidemica (NE) and hantavirus pulmonary syndrome (HPS) or hantavirus cardiopulmonary syndrome (HCPS). Old World hantaviruses are responsible for causing HFRS and NE whereas New World hantaviruses are responsible for HPS or HCPS

The first serological evidence of hantavirus infections in the Caribbean was observed in Barbados among clinical cases suspected of leptospirosis and rodents (*Rattus* spp.) however the exact identity of the circulating strain remained unknown (6). Other serological and molecular evidence of hantavirus circulation in the Caribbean including in Grenada, Trinidad & Tobago and a single exported case from Cuba (7-10). Recent hantavirus outbreaks in adjacent regions including 4 fatal HPS cases observed in French

Guiana (Fig. 1, on the eastern border of Suriname) in 2016 enhancing the risk of new and more lethal hantavirus strains entering the Caribbean region via trade and travel (11). To our knowledge no published hantavirus epidemiology studies on an entire population exist for the Caribbean.

We analysed clinical data from a centralized database for hantavirus cases (laboratory confirmed IgM seropositive) identified in Barbados during 2008 to 2016 and report relevant epidemiological characteristics of hantavirus infections. The aim of the study was to study the epidemiology of hantavirus infections in Barbados examining the demographic, temporal and seasonal factors involved. This should provide useful data to aid in the control and prevention of hantavirus infections in Barbados and the wider Caribbean.

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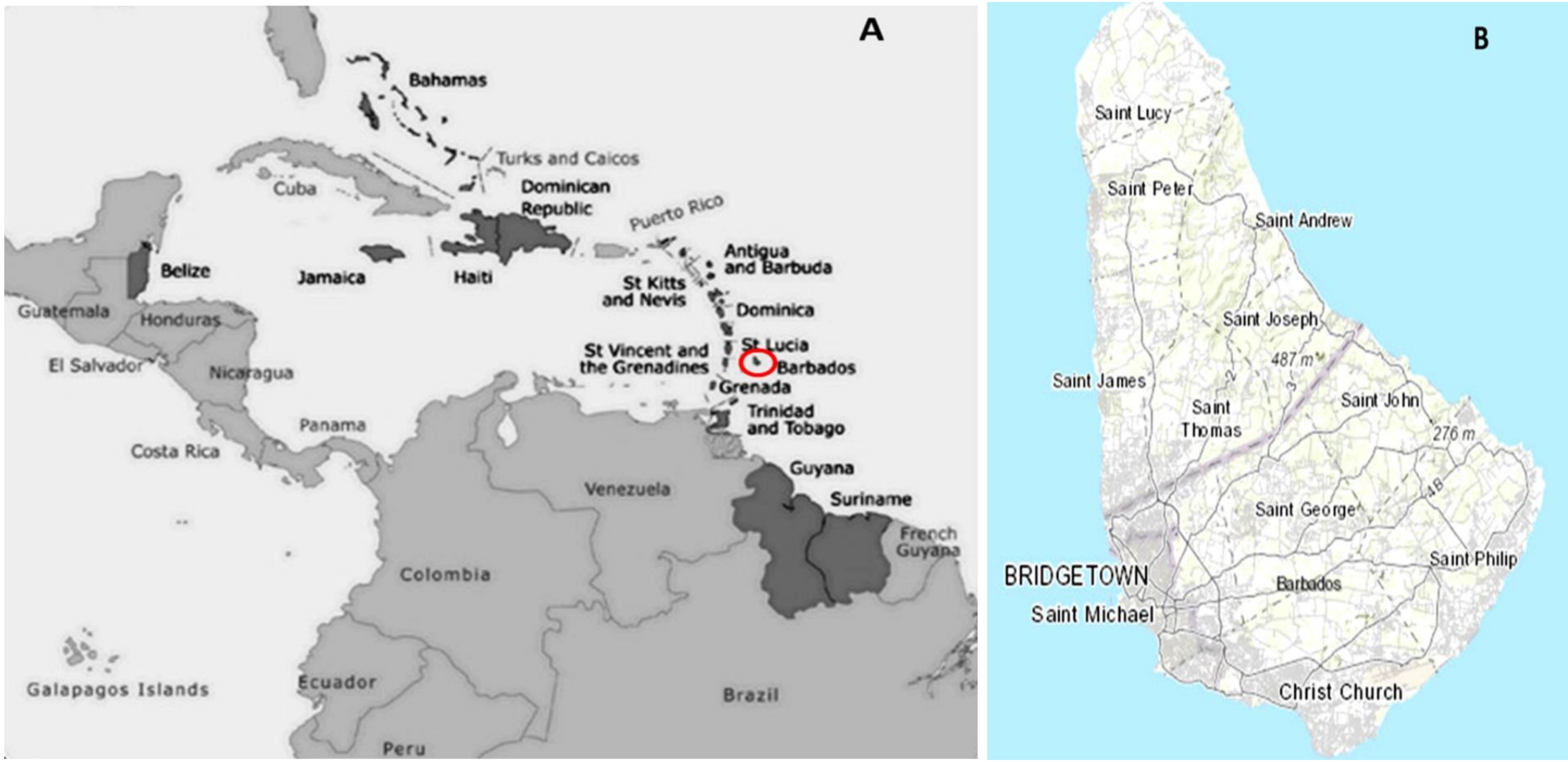

Figure 1A. Geographic location of Caribbean **1B**. Map of the island of Barbados.

Materials & Methods

National Surveillance Program

In Barbados, all suspected febrile patients (Fig. 2) are referred to the Best-dos Santos Public Health Laboratory based on the similarity of clinical symptoms of dengue virus (DENV), chikungunya virus (CHIKV), Zika virus (ZIKV), *Leptospira* and hantavirus infections which are characterized by fever, malaise, myalgia, arthralgia, rash, retro-orbital pain, abdominal pain, nausea and vomiting. Sampling of patients from this database then permits a good representation of the entire population in Barbados with febrile illness. Hantavirus is a reportable disease in the Barbados public health surveillance system. All probable and confirmed cases of hantavirus infections are submitted to a central laboratory Best-dos Santos Public Health Laboratory.

Case Definition

Hantavirus cases were confirmed by detection of hantavirus specific IgM and IgG in patients' serum (samples within 5-15 days of illness) with a hantavirus IgM and IgG ELISA kit (Focus Diagnostics, CA, USA) along with kit and patient sera positive and negative controls following the manufacturer's instructions. A clinical laboratory hantavirus case was assigned according to the CDC hantavirus case definition for non-Hantavirus Pulmonary Syndrome (HPS) specifically a) "the detection of hantavirus-specific immunoglobulin M or b) rising titers of hantavirus-specific immunoglobulin G, or c) the detection of hantavirus-specific ribonucleic acid in clinical specimens, or d) the detection of hantavirus antigen by immunohistochemistry in lung biopsy or autopsy tissues" with the focus on part (a)(44). These hantavirus cases were from suspected febrile patients tested for suspected infections including DENV, *Leptospira*, CHIKV, ZIKV and hantavirus between 2008 and 2016.

Study design and sampling

Data analysis

Following the relevant ethical approval (IRB), using centralized database at Best-Dos Santos Public Health Laboratory, St. Michael, Barbados, a list of 861 laboratory confirmed hantavirus cases, identified in Barbados during 2008 to 2016, was generated (Fig. 2). The list of patients was exported from Microsoft Access as a Microsoft Excel file for epidemiological analysis. The list of hantavirus cases was sorted and grouped by the year of hantavirus disease/symptom onset 2008-2016. For each year the cases were analysed by age, gender, geographical location, date and hospitalization. Within these epidemiological categories, incidence and hospitalization rates (per 100,000 population) were calculated using the Barbados 2010 census data as the denominator. Age standardisation was done using the World Health Organization (WHO) standard (12). For geographic and gender analysis, parish, male and female populations from the Barbados 2010 national census were used, as the denominator, to calculate the respective incidence rates. Confidence intervals (95%) were calculated for each incidence rate using Microsoft Excel.

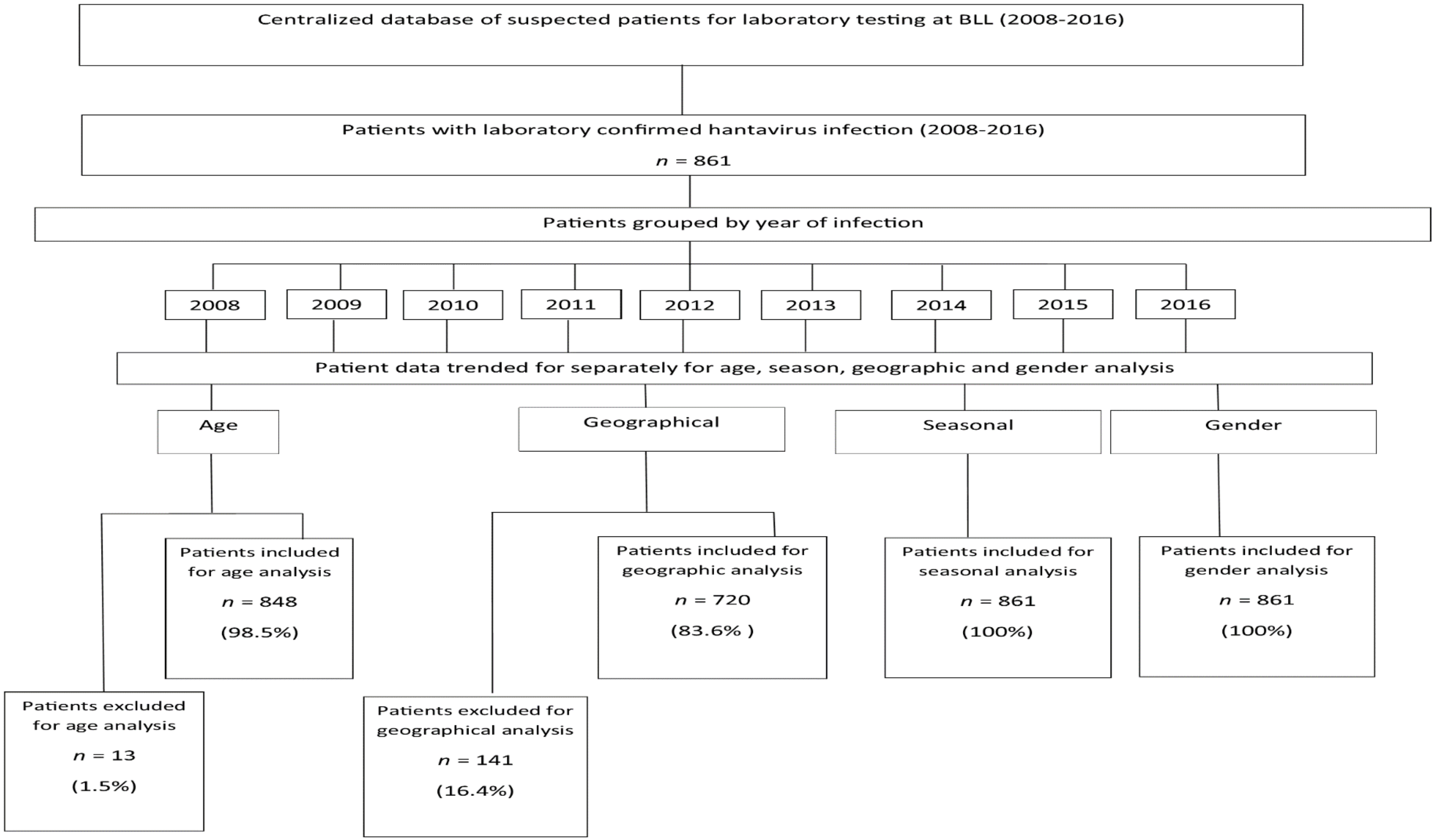

Figure 2. Hantavirus epidemiology study, Barbados, 2008-2016.

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Ethical approval

The study was approved by Institutional Review Board (IRB) on Ethics in Research on Human Subjects at The University of the West Indies (UWI), Cave Hill, St. Michael, Barbados combined with the Ministry of Health on 11th July 2013 and the Ethics Committee at the Queen Elizabeth Hospital (QEH), Martindale's Road, St. Michael, Barbados on 19th August 2013 prior to the start of data collection.

Results

Epidemiology of hantavirus infections in Barbados

During 2008–2016, a total of 861 laboratory confirmed hantavirus cases, including 297 hospitalised cases, were reported in Barbados (Fig. 3). The crude incidence rate of hantavirus infections varied by year from 5.52 (95% CI, 2.94-8.58) to 100.16 (95% CI, 88.64-112.21) cases per 100,000 population annually (Fig. 3). The mean annual incidence rate was 33.03 (95% CI, 27.53-41.34) cases per 100,000 population. The hantavirus incidence rate peak was observed in 2010 with a crude incidence rate of 100.16 (95% CI, 88.64-112.21) cases per 100,000 population indicating a major hantavirus epidemic as this represented the largest number of cases observed (Fig. 3). The mean annual incidence rate was 33.03 (95% CI, 27.53-41.34) cases per 100,000 population.

Hantavirus and hospitalization

All patients were included in this analysis (100%) (Fig. 2). The highest number of hospitalized hantavirus cases occurred during 2010 and 2016 and the incidence rates followed a similar pattern (Fig. 4). The incidence rates ranged from 9.67 (95% CI, 6.35-13.81) to 29.00 (95% CI, 23.78-36.70) cases per 100,000 population. The highest hospitalization rates were observed in 2010, 29.00 (95% CI, 23.78-36.70) cases per 100,000 population, which was significantly higher than all other years except for 2016 [19.33 (95% CI, 14.88-25.44) cases per 100,000 population]. Both cases and incidence

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rates did not different greatly during 2011-2015 (Fig. 4). Hospitalization rates were highest among the 0-4 years age group [46.10 (95% CI, 35.45-56.75) cases per 100,000 population] and the 10-19 years age group [19.89 (95% CI, 15.12-24.65) cases per 100,000 population].

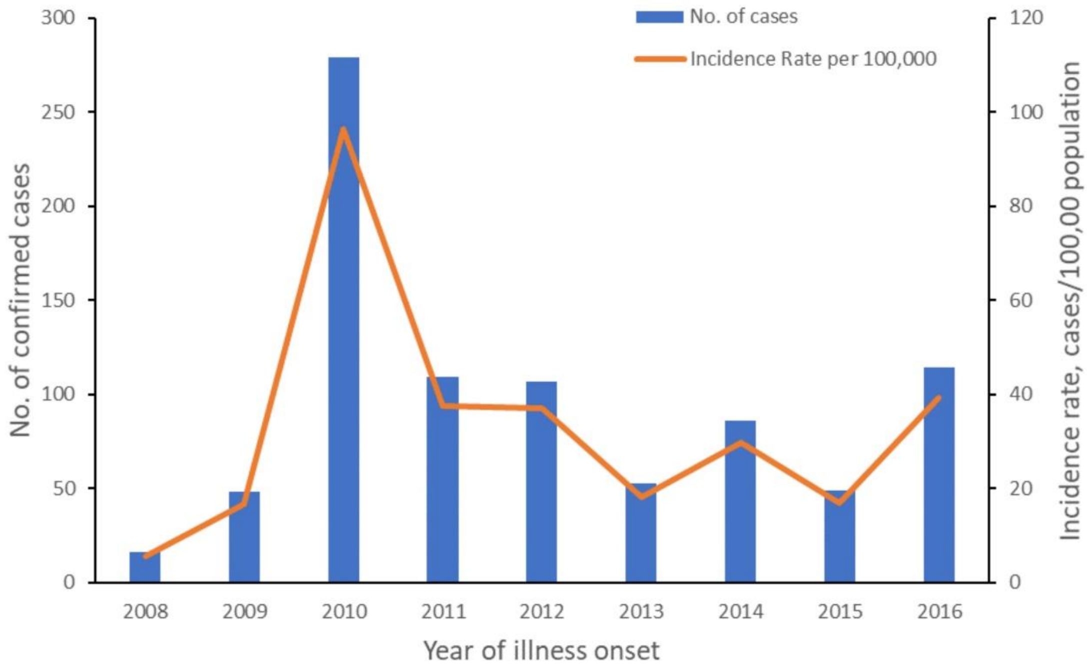

Figure 3. Cases and incidence rates of hantavirus infections in Barbados, 2008 – 2016.

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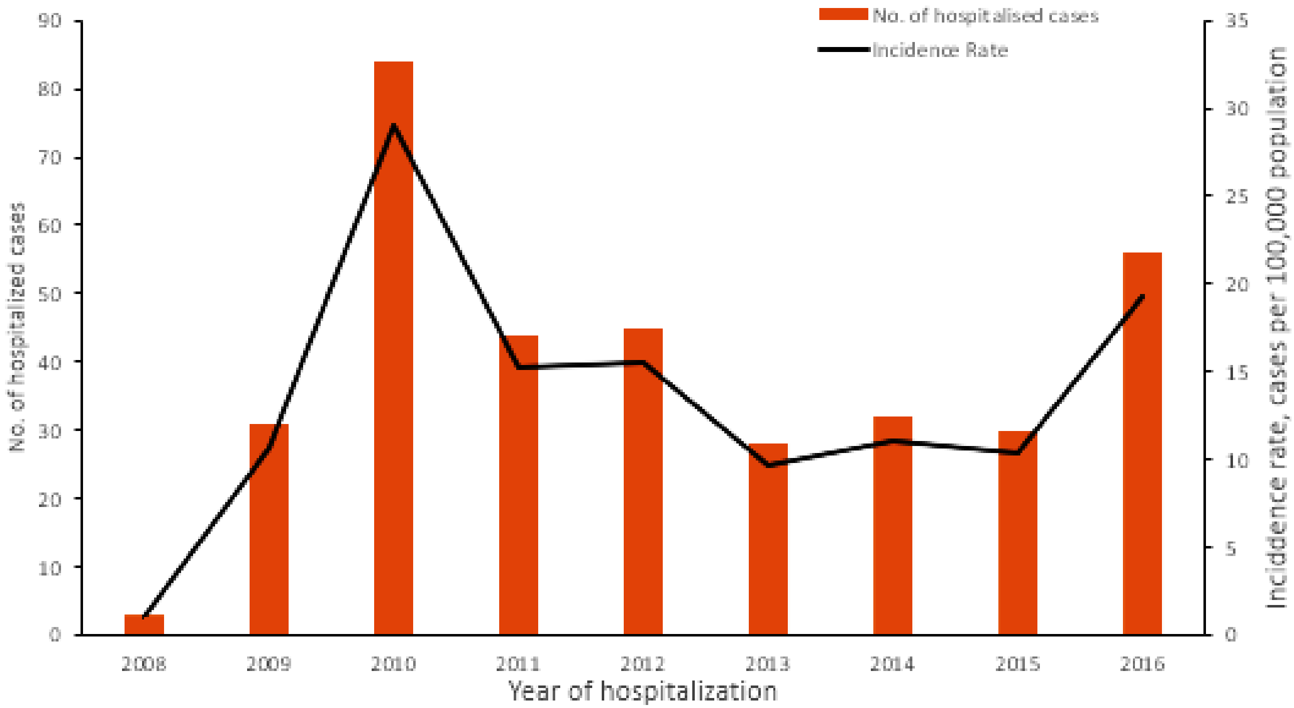

Figure 4. Hospitalized cases and hospitalization rates of laboratory confirmed hantavirus infections in Barbados, 2008 – 2016.

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Seasonality

All patients were included in this analysis (100%) (Fig. 2). Hantavirus transmission occurred year-round in Barbados (Fig. 5). The mean hantavirus incidence rate in Barbados was higher during the rainy season (June to November), 3.84 (95% CI, 1.54-6.14) cases per 100,000, than the dry season (December to May), 1.86 (95% CI, 0.26-3.46) cases per 100,000, however this difference was not significant. Mean incidence rates peaked in August [6.12 (95% CI, 3.21-9.02) cases per 100,000 population] during the study (Fig. 5). The highest incidence rate, 40.31 (95% CI, 32.85-47.78) cases per 100,000 population, occurred during August 2010 (Fig. 5).

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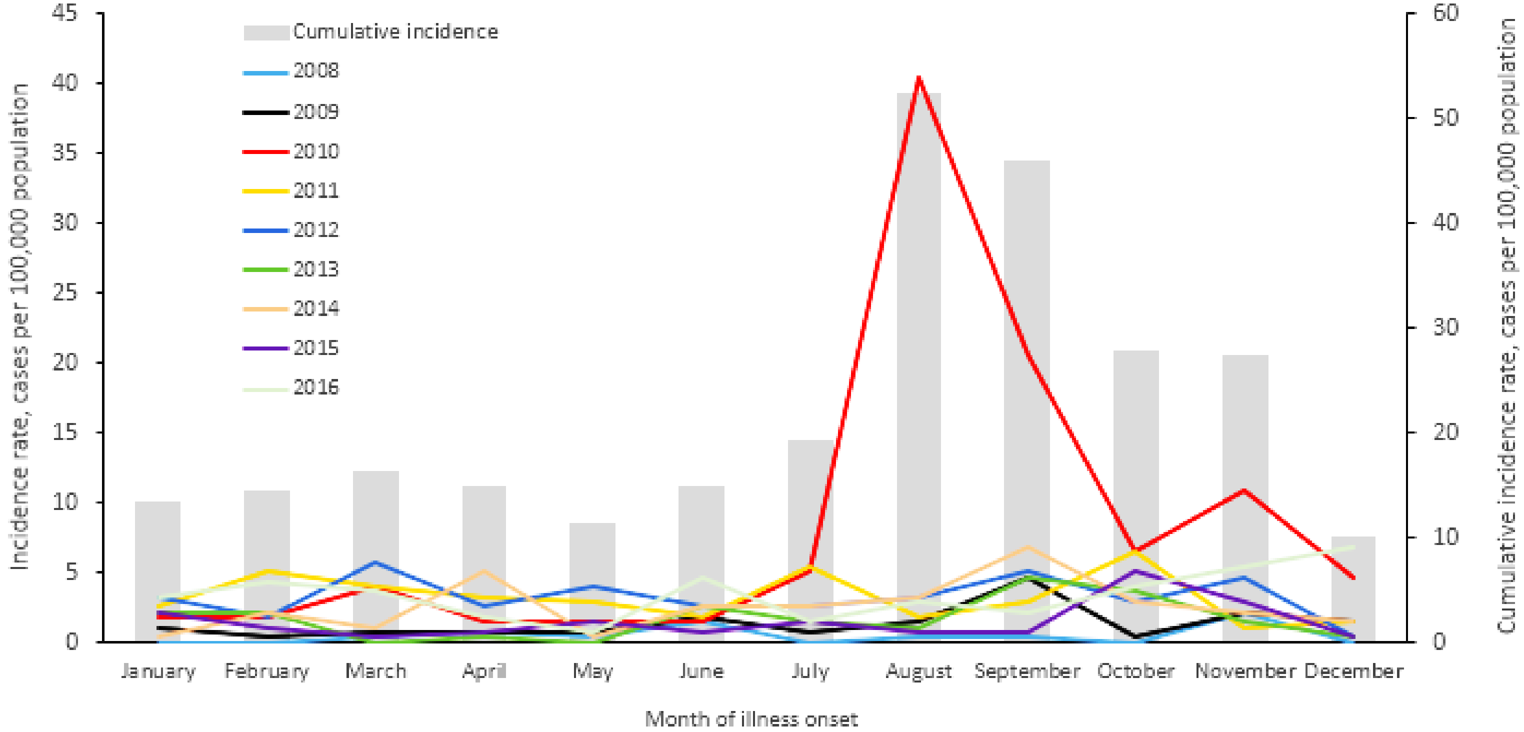

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12
13 **Figure 5.** Monthly distribution of laboratory confirmed hantavirus cases in Barbados, 2008 – 2016.

Demographic

The highest mean incidence rate of 63.36 (95% CI, 50.91-75.88) cases per 100,000 population was observed among patients 0–4 years of age with a similar incidence rate of 57.56 (95% CI, 49.44-65.68) cases per 100,000 population in the 20-29 age group (Fig. 6). Excluding 2008 persons 20 years or less comprised more than 50% of persons and those < 40 years old comprised 75% of persons acutely infected with hantaviruses in Barbados (Fig. 7). The crude and mean gender-specific hantavirus incidence rates were higher in females than males during every year of the study period ($\chi2$=7.75, 28.59, 8.86, 72.98, 53.25, 13.80, 82.85, 8.86; $P<0.01$, Fig. 8). The mean male specific hantavirus incidence rate was 22.89 (95% CI, 14.76-31.02) cases per 100,000 population and the mean female specific incidence rate was 40.36 (95% CI, 30.01-50.71) cases per 100,000 population (Fig. 8). The male: female hantavirus infection ratio was approximately 1:1.8.

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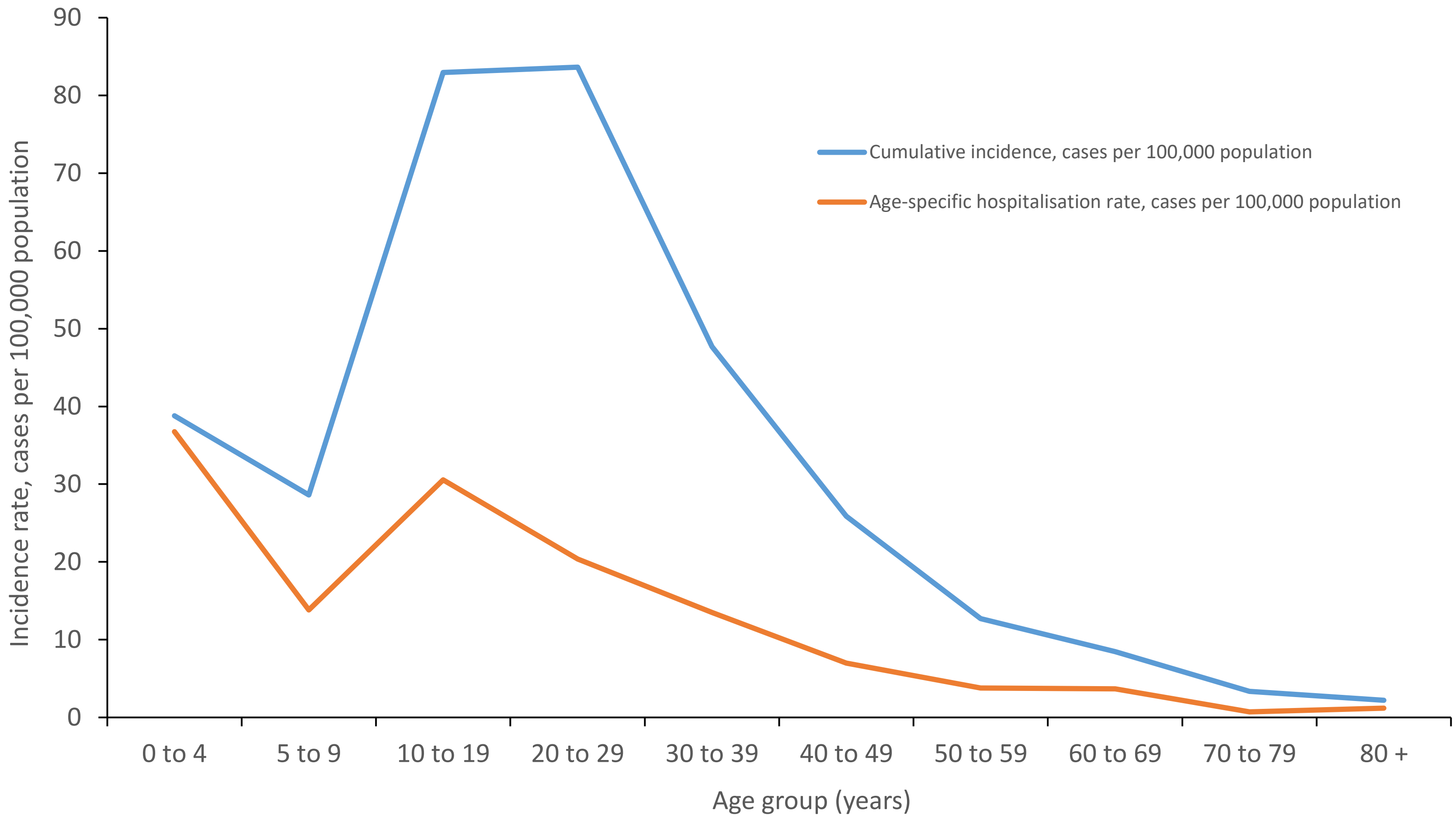

Figure 6. Cumulative and age specific hospitalization incidence rates of hantavirus infections in Barbados, 2008 – 2016.

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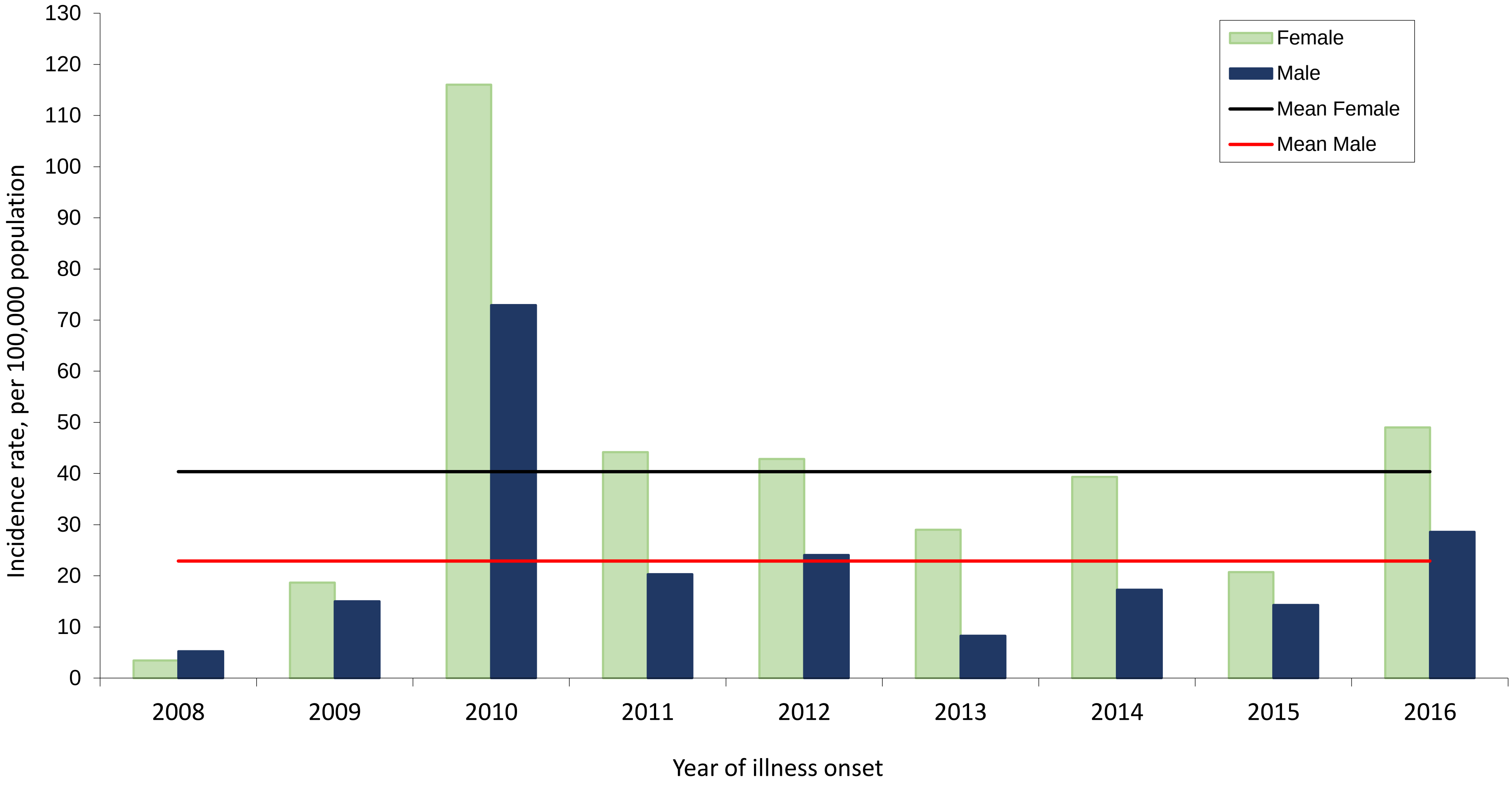

Figure 7. Crude and mean hantavirus incidence rates by gender, Barbados, 2008-2016.

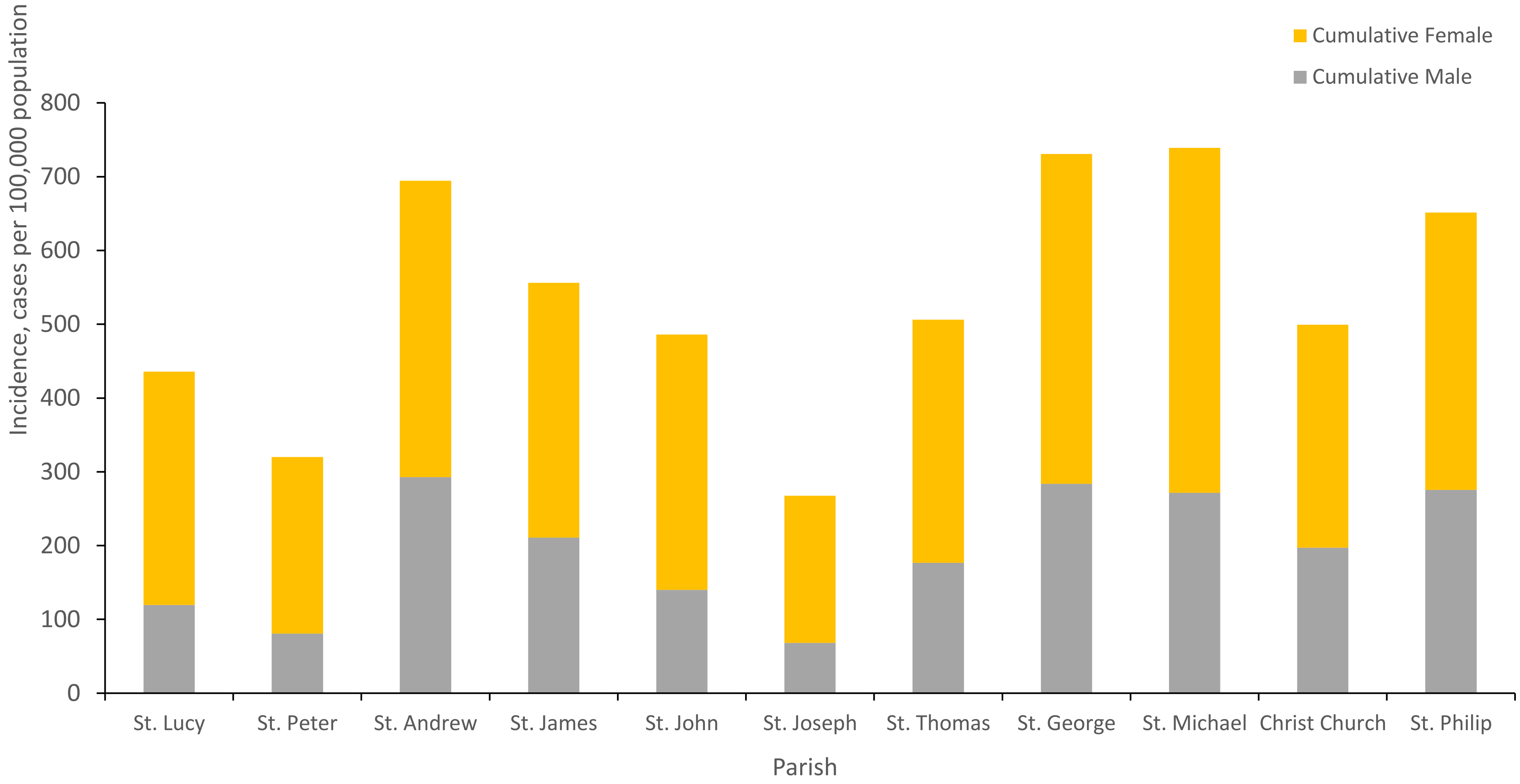

Figure 8. Cumulative hantavirus incidence rates by gender and geographic location, Barbados, 2008 – 2016.

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Geographic Distribution

The highest mean incidence rates (> 40 cases per 100,000 population) were observed in St. Michael [45.73 (95% CI, 29.73-61.74) cases per 100,000 population], St. George [45.32 (95% CI, 14.40-76.25) cases per 100,000 population], St. Philip [40.51 (95% CI, 14.92-66.10) cases per 100,000 population] and St. Andrew [40.49 (95% CI, 0-98.44) cases per 100,000 population] (Fig.9). During the 2010 hantavirus epidemic incidence rates in three parishes were > 100 cases per 100,000 population; St. George [131.85 (95% CI, 79.10-184.60) cases per 100,000 population], St. Lucy [127.78 (95% CI, 52-203.28) cases per 100,000 population], and St. Philip [109.42 (95% CI, 67.36-151.48) cases per 100,000 population] (Fig. 9). However, these parishes are not the most densely populated parishes (Fig. 9). Incidence rates were highest in males in St. Andrew, St. George and St. Philip and highest in females in St. George, St Michael and St. Philip (Figure 10).

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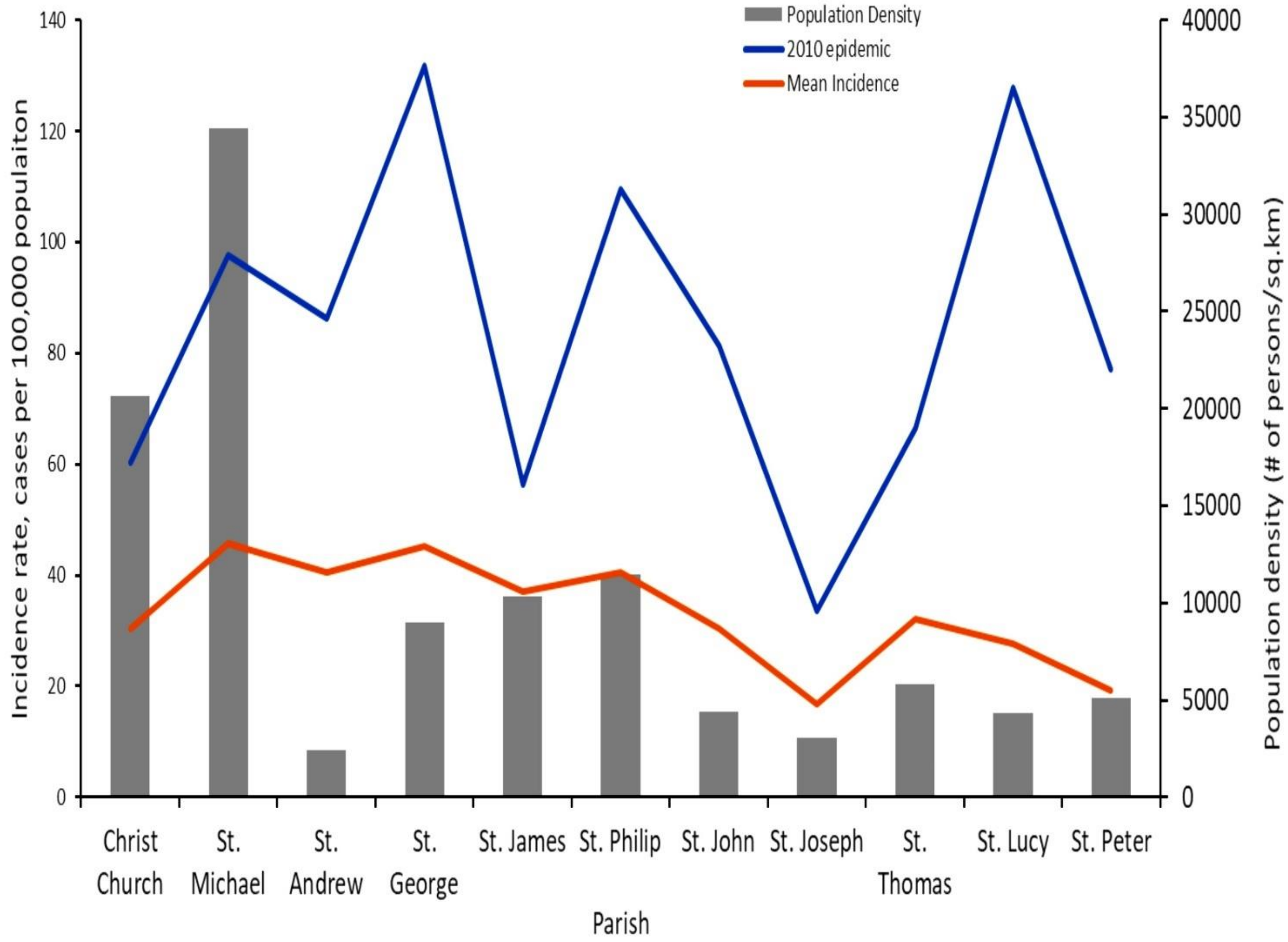

Figure 9. Population density, hantavirus incidence rates and geographic distribution of hantavirus cases in Barbados.

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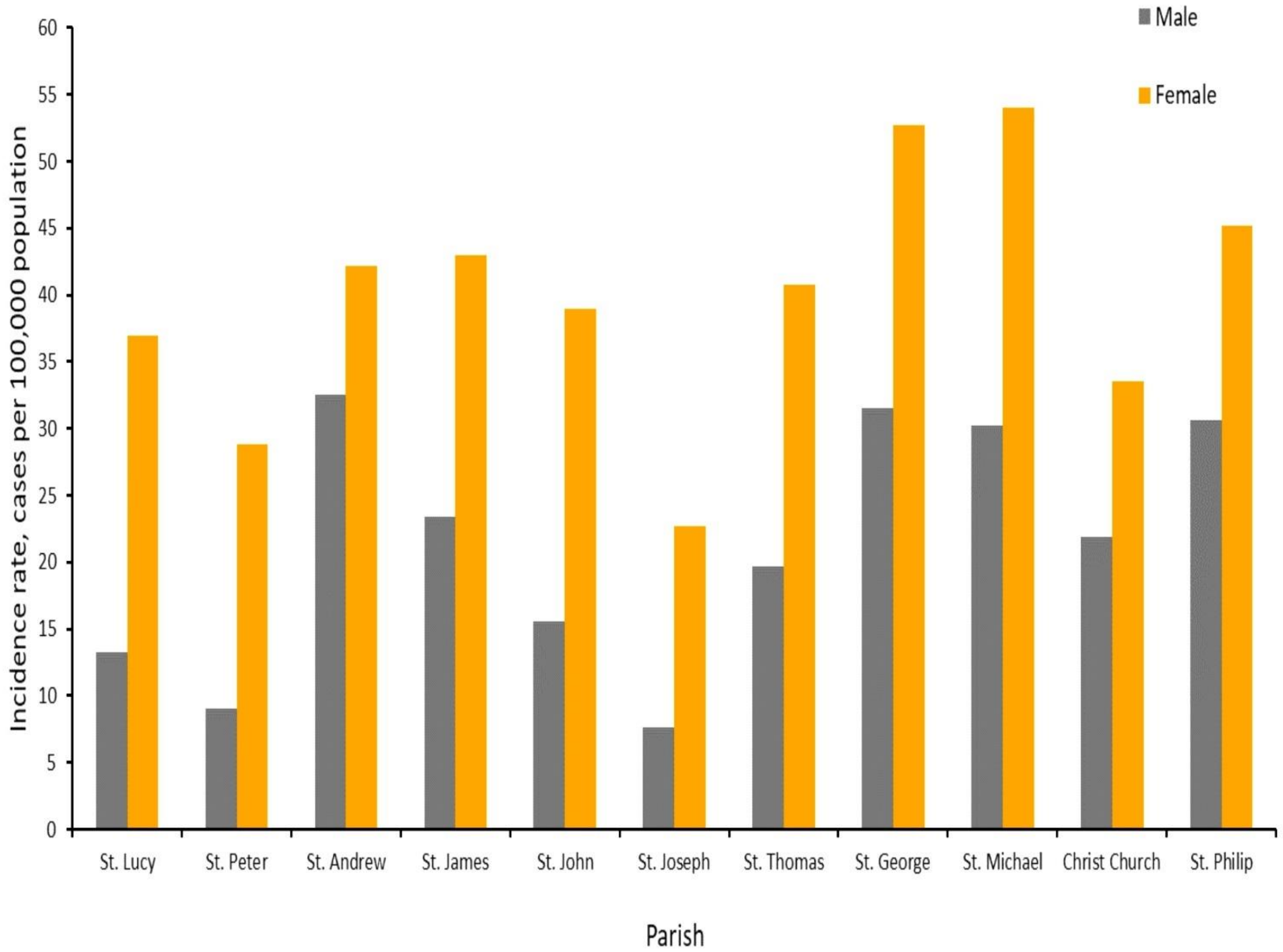

Figure 10. Hantavirus incidence rates by gender and geographic distribution of hantavirus cases in Barbados.

Discussion

Hantavirus epidemiology studies in the Caribbean region countries have been sparse. We present the first population-wide hantavirus epidemiology study (2008-2016) in Barbados and the Caribbean. This study is useful as it presents epidemiological data that has been absent from the region since its first report of hantavirus serological detection in 2002. It adds interesting insights into hantavirus epidemiology including an unusually higher incidence in females than males, the occurrence of a hantavirus outbreak in 2010, year-round hantavirus transmission with a seasonal peak in August and a possible role of land usage such as sugarcane cultivation in hantavirus transmission dynamics.

Hantavirus epidemics are influenced by environmental and behavioural factors including rainfall, topography, vegetation, occupational factors (4, 5). A significant increased rise in hantavirus incidence rate occurred in 2010 (coincidentally during 2010 dengue epidemic. During 2010, hantavirus epidemics were also observed in other countries including Germany and Brazil (13, 14). The increase of hantavirus incidence rate observed during 2010 in Barbados could be due to enhanced surveillance due to an ongoing dengue epidemic and thus greater awareness among physicians for persons presenting with dengue-like symptoms. The mean annual incidence rate observed in this study 33.03 cases per 100,000 person-years is higher than that reported from other countries including Brazil (1.0 cases/100,000 population), USA (0.009 cases/100,000 population), Chile (0.29 cases/100,000 population) even China (1.5 cases/100,000 population)(13, 15, 16). This may be due to a difference in the level of clinical suspicion, testing available and offered or the type of hantavirus infection, mild HFRS compared to HPS. In areas where non-HPS hantavirus disease was examined e.g. China (28.62 cases/100,000 population) a higher incidence rate was observed (17).

Approximately 150,000 to 200,000 patients with HFRS are hospitalised each year (18). The hospitalised hantavirus incidence rates ranged from 9.67 (95% CI, 6.35-13.81) to 29.00 (95% CI, 23.78-36.70) cases per 100,000 population; it was highest in 2010 during dengue and hantavirus epidemics in Barbados. Severe HFRS cases do occur resulting in hospitalization and the risk factors include pre-existing co-morbidities, home proximity to heavily vegetated/wooded area, virus strain, gender, smoking and age (19-22). A higher hantavirus case fatality rate (CFR) among females than males has been observed with HPS, HFRS & NE (23-25).

Among hantavirus cases the highest incidence rates were observed in persons 0-4 years of age [63.39 (95% CI, 50.91-75.88) cases per 100,000 population] which agrees with a study conducted among children in Barbados (26). Excluding 2008 persons < 30 years old comprised > 50% of persons acutely infected with hantaviruses in Barbados. This shows hantaviruses infect the younger portion of the population who lack substantial immunity due to immunological naivety however, but this immunity does increases with age. The decline in hantavirus incidence rates does occur with increasing age but other factors such as reduced exposure with age may also be occurring. Hospitalization rates were highest, 63.39 (95% CI, 50.91-75.88) cases per 100,000 population, among the 0-4 years age group and this may reflect the clinical perspective of acute infections in very young children. Physicians are more likely to hospitalize young babies and toddlers to monitor their clinical progression during febrile illness as such illnesses can be more life threatening so early in life.

Sex bias does occur in infectious disease epidemiology including hantavirus infections (24, 27). In Barbados, a higher hantavirus incidence rate was observed in females [40.36 (95% CI, 30.01-50.71) cases per 100,000 population] than males [22.89 (95% CI, 14.76-31.02) cases per 100,000 population] but was not significant. This agrees with seroprevalence data in the Netherlands where females exhibited a higher seroprevalence than males even though males presented more often clinically (28). A retrospective hantavirus prevalence study in Brazil found a similarly higher IgG seroprevalence rate among females than males (29). This indicated greater exposure to hantavirus infection in females than males with more urban than rural cases and was concluded to be due to occupation (housewives). This hantavirus gender bias towards females differs from hantavirus infections in China and Europe where men were more likely than females to be infected (24, 30). The male to female infection ratio observed in this study was 1:1.8. Gender bias of infection among females in Barbados may occur as more females are employed in the harvesting of sugarcane than males. Forestry work in Europe is associated with higher risk of HFRS yielding a high male:female infection ratio greater than 1.5:1 (30). This is not the case in North America where a male:female ratio of 1.0 is observed due to frequent peridomestic exposure and is supported by molecular epidemiology (31, 32). In Panama, the male:female ratio of hantavirus infection is also close to 1:1 (1.2:1) (33). Different behavioural dynamics could be at play where females are more likely to be exposed to hantavirus infection. For example, females might be more exposed to rodents and rodent droppings inside the home than males especially during cleaning activities thus more likely to be infected as was observed in Brazil (29). Mice (*Mus musculus*) have been identified as hantavirus hosts in China and could be a possible host in Barbados (34). Also given the lower age of hantavirus cases the possibility of a higher risk of exposure to rodent faeces and urine for children in day care, primary and secondary schools should be investigated.

Hantavirus transmission is influenced by environmental and climatic factors including rainfall, topography and vegetation (4, 5, 35). El Niño Southern Oscillation (ENSO) is a periodic shift of the ocean-atmosphere system in the tropical Pacific that impacts weather globally (36). ENSO events can influence transmission of infectious diseases and in the context of the Caribbean influence hurricane/tropical cyclone activity as well (36). Specific climatic events such as El Niño can result in ideal climatic conditions that fuel rapid vector population growth due to increase food availability, ideal breeding conditions and increase the risk of hantavirus transmission (37). An El Niño event occurred in 2010 coincidentally the same year the highest hantavirus incidence rate in Barbados was observed (38). A dengue epidemic also occurred during 2010 in Barbados. Increased monthly hantavirus incidence rates in Barbados occurred during the rainy season months (June to November) whilst during the drier months, hantavirus transmission was lower as observed with lower incidence rates during December to May. This highlights rainfall as a factor in the transmission of hantaviruses in Barbados as it permits moist soil which facilitates rodent burrowing, breeding, survival and the proliferation of vegetation and food for rodents (5, 35). Conversely, excessive rainfall and or extreme weather events including flooding can result in the reduction of rodent population, reduced risk of hantavirus transmission and reduced hantavirus incidence (39). However, it should be noted that hantavirus specific IgM and IgG can persist in humans so their detection by ELISA may not be exactly in sync with the time of infection and thus limits the soundness of this data analysis nonetheless in absence of other data it offers a starting mark for future research. Other climatic factors influencing hantavirus transmission include atmospheric moisture variability and temperature (5). It is likely the increased rainfall caused by El Nino event in 2010 contributed to the 2010 hantavirus outbreak in Barbados. Using sensitivity analysis if 2010 data is excluded the highest incidence peak is September followed by October and November (data not shown). Rainfall is thus likely the major determinant of hantavirus case distribution similar to leptospirosis in Barbados (40, 41).

In Barbados, the mean hantavirus incidence rates varied by parish with the four-highest mean hantavirus incidence rates observed in St. Michael [45.73 (95% CI, 29.73-61.74) cases per 100,000 population], St. George [45.32 (95% CI, 14.40-76.25) cases per 100,000 population], St. Philip [40.51 (95% CI, 14.92-66.10) cases per 100,000 population] and St. Andrew [40.49 (95% CI, 0-98.44) cases per 100,000 population]. A higher population density and urbanisation in St. Michael, the most populous parish, are likely reasons for the mean hantavirus incidence observed with the higher risk of contact with rodents, their droppings and urine. Urbanisation likely contributes to generation of more waste and increased proliferation of rodents. However in more rural areas large swaths of land are unused or in agricultural use and could also favour rapid rodent population growth (42). (43). Sugarcane harvesting occurs from January to May/June of each year in Barbados and this activity can disturb rodents and reduce their food supply (44). Sugarcane cultivation density i.e. the proportion of area planted with sugarcane, has been associated with increased risk of hantavirus infection in Brazil (45). Sugarcane workers have been suggested as targets for preventative measures and allocation of resources to reduce hantavirus transmission (45). One risk factor associated with hantavirus infection is an occupation in agriculture/forestry (46). The parishes with the highest density of sugarcane plantings in Barbados are St. George, St. Joseph, St. Andrew, St. Philip and St. Lucy (pers. comm., S. Norville, Barbados Agricultural Development & Marketing Corporation (BADMC), 2016). St. George has the highest density of sugarcane field plantings among all parishes in Barbados thus offering a possible explanation for the high mean hantavirus incidence rate observed in this parish along with St. Philip even with low population density (pers.comm., S. Norville, Barbados Agricultural Development & Marketing Corporation (BADMC), 2016). Rats are estimated to have arrived in Barbados circa 1536 on discovery or 1626 during settlement with rat control efforts commencing as early as 1745 (47). Rats can live in sugar cane fields and cause notable damage to sugarcane plantings (44). This can result increased foraging behaviour of rodents (e.g. in domestic refuse) and increased risk of rodent contact by humans and hantavirus transmission via rodent excreta (urine or faecal droppings) (44).

With leptospirosis, another rodent borne zoonosis, rainfall was the major determinant of the distribution of leptospirosis cases in Barbados and the highest incidence was observed in St. Andrew (40, 41). The association of hantavirus incidence with sugarcane harvesting and cultivation may have occurred during the 2010 hantavirus epidemic where the highest hantavirus incidence rates were observed in St. George, St. Lucy and St. Philip even with their respective low population densities. In Barbados, the combination of disturbed rodents, reduced food supply (sugar canes) and increased rainfall during the rainy season may all contribute to increased hantavirus transmission and higher hantavirus incidence rates observed during the rainy season over the study period.

Strengths

This was a population based, national and multi-year study examining the dynamics of hantavirus epidemiology in a Caribbean country for the first time. It provides data previously absent in the region and offers the structure for future hantavirus studies within the region to permit comparability of data.

Study limitations

Initially all submitted clinical samples were tested for dengue and hantavirus infection but around 2014-2015 due to financial constraints hantavirus tests were performed only on request. This led to an underestimation of hantavirus infection rates in Barbados from 2014-2015 onwards however in the absence of any prior data these data are still useful in understanding hantavirus epidemiology in the Caribbean. The persistence of hantavirus-specific IgM and IgG in infected patients limits the depth of analysis that can be gleaned from ELISA data where time-based factors are concerned. With the paucity of hantavirus epidemiological data for the region and genetic analysis of infecting hantavirus strains this can viewed as seminal research which can be built upon in future studies examining possible rodent hosts and animal reservoirs.

Recommendations

Public health awareness campaigns would aid in educating the population on the possible risks of infection, modes of infection, gender bias, affected age groups, how to prevent infection and what to do if infection does occur. The use of social media platforms may be effective in such campaigns as more than 50% of hantavirus cases in Barbados are less than 30 years of age. Continuing medical education on the circulation of hantaviruses in the region and the risk posed to younger persons should be communicated. Qualitative public health research is required to determine the reason(s) for this disparity between sexes and the role of occupation as a risk factor of hantavirus infection.

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Biographical sketch

Mr. Kirk Douglas is a Ph.D. medical microbiology candidate at the University of the West Indies (Cave Hill) with an avid interest in clinical virology and vector-borne and zoonotic disease research.

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