

Ten years of a hantavirus disease emergency in the Federal District, Brazil

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ABSTRACT

Introduction: Hantavirus diseases are emerging human diseases caused by *Hantavirus* spp. of the Bunyaviridae family. Hantavirus pulmonary syndrome (HPS) has been detected in the Federal District (DF) of Brazil since 2004. Among the 27 Brazilian Federal Units, DF has the highest fatality rate. More than 10 years have already passed since then, with confirmation of cases caused by the *Araraquara* and *Paranoa* species. The reservoir is *Necromys lasiurus*. **Methods:** Local surveillance data of the confirmed cases were analyzed, including age, sex, month and year of occurrence, clinical symptoms, syndromes and outcomes, and probable transmission place (PTP). The cases were mainly confirmed by IgM detection with a capture enzyme immunoassay. The cases were classified as autochthonous if PTPs were in the DF area. **Results:** From 2004 to 2013, in the DF, 126 cases of hantavirus were confirmed, and the cumulative incidence was 5.0 per 100,000 inhabitants. The occurrence of cases was predominantly from April to August. At least 75% of the cases were autochthonous. Acute respiratory failure was reported in 47.5% of cases, and the fatality rate was 40%. **Conclusions:** In the DF, the cumulative incidence of HPS was one of the highest worldwide. A seasonal pattern of hantavirus disease in the dry season is clear. There was a high frequency of severe clinical signals and symptoms as well as a high fatality rate. For the near future, visitors and inhabitants of DF rural areas, particularly male adults, should receive continuous education about hantavirus transmission and prevention.

Keywords: Hantavirus. Infectious disease. Epidemiological surveillance.

INTRODUCTION

Hantavirus diseases are emerging infectious diseases caused by the genus *Hantavirus*, of the family Bunyaviridae⁽¹⁾. First described in South Korea in the 1950s, as Korean hemorrhagic fever, the etiologic agent was only isolated in 1977⁽²⁾. Rodents are the main reservoirs of hantavirus, and transmission occurs through contact with blood or excreta of infected rodents or by inhaling aerosols containing the virus⁽³⁾.

The geographic distribution of the two distinct major clinical syndromes between the different continents is very distinct. Hantavirus pulmonary syndrome (HPS) occurs in the Americas^{(4) (5)}, while hemorrhagic fever with renal syndrome (HFRS) occurs in Europe and Asia^{(2) (3) (6)}, with occasional reports of cross occurrence⁽⁷⁾.

In Brazil, the first confirmed cases were reported in 1993, and 1,906 cases were reported nationwide until 2014; of these, 448 (25.6%) cases were reported in the Brazilian Midwest region. Cases have been reported in all five regions of the country and distributed in 14 (51.9%) of the 27 Brazilian Federal Units (BFUs)^{(8) (9)}. In 2004, cases were first reported in the Federal District (DF), as an outbreak⁽¹⁰⁾, and during recent years, the DF has had the highest fatality rates among the BFUs⁽¹¹⁾.

At least three different monophyletic clades of hantavirus have been detected in South America and are also found throughout Brazil. However, in the DF, only the Andes clade, which includes the *Araraquara* and *Paranoa* genotypes, has been found so far^{(12) (13)}. There are different clinical and epidemiological patterns related with the diversity of the etiologic agent⁽¹⁴⁾. Some hantavirus species are linked with HFRS and others with HPS, each with specific environmental scenarios and climate patterns. In the rural areas of the DF, the reservoir for hantavirus transmission is the wild rodent *Necromys lasiurus*^{(15) (16) (17)}.

The DF has a population of over 2.8 million inhabitants and includes the Brazilian capital City of Brasília⁽¹⁸⁾. Limited by the parallel 15°30' S and 16°03' S, with altitude ranging from 750

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to 1,344 meters above sea level, the DF has an area of nearly 5,800km². The climate is tropical, with a dry winter, monthly mean temperatures of 13-22°C, and environmental relative humidity of 11-75%. The vegetation is typical of the savanna⁽¹⁹⁾. There is a high proportion of agricultural activities in rural areas. During the 10-year period between the emergence of hantavirus disease in the DF in 2004⁽¹⁰⁾ ⁽²⁰⁾ and 2013, cases have been confirmed every year, and there has been territorial expansion. This study describes the main epidemiological aspects of hantavirus cases in the DF during these 10 years of detection.

METHODS

This epidemiological, descriptive, observational study used data collected by the DF surveillance system teams in 2004-2013. The data sources were records from the National Notifiable Diseases System (SINAN) and reports from visits to households and sites of activity of cases by the environmental health surveillance team.

For confirmed cases, the following variables were analyzed: age, sex, month and year of occurrence, clinical symptoms, syndromes and outcomes, and probable transmission place (PTP). All cases were confirmed using laboratory tests, mainly with a capture enzyme-linked immunosorbent assay (ELISA) designed to detect the anti-hantavirus class M (IgM) antibody⁽²¹⁾. The suspected cases in the DF were tested using ELISA with the recombinant nucleocapsid protein of Andes and Araraquara, which are native South American species⁽²²⁾ ⁽²³⁾. For a few cases, sera were not available; therefore, immunohistochemistry for hantavirus was used. Laboratory tests were performed at a reference institution for the Brazilian National Surveillance System⁽²⁴⁾.

The PTPs for hantavirus disease are geographic points that are considered places of exposure reported by confirmed cases or their *proxies*, verified by the specialized environmental health surveillance, and classified as receptive for transmission. The PTPs were marked with geographical positioning devices, and the coordinates were recorded in the Universal Transverse Mercator⁽²⁵⁾. The cases were classified as autochthonous if PTPs were in the DF area, regardless of the place of residence. The cases treated in Brasília, with one or more PTPs outside the DF, were considered allochthonous. Notified inpatient cases with acute disease who did not survive were classified as *death*. Notified cases with an address in the DF territory were classified as inhabitants.

Absolute and relative frequencies were calculated, including simple proportions and incidence rates by year and as averages for each month during the study period. The results are graphically depicted. The study was approved by the Ethics Committee for Research with Humans Beings of DF Health Secretariat.

RESULTS

During the first 10 years of detection, 126 cases of hantavirus disease were confirmed, resulting in a cumulative incidence rate of 5.0 cases per 100,000 inhabitants.

There were no cases aged <10 years. The incidence for those aged 20-49 years was almost double that of the other age groups. The incidence for men was also almost double that of women, except for persons aged <20 years (Table 1).

The curves of the cases by year for all inpatient cases, regardless of residence, and residents of the DF were both bimodal, with similar shapes and considerably more cases in 2004 (Figure 1). In the months from April to August, the mean numbers of cases were at least two times higher than those in the other months (Figure 2).

The PTP was classified by the environmental health investigation for 104 (82.5%) cases: 85 (81.7%) in the DF and/or another BFU and 78 (75%) only in the DF (Figure 3). The other BFUs included the rural areas of 11 municipalities of State of Goiás and two municipalities of the State of Minas Gerais, all of which are very close to, and even border, the DF.

Fever, dyspnea, and myalgia were recorded for 94.2%, 87.5%, and 85.8% of cases, respectively. Acute respiratory failure (47.5%), hemorrhagic signs (25.8%), circulatory shock (15%), and renal failure (10%) were also reported (Figure 4). The hantavirus disease fatality rate in the DF during the study period was 40%.

TABLE 1 - Absolute numbers and incidence rates per 100,000 inhabitants of hantavirus disease confirmed in the Federal District, Brazil, 2004-2013.

Age group (years old)	Female		Male		Total	
	(n)	(rate)	(n)	(rate)	(n)	(rate)
< 10	-	-	-	-	-	-
10-19	9	4.0	7	3.2	16	3.6
20-49	31	4.6	64	10.6	95	7.4
≥ 50	6	2.8	9	5.4	15	3.9
Total	46	3.5	80	6.7	126	5.0

DISCUSSION

The cumulative incidence rate of HPS in the DF from 2004 to 2013 was 5.0 cases per 100,000 inhabitants. In Brazil, there were 1,486 cases of HPS reported from 2001 to 2011, for a cumulative incidence rate of 0.080⁽²⁶⁾. Comparatively, from 1995 to 2008 in Argentina, there were 750 HPS cases⁽²⁷⁾, for a cumulative incidence rate of 1.955 per 100,000 inhabitants. In Chile, which is the most endemic country in the Americas, the mean incidence rate by year was 0.290 per 100,000 inhabitants, and in the USA it was 0.009 per 100,000 inhabitants⁽⁵⁾. During the 20 years since the 1993 Four Corners outbreak in the USA,

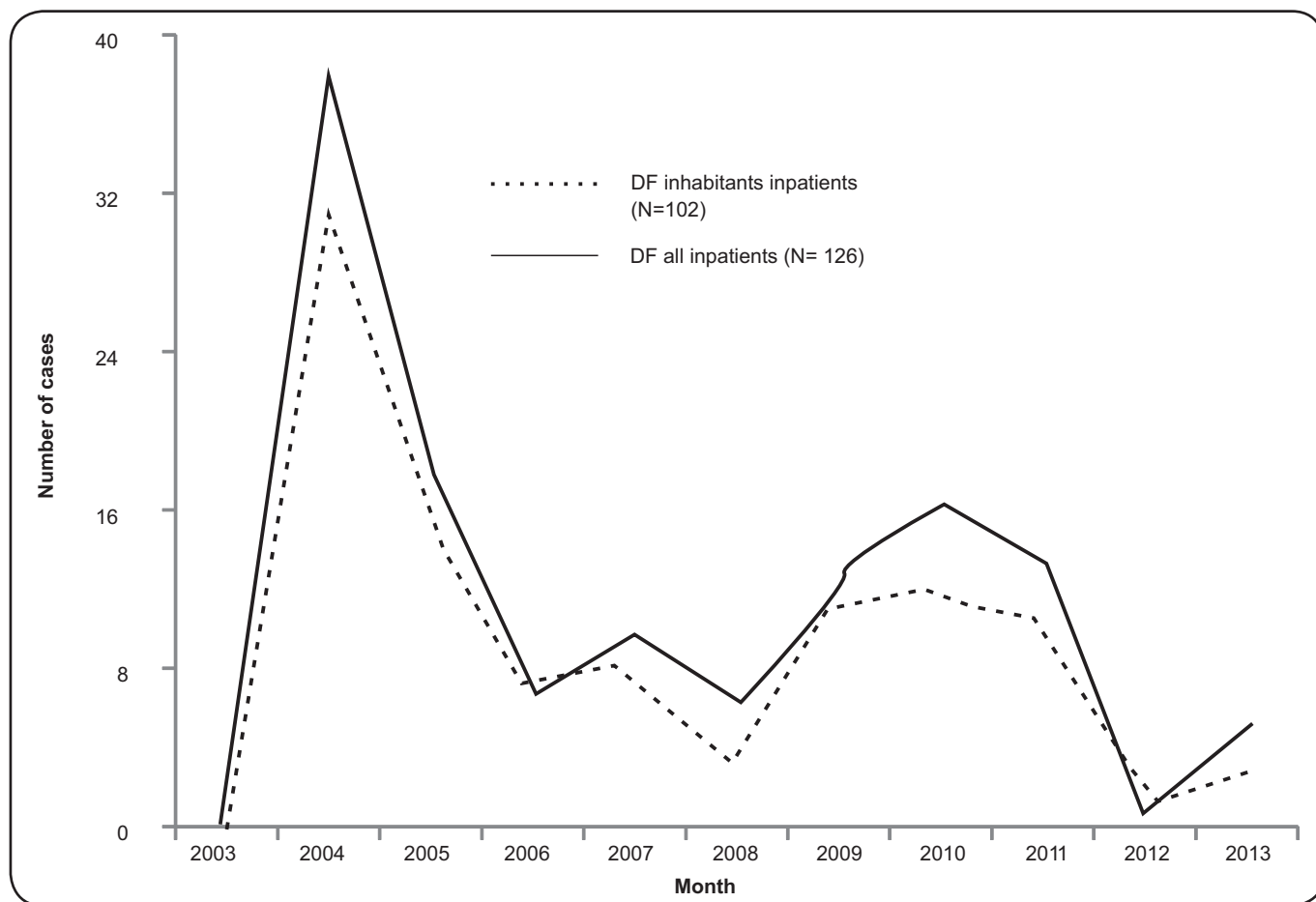


FIGURE 1 - Hantavirus disease by year and inpatients status, in the Federal District (DF) of Brazil, 2004-2013.

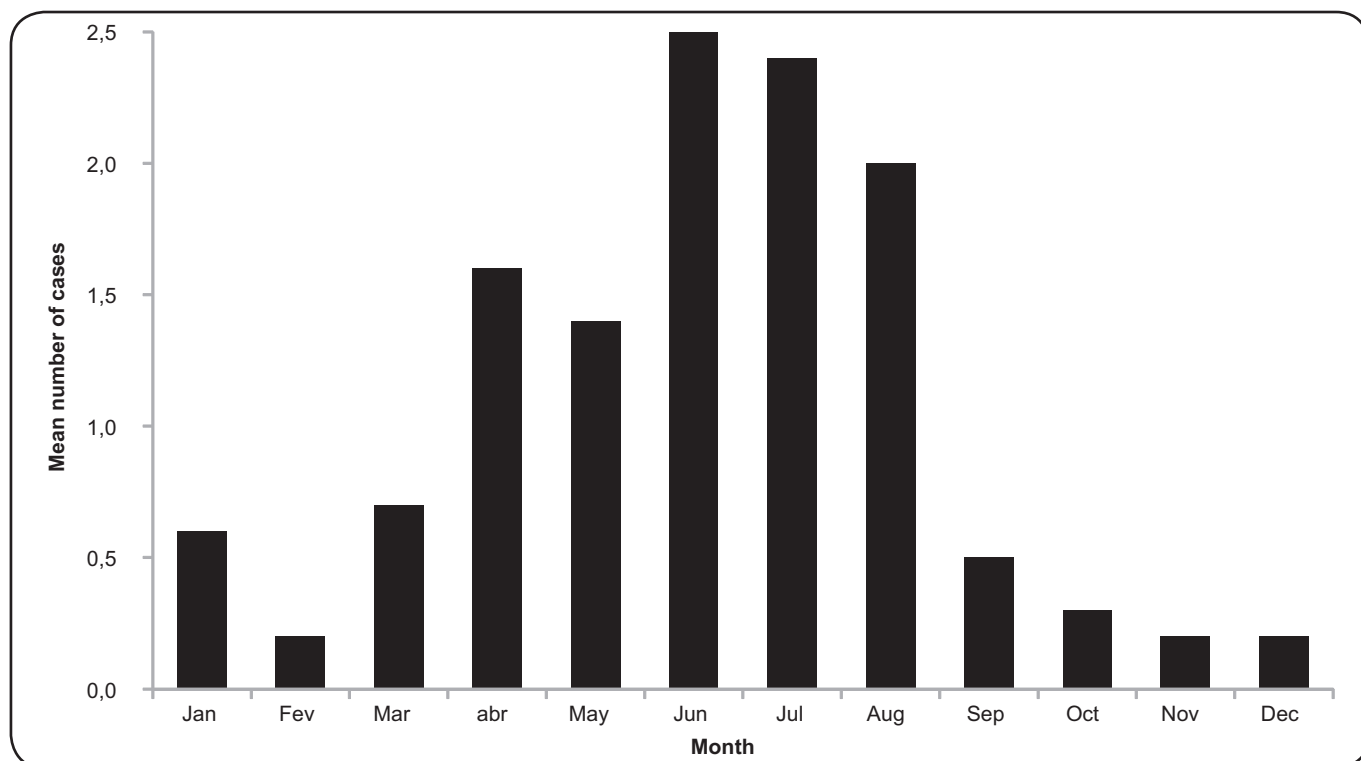


FIGURE 2 - Mean monthly curve for confirmed cases of hantavirus disease, Federal District (DF), Brazil, 2004-2013.

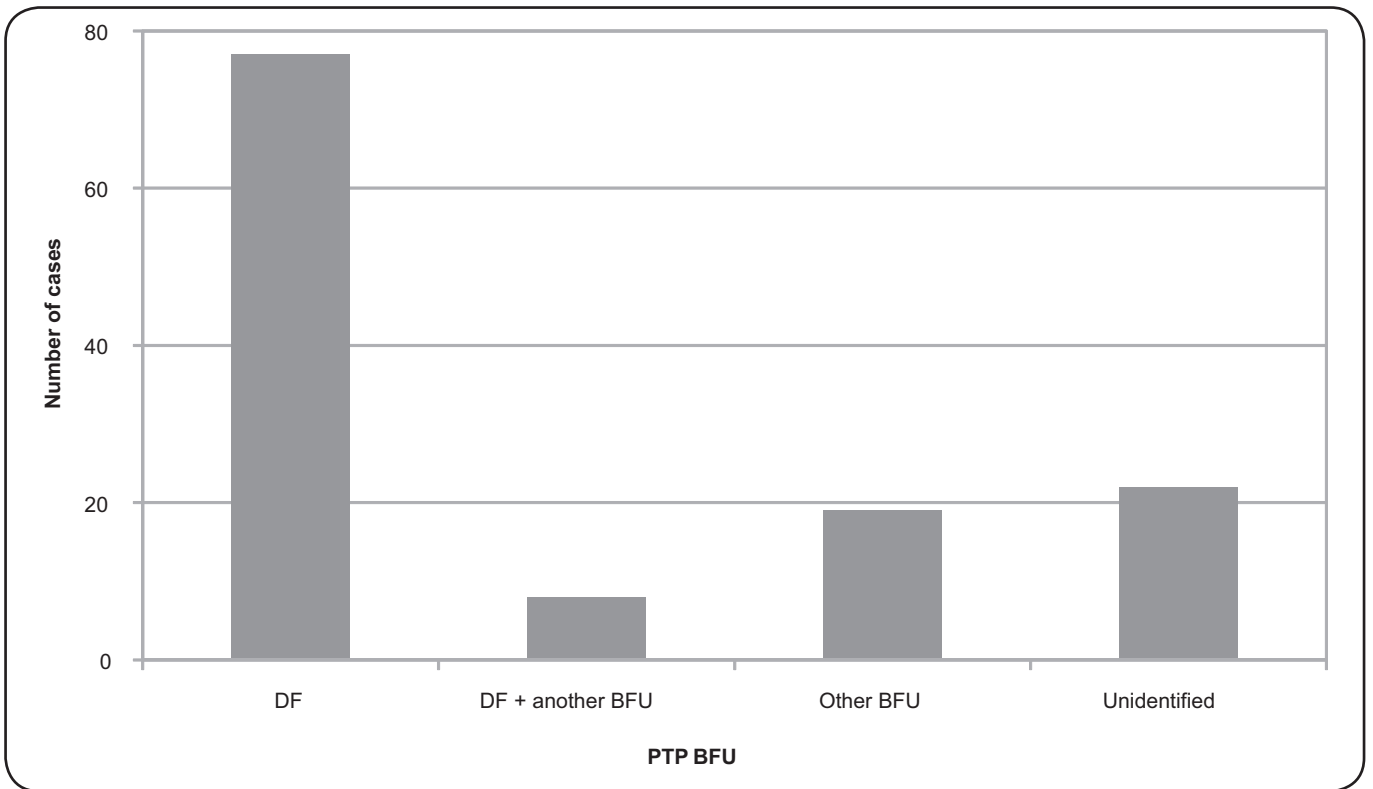


FIGURE 3 - Probable transmission places (PTP) of confirmed cases of hantavirus disease in the Federal District (DF) and other Brazilian Federal Units (BFU), 2004-2013.

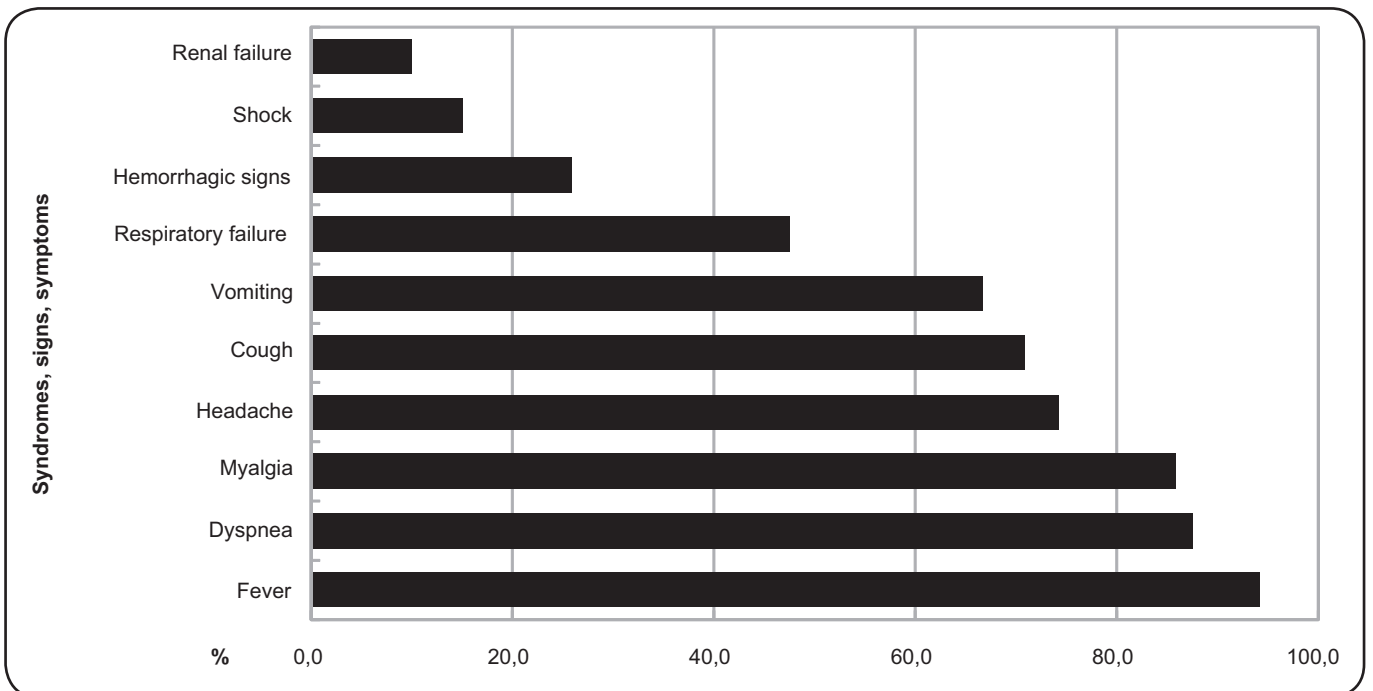


FIGURE 4 - Most frequent symptoms and relevant syndromes detected in confirmed hantavirus disease cases, Federal District (DF), Brazil, 2004-2013.

there were 624 HPS confirmed cases, scattered throughout 34 states⁽¹²⁾.

In 2014, the incidence rate in Brazil was 0.092 per 100,000 inhabitants, and the incidence in the affected BFUs ranged from 0.028 to 1.343 per 100,000 inhabitants. According to the Brazilian Ministry of Health, the DF had the highest incidences among the 11 affected BFUs in 2004 and 2005, with 1.343 and 0.686 per 100,000 inhabitants, respectively⁽²⁸⁾ ⁽²⁹⁾. By 2009, 5.6% of all of the hantavirus disease cases reported nationwide in Brazil were in the DF⁽²⁴⁾.

Regarding age, the incidence was much higher in those aged 20-49 years in the present study; the same age group accounted for 67.7% of confirmed HPS cases in 2004 and >70% of confirmed HPS cases in 2005 in Brazil⁽²⁸⁾ ⁽²⁹⁾. In the DF, HPS was not confirmed in persons younger than 10 years old. In Brazil, there were only 19 (1.6%) confirmed cases of HPS in persons younger than 10 years old from 1993 to 2009.

Eighty (63.5%) HPS cases in the DF were men, and the number of male cases of HPS was twice as high as the number of female cases in those aged ≥ 20 years. In Brazil, 80% of the HPS cases were men⁽²⁴⁾.

The curves for number of cases by year for DF inhabitants and all persons treated in the DF peaked in 2004 and 2010 for both groups, mainly in 2004, indicating that the small portion of cases that originated from outside the DF had the same context of transmission as the inhabitants. The number of cases in the DF in 2004 was equivalent to that registered in Brazil from 1993 to 2000⁽²⁴⁾. Because there are no reports of hantavirus before 2004, the detection of HPS cases in the DF started in 2004. A retrospective study in the US using laboratory tests of tissue samples from fatal cases with unclear causes detected >30 cases in the 15 years before the Four Corners outbreak⁽³⁰⁾. In Europe, hantavirus disease has demonstrated a particular cyclical temporal pattern; in boreal regions, the number of cases increases every three years⁽³¹⁾. The bimodal pattern demonstrated in the DF might indicate that the occurrence is also cyclical.

There were reports of HPS in the DF in every month of the year from 2004 to 2013. However, the monthly means for the months from April to August were at least two times higher than those in other months, indicating a seasonal pattern. The DF climate is characterized by two seasons: rainy and dry⁽¹⁹⁾. The peak incidence of HPS was reported during the dry and cold season, which was also observed in a presumably descriptive study in Uberlândia, Minas Gerais that included only 23 cases during an 8-year period⁽³²⁾ and in the State of São Paulo, as reported using a sophisticated scientific method⁽³³⁾. In contrast, a seasonal pattern was not found in another study of Brazilian geographical regions (BGRs)⁽²⁶⁾. However, BGRs have different biomes, landscapes, and climates, such as the Midwest, where hantavirus occurs in two very different climatic contexts.

In this study, the HPS fatality rate in the DF was similar to the Brazilian fatality rate of 42% from 1993 to 2009⁽²⁴⁾. Comparatively, the fatality rates in the USA, Chile, and Argentina were 35%⁽³⁴⁾, 30%⁽⁵⁾, and 25.8%⁽²⁷⁾, respectively. The differences in the fatality rates by country might be explained by the higher virulence of some hantavirus species⁽³⁵⁾ or the clinical spectrum

of hantavirus disease, which ranges from a mild clinical course to cardio-respiratory failure and death⁽³¹⁾. In some severe cases, the patients also had an underlying illness, such as chronic pulmonary disease⁽⁴⁾. Whereas 90% of HPS deaths occur within 48 hours from symptom onset⁽⁵⁾, the differences in the quality of care among hospitals should also be considered.

Fever, dyspnea, and myalgia are included in the case definition⁽²⁴⁾ and were reported in a high percentage of the cases in the DF. The severe signs and symptoms, such as acute respiratory failure, hemorrhagic signs, and circulatory shock, also affected many cases. The severe pattern of signs and symptoms in the DF, including respiratory symptoms, indicates that HPS is primarily present. All 12 cases with renal failure also had respiratory failure or dyspnea. Renal failure appeared in approximately 20% of the cases registered in Brazil from 1993 to 2006⁽⁸⁾. Therefore, renal failure in cases in the DF might be a late complication, similar to pre-renal acute failure⁽⁵⁾ ⁽³¹⁾. However, HFRS cases confirmed in the USA⁽¹²⁾ may also suggest the presence of this form of disease in other countries in America.

Regarding the limitations of this study, the Brazilian national databases have been in a constant adaptation process to the technological resources, creating instability in the information system. The spread of epidemiological information in different institutions, with no concatenate records, accentuate this instability. Calculations of the incidence rates in the DF used all cases treated in DF hospitals, regardless of BFU address. Autochthonous cases represented at least 75% among those whose PTP was identified. Also, the frequent changes in DF territorial occupation create some difficulty for epidemiological analysis⁽²⁰⁾.

From 2004 to 2013, HPS in the DF presented with great severity, even higher than other regions of America, despite the low incidence, when compared with all other health problems. The high fatality rate and predominance among men and young adults in the DF were similar to what occurs in Brazil. Nevertheless, the fatality rate was higher than in other countries.

There was a bimodal distribution in the DF, suggesting that hantavirus disease should have a cyclical temporal pattern in this area. Seasonality was also observed, and the cases originated from DF and nearby, although the PTPs were predominantly in the DF.

A human hantavirus infection seroprevalence based-population study in the DF would provide some answers regarding the epidemiological pattern of this disease in this area. For the near future, visitors and inhabitants of rural areas in the DF, particularly male adults, should receive continuous education about hantavirus transmission and prevention. Medical assistance should be sought immediately after onset of symptoms in a suspected case of hantavirus disease.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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