Trans R Soc Trop Med Hyg
doi:10.1093/trstmh/trt014

ORIGINAL ARTICLE

Demographic profile of sylvatic yellow fever (SYF) in Brazil from 1973 to 2008

Fernando Portela Câmara[a,*], Luiz Max de Carvalho[a] and Ana Luisa Bacellar Gomes[b]

[a]*Sector for Infectious Diseases Epidemiology, Institute of Microbiology, Federal University of Rio de Janeiro (UFRJ), Health Sciences Center - Block I, University City - Fundão Island, Rio de Janeiro - RJ - CEP: 21941-590, Brazil;* [b]*Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, Brazil*

*Corresponding author: Tel: +55 21 2560-8344; Fax: +55 21 2560-8028; E-mail: portela@micro.ufrj.br

Received 19 July 2012; revised 4 January 2013; accepted 7 January 2013

Background: Yellow fever is an acute, frequently fatal, febrile arbovirosis that in Brazil occurs only in the sylvatic form. Sylvatic yellow fever (SYF) appears in sporadic outbreaks over a large area of Brazil. In this paper, we analyze the demographic profile of 831 SYF cases that occurred between 1973 and 2008, to determine which segments of the exposed population are at greater risk.

Methods: Data were statistically analyzed and were also geo-referenced in order to observe their spatial pattern. The basic reproductive number of infections, R_0, was estimated by the ratio between average life expectancy and the average age of the cases.

Results: SYF cases showed a modal profile of young male adults, approximately 30 years of age, living in rural areas of the states of Pará, Goiás, Maranhão and Minas Gerais, who were unvaccinated or whose vaccination was out of date. The disease showed a high mortality rate (51%, 421/831) among the notified cases, with death occurring on around the seventh day of illness for most patients. The R_0 for SYF was estimated at approximately 2.4.

Conclusion: The results of this study suggest that lack of vaccination coverage is a major risk factor for SYF, and that the groups most at risk are migrant laborers, farm workers and tourists.

Keywords: Sylvatic yellow fever, Yellow fever vaccine, Demographic profile, Brazil

Introduction

Yellow fever is an acute infectious disease caused by an arbovirus of the family Flaviviridae, genus *Flavivirus*, transmitted by mosquito vectors of the genera *Aedes*, *Haemagogus* and *Sabethes*.[1,2] Epidemiologically, yellow fever exists in two forms: sylvatic yellow fever (SYF), transmitted through a cycle that involves non-human primates and vectors of the genus *Sabethes* and *Haemagogus*; and urban yellow fever, in which the transmission cycle is adapted to urban ecology and involves the human host and *Aedes aegypti* mosquitoes.[3] In Brazil, only SYF has been detected in recent years.[4] Câmara and colleagues[5] detected a major 7-year cycle of human SYF in the Mid-West region of the country, where most cases occur, and a 14-year cycle in the North region, which has predominant Amazon (tropical rainforest) ecology and the country's lowest population density.

SYF is active in the rainforests of Africa and the Americas, occupying much of the Brazilian territory and causing sporadic outbreaks in the Mid-West and South East regions of Brazil with recent increase in cases in the states of Pará (North region), Goiás (Mid-West), Maranhão (North East) and Minas Gerais (South East).[4] The outbreaks are small in magnitude, with high mortality among the notified cases.[4] However, the total mortality is unknown, because probably in most cases the illness evolves as a fever without complications and is not notified. In the past, the total mortality in urban outbreaks was low, with high rates occurring only in non-Brazilian Caucasian individuals (Câmara; in preparation). Yellow fever has an incubation period of 3–6 days after the bite of the infected mosquito vector and the symptoms at this stage of the illness (the infectious phase) are similar to those of dengue. Some patients recover spontaneously after this phase but others, after a brief improvement, enter a toxemic phase; they experience a second peak of fever with serious hemorrhagic phenomena and visceral damage that are often fatal. The classical picture of yellow fever in humans includes severe hepatitis, jaundice, hematemesis ('black vomit'), renal failure and sometimes encephalitis, on a background of mucocutaneous bleeding.

Surveillance of human cases of SYF in Brazil relies on compulsory notification (within 24 h) and case confirmation (within

60 days). The surveillance is based on the case definition adopted by the Ministry of Health of Brazil, which is in line with the recommendations of the Pan American Health Organization (PAHO) but wider, to improve the power of detection of the surveillance system.[6] (This case definition is described in detail in a paper by Tsuboi and colleagues and the references therein.[7]) Even so, illness causing few symptoms is liable not to be attributed to yellow fever.[6]

Re-emergence of yellow fever in areas where the virus had been eradicated has caused considerable concern. In 2008 and 2009, outbreaks occurred in São Paulo (South East region) and Rio Grande do Sul (South region) years after the last reported yellow fever cases in these areas,[7] with human cases and epizootics in monkeys being reported. Control measures are needed urgently to avoid the spread of yellow fever to the Brazilian coastal area.[8]

The purpose of this study was to describe and analyze the demographic profile of SYF patients in Brazil between 1973 and 2008, aiming to define possible risk factors in the exposed population. Surveillance of SYF is a priority, given the current construction of dams and highways, expansion of agribusiness, mining and the increase in ecotourism into endemic areas in Brazil, with the risk of re-emergence of this disease,[9–12] particularly as *A. aegypti* infests almost all urban areas of the country.[13,14]

Methods

Data were obtained from the Ministry of Health of Brazil covering the period from 1973 to 2008, and entered into a spreadsheet (Microsoft Excel, Microsoft Corporation, Redmond, WA, USA), with the categories for each case being: state, vaccination status, death, sex, age, duration of illness until death, and diagnosis. Each variable present in this dataset was checked for the presence and amount of missing data, and cases for which there was insufficient information were excluded from posterior analysis. Statistical analyses were performed using Minitab V.16 (Minitab Inc., State College, PA, USA).

Cases were geo-referenced to the highest spatial definition available, at municipality level. Using this scheme we were able to recover spatial coordinates for 99.39% (826 of 831) cases reported. Additionally, the point map of case locations was overlaid to a risk map for yellow fever in Brazil.[15,16]

To gain an insight into the dynamic characteristics of SYF we calculated the basic reproductive number of infections, R_0. This parameter was estimated using the approximation proposed by Anderson and May,[17] using the ratio between the male average life expectancy for the affected regions[18] and the average age of the male cases. We considered that the exposed population had a uniform distribution because of its relatively small size and homogeneous life pattern.

Results

We analyzed 831 cases of yellow fever, most of which were concentrated in the states of Pará (North region) and Goiás (Mid-West region), followed by the respective border states of Maranhão and Minas Gerais. Figure 1 shows the geographic distribution of the 826 cases that allowed for geo-referencing. Most of the cases were concentrated in the Mid-West and South East regions, where the largest outbreaks of recent years occurred. Noticeably, there were two well defined clusters within Minas Gerais state, which is within the boundaries of the endemic region.

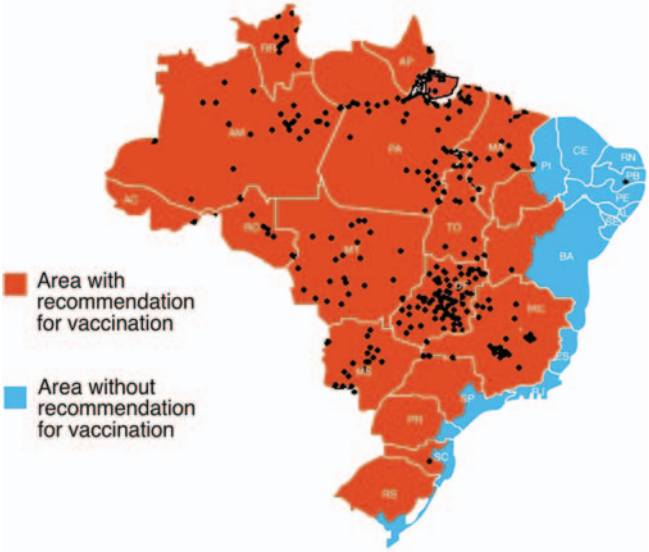

Figure 1. Distribution of notified cases of sylvatic yellow fever on the Brazilian territory from 1973 to 2008. The areas with and without recommendation for vaccination are based on the recent findings of Hill[15] and the recommendations of the Centers for Disease Control, Atlanta, FA, USA,[16] available at http://wwwnc.cdc.gov/travel/pdf/yellow-fever-vacc-brazil.pdf. Points show the localization of the 826 yellow fever cases where data allowed geo-referencing at the municipality level.

With regard to vaccination status, 52% (432/831) of the reported cases were individuals who had been vaccinated >10 years earlier and 3% (27/831) had been vaccinated <10 years earlier; 45% (372/831) did not declare their immunization status. Most cases belonged to the age group 10–40 years, with a peak between 20 and 30 years. The age range was 0–75 years with a mean of 30.5 years and standard deviation of 15.2 years. Most of the yellow fever cases (80%, 660/831) were male. Table 1 shows the demographic data of cases. The average life expectancy for these regions is 73.2 years (Mid-West, 74.3; North, 72.2), and the basic reproductive number, R_0, for SYF in this period can be estimated as approximately 2.4.

The death rate in the notified yellow fever cases was 51% (420/831), death being more frequent in males than in females ($\chi^2 = 23{:}19$, $p < 0.001$). The median time between symptom onset and death was 7 days, with 86% (661/831) of deaths occurring in the first 10 days of illness.

Discussion

All the cases of yellow fever were virologically confirmed, but there were insufficient data on symptoms to determine a clinical profile. However, as the demographic data were well documented, it is possible to make indirect inferences about risk. The considerable missing data on occupation and vaccination status

Table 1. Summary statistics for 831 yellow fever cases in the period 1973–2008

Variable	
Age (years)	28.79 (14.78)
Deaths	420 (50.54)
Time from symptom onset to death (days)	7.81 (5.14)
Occupation	
Handyman	273 (32.85)
Tourist	40 (4.81)
Housewife	33 (3.97)
Other	190 (22.86)
Data missing	295 (35.49)
Vaccination status	
Vaccinated	27 (3.24)
Non-vaccinated	432 (51.98)
Patient did not know status	58 (6.97)
Data missing	314 (37.78)
Gender	
Male	660 (79.42)
Female	170 (20.45)
Question ignored	1 (0.12)

Data are mean (SD) or no. of cases (%).

(Table 1) did not preclude overall conclusions. There is a possibility of bias, because the information recorded on cases was collected from fully symptomatic individuals according to the case definition adopted by the yellow fever surveillance scheme.[6] Cases with few symptoms are poorly detected because the surveillance system focuses on outbreak detection.[6]

Only a few cases (3%) were from patients with an in-date vaccination; the remainder did not state their vaccination status or were overdue for a booster vaccination. This suggests that exposure to SYF was conditional on the absence of vaccine protection, and this defines the main condition of risk for these populations. Most cases were from the local population, probably immigrants. Among the reported cases 40 were tourists, 34 of whom were not vaccinated. These data suggest that the occurrence of SYF in unvaccinated workers and tourists is the main risk for the re-urbanization of this arbovirus.

The risk group showed a typical profile, as observed in other surveys[3,6,8] most (80%, 660/831) were young adult males, about 30 years old, unvaccinated, living in transition areas in the North and Mid-West regions, especially in the states of Pará, Goiás, Maranhão and Minas Gerais. This profile corresponds to a farmer, family man, habitually or temporarily working in areas with a higher risk of exposure to infection.

The death rate was high among the reported cases, around 51% (421/831), mostly on the seventh day of illness. This suggests the circulation of highly virulent viral strains in the South American tropical ecosystem. This death rate also requires early medical intervention; this is problematic, as at the onset of yellow fever the symptoms can be confounded with those other common infections in the region, and the interval between confirmation of SYF and death is short. The R_0 of approximately to 2.4 is sufficient to allow efficient spread of the disease.

Plotting the geographic coordinates of the geo-referenced cases showed a high intensity of cases in the Mid-West region (Figure 1), especially in Goiás state (DF), the federal district that includes the national capital (Brasília). This pattern, coupled with the clusters observed in Minas Gerais state (South East region) may suggest a trend of westward expansion of SYF, which may increase the risk of re-urbanization as disease flows toward densely populated areas where the urban mosquito vector is abundant. This same pattern occurred during the mid-1940s,[13] and may reflect the migration routes of human populations towards the more populated coastal region. The detection of virus circulation in the South East region in 2008[19] reinforces concerns about the spread of yellow fever to the coast.[13]

The only possible defense against SYF outbreaks is the vaccination of exposed individuals. The expansion of Brazilian agriculture into native forest and savannah is an important factor that increases human exposure to the virus. The decrease in forest coverage can trigger spread of the vectors of SYF to peri-urban and rural areas, thus increasing the chance of human transmission of the disease.[20] Taken together with previous studies,[3,6] our findings show a recurrent demographic pattern of SYF. Despite the massive vaccination policy carried out by the Ministry of Health, the available data suggest that migrant laborers, farm workers and tourists are at greater risk and therefore should be specially targeted by vaccination campaigns.

Acknowledgements: We thank Gualberto dos Santos for providing access to the data used in this work and Professor Andrew Macrae for critical review of the text.

Authors' contributions: FPC conceived the study; ALBG and LMF compiled the data; ALBG, FP and LMFC analyzed the data; FPC and LMFC wrote the manuscript. FPC is guarantor of the paper.

Funding: MS/SUS/CNPq/UNESCO [process no. 501553/2003-7].

Competing interests: None declared.

Ethical approval: Not required.

References

1 Barrett AD, Higgs S. Yellow fever: a disease that has yet to be conquered. Annu Rev Entomol 2007;52:209–29.

2 Gomes AC, Torres MAN, de Paula MB et al. Ecologia de *Haemagogus* e *Sabethes* (Diptera: Culicidae) em áreas epizoóticas do vírus da febre amarela, Rio Grande do Sul, Brasil. Epidemiol Serv Saud 2010;19:101–13.

3 Prata A. Yellow fever. Mem Inst Oswaldo Cruz 2000;95:183–87.

4 Jentes ES, Poumerol G, Gershman MD et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. Lancet Infect Dis 2011;11:622–32.

5 Câmara FP, Gomes ALBB, Carvalho LMF et al. Dynamic behavior of sylvatic yellow fever in Brazil (1954-2008). Rev Soc Bra Med Trop 2011;44:297–99.

6 Costa ZG, Romano AP, Elkhoury AN et al. Evolução histórica da vigilância epidemiológica e do controle da febre amarela no Brasil. Rev Pan-Amaz Saude 2011;2:11–26.

7 Tuboi SH, Costa ZG, Vasconcelos PF et al. Clinical and epidemiological characteristics of yellow fever in Brazil: analysis of reported cases 1998-2002. Trans R Soc Trop Med Hyg 2007;101:169–75.

8 Vasconcelos PF. Yellow fever in Brazil: thoughts and hypotheses on the emergence in previously free areas. Rev Saud Pub 2010; 44:1144–9.

9 Franco O. História da Febre Amarela no Brasil. Rio de Janeiro (Guanabara): Ministério da Saúde, Departamento de Endemias Rurais, 1969.

10 Adams B, Kapan DD. Man bites mosquito: understanding the contribution of human movement to vector-borne disease dynamics. PLoS One 2009; 4:e6763.

11 Codeço CT, Luz PM, Struchiner CJ. Risk assessment of yellow fever urbanization in Rio de Janeiro, Brazil. Trans R Soc Trop Med Hyg 2004;98:702–10.

12 Pedroso ER, Rocha MOC. Infecções emergentes e reemergentes. Rev Med Minas Gerais 2009;19:140–50.

13 Câmara FP, Theophilo RL, dos Santos GT et al. Regional and dynamics characteristics of dengue in Brazil: a retrospective study. Rev Soc Bras Med Trop 2007;40:192–96.

14 Câmara FP, Gomes AF, dos Santos GT et al. Climate and dengue epidemics in state of Rio de Janeiro. Rev Soc Bras Med Trop 2009;42:137–40.

15 Hill DR. Mapping the risk of yellow fever infection. Curr Infect Dis Rep 2012;14:246–55.

16 Centers for Disease Control. Brazil yellow fever vaccination map. Atlanta: CDC; 2012. http://wwwnc.cdc.gov/travel/pdf/yellow-fever-vacc-brazil.pdf [accessed 22 November 2012].

17 Anderson RM, May RM. Infectious Disease in Humans: Dynamics and Control. 2nd ed. London: Oxford University Press; 1991.

18 Instituto Brasileiro de Geografia e Estatística (IBGE). 2010 Population Census. http://www.ibge.gov.br/cidadesat [accessed 5 July 2012].

19 Moreno ES, Rocco IM, Bergo ES et al. Reemergence of yellow fever: detection of transmission in the State of São Paulo, Brazil, 2008. Rev Soc Bras Med Trop 2011;44:290–6.

20 Monath TP. Yellow fever. In: Monath TP, editor. The Arboviruses: Epidemiology and Ecology, Vol. 5. Boca Raton, FL: CRC Press; 1989. pp. 139–231.