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

Fernando Portela Câmara[1], Luiz Max de Carvalho[1], Ana Luisa Bacellar Gomes[2].

1- Sector for Infectious Diseases Epidemiology, Institute of Microbiology, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil.

2- Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro (UERJ).

SUMMARY

Background

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

Methods

Data were statistically analyzed and were also georeferenced 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, of approximately 30 years old, living in rural areas of the states of Pará, Goiás, Maranhão, and Minas Gerais, who were unvaccinated or with vaccination out of date. The disease showed a high mortality rate (51%, 421/832) amongst the notified cases, with death occurring on around the seventh day for most patients. The R0 for SYF was estimated as approximately 2.4.

Conclusion

The results of this study suggested that the lack of vaccination coverage as major risk factor, many of which are migrant labourers, farm workers and tourists.

Keywords: Sylvatic yellow fever, yellow fever vaccine, demographic profile.

INTRODUCTION

Yellow fever is an acute infectious disease whose etiologic agent is an arbovirus of the family *Flaviviridae*, genus *Flavivirus*, transmitted by mosquito vectors of the genera *Aedes*, *Haemagogus* and *Sabethes*[1,2]. Epidemiologically, it exists in two forms: sylvatic yellow fever (SYF) through a cycle involving nonhuman primates and vectors of the genus *Sabethes* and *Haemagogus*; and urban yellow fever, through a cycle sustained by the human host and *Aedes aegypti* mosquitoes, adapted to the urban ecology[3]. In Brazil, only the first epidemiological form has been detected in recent years[4]. Câmara et al (2011)[5] detected a major cycle of seven years of human SYF in the Midwest region of

51 the country, where most of the cases occur, and a fourteen years cycle in the
52 North region, dominated by the Amazon ecology, with the lowest demographic
53 density of the country.

54 SYF is active in the rainforests of Africa and the Americas, occupying
55 much of the Brazilian territory causing sporadic outbreaks in the Midwest,
56 Southeast, with recent increase in cases in the states of Pará, Goiás, Maranhão
57 and Minas Gerais[4]. The outbreaks are small in magnitude, with very high
58 mortality among the notified cases[4]. However, total mortality is not known
59 because most of cases probably evolve as a fever without complications. In the
60 past, the total mortality in urban outbreaks was low, with high rates occurring
61 just in non-brazilian caucasians (Câmara, FP, in preparation). Yellow fever has
62 an incubation period of three to six days after the bite of the infected mosquito
63 vector and the initial symptoms (infectious stage) are similar to that of dengue.
64 Part of the patients heal spontaneously after this phase, however, the other part
65 suffers, after a brief improvement, a second peak of fever with serious
66 haemorrhagic phenomena and visceral damages, that are often fatal (toxemic
67 phase). The classical picture of yellow fever in humans includes severe
68 hepatitis, jaundice, hematemesis ("black vomit"), renal failure, and sometimes
69 encephalitis, on a background of muco-cutaneous bleeding.

70 Surveillance of human cases in Brazil is based on compulsory notification
71 (24h), and case confirmation has to be done in maximum 60 days. This
72 surveillance is based on the case definition adopted by the Ministry of Health of
73 Brazil, according to the recommendations by the Pan American Health
74 Organization (PAHO), but which is wider, in order to improve the power of
75 detection of the surveillance system[6]. This case definition is described in detail

in Tsuboi et al (2007)[7] and references therein. However olygossymptomatic cases are prone not to be attributed to YF, due to the sparse nature of YF outbreak occurrence and reporting[6].

Reemergence of YF in areas where the virus has been eradicated has caused severe preoccupation. In 2008 and 2009 outbreaks emerged in São Paulo and Rio Grande do Sul years after the last report yellow fever in these areas[7]. In these municipalities human cases and epizootics in monkey were reported. These facts point to urgent control measures to avoid the spread of YF to the Brazilian coast[8].

The purpose of this study was to describe and analyze the demographic profile of cases of SYF in Brazil between 1973 and 2008, aiming to define possible risk factors in the exposed population. Surveillance of SYF is a priority, given the construction of dams and highways, expansion of agribusiness, mining and the increase in ecotourism into endemic areas in Brazil, with the risk of reemergence of this disease[9,10,11,12], since *A. aegypti* infests almost all urban areas of the country[13,14].

METHODOLOGY

Data were obtained from the Ministry of Health of Brazil from the Ministry of Health of B razil (MS/FNS/DEOPE/CCDTV/GT-FAD), covering the period from 1973 to 2008. Data handling carried out using a Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheet in the categories of each 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 those which had insufficient information were

excluded from posterior analysis. Statistical analyses were performed using the Minitab package version 16 (Minitab Inc., State College, PA, USA).

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

To gain an insight into the dynamical characteristics of SYF we calculated the basic reproductive number of infections, R_0. This parameter was estimated using the approximation proposed by Anderson & May (1991)[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 exposed population had a square age distribution due its relative small sizes and homogeneous life pattern.

RESULTS

We analyzed 831 cases in total, most of which concentrated in the states of Pará and Goiás, followed by the respective border states of Maranhão and Minas Gerais. Figure 1 shows the geographic distribution of the 826 cases that allowed for georeferencing. Most of the cases were concentrated in Midwest and Southeast regions, where the largest outbreaks of the recent years occurred. Noticeably, there were two well-defined clusters within Minas Gerais state, which is within the boundaries of the endemic region.

With regard to vaccination status, 52% (432/832) of the reported cases were from individuals who had been vaccinated more than 10 years earlier, 3% (27/832) less than 10 years, and 45% (372/832) did not declare their immunization status. Most cases belonged to the age group 10-40 years, with

peak between 20 and 30 years. The range of ages studied was 0-75 years with a mean of 30.5 years and standard deviation of 15.2 years. 80% (660/832) of yellow fever cases were males. Table I shows the demographic data of cases. The average life expectancy for these regions is 73.2 years (Midwest, 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 cases was 51% (420/832), being more frequent in males compared to females (X^2 = 23:19 p <0.001). The median time between symptom onset and death was 7 days, with 86% (661/832) occurrences in the first 10 days.

DISCUSSION

Although all cases were virologically confirmed, a clinical profile could not be determined due the lack of data on symptoms. On the other hand, as the demographic data on the cases are well-documented, it is possible to make indirect inferences about risks. Missing data on occupation and vaccination status was high (Table 1), but did not preclude overall conclusions. The possibility of bias must be acknowledged and may be due to the fact that information on the cases were collected from fully symptomatic persons according to the case definition adopted by the YF surveillance[6]. Oligosymptomatic cases are poorly detected because the surveillance system focuses on outbreak detection[6].

Only a small proportion of cases (3%) were from patients with an in-date vaccine, and the remainder either did not inform or their vaccine was out-of-date. 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 38 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 reurbanization of this arbovirus.

The risk group showed a typical profile, as observed in other surveys[3,6,8] the majority (80%, 660/832) was of young adult males, with approximately 30 years old, unvaccinated, living in transition areas at the North and Midwest 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 higher risk of exposure to infection.

The death rate was high among the reported cases, around 51% (421/832), mostly on the seventh day of illness. This suggests the circulation of very virulent viral strains in South American tropical ecosystem. This death rate also requires early medical intervention, which is problematic since the onset of symptoms of yellow fever can be confounded with other common infections in the region, and also the time lapse between confirmation of SYF and death is very small. On the other hand, the R_0 of approximately to 2.4 is sufficient to efficient spreading of the disease.

By plotting the geographic coordinates of the georeferenced cases we could notice a high intensity of cases (points, see Fig. 1) in the Midwest region, especially in Goiás state, that bears the federal district and the national capital (Brasília). This pattern, coupled with the clusters observed in the Minas Gerais state (Southeast region) may suggest a trend of westward expansion of SYF, which may increase the risk of reurbanization as disease flows toward densely

176 populated areas where the urban mosquito vector is abundant. It is worth noting
177 that this same pattern occurred during the mid 1940's[13], and may reflect the
178 migration routes of human populations towards the more populated coastal
179 region. Detection of virus circulation in the Southeast region in 2008[19] reinforces
180 the concerns about the expansion of YF to the coast[13].
181
182 The only possible defense against SYF outbreaks is the vaccination of
183 exposed individuals. The expansion of Brazilian agriculture into native forest
184 and savannah is an important factor which increases human exposure to the
185 virus. The decrease in forest coverage can lead the expansion of the vectors of
186 SYF to peri-urban and rural areas, thus increasing the chance of human
187 transmission of the disease[20]. Taken together with previous studies[3, 6], our
188 findings show a recurrent demographic pattern of SYF. Despite the massive
189 vaccination policy carried out by the Ministry of Health, the available data
190 suggest that migrant labourers, farm workers and tourists are at greater risk and
191 thus should be specially targeted by vaccination campaigns.
192
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198 Author contributions: conceived the study: FPC; compiled the data: ALBG, LMF;
199 analyzed the data: ALBG ,FPC, LMFC; wrote the manuscript: FPC,LMFC.
200

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Table 1

Variable	Mean (SD)	Cases (%)
Age (years)	28.79 (14.78)	-
Death	-	421 (50.54)
Time from symptom onset to death (days)	7.81 (5.14)	-
Ocupation		
Handyman	-	273 (32.85)
Tourist	-	40 (4.81)
Housewife	-	33 (3.97)
Other		190 (22.86)
Missing		295 (35.49)
Vaccination Status		
Vaccinated	-	27 (3.24)
Non-Vaccinated	-	432 (51.98)
Ignored	-	58 (6.97)
Missing		314 (37.78)
Gender		
Males	-	660 (79.42)
Females	-	170 (20.45)
Ignored	-	1 (0.12)

Table. Summary statistics for 832 YF cases in the period 1973-2008.

Figure
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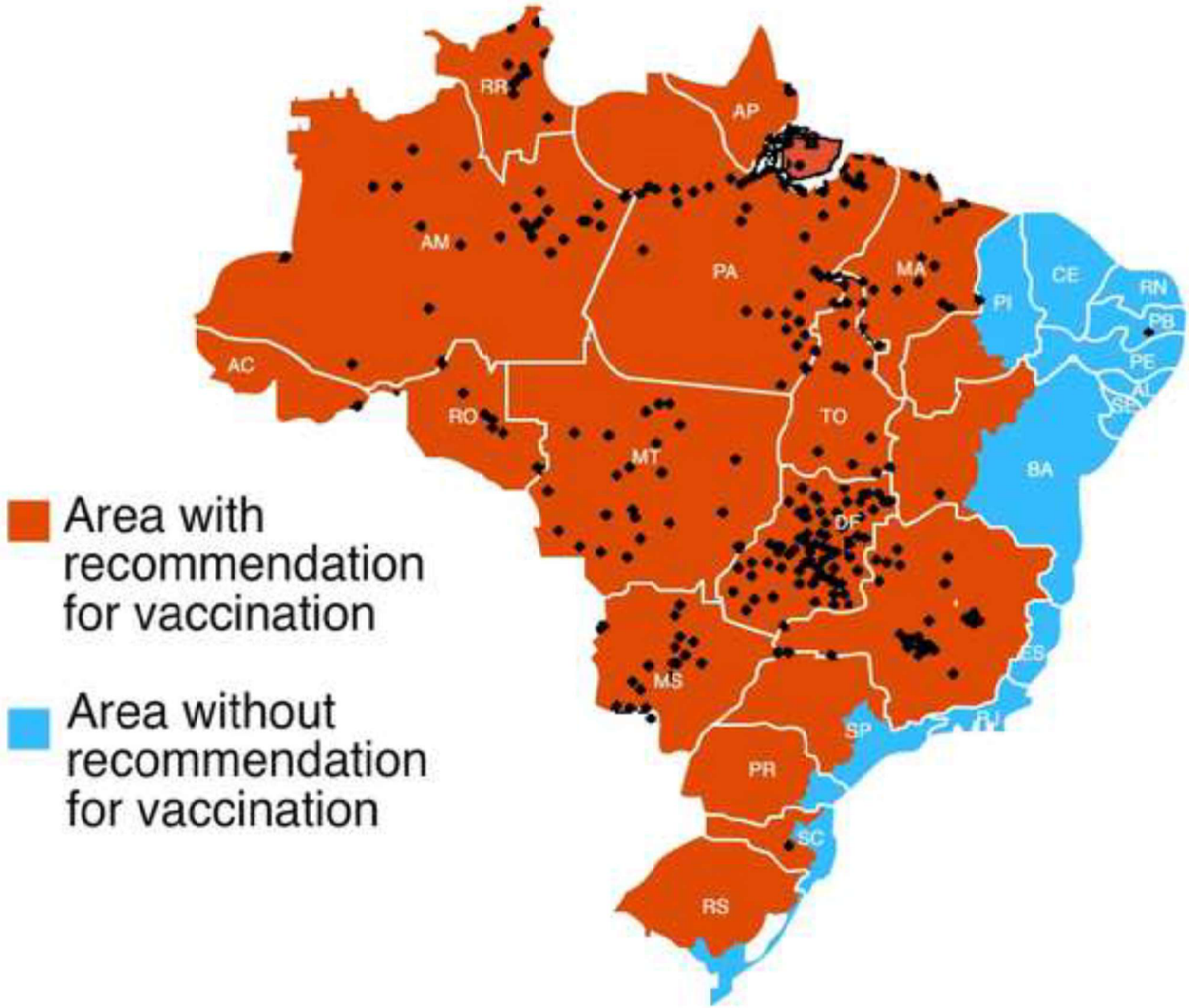

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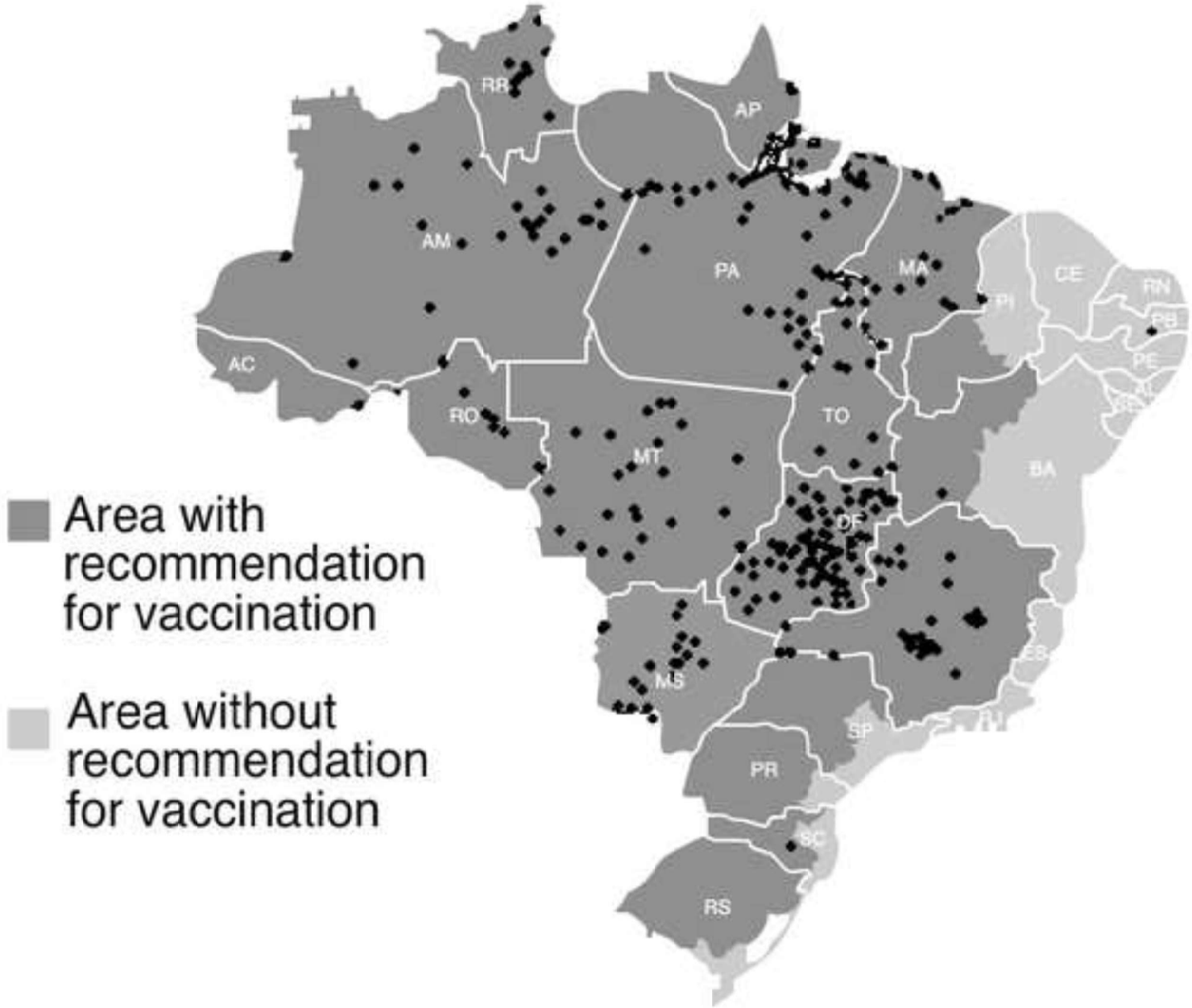

FIGURE 1. Distribution of notified cases of sylvatic yellow fever on the Brazilian territory from 1973 to 2008. Colors depict the areas with and without recommendation for vaccination, based on Hill, DR (2012)[15] and the recommendation of the Centers for Disease Control (CDC, 2012)[16], available at http://wwwnc.cdc.gov/travel/pdf/yellow-fever-vacc-brazil.pdf. Points show the localization of the 826 cases that allowed for georreferencing, at the municipality level.