Urbanisation of yellow fever in Santa Cr uz, Bolivia

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Summary

Background Reinvasion by *Aedes aegypti* of cities in the Americas poses a threat of urbanisation of yellow fever. After detection of yellow-fever infection in a resident of the city of Santa Cruz, Bolivia, in December, 1997, we investigated all subsequent suspected cases.

Methods We introduced active surveillance of yellow fever in the Santa Cruz area. Hospitals and selected urban and rural health centres reported all suspected cases. Patients were serologically screened for yellow fever, dengue, hepatitis A and B, and leptospirosis. We collected clinical and epidemiological information from patients' records and through interviews. We also carried out a population-based serosurvey in the neighbourhood of one case.

Findings Between December, 1997, and June, 1998, symptomatic yellow-fever infection was confirmed in six residents of Santa Cruz, five of whom died. Five lived in the southern sector of the city. Two had not left the city during the incubation period, and one had visited only an area in which sylvatic transmission was deemed impossible. Of the 281 people covered in the serosurvey 16 (6%) were positive for IgM antibody to yellow fever. Among five people for whom this result could not be explained by recent vaccination, there were two pairs of neighbours.

Interpretation Urban transmission of yellow fever in Santa Cruz was limited in space and time. Low yellow-fever immunisation coverage and high infestation with *A aegypti* in the city, and the existence of endemic areas in the region present a risk for future urban outbreaks. We recommend immediate large-scale immunisation of the urban population, as well as tightened surveillance and appropriate vector control.

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See Commentary page 1541

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Introduction

Urban yellow fever has not been reported from the Americas since 1954, but jungle yellow fever transmitted by *Haemagogus* vectors increasingly affects forest dwellers in Bolivia, Brazil, Columbia, Ecuador, and Peru, and periodically causes small outbreaks.[1–3] The reinvasion of South America by *Aedes aegypti* after relaxation of the eradication programme in the 1970s, and presence of *A aegypti* in cities near areas in which sylvatic yellow fever is endemic, poses a threat of urbanisation of yellow-fever transmission.[1,4]

In 1980, *A aegypti* reappeared in Santa Cruz de la Sierra, a city situated in the tropical lowland areas of Bolivia,[5] and was implicated in epidemics of dengue fever in 1987–88[6] and 1996–97.[7] Jungle yellow fever is endemic in many focal areas of the region around Santa Cruz. During the yellow-fever epidemic in 1981–82,[8] there was a small sylvatic focus less than 10 km from the city.[9] In response to this outbreak, a massive immunisation campaign was launched.

In 1991, a serosurvey in Santa Cruz de la Sierra estimated the proportion of urban residents with protective antibodies against yellow fever, mainly reflecting past immunisations, at 34% (F Balderrama, personal communication) and occasional immunisation efforts between 1991 and 1997 did not specifically target the urban population. In March, 1997, a random serosurvey was carried out in a unidad vecinal (neighbourhood) of the city to estimate dengue attack rates and coverage of yellow-fever vaccination.[7] Only 102 (41%) of 248 adults and six (3%) of 195 children aged between 5 years and 7 years had protective antibodies against yellow fever.

Bolivia has difficulties in financing the purchase of yellow-fever vaccines to protect the at-risk population. With the assistance of the Pan American Health Organization and partial financial support from the World Bank, the Bolivian Ministry of Health decided, at the end of 1998, to include the yellow-fever antigen in the Expanded Programme on Immunization,[10] but this decision is yet to be implemented.

In December, 1997, the laboratories of the Centro Nacional de Enfermedades Tropicales (CENETROP) confirmed yellow-fever infection in an urban resident. In response, we started active surveillance of yellow fever in the city and the surrounding endemic areas and investigated all reported suspected cases.

Methods

In 1998, the total population of the Santa Cruz region was 1 721 332, of which the city of Santa Cruz de la Sierra accounted for 891 287 inhabitants. The city is divided in 246 neighbourhoods, which vary in population size (3000–10 000 inhabitants). The mean population density of the town is 2903 inhabitants per km^2.

Until December, 1997, the Ministry of Health relied on passive surveillance and confirmation of suspected deaths by liver necropsy for the notification of yellow-fever cases. In January, 1998, after detection of yellow-fever infection in an

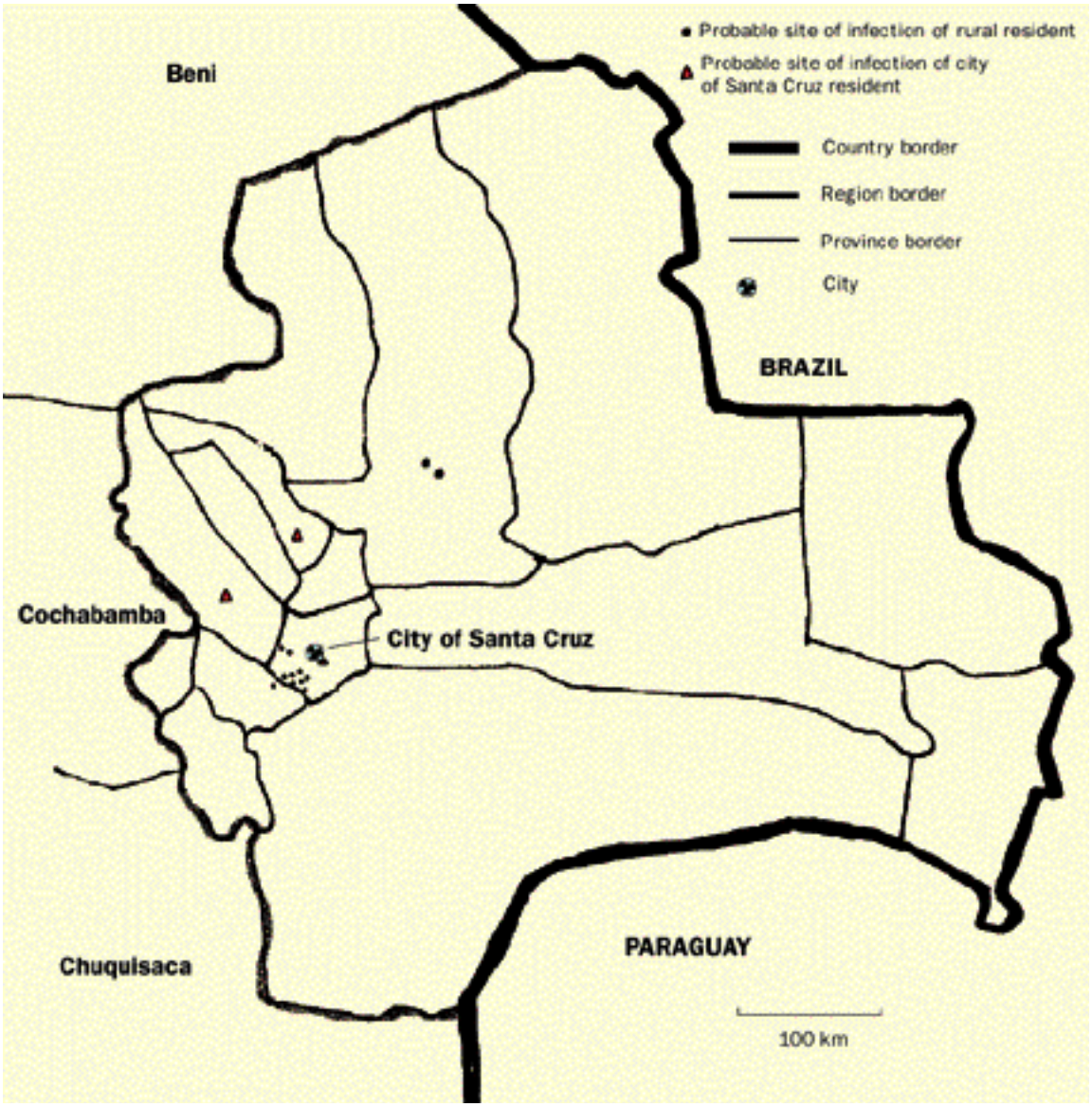

Figure 1: **Region of Santa Cruz and probably site of infection of 18 confirmed cases of yellow fever between July 1, 1997, and Dec 12, 1998**

urban resident, we introduced active surveillance and serological confirmation in the Santa Cruz area. We launched an information campaign to raise awareness among medical staff working in the city hospitals, in selected urban health centres, and in the health centres of the surrounding endemic areas and they agreed to report immediately each suspected case of yellow fever. Suspected cases were defined as temperature of 38°C or higher with jaundice, haemorrhagic symptoms, oliguria, albuminuria, or a fatal outcome. We visited health facilities periodically, and direct telephone links were set up with the virology and epidemiology units of CENETROP.

5 mL venous blood samples were taken from all suspected cases on the day of notification. Samples were analysed on the same day in the CENETROP laboratory. Serum samples were tested for IgM antibody by a previously described antibody capture ELISA.[11] All serum samples taken from patients and human control samples that were negative for IgM antibody to yellow fever, from the US Naval Medical Research Institute Detachment's diagnostic testing reference serum collection, were tested at a dilution of 1 in 100. Serum samples with corrected absorbance values higher than the reference cut-off value, estimated for each assay as the mean absorbance of two antibody-negative serum samples plus three SD, were taken to

	1	2	3	4	5	6
Date of onset of symptoms*	Dec 19, 1997	Jan 11, 1998	Jan 26, 1998	Feb 3, 1998	March 2, 1998	June 17, 1998
Neighbourhood of residence	183	160	160	128	183	30
Outcome	Survived	Died	Died	Died	Died	Died
Age (years)	10	4	26	23	22	58
Sex	Male	Male	Male	Male	Male	Male
Ever vaccinated against yellow fever	No	Reportedly	No	No	No	Reportedly
Left the city†	Yes	Yes	Yes	Yes	No	No
Classification of area visited	B	C	A	A	None	None

A=sylvatic yellow fever ever reported in past 20 years; B=sylvatic transmission deemed possible because of entomological and ecological characteristics; C=sylvatic transmission seemed impossible.
*First (possbily atypical) symptoms: fever, malaise, headache, nausea, myalgia. †During 10 days before onset of first symptoms.

Epidemiological findings in six confirmed yellow-fever cases resident in Santa Cruz de la Sierra

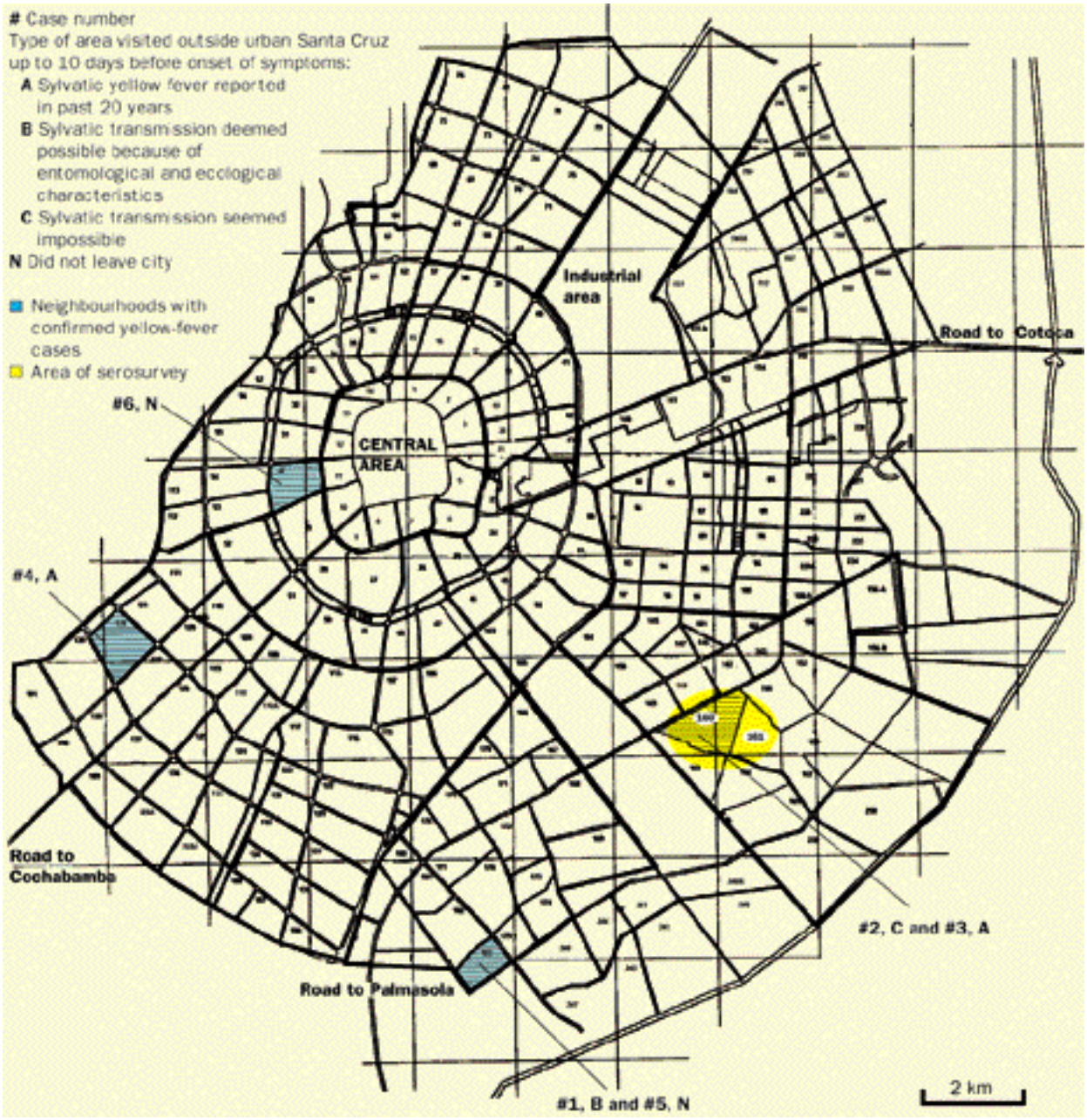

Figure 2: **Neighbourhoods of residence in Santa Cruz and exposure to sylvatic transmission of confirmed yellow-fever cases**

be antibody positive. All samples were also screened for dengue (with the IgM MAC ELISA technique), hepatitis B surface antigen (ETI-MAK–3, Diasorin, Saluggia, Italy), leptospirosis (IgM ELISA, Pan Bio, Brisbane, Australia), and, in children, hepatitis A (ETI-HA-IgMK–2, Diasorin). Confirmed cases of yellow fever were defined, according to the WHO case definition,[12] as clinically suspected cases with positive yellow-fever IgM results, virus isolation, or both.

We collected clinical and epidemiological information from patients' records and through interviews with the physicians in charge and family members. We recorded atypical onset signs and symptoms (malaise, headache, nausea, and myalgia), symptoms included in the case definition, and yellow-fever vaccination status. Journeys outside the urban area of Santa Cruz during the maximum incubation period (10 days before the onset of first symptoms) were investigated. Areas visited were investigated by the chief entomologist (JC) and classified as A (cases of sylvatic yellow fever reported in human beings in the past 20 years), B (sylvatic yellow-fever transmission deemed possible because of entomological and ecological characteristics of the site), or C (sylvatic transmission seemed impossible).

Between March 13 and 17, 1998, 2 months after the first case of yellow fever was confirmed in neighbourhood 160, we carried out a serosurvey in an area of about 1000 m around the house in which the case lived. We visited 50% of houses in the area. After obtaining informed consent, we recorded the yellow-fever vaccination status of all present residents and collected two drops of capillary blood on Whatman number 1 filter paper. All unimmunised inhabitants of the neighbourhood were offered yellow-fever vaccination. Filter papers were dried and stored at 4°C until processing. Within 1 month a circle of 1 cm diameter cut out of the filter paper was resuspended overnight in 1 mL phosphate-buffered saline. Serological analyses were done first in the CENETROP laboratory, with the techniques described above. These analyses were repeated in CDC Puerto Rico, following procedures described by Innis and colleagues,[13] and in the case of discordance, we used the Puerto Rico result.

People were classified as recently infected if they had a positive yellow-fever IgM antibody result without evidence of cross-reaction with dengue antigens and did not report yellow-fever vaccination in the previous 2 years.

Results

Between July 1, and Dec 31, 1997, two suspected cases of yellow fever were reported to the Santa Cruz health authorities. The first, a clinical suspect in whom no laboratory tests were done, was reported after he died on Dec 20. This man lived in a area in which yellow fever was endemic and had been referred to a hospital in Santa Cruz, possibly in the viraemic phase. The second case, a boy aged 10 years, was reported on Dec 30. He presented with fever, jaundice, thrombocytopenia, and haemorrhagic symptoms. He had a positive yellow-fever IgM antibody result at CENETROP on Dec 31 (case one, table). After this case was confirmed, we started active surveillance.

Between Jan 1 and Dec 31, 1998, under active surveillance, 51 suspected cases living in the Santa Cruz region were investigated. Yellow-fever IgM antibodies were detected in 16 (31%) of these cases. In two of the 16, permission for necropsy was granted and histopathology of liver tissue was compatible with yellow fever. Attempts at virus isolation in four cases were negative, but blood samples were taken 4 days after onset of symptoms (end of the viraemic phase).

11 of the 16 cases lived in areas with known sylvatic transmission, one as close as 15 km to the southern edge of town (figure 1). Five were urban residents (cases two to six, table) and all presented with a temperature of 38°C or higher, jaundice, and haemorrhagic symptoms, and the overall course of illness was compatible with yellow fever; all died. Hepatitis A, hepatitis B, and leptospirosis serology were negative in all cases. Cross-reaction with dengue antigens was found in case six only. Apart from the listed symptoms, this patient had also myalgia and arthralgia, hypotension, a packed-cell volume of 51%, thrombocytopenia, and a leucocyte count of 7300 per μL, but no albuminuria. He died 7 days after the onset of symptoms. Reportedly, he had been vaccinated against yellow fever 6 months to 1 year before his illness. The pattern of reaction with dengue and yellow-fever antigen, respectively, made yellow fever the most likely diagnosis.

The epidemiological findings in the six confirmed cases of yellow fever are summarised in the table. Five cases lived in peripheral neighbourhoods in the southern sector of Santa Cruz (figure 2) and one in a neighbourhood near the centre of the city. The more peripheral neighbourhoods of Santa Cruz de la Sierra are the most recently urbanised and have a population density around 6000 inhabitants per km^2, which is lower than that of central neighbourhoods, in which there are fewer green areas. The distance between houses of cases originating from the same neighbourhood was less than 800 m. For two cases, journeys had been made into areas endemic for yellow fever (class A areas) within the 10 days before the onset of symptoms. Two other cases each visited different class B or C areas close to Santa Cruz City. Cases five and six had not left town and the urban area was, therefore, the only plausible site of infection.

All of the 281 people covered by the seroepidemiological survey around the house of case two were in good health, but 16 (6%) were positive for yellow-fever IgM antibody, which suggested recent infection with yellow fever or vaccination less than 2 years earlier. Ten of the 16 had reportedly been vaccinated in the preceding 2 months, one about 1 year, and one more than 4 years before the survey, and four had never been vaccinated. Among the five people with yellow-fever IgM antibodies that could not be explained by vaccination, there were two pairs of neighbours. The distance between the pairs was less than 500 m.

Discussion

Haemorrhagic dengue fever cannot be completely excluded in case six, but all other results point directly towards urban yellow-fever transmission in Santa Cruz. Five of the six confirmed cases of yellow fever occurred within 4 months of each other in the southern sector of the city, with no likelihood of sylvatic transmission in three cases, and evidence of recent symptomless yellow-fever infection in five of 281 people in the serosurvey. The plausibility of urban yellow-fever transmission is further strengthened by the low immunisation coverage of the urban population and by the finding that 33% of the city compounds sampled in January, 1998, were infested with *A aegypti* (Ministry of Health, unpublished data).

Judging from the distribution of clinical cases, yellow-fever transmission was limited in space and time. Only one case was reported outside the southern sector of the city. The peak incidence (December to April) matches the maximum density of *A aegypti* in the city and correlates with yellow-fever transmission in the surrounding endemic areas of the province,[8] in which, excluding the epidemic in 1990–91, an average of five clinically suspected cases have been reported yearly in the past decade (Ministry of Health unpublished data). The apparently limited geographical spread in the city is compatible with the reported absence, for reasons not well understood,[1,4] of current urban yellow-fever transmission in the Americas, and with the historically documented short duration (18 days when half of the population was immune) of previous urban epidemics of yellow fever.[1] Emergency vaccination of urban residents living close to yellow-fever cases and intensified vector control in the neighbourhood may also have contributed to limiting the propagation of the virus.

Cases were detected less than 10 km from Santa Cruz during the 1981–82 epidemic.[9] The more intensive surveillance in our study could, therefore, have enabled the identification of urban cases during the present epidemic (although under-reporting is still probable), and suggests that in-depth entomological studies would provide definite proof of *A aegypti* involvement in transmission. Nevertheless, the potential for a large urban yellow-fever outbreak in Santa Cruz remains beyond doubt. The vector, as shown by a dengue epidemic in 1998,[7] is present in abundance, immunity in the population is low, and journeys to nearby endemic areas are frequent. Our results show that the threat of urbanisation of yellow fever in the Americas is less hypothetical than in some forecasts,[1,4,14,15] and that urgent intervention is needed.

In early 1999, a new outbreak of 98 cases of yellow fever occurred in two rural provinces of the region, and led to 21 deaths.[10,16,17] The response to the outbreak was delayed and, because of lack of vaccines, largely confined to the affected areas. The limited impact of such strategies has long been recognised.[1,4,18] Despite the risk of urbanisation and international calls by the health

authorities for vaccine donation, the planned campaign of mass yellow-fever vaccination in Santa Cruz city has not yet been possible. Between January, 1998, and April, 1999, less than 150 000 doses of vaccine were dispensed in the urban area; extrapolation from 1997 immunisation coverage data suggests a need for a minimum of 600 000 doses. The population most at risk should be targeted first, encompassing those living in peripheral neighbourhoods of the town, especially migrants and people born after the 1982 emergency mass vaccination campaign (the Santa Cruz population has increased by 230% since then).

Our recommendations for future actions are two-fold. First, the Ministry of Health's decision to include yellow-fever vaccine in the Bolivian Expanded Programme on Immunization, a strategy advocated by WHO should be implemented without further delay.[12,19] This approach would lead to minimum increases in the per-dose cost of vaccines delivered.[20] Second, in agreement with the Yellow Fever Technical Consensus meeting recommendations,[19] and as well as tightened yellow-fever surveillance and continued vector control efforts,[16] a catch-up mass immunisation campaign of all the urban residents of Santa Cruz de la Sierra, should be started urgently.

Contributors

P Van der Stuyft, A Gianella, J Cespedes, V Vorndam, and M Boelaert initiated the study. A Gianella, M Pirard, J Cespedes, and C Peredo collected the data. The laboratory analyses were done by C Peredo, J L Pelegrino, and V Vorndam. All the authors participated in data analysis and interpretation. P Van der Stuyft, M Pirard, and M Boelaeert wrote the first draft of the manuscript and all the investigators had input to the later drafts.

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