Documentos

VIII International Colloquium on Invertebrate Pathology and Microbial Control

VI International Conference on Bacillus thuringiensis

35th Annual Meeting of the SIP

Foz do Iguassu, Brazil
18 - 23 August 2002

PROCEEDINGS

Society for Invertebrate Pathology

Embrapa

Universidade Estadual de Londrina

Foz do Iguassu, Brazil
2002
Yellow fever in South America

P.F.C. Vasconcelos

Who Collaborating Center for Reference and Research on Arbovirus, Department of Arbovirus of the Instituto Evandro Chagas/FUNASA, Av. Almirante Barroso, 492, 66090-000, Belém, PA, Brazil e-mail: pedrovasconcelos@iec.pa.gov.br

Yellow fever, the original viral hemorrhagic fever, is endemic in tropical regions of Africa and South America where the virus is maintained as a zoonotic infection, within complex cycles involving jungle mosquitoes and monkeys (Monath, 2001; Robertson et al., 1996; Vasconcelos et al., 1999). It is estimated that approximately 200,000 yellow fever infections occur annually, with several thousand deaths. But, the disease is grossly underreported and only about 5000 and 300 cases reported annually in Africa and South America, respectively (Monath, 2001).

Yellow fever virus is the prototype of the genus Flavivirus of the family Flaviviridae; it is a single-stranded RNA virus positive sense (Westaway et al., 1985). The virus genome contains a single open-reading frame with 10,233 nucleotides that encodes three structural (prM, C, and E) and seven non-structural (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5) proteins, and two short non-coding regions (3' and 5’ NCRs) (Rice et al., 1985; Hahn et al., 1987). Presently, seven yellow fever virus genotypes (five in Africa and two in South America) are recognized within a single serotype (Wang et al., 1996; Mutebi et al., 2001).

The diagnosis of yellow fever, is based on the clinical symptoms and plus at least detection of specific IgM antibodies in unvaccinated persons (Kuno et al., 1987), virus isolation in animals or cell cultures (Tesh, 1979; Tesh et al., 2001), detection of antigens by immunohistochemistry (Hall et al., 1991), and/or genome recovery by RT-PCR (Lanciotti et al., 1992).

Clinically, yellow fever occurring during an epidemic or in a patient having the classical signs of severe disease is relatively easy to diagnose. The problem is that only 10-20% of people developing yellow fever virus infection shows the classical signs of yellow fever. Abortive infections are difficult to recognize, except during epidemics when multiple cases alert physicians to its presence. In classical yellow fever, patients show a severe systemic illness with fever, headache, myalgia, Faget's sign, conjunctival congestion, flushing of neck and face, and other non specific symptoms/signs that can not be easily differentiated from other febrile illnesses.

The early phase of more severe forms shows similar symptoms/signs and is called the "period of infection". This phase lasts about three days. During this period, yellow fever virus can be detected in blood; therefore patients in this stage are infectious for mosquitoes. After this period, patients with abortive forms show rapid recovery, while those with severe forms have apparent improvement of symptoms that lasts several hours to one or two days and is known as "period of remission". This brief period is immediately followed by the "period of intoxication" that is characterized by low viremia or absence of it, return of high fever, and presence of jaundice, vomiting, epigastric pain, dehydration, hemorrhagic diathesis, prostration and renal failure. Other symptoms/signs commonly present at this stage include thrombocytopenia, albuminuria, tachycardia, hypotension, encephalopathic signs, and azotemia. The picture is easily recognized when, coffee-ground hematemesis, oligo-anuria and jaundice are evident. About 50% of these patients have a fatal outcome. Other intermediate more or less severe forms have also been described (Serié et al., 1968; Monath, 1988; Vasconcelos et al., 1997; Monath, 2001; Vasconcelos, 2000).
Yellow fever virus is transmitted in different cycles in Africa and South America. In Africa, a third or intermediate cycle has been recognized in addition to the urban and jungle cycles (Digoutte et al., 1995). In South America, only two cycles (urban and jungle) has been recognized until now. In Africa, the vectors are mosquito species of the genus Aedes; in South America, Haemagogus and Sabethes species are responsible for the jungle cycle transmission (Monath, 1988).

The recent increases in distribution and density of Aedes aegypti in urban areas of the Americas with resulting epidemics of dengue fever and dengue hemorrhagic fever, brings again the concern of the re-urbanization of yellow fever (Mondet et al., 1996; Vasconcelos et al., 1999; Travassos da Rosa et al., 2000). It is worthy of note that the last urban epidemic in the Americas occurred in Rio de Janeiro in 1929-30, and the last case was reported in Port-of-Spain (Caribbean region) in 1954 (Nobre et al., 1994; Dégallier et al., 1996; Vasconcelos et al., 1999).

In South America, in the last two decades, yellow fever has been reported in Bolivia, Brazil, Colombia, Ecuador, French Guyana (a single fatal case reported in 1998), Peru and Venezuela (Figure 1), and excepting for a few urban cases reported in Bolivia (Van der Stuyft et al., 1999), all of them were of jungle yellow fever. However, more than 93% of the total have been reported by three countries: Bolivia, Brazil and Peru. While Bolivia reported about 20% and Brazil almost 18%, Peru reported more than 50% of all cases on the continent (Figure 2). The case-fatality rate was high, reaching 49.6%, and clearly represents an underestimate, since almost all reported cases were due to classical yellow fever, and in general was diagnosed after the patient’s hospitalization. Only exceptionally is the case-fatality rate in sylvan cases under 30%, which was observed in Brazil in 1993 and 1994 (Figure 3) (Vasconcelos et al., 1997; Vasconcelos et al., 1999). The overall case-fatality rate ranges from 33.3% in Venezuela through 79% in Colombia (Figure 4).

Yellow fever, in South America, is transmitted mainly in Amazon, Araguaia-Tocantins and Orinoco basins, especially by Haemagogus janthinomys; but other Haemagogus and Sabethes species have also been recognized to be potential vectors of yellow fever virus in the region (Monath, 1988; Monath, 2001; Vasconcelos et al., 2001b).

The coastal zone of South America, the most populated area, is in general yellow fever free, but the presence of Aedes aegypti, sometimes in increased indexes is noteworthy. The
**FIG. 2.** Frequency of yellow fever by country in South America, 1980-2002 (figures for March).
Source: PAHO/WHO.

**FIG. 3.** Yellow fever reported cases, deaths, and case-fatality rate in Brazil, 1982-2002 (figures for March).
Source: CENP/ES/FUNASA/MS

**FIG. 4.** Yellow fever cases, deaths and case-fatality rate by country in South America, 1985-2002 (figures for March).
Source: PAHO/WHO.
reintroduction of this mosquito species has increased the risk of urban yellow fever, especially in the last five years when an increased reemergence of virus transmission was observed in the continent, mainly in Brazil. This country, like several others in South America, has an extensive Amazonian forest region in which jungle yellow fever is endemic and a coastal zone in which yellow fever does not currently occur (Robertson et al., 1996; Vasconcelos et al., 1997). The boundary between these two zones designated as pre-Amazon forest, and intermediate savanna and gallery forests may be affected by periodic expansions in epizootic activity (Mondet et al., 1996; Vasconcelos et al., 2001 b).

In Brazil, the endemic area includes 12 states in the western two-thirds of the country inhabited by 29.3 million people. Beginning in the first quarter of 1998 and continuing to 2001, one of the largest epizootics in history has occurred, leading to the occurrence of 236 registered human cases of jungle yellow fever; 105 of them or 44.5% had a fatal outcome (Vasconcelos et al., 2001a; Vasconcelos et al., 2001b). The epizootic has expanded beyond traditional boundaries of the endemic zone, to involve the western regions of the states of Minas Gerais, São Paulo, Bahia, Paraná, Santa Catarina and Rio Grande do Sul States (Vasconcelos et al., 2001b; Vasconcelos et al., 2002-in press). About 20 million persons inhabit this transitional epizootic region. The remaining receptive, non-endemic coastal zone includes 15 states and is inhabited by 126.3 million persons (Costa et al., 2002).

Considering the annual disease occurrence of yellow fever and actual figures of Aedes aegypti indexes in the South America, the risk of re-urbanization raises the question of massive use of yellow fever vaccine to prevent it. Thus, in the last four years (1998-2001), Brazil has used more than 60 million doses of the 17DD vaccine especially in endemic and transitional yellow fever zones (Figure 5). This massive use, resulted in the appearance of several serious adverse events, including deaths due the vaccine (Vasconcelos et al., 2001c; Galler et al., 2001). In consequence, Brazilian authorities reviewed the policy for vaccine utilization and yellow fever vaccination is now only recommended to people living in the high risk areas (endemic and transitional zones), and for those that are travelling or will travel to these areas, focusing on tourists, agricultural workers, and migrants, the groups most affected by the disease (Vasconcelos et al., 2001b).
To conclude, we suggest that other South American countries establish national policies for the use of yellow fever vaccine. But, it is important to emphasize, that the most important step is trying to control the *Aedes aegypti* levels. This is the best way to avoid re-urbanization of yellow fever and to prevent the lost of many human lives.

References


