Yellow fever

Febre amarela

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http://dx.doi.org/10.1590/1806-9282.63.04.291

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Yellow fever is a potentially very serious disease, with high mortality, caused by a Flavivirus, which is a genus of the *Flaviviridae* family, inoculated in humans by arthropod vectors with two cycles of transmission: urban and sylvatic (jungle).[1] In Brazil, there is no record of urban transmission of the disease since 1942, but human cases in the sylvatic cycle do occur.[2]

Yellow fever is still relevant in countries on three continents: Africa, South America and Central America, with an annual estimate of 84,000 to 170,000 serious cases and about 29,000 to 60,000 deaths, according to the World Health Organization (WHO).

The peak transmission season in Brazil is between December and May, with epizootic cases having occurred in non-human primates in atypical periods in the last year.

Cases of sylvatic yellow fever were recorded in the states of Goiás, Mato Grosso do Sul, Pará, Tocantins, Distrito Federal, Minas Gerais and São Paulo. The Brazilian Ministry of Health issued an official document, Informative Note No. 02/2017, which regulated the expansion of the areas of obligatory vaccination coverage in the country, also vaccinating its inhabitants and visitors.

It should be noted that myths, misinformation and neglect about yellow fever have caused diffuse panic in several countries.[3]

Epidemiology

Two distinct cycles of disease transmission occur in endemic areas (sylvatic and urban), with symptoms indistinguishable from each other. In sylvatic-cycle infections, the vector species are necessarily of the *Haemagogus* and/or *Sabethes* genera, which normally inhabit the tree canopy, as well as the susceptible reservoir, non-human primates, and occasionally humans. In urban-cycle infections, the vector responsible for the transmission of the virus is of the *Aedes* genus, with *Aedes aegypti*, an insect extremely adapted to urban conditions, as the main disease transmitter. In this case, humans are the only susceptible reservoir. In terms of transmission potential, sylvatic-cycle vectors are more efficient than those of the urban cycle. This, combined with mass vaccination campaigns in the country, led to the last case of urban-cycle infection in Brazil occurring more than seven decades ago, precisely in 1942, in the state of Acre. It is worth remembering that epizootic (death of monkeys due to yellow fever) is a red flag to verify the circulation of yellow fever virus in the region, which, *per se*, can generate immediate action of the sanitary authorities to elaborate contingency plans for halting transmission to humans.

The sylvatic form of transmission does not occur so markedly in other endemic countries as it does in Brazil. This is particularly true for the African continent, where approximately a thousand cases occurred in 2016 with urban transmission, with the countries most affected, in descending order, being Angola, Democratic Republic of Congo, Ethiopia and Uganda (http://www.who.int/emergencies/yellow-fever/en/).

In Latin America, apart from Brazil, a recent outbreak struck Peru, which notified health authorities of more than twice as many cases of yellow fever as normal.

In Brazil, an increase in the number of cases of yellow fever started to be noticed at the end of 2016, extending from the summer of 2017 to the present, with more than 680 cases reported and a case fatality rate of 34% (monitoring of yellow fever cases and deaths – Report 37, Ministry of Health). As previously reported, all cases have sylvatic transmission. The most affected states are Minas Gerais and Espírito Santo, but São Paulo and Rio de Janeiro (which traditionally does not register cases of the disease) are also on the list.

The intensification of sylvatic transmission of yellow fever with increasing numbers of patients every 5 to 8 years is a known fact that can be explained by the increase

in the number of unvaccinated susceptible individuals who enter or live in endemic areas. This leads to the immediate call for action by health authorities in order to contain the disease's progress through blocking vaccination campaigns.

Immunization

In 1937, an attenuated virus vaccine, specific for yellow fever, was developed conferring lifelong immunity in up to 99% of those vaccinated. Max Theiler, of the Rockefeller Foundation, received in 1951 the Nobel Prize of Medicine for such discovery.[4] Since then, vaccination campaigns in endemic countries have been the central axis that has significantly reduced the number of cases in the world and in Brazil.[5]

Today, being vaccinated against yellow fever is a condition for entry into several countries due to the risk of contracting the disease at the destination or the possibility of introducing the virus into an epidemiologically compatible environment.

In Brazil, two vaccines are distributed against yellow fever, one produced by Biomanguinhos (Fiocruz) and another by the Sanofi-Pasteur laboratory. For the list of centers authorized to issue an official vaccination document, visit the website of the National Health Surveillance Agency, www.anvisa.gov.br. For the list of countries requiring vaccination against yellow fever as a condition for issuing the entry visa, visit the World Health Organization website, or the US Centers for Disease Control and Prevention, www.who.int and www.cdc.gov/travel, respectively. Travelers with contraindications to the vaccine and who are going to countries that require the International Certificate of Vaccination against Yellow Fever must present a medical statement attesting to the fact to one of the authorized centers for the emission of the vaccine exemption affidavit form, valid internationally.

The yellow fever vaccine consists of attenuated live virus, strain 17D, with two sub-strains: 17DD, used in Brazil, and 17D-204, used in other countries. Protection, which reaches levels above 95%, begins after the tenth day of application and probably extends for decades. Current evidence shows that the protection conferred by the vaccine is long-lasting, probably lifelong, and therefore there is no recommendation for revaccination, even if there is new displacement to endemic areas.[6] Contraindications include: children under 6 months of age; gestation; immunosuppression associated with disease or therapy (cancer, including lymphomas and leukemias, AIDS, systemic corticosteroid therapy, chemotherapy and radiotherapy), previous history of egg anaphylaxis, and allergic reaction to the previous dose of the vaccine. For those with contraindications, regions where the disease is endemic should be avoided; if the trip is essential, follow the methods of individual protection against mosquitoes.

Non-serious reactions are common, including pain at the site of application, fever, myalgia and headache, which generally appear after vaccination between the second and fifth day after receiving the dose. Serious adverse events such as yellow fever vaccine-associated viscerotropic and neurotropic disease, although infrequent, may arise. Cases similar to the disease, with visceral involvement, have been described since 1996, with an approximate incidence of 1 for every 40,000-50,000 doses in the United States, especially in individuals over 60 years of age, with mortality around 65%. Likewise, rare cases of encephalitis have been reported, with a higher frequency in children, particularly those under 6 months. Such occurrences are probably linked to individual immune responses and not to changes in the vaccine virus. The fact that four of the 62 cases of viscerotropism already reported in the world (up to the year 2016) were linked to diseases leading to thymus dysfunction or previous thymectomy corroborates this assumption.[7]

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