RAPID RISK ASSESSMENT

Outbreak of yellow fever in Brazil

Second update, 18 January 2018

Conclusions

The 2016/2017 yellow fever outbreak in Brazil was declared over in September 2017, yet the upsurge of human cases since December 2017 and non-human primate epizootics since September 2017 indicate a resurgence of yellow fever virus circulation in Brazil, particularly in São Paulo state.

The detection of non-human primate cases in the vicinity of the metropolitan regions of São Paulo and Rio de Janeiro is of concern, particularly in light of the start of the mosquito activity season in December 2017 and the suboptimal vaccination coverage in some areas. There is an increased likelihood of peri-urban or urban cycles of yellow fever transmission, which significantly increases the number of potentially exposed people.

The Carnival, one of the largest international mass gatherings in Brazil, will take place from 9 to 14 February 2018. During the Carnival, the number of EU/EEA travellers to Brazil is expected to increase, hence the number of travel-related cases among unvaccinated travellers may increase in the coming month.

The risk of yellow fever importation and subsequent transmission in the continental EU/EEA is currently very low because the virus has to be introduced by viraemic travellers in an area with an established, competent and active mosquito vector population.

Options for response

Advice to travellers

EU/EEA citizens who travel to, or live in, areas at risk of yellow fever in Brazil and other countries in South America are advised to:

- check their vaccination status and get vaccinated if necessary, in accordance with national and WHO recommendations. Vaccination against yellow fever is recommended for people visiting or living in yellow fever risk areas [1-9], from nine months of age and without contraindication. An individual risk–benefit analysis should be conducted by professionals in tropical or travel medicine prior to vaccination, taking into account the period, destination, duration of travel and likelihood of being bitten by mosquitoes as well as individual risk factors for adverse events following yellow fever vaccination;

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- take measures to prevent mosquito bites indoors and outdoors, especially between sunrise and sunset when mosquito vectors are most active [10]. These measures include:
  - the use of mosquito repellent in accordance with the instructions indicated on the product label;
  - wearing long-sleeved shirts and long trousers;
  - sleeping or resting in screened/air-conditioned rooms or using mosquito nets at night and during the day.

International travellers returning from affected areas may be requested to show proof of yellow fever vaccination (or a contraindication certificate) when entering countries or territories infested with *Aedes aegypti* mosquitoes.

Vaccination requirements and recommendations for international travellers are available from the World Health Organization's website [1-8].

Advice to health professionals

Physicians, health professionals and travel health clinics should be provided with, or have access to, regularly updated information on areas with ongoing yellow fever transmission and should consider yellow fever in the differential diagnoses for illnesses in relation to unvaccinated travellers returning from at risk areas.

To reduce the risk of adverse events following immunisation, healthcare practitioners responsible for yellow fever vaccinations should be aware of the contraindications and follow the manufacturers' advice on precautions before administering yellow fever vaccine [11,12].

Option for the EU Overseas Countries and Territories and Outermost Regions with presence of *Aedes aegypti*

In the EU Overseas Countries and Territories and Outermost Regions where *Aedes aegypti* is established or has been introduced, yellow fever vaccination checks should be considered for travellers coming from Brazil in order to reduce the risk of yellow fever importation.

Options for the safety of substances of human origin (SoHO)

Deferral of blood donors returning from areas affected by malaria will be sufficient to prevent most yellow fever infectious donations. In addition, precautionary deferral of non-vaccinated blood donors is suggested for 28 days after returning from an area affected by yellow fever but non-endemic for malaria. Potential blood donors should be deferred from donation for two weeks after live virus immunisation with the yellow fever 17D vaccine.

For organs, tissues and cells, the risk of yellow fever transmission from a donor who may have visited an affected area should be balanced with the likelihood of virus transmission. If an organ donor has received yellow fever vaccine during the four weeks before donation, an individual risk assessment of the immune status of all prospective recipients is mandatory. Yellow fever vaccination is contraindicated for immunocompromised patients after solid organ and haematopoietic stem cell transplantation. Potential transplant patients living in countries endemic for yellow fever or planning travel to endemic countries should be immunised before transplantation.

There are no specific criteria for the deferral of a prospective SoHO donor with a history of yellow fever. Therefore, it is suggested that a general recommendation be applied that donors must have recovered, be afebrile and asymptomatic on the day of donation and may donate SoHO 14 days after full recovery.

Source and date of request

ECDC internal decision, 15 January 2018.

Public health issue

This is the second update of a rapid risk assessment originally produced on 25 January 2017 and updated on 13 April 2017. It assesses the risk to EU/EEA countries and citizens associated with the ongoing outbreak of yellow fever in Brazil. It was triggered by the evolution of the epidemic in São Paulo state and reports of an imported case into the EU/EEA from Brazil.

Consulted experts

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Disease background information

Background information on yellow fever can be found on the ECDC website: Facts about yellow fever.

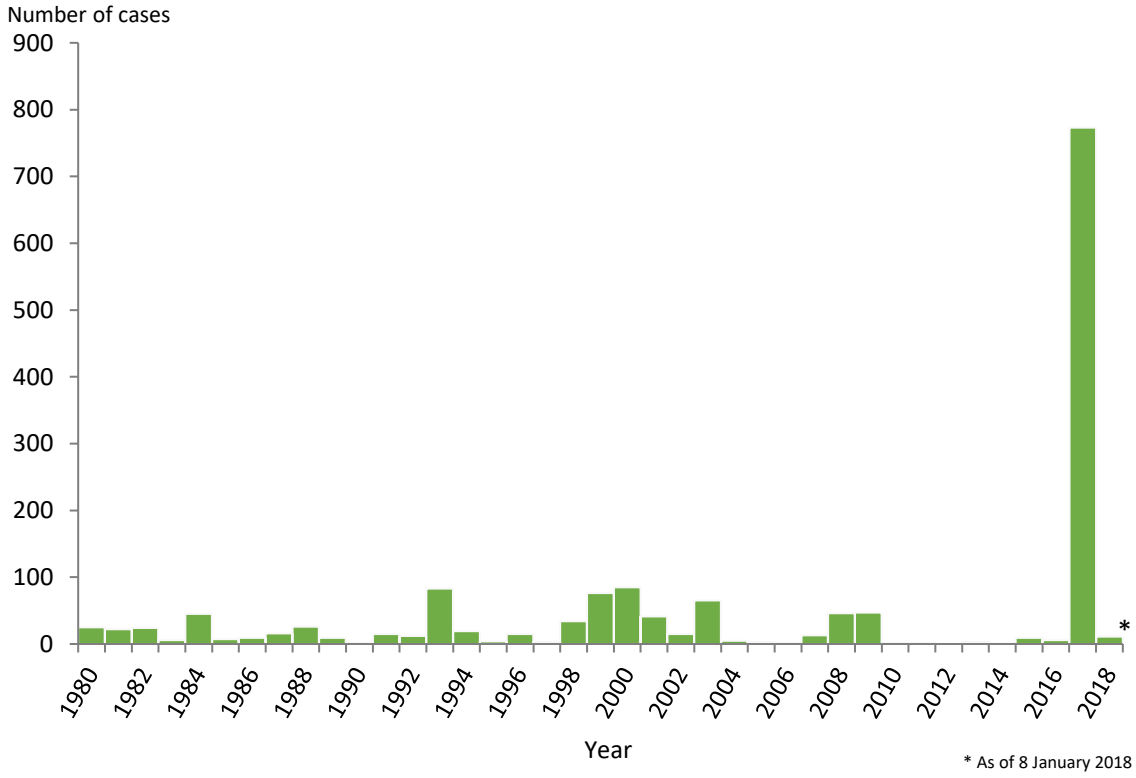
Event background information

Epidemiological background of yellow fever in Brazil

In the Americas, yellow fever transmission is maintained through a sylvatic cycle involving non-human primates (monkeys) and mosquitoes of two genera, *Haemagogus* and *Sabethes*. Humans can be infected after being bitten by yellow-fever-infected mosquitoes of these two genera when they stay close to, or enter, forest areas. In Brazil, this cycle occurs in a large part of the country, but the most affected locations are forested and rural areas including the hydrographic basins of the Amazon, Rios Araguaia-Tocantin and Paraná [13].

Yellow fever has a cyclical pattern in forested areas of South America, with alternating endemic periods as seen in Brazil (Figure 1) [14]. These cyclical intervals from three to seven years are the result of cyclical epizootics in non-human primates [15]. The observation of deaths in monkey populations is considered as a sentinel event for human cases of sylvatic origin and is used to define the priority areas for disease prevention and control [13,15]. Prior to the 2016/2017 outbreak, the last epidemic occurred between 2007 and 2009 [16]. The case fatality rate during the period 1980 to 2016 was 52%. Onset of yellow fever cases in Brazil follows a marked seasonal pattern, with the majority of the cases detected between January and June [13].

Figure 1. Distribution of confirmed human cases of yellow fever by year, Brazil, 1980 – January 2018



Source: Adapted from Ministry of Health, Brazil

* Experts from WHO reviewed this risk assessment, however the views expressed in this document do not necessarily represent the views of WHO.

When infectious humans returning to urbanised areas are bitten by *Aedes aegypti* mosquitoes, an urban transmission cycle can establish and spread rapidly in human populations with low vaccination coverage. *Aedes aegypti* is present in all Brazilian states [17]. The season for the highest mosquito vector activity lasts from December to July in the southern part of Brazil.

Since the outbreak of urban yellow fever in Acre in 1942, Brazil has only reported sylvatic yellow fever cases [18].

Entomological investigations conducted during the 2016/2017 outbreak in some of the affected states isolated *Haemagogus* mosquitoes positive for yellow fever virus, but no evidence of transmission by *Aedes aegypti* was found [19].

Outbreak of yellow fever in Brazil 2016/2017

From July 2016 to June 2017, 779 human yellow fever cases and 262 deaths were reported. In addition, 1 659 epizootics in non-human primates were reported, leading to the death of at least 2 504 animals [20]. The first laboratory-confirmed cases were reported on 19 January 2017. In March 2017, a decreasing trend in yellow fever cases was observed in the states of Minas Gerais and Espírito Santo, while an increasing trend was observed in the state of Rio de Janeiro [16]. During the 2016/2017 outbreak, confirmed cases were reported in the states of Minas Gerais, Espírito Santo, São Paulo, Rio de Janeiro, Pará, Distrito Federal, Goiás, Mato Grosso and Tocantins [21]. The 2016/2017 yellow fever outbreak in Brazil was declared over in September 2017 [22].

Upsurge of yellow fever cases in Brazil – 2017/2018

Between 1 September 2017 and 14 January 2018, 34 laboratory-confirmed cases, including 20 deaths (CFR=57%), were reported by the Brazilian national authorities [23]. Four cases occurred between September and November 2017 and 30 cases in December 2017/January 2018. The confirmed cases were reported in the states of São Paulo (20 cases, including eleven deaths), Minas Gerais (eleven cases, including seven deaths), Rio de Janeiro (two cases, including one death) and in the Federal District (one fatal case).

The probable sites of infection of all confirmed human cases are areas with documented cases in non-human primates [23]. Between 1 July 2017 and 8 January 2018, 2 242 yellow fever suspicions of epizootics among non-human primates were reported, 411 of which were confirmed [23]. Confirmed non-human primate epizootics were reported from the states of São Paulo (360 cases), Minas Gerais (47), Rio de Janeiro (3) and Mato Grosso (1). The upsurge of epizootics among non-human primates has been observed since mid-September in São Paulo state.

In December 2017, non-human primates infected with yellow fever were detected in urban parks in the Greater São Paulo [24]. As a consequence, the authorities closed several parks in the area [25]. In addition, the news media reported the deaths of four monkeys near one of the access points to the urban Tijuca Forest, in the northern part of Rio de Janeiro city. These four animal cases are being investigated for suspicion of yellow fever [26].

A recent phylogenetic analysis of the south-eastern Brazilian outbreak of yellow fever in 2016/2017 suggests that the outbreak was a result of the reintroduction of a modern-lineage (genotype I) variant from Venezuela or from some endemic region in Brazil [27]. The genomic analysis of two complete yellow fever virus sequences from two naturally infected howler monkeys from Espírito Santo state in 2017 showed an identical virus sequence. Seven amino acid changes were identified by the alignment of the precursor polyproteins from Brazilian and Venezuelan yellow fever viruses detected since 1980. Further investigations would be needed to asses if these genetic modifications are found in other locations of the 2017 and current 2018 yellow fever outbreaks in Brazil. The potential implications of these findings on infectivity and viral fitness remain to be determined [27].

Travel data and travel-related cases

Based on 2015 data from the International Air Transport Association (IATA), 940 000 travellers from the EU/EEA are estimated to travel to Brazil by air during the period January to May. In 2015, countries of origin included Italy (17%), Portugal (16%), France (15%), the United Kingdom (12%), Spain (12%) and Germany (12%).

The Carnival, one of the largest international mass gatherings in Brazil, will take place from 9 to 14 February 2018. This event brings together millions of people throughout the country and an increased number of international travellers, including travellers from the EU/EEA, is expected.

Since January 2017, three travel-associated cases of yellow fever have been identified among unvaccinated EU/EEA travellers: one case in January 2017 returning from Bolivia, one case in March 2017 returning from Suriname, and one case in January 2018 returning from Brazil (i.e. the surroundings of São Paulo city) [28-31]. By comparison, there were six travel-related cases of yellow fever among EU/EEA travellers between 1999 and 2016, highlighting an increased circulation of yellow fever virus in the Americas in 2017 [32].

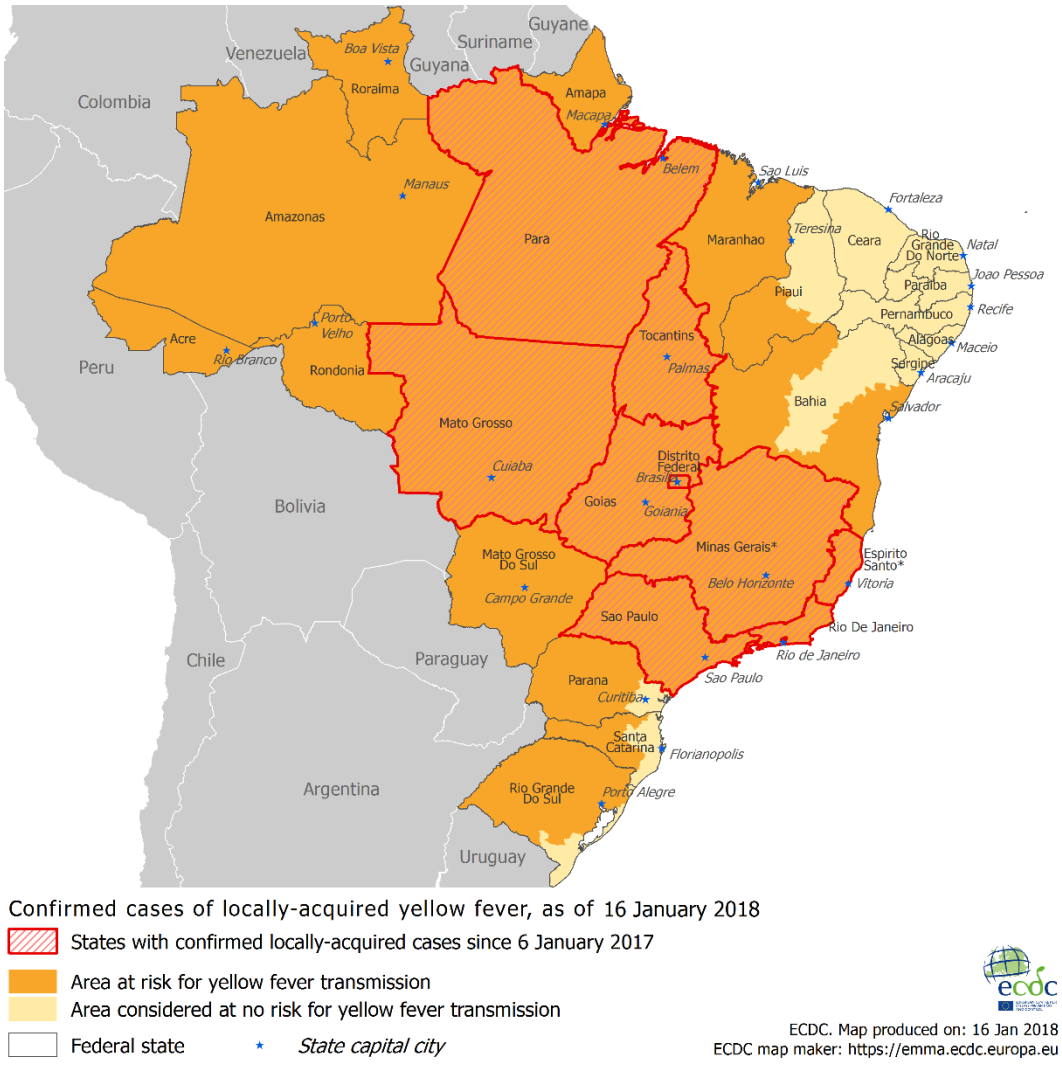
Yellow fever vaccination

Yellow fever vaccination is not recommended universally in Brazil. WHO recommends vaccination to all unvaccinated travellers aged above nine months and without contraindication who are travelling to at-risk areas [33]. Vaccination should be obtained ten days prior to travelling [21]. On 16 January 2018, WHO revised the areas at risk for yellow fever transmission and included the entire state of São Paulo in the list. Consequently, vaccination is recommended for travellers visiting any area in the state of São Paulo [21]. Individuals who cannot be vaccinated because they do not meet the vaccination criteria are of particular concern (e.g. babies under nine months of age and people with underlying health conditions). These individuals should strictly apply personal protection measures to prevent mosquito bites [21].

The countries with risk of yellow fever transmission and countries requiring yellow fever vaccination are listed on the WHO International Travel and Health website [1-8].

Between 3 and 24 February 2018, the Brazilian health authorities intend to vaccinate 7.6 million people. Following previous recommendations to increase the availability of vaccines in response to an outbreak or in settings where the extension of the outbreak is imminent [34], the campaign will use fractional doses of the vaccine and will cover 54 cities in the regions of Greater São Paulo, Vale do Paraíba and Baixada Santista. In addition, conventional doses will be made available to children between the age of nine months and two years, those who travel to countries with vaccination requirements, pregnant women living in yellow fever risk areas, patients with a transplant history and those with chronic diseases, such as diabetes, heart diseases or chronic renal failure [35].

Figure 2. Distribution of confirmed yellow fever cases by municipality, Brazil, 6 January 2017 – 16 January 2018



Source: Adapted from [1-7,35]

ECDC threat assessment for the EU

Yellow fever risk in Brazil

The upsurge of human cases since December 2017 and non-human primate epizootics since September 2017 indicate a resurgence of yellow fever virus circulation in Brazil, particularly in São Paulo state.

The relatively high number of epizootics among non-human primates that occurred between September and December 2017 – a period of lower vector activity – indicates continued viral circulation among non-human primates and therefore a risk for human populations.

The detection of non-human primate cases in the vicinity of the metropolitan regions of São Paulo and Rio de Janeiro is of concern, particularly in light of the start of the mosquito activity season in December 2017 and the suboptimal vaccination coverage in some areas [23].

So far, the transmission cycle in Brazil has been sylvatic, and the centres of the metropolitan areas of São Paulo and Rio de Janeiro have remained unaffected. With non-human primate cases being detected closer to city centres and a high density of *Aedes aegypti* mosquitoes in Brazil (which were also responsible for a number of dengue, zika and chikungunya outbreaks), there is an increased likelihood of peri-urban or urban cycles of yellow fever transmission, which significantly increases the number of potentially exposed people [37].

Yellow fever risk for EU/EEA citizens travelling to/residing in affected areas

During the Carnival, the number of EU/EEA travellers to Brazil is expected to increase. Unvaccinated travellers visiting affected areas and EU/EEA residents living in affected areas are at risk of infection. Hence, an increased number of travel-related cases among unvaccinated EU/EEA travellers may be reported in the coming month.

Risk of transmission in the continental EU/EEA

The likelihood of yellow fever virus being introduced to EU/EEA countries by viraemic travellers returning from Brazil is considered low, as most travellers are likely to have been immunised. However, importation of yellow fever remains possible through infected returning travellers, as demonstrated recently. The establishment of an urban cycle of yellow fever transmission in Rio de Janeiro or São Paulo would increase the number of exposed travellers and the likelihood of importation to EU/EEA countries.

The probability of local yellow fever transmission in the EU/EEA following introduction by a viraemic traveller is currently considered very low as weather conditions during the winter season in continental EU/EEA are not favourable to vector activity. Recent studies conducted in France have shown that *Aedes albopictus* mosquitoes, which are already established in the southern part of the EU, can transmit yellow fever virus in laboratory settings [38]. To date, yellow fever transmission via *Aedes albopictus* has not been observed in nature.

Risk of transmission in the EU overseas countries and territories (OCT) and outermost regions (OMR)

French Guiana is endemic for yellow fever. The most recent locally acquired case was identified in 2017 in a person who was most likely infected in the border region of French Guiana and Brazil [39]. Yellow fever vaccination has been mandatory for residents since 1967 and is compulsory for people entering French Guiana [40]. Vaccination coverage through routine vaccination is high, as demonstrated by an exhaustive coverage survey in schools in 2009, showing a coverage of 95.6% [CI 95%: 95.5–96.3%] in children aged 6 to 16 years [40].

Aedes aegypti is established in the British, French and Dutch OCTs and OMRs of the Caribbean region and in the Portuguese OMR of Madeira. Recently, *Aedes aegypti* has been detected in the Spanish OMR of Fuerteventura, Canary Islands [41]. In the northern hemisphere (e.g. in Madeira) vector activity is currently low. However, the risk may increase towards the summer months.

The French High Council for Public Health has published guidelines for reducing the risk of importing yellow fever into receptive areas (where *Aedes aegypti* is present). Recommendations include:

- vaccination of travellers to risk areas
- integrated vector management
- enhancement of clinicians' awareness to facilitate early detection of suspected cases [8].

Yellow fever and safety of SoHO

The risk of yellow fever transmission via substances of human origin (SoHO) is merely theoretical. Transmission of yellow fever through transfusion or transplantation has not been reported although a risk of infectious SoHO donations from an unvaccinated asymptomatic viraemic donor cannot be excluded. The yellow fever attenuated virus from the 17D vaccine has been transmitted through transfusion of blood donated by recently immunised donors [42]. Donation of blood is possible four weeks after vaccination with attenuated viral vaccine [43].

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