

RAPID RISK ASSESSMENT

Outbreak of yellow fever in Brazil

25 January 2017

Conclusions and options for response

The risk of yellow fever transmission in the EU/EEA is currently very low as it depends on the virus being introduced by viraemic travellers to an area with an established, competent and active mosquito vector population.

In Brazil, the authorities have reported only sylvatic cases in 2016 and 2017. However, this outbreak should be carefully monitored as the establishment of an urban yellow fever cycle would have the potential to quickly affect a large number of people. Therefore, EU/EEA Member States should consider a range of options for response.

EU citizens who travel to, or live in, areas where there is evidence of periodic or persistent yellow fever virus transmission, especially those in outbreak-affected regions, are advised to:

- Be aware of the risk of yellow fever in endemic areas of Brazil, particularly in the states with confirmed autochthonous cases: Minas Gerais, Espírito Santo and São Paulo;
- Check their vaccination status and get vaccinated if necessary. Vaccination against yellow fever is recommended from nine months of age for people visiting, or living in yellow fever risk areas. An individual risk benefit analysis should be conducted prior to vaccination, taking into account the season (December to July in Brazil), destination, duration of travel and the likelihood of exposure to mosquitoes (e.g. rural areas, forests).
 - WHO publishes a list of countries, territories and areas with yellow fever vaccination requirements and recommendations [1], which includes the Brazilian states of Minas Gerais, Acre, Amapá, Amazonas, Distrito Federal (including the capital Brasília), Goiás, Maranhão, Mato Grosso, Mato Grosso do Sul, Pará, Rondônia, Roraima and Tocantins, and designated areas of Bahia, Paraná, Piauí, Rio Grande do Sul, Santa Catarina and São Paulo. Vaccination is also recommended for travellers visiting Iguazu Falls.
 - Given the geographical extension of the outbreak to states previously considered low risk, such as Espírito Santo, in addition to considering recommending vaccination in line with the WHO recommendations on yellow fever vaccination related to the states listed above, Member States should also consider recommending yellow fever vaccination for travellers aged over nine months going to rural areas in Espírito Santo State.
- Take measures to prevent mosquito bites indoors and outdoors, especially between sunrise and sunset when *Aedes* mosquito vectors are most active. 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 or air-conditioned rooms, or using mosquito nets at night and during the day.

To reduce the risk of adverse events following immunisation, healthcare practitioners should be aware of the contraindications and follow the manufacturers' advice on precautions before administering yellow fever vaccine [2].

ECDC will publish and update regularly a map and a list of states reporting confirmed cases of yellow fever in Brazil related to the current outbreak at the following link: http://ecdc.europa.eu/en/healthtopics/yellow_fever/current-transmission/Pages/yellow-fever-map.aspx.

Source and date of request

ECDC internal decision, 19 January 2017.

Public health issue

This document assesses the risk to EU/EEA countries and citizens associated with the ongoing outbreaks of yellow fever in Brazil.

Consulted experts

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Disease background information

Background information on yellow fever can be found in the ECDC factsheet for health professionals:

http://ecdc.europa.eu/en/healthtopics/yellow_fever/factsheet-health-professionals/Pages/factsheet_health_professionals.aspx

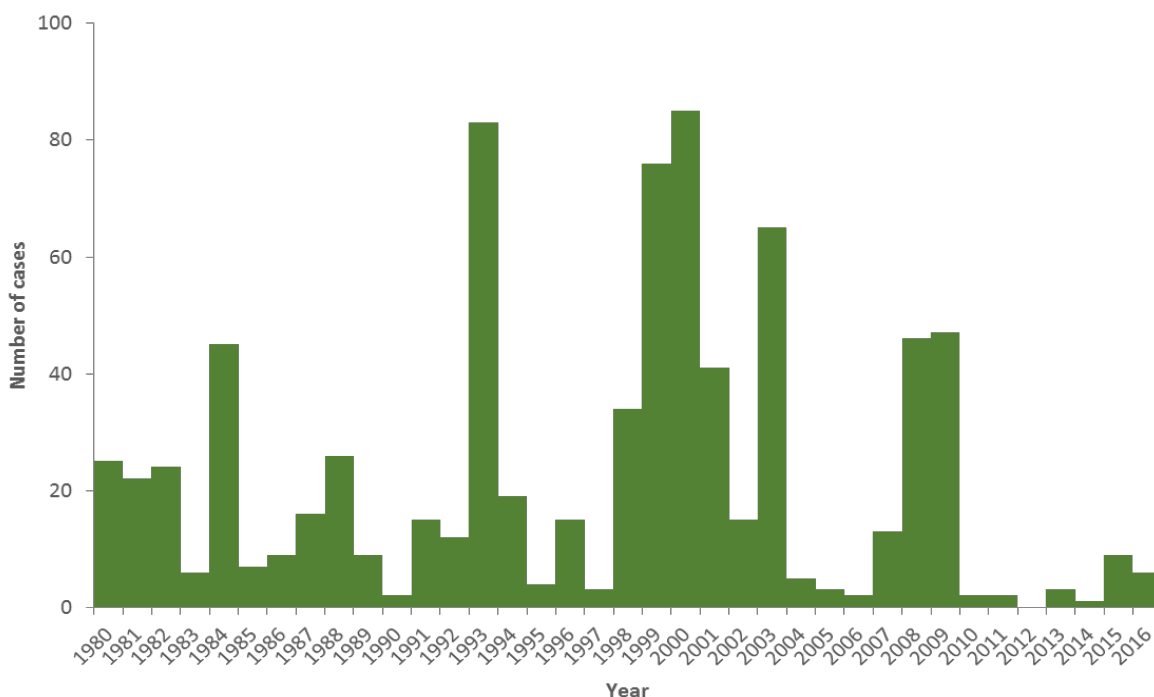
Epidemiology of yellow fever in the Americas and Brazil

Over the past 10 years in the Americas, human cases of yellow fever have been reported in Argentina, Bolivia, Brazil, Colombia, Ecuador, Paraguay, Peru and Venezuela [3]. In 2016, human cases of yellow fever were recorded in Brazil (six confirmed cases prior to the current outbreak), Colombia (seven confirmed and five probable cases) and Peru (62 confirmed and 17 probable cases) [4].

On 10 August 2016, the World Health Organization (WHO) reported through the International Health Regulations (IHR) two laboratory-confirmed cases of yellow fever, including one fatality in a French national who visited several endemic areas for yellow fever in Peru [5]. Neither individual was vaccinated against yellow fever, despite the French health authorities' recommendation of yellow fever vaccination for those visiting endemic areas in Peru.

Yellow fever has a cyclical pattern in Brazil, with alternating endemic periods (i.e. isolated cases in unvaccinated individuals) and epidemic periods (i.e. outbreaks in populations with low vaccine coverage) (Figure 1) [6]. These cyclical intervals from three to seven years are the result of cyclical epizootics in non-human primates [7]. The last epidemic occurred between 2007 and 2009 [6]. The case fatality rate (CFR) during the period 1980 to 2016 was 52%.

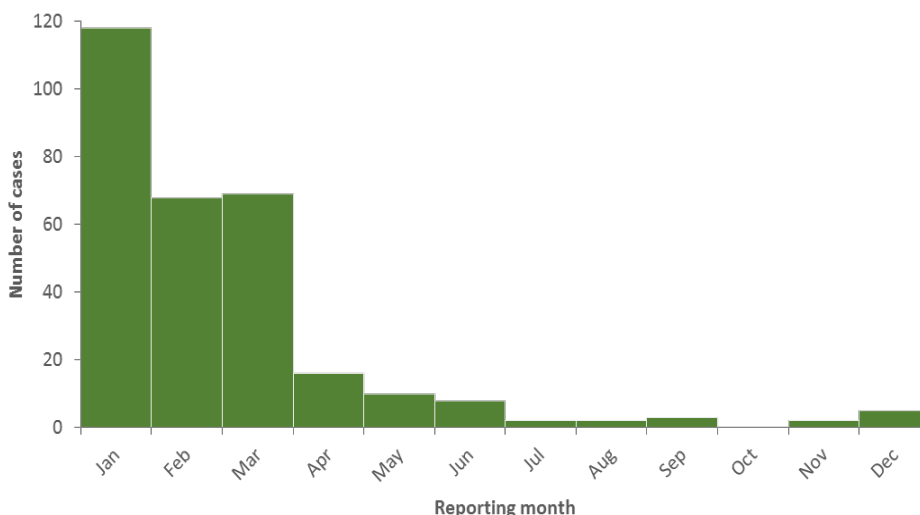
Figure 1. Distribution of confirmed human cases of yellow fever, by year, Brazil, 1980–2016



Source: adapted from *Ministry of Health, Brazil*

According to the Ministry of Health, as of 6 June 2016, Brazil had only reported cases of sylvatic yellow fever since the last outbreak of urban yellow fever reported in Acre in 1942 [8]. During the period 2000–2012, cases followed a marked seasonal pattern, with 95% detected between January and June (Figure 2) [9].

Figure 2. Distribution of the human cases of yellow fever by month of reporting, Brazil, 2000–2012



Source: adapted from [9]

Between July 2014 and December 2016, Brazil reported 15 confirmed human cases from 769 notifications, and 49 confirmed epizootic cases in non-human primates from 849 notifications (Figure 3) [6]. Among these, the state of Minas Gerais recorded no confirmed human cases from 38 notifications and five confirmed epizootic cases in non-human primates from 114 notifications). The last autochthonous human case of yellow fever in Minas Gerais occurred in 2009 [10].

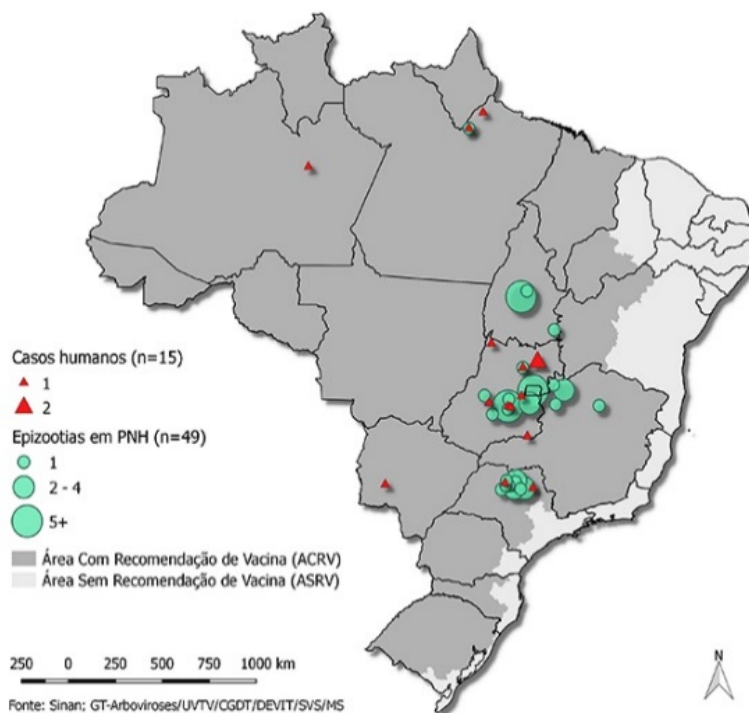
The observation of deaths in monkey populations is considered a sentinel event for human sylvatic cases [9] and is used to define the priority areas for preventing and controlling the disease [7].

The state of Espírito Santo, bordering Minas Gerais, is not considered endemic. However, sylvatic yellow fever cases have been reported previously in this state in 1933 [11].

In January 2017 several municipalities in the State of Espírito Santo reported the death of monkeys. More than 80 monkeys were found dead in the municipalities of Irupi and Colatina close to the border with Minas Gerais. On 20 January 2017, the State Department of Health reported positive tests for yellow fever, confirming an epizootic and the transmission of yellow fever in the state of Espírito Santo [12].

According to media reports, five monkeys were found dead between 17 and 19 January 2017 with suspected yellow fever in a southern neighbourhood of the city of São José do Rio Preto, in the centre of São Paulo state. Laboratory test results are still pending [13]. Confirmed yellow fever cases in both humans and animals have been reported in this region in the past few years (Figure 3) [4].

Figure 3. Distribution of confirmed human cases and confirmed epizootics in non-human primates by municipality, Brazil, July 2014 – December 2016



Source: *Ministry of Health of Brazil*

Event background information

Current event

On 6 January 2017, the Ministry of Health of Brazil notified the Pan American Health Organization of the occurrence of 23 suspected and probable cases of yellow fever, including 14 deaths, from 10 municipalities in the state of Minas Gerais [4]. The index case had onset of symptoms on 18 December 2016.

The first laboratory-confirmed cases were reported on 19 January 2017 by the Ministry of Health of Brazil.

As of 23 January, three states (Minas Gerais, Espírito Santo and São Paulo) have reported confirmed cases of yellow fever:

- Minas Gerais: 391 cases (333 suspected and 58 confirmed) in 39 municipalities, including 83 deaths (52 suspected and 31 confirmed). The case fatality rate (CFR) is 21.2% among all cases and 53.4% among confirmed cases. This is an increase of 119 cases, including 11 confirmed cases, since 20 January.
- Espírito Santo: 19 cases (18 suspected and one confirmed) in 12 municipalities, including one death in a suspected case. The CFR is 5.3%. This is an increase of seven cases since 20 January.
- São Paulo: three cases (three confirmed) in three municipalities, including three deaths. This is the first report of cases in this state for 2017. According to the media, ten additional suspected cases are still under investigation [14].

On 23 January 2017, Bahia state also reported six suspected cases in three municipalities and the Federal District reported other suspected cases under investigation.

Figure 4. Distribution of suspected and confirmed human cases of yellow fever by week of reporting and state, Brazil, 2017, as of 23 January 2017

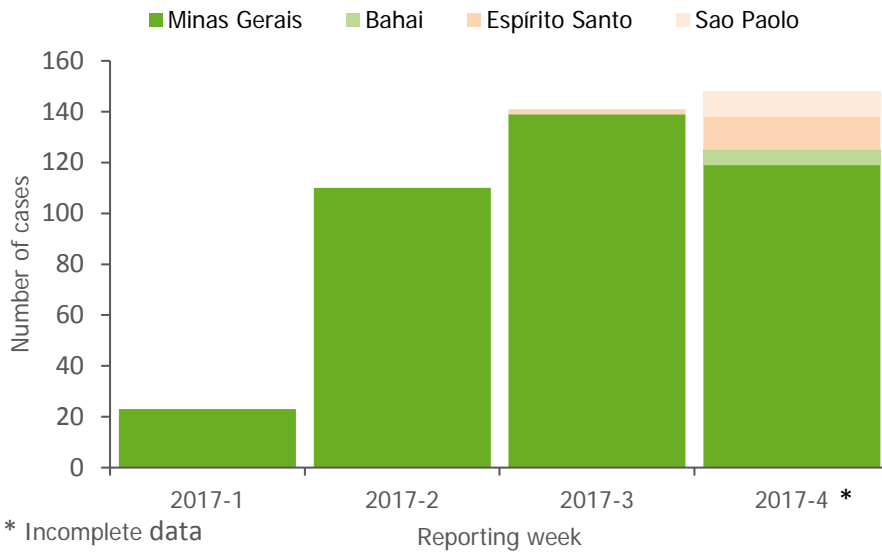
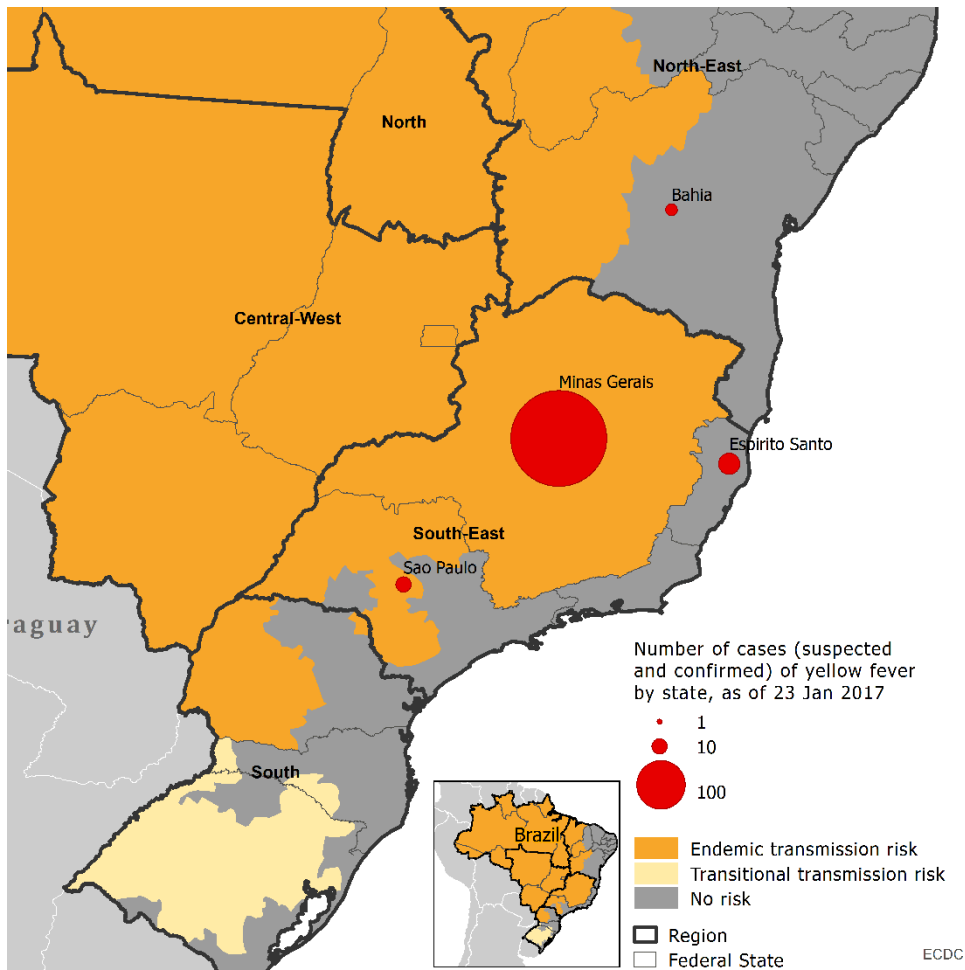


Figure 5. Human suspected and confirmed cases of yellow fever by municipality, Brazil, 2017, as of 23 January 2017



Source: adapted from [15]

Vector distribution and seasonality

In the Americas, yellow fever is maintained in a sylvatic cycle involving non-human primates (monkeys) and mosquitoes of two genera, *Haemagogus* and *Sabethes*. Humans can become infected after being bitten by 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 forested and rural areas are the hydrographic basins of the Amazon, Araguaia-Tocantim and Parana [9].

When infectious humans returning to urbanised areas are bitten by *Aedes aegypti* mosquitoes, an urban cycle can establish and spread quickly in human populations with low vaccine coverage. Currently, *Aedes aegypti* is present in all Brazilian states [16]. The season for the highest vector activity lasts from December to July.

Vaccine coverage

The Brazilian national vaccination schedule includes two doses of the yellow fever vaccine, one dose at the age of nine months and one booster dose at four years. More than 16 million doses of yellow fever vaccines were distributed nationally in 2016.

Brazilian Health authorities are recommending vaccination for rural or forested areas and for people who travel to these areas. The states of Ceará, Rio Grande do Norte, Paraíba, Pernambuco, Alagoas, Sergipe, Espírito Santo and Rio de Janeiro are outside of the area of recommended vaccination.

Within the municipalities of Minas Gerais, the vaccination coverage rate varies significantly, from 9 to 100%. The vaccination coverage in the four most affected areas is reported to be 83% in Caratinga, 70% in Ladainha, 66% in São Sebastião do Maranhão and 33% in Imbe de Minas respectively. Significant year-to-year changes have been reported for vaccine coverage rates [17].

In the neighbouring states of Minas Gerais, such as Espírito Santo, Rio de Janeiro and the south of Bahia, previously considered to be at low risk of transmission, yellow fever vaccination is not included in the childhood immunisation schedule. However, yellow fever vaccination is currently being intensified in 26 municipalities of the western part of the state of Espírito Santo, close to the eastern border with Minas Gerais where suspected human cases have been reported [18]. Immunisation campaigns are also planned in the north-western municipalities of the state of Rio de Janeiro and the western municipalities of the state of Bahia [18].

Immunisation campaign in Minas Gerais

The State Health Department of Minas Gerais (SES/MG) has distributed 266 075 doses for the routine yellow fever vaccination programme to the 28 regional health units of Minas Gerais. Under the intensified immunisation campaign, SES/MG and the Ministry of Health have made available 1 356 000 doses of yellow fever vaccine to the four priority regional health centres. Through a combination of routine and intensified action, the state has to date distributed 1 622 075 doses [19]. The Ministry of Health intends to distribute 350 000 additional doses during the week of 23 January 2017 [20].

The doses are being distributed to the following municipalities in Minas Gerais:

Municipality in Minas Gerais	Estimated population	Doses distributed in intensified action
Coronel Fabriciano	838 603	430 000
Governador Valadares	697 988	205 000
Manhumirim	474 254	311 000
Teófilo Otoni	523 497	410 000
Total	2 534 342	1 356 000

Immunisation campaign in Espírito Santo

According to the State Health Department of Espírito Santo, the state has recently received 500 000 doses of vaccine from the Health Ministry of Brazil. The State Health Department of Espírito Santo is expecting an additional 500 000 doses to be received during the week of 23 January 2017 to increase the area protected by vaccination [21].

The state of Espírito Santo has currently distributed vaccine to 26 municipalities: Água Doce do Norte, Alto Rio Novo, Baixo Guandu, Barra de São Francisco, Brejetuba, Divino de São Lourenço, Dolores do Rio Preto, Guaçuí, Ibatiba, Ibitirama, Irupi, Iúna, Laranja da Terra, Mantemópolis, Montanha, Mucurici, Pancas, Afonso Cláudio, Ecoporanga, Colatina, Itaguaçu, Governador Lindenberg, Conceição do Castelo, Venda Nova do Imigrante, São Roque do Canaã and São Gabriel da Palha [21]. The state health department recommends municipalities to first vaccinate the rural population and then the population in cities.

The additional doses will be used for protective vaccination in 11 municipalities (Marilândia, Domingos Martins, Itarana, Santa Teresa, Castelo, Iconha, Muniz Freire, Águia Branca, São Domingos do Norte, Santa Leopoldina and Santa Maria de Jetibá), as well as to vaccinate travellers to risk areas outside of the state [21].

Immunisation campaigns in the other affected states

The Ministry of Health has distributed 400 000 extra doses of vaccine to Bahia, 400 000 extra doses to São Paulo, and 42 000 extra doses to the Federal District [18].

Travel data

In 2015, according to data from the International Air Transport Association (IATA), an estimated 940 000 travellers from the EU/EEA travelled by air to Brazil between January and May. Countries of origin include Italy (17%), Portugal (16%), France (15%), the United Kingdom (12%), Spain (12%) and Germany (12%). Among these, an estimated 40 000 travellers flew to Minas Gerais, departing from Portugal (28%), Italy (18%), France (14%), Spain (11%), Germany (9%) and the United Kingdom (8%).

The largest mass gathering planned in Brazil during the coming weeks is Carnival, which starts on 24 February 2017.

Vaccine recommendations

The vaccination recommendations of the six EU Member States with the highest numbers of travellers to Brazil (France, Germany, Italy, Portugal, Spain and the United Kingdom), follow current WHO recommendations [1]. The validity of a yellow fever vaccination certificate has now been extended from 10 years to life [22].

Vaccination against yellow fever is recommended for people aged ≥ 9 months who are travelling to areas considered at risk for yellow fever transmission in Brazil:

- Acre, Amapá, Amazonas, Distrito Federal (including the capital city of Brasília), Goiás, Maranhão, Mato Grosso, Mato Grosso do Sul, Minas Gerais, Pará, Rondônia, Roraima and Tocantins, and designated areas of the following states: Bahia, Paraná, Piauí, Rio Grande do Sul, Santa Catarina and São Paulo [1].
- Vaccination is also recommended for travellers visiting Iguazu Falls) [1].

According to Brazilian health authorities, neighbouring states such as Espírito Santo and Rio de Janeiro are considered to be at low risk of transmission [15]. Therefore Brazilian authorities are currently not recommending vaccination for travellers visiting only these areas.

Yellow fever vaccine is a live-attenuated vaccine that is considered to have a satisfactory safety profile. However, it can be associated with adverse reactions on rare occasions, which include anaphylaxis, yellow fever neurotropic disease and adverse viscerotropic disease [23]. These adverse reactions have been reported only following primary vaccination with a reported rate of 0.25–0.8 per 100 000 vaccine doses for neurotropic disease and 0.25–0.4 per 100 000 vaccine doses for viscerotropic disease. The risk of lethality of these adverse events is higher than for wild-type yellow fever disease. These adverse events are believed to be due to host susceptibility rather than viral vaccine strain mutations causing an increase in virulence [24]. Anaphylactic reactions have been estimated to occur in 0.8 per 100 000 vaccinations, most commonly in people with allergies to eggs and gelatine.

Clinicians should be aware of the potential risk of adverse viscerotropic disease, particularly in patients with autoimmune diseases, immune-deficiencies or other related underlying conditions, and also among the elderly.

A individual risk benefit analysis should be conducted prior to vaccination taking into account the season (December to July in Brazil), destination and duration of travel, and the likelihood of exposure to mosquitoes (e.g. rural areas, forests.) [25].

ECDC threat assessment for the EU

The geographical extension of the outbreak from Minas Gerais to Espírito Santo and São Paulo states is of concern since the low vaccination coverage in some areas creates a risk of further cases among the local population.

Authorities have launched a mass vaccination campaign targeting the main affected areas, as well as cities in states bordering Minas Gerais and Espírito Santo [26–28].

Risk to travellers and residents of affected areas

Unvaccinated travellers to affected areas or residents in the affected areas are at risk of becoming infected. Of particular concern are individuals who cannot be vaccinated because they do not meet the vaccination criteria – e.g. babies under nine months of age and people with underlying health conditions, for whom strict personal protection measures should be enforced to mitigate the risks of being infected.

Importation of infected cases into the EU remains possible. The frequency of such an event would depend on whether there is further geographical extension of the epidemic, which would increase the number of potentially exposed travellers.

Yellow fever vaccination is currently not mandatory for EU travellers to Brazil. In the EU, the main countries with travellers to Brazil (Italy, Portugal, France, UK, Spain, Germany) and WHO recommend yellow fever vaccination for travel to thirteen states and designated areas in six other states of Brazil, including Minas Gerais, Bahia and São Paulo states but not Espírito Santo state [1].

Risk of transmission in the EU

The primary vector of yellow fever in urban settings (*Aedes aegypti*) is present in Madeira, Portugal, and recent studies have shown that *Aedes albopictus* from France can potentially transmit yellow fever virus [29]. However, the risk of the virus being introduced into local competent vector populations in the EU through viraemic travellers from Brazil is considered to be very low as the current weather conditions in Europe are not favourable for vector activity.

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