RAPID RISK ASSESSMENT

Outbreak of yellow fever in Brazil

First update, 13 April 2017

Conclusions and options for response

Brazil has been experiencing a yellow fever outbreak since January 2017 and vaccination requirements and recommendations for international travellers, including yellow fever, have been updated by WHO accordingly [1-6]. The Brazilian authorities have only reported yellow fever cases related to sylvatic transmission 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.

EU travellers travelling to areas at risk of yellow fever in South America should be informed of the potential exposure to yellow fever virus and an individual risk benefit analysis should be conducted during pre-travel medical consultation.

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.

Advice to travellers

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 throughout South America, including recently affected States in Brazil (Minas Gerais, Espírito Santo, Pará, Rio de Janeiro and São Paulo). WHO publishes and provides an updated list of countries, territories and areas with yellow fever vaccination requirements and recommendations [1,7,8].
- Check 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 period, destination, duration of travel and likelihood of exposure to mosquitoes (e.g. visits to rural areas, forests) as well as individual risk factors for adverse events following yellow fever vaccination.
- Take measures to prevent mosquito bites indoors and outdoors, especially between sunrise and sunset when *Aedes* and sylvatic yellow fever mosquito vectors are most active [9]. 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 should be able to show proof of yellow fever vaccination (or a contraindication certificate) as these could be requested by countries or territories infested with *Aedes aegypti* mosquitoes.

Suggested citation: European Centre for Disease Prevention and Control. Outbreak of yellow fever in Brazil, First update – 13 April 2017. Stockholm: ECDC; 2017.

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 affected areas.

According to the updated recommendation from WHO (4 April 2017), vaccination against yellow fever for international travellers has been extended to the coastal area of Bahia State, Rio de Janeiro State and to the urban area of Campinas in São Paulo State [6]. ECDC will publish and regularly update a map of risk areas for yellow fever transmission in accordance with WHO recommendations. This map will also show distribution by State of confirmed yellow fever cases in Brazil* [10].

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 [11,12].

Options for safety of SoHO

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 in the future 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. Deferral of donors returning from areas affected by malaria will be sufficient to prevent yellow fever infectious donations. Precautionary deferral is suggested for 28 days of non-vaccinated donors returning from an area affected by yellow fever but non-endemic for malaria.

Source and date of request

ECDC internal decision, 6 April 2017.

Public health issue

This document assesses the risk to EU/EEA countries and citizens associated with the ongoing outbreak of yellow fever in Brazil. The update of this rapid risk assessment was triggered by the evolution of the epidemic towards new Brazilian States and the consequent update of the yellow fever vaccination requirements for travellers.

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/current-transmission/Pages/yellow-fever-map.aspx

Event background information

Epidemiology of yellow fever in the Americas

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, Rios Araguaia-Tocantin and Paraná [13].

Yellow fever has a cyclical pattern in forested areas of South America, with alternating endemic periods and epidemic 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 [13] and is used to define the priority areas for disease prevention and control [15]. The last epidemic occurred between 2007 and 2009 [14]. The case fatality rate (CFR) during the period 1980 to 2016 was 52%. During the period 2000 to 2012, onset of yellow fever cases in Brazil followed a marked seasonal pattern, with 95% detected between January and June [13].

When infectious humans returning to urbanised areas are bitten by *Aedes aegypti* mosquitoes, an urban cycle can establish and spread rapidly in human populations with low vaccine coverage. Currently, *Aedes aegypti* is present in all Brazilian States [16]. According to the Ministry of Health, Brazil has only reported cases of sylvatic yellow fever since the last outbreak of urban yellow fever reported in Acre in 1942 [17]. The season for the highest mosquito's vector activity lasts from December to July.

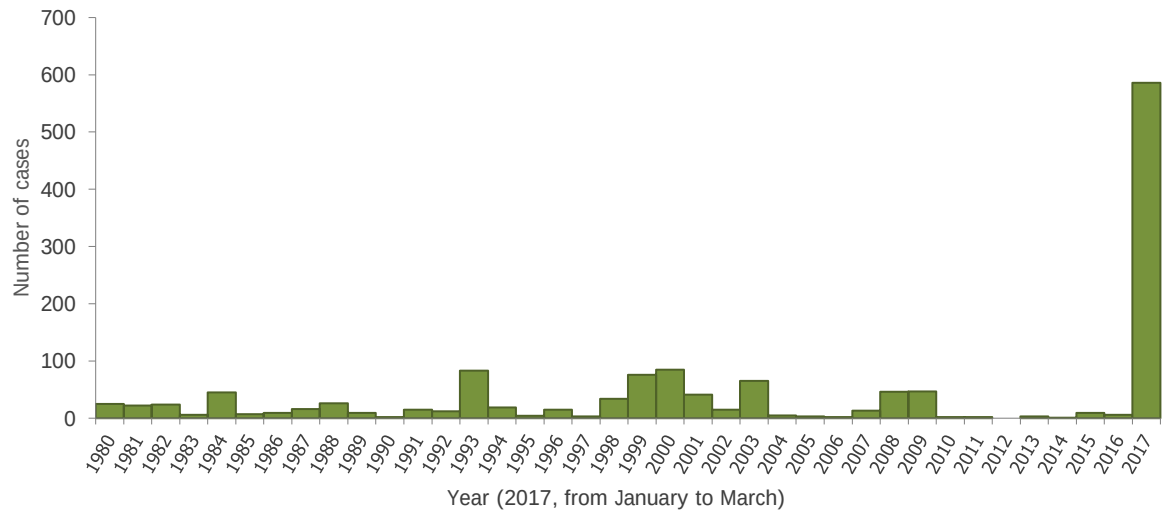
Over the past 10 years in the Americas, human cases of yellow fever have been reported in Argentina, Bolivia, Brazil, Colombia, Ecuador, Paraguay, Peru and Venezuela [18]. Between 1980 and 2016, the number of confirmed yellow fever cases remained below one hundred per year, while a significant increase has been observed in 2017.

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 [14]. In 2016, human cases of yellow fever were recorded in Brazil (only six confirmed cases prior to the current outbreak), Colombia (seven confirmed and five probable cases) and Peru (62 confirmed and 17 probable cases) [19].

In the first three months of 2017, six countries, in the Americas have reported suspected or confirmed cases of yellow fever: Bolivia (1), Brazil (1 036), Colombia (two suspected cases), Ecuador (1), Peru (9) and Suriname (1) [10,21-23].

During the past eight months, four travel-associated cases of yellow fever have been identified among unvaccinated EU travellers: two during a visit to Peru in August 2016, one case in March 2017 following travel to Bolivia and one case in March 2017 following travel to Suriname [20]. Compared to the historical baseline of four travel associated cases of yellow fever among EU travellers for the period 1999 to July 2016, this unusual increase in travel-associated cases reflects a significant increase in the circulation of yellow fever virus in South America [20].

Figure 1. Distribution of confirmed human cases of yellow fever, by year, Brazil, 1980 – March 2017



Source: adapted from Ministry of Health, Brazil

Epidemiological situation in Brazil in 2017

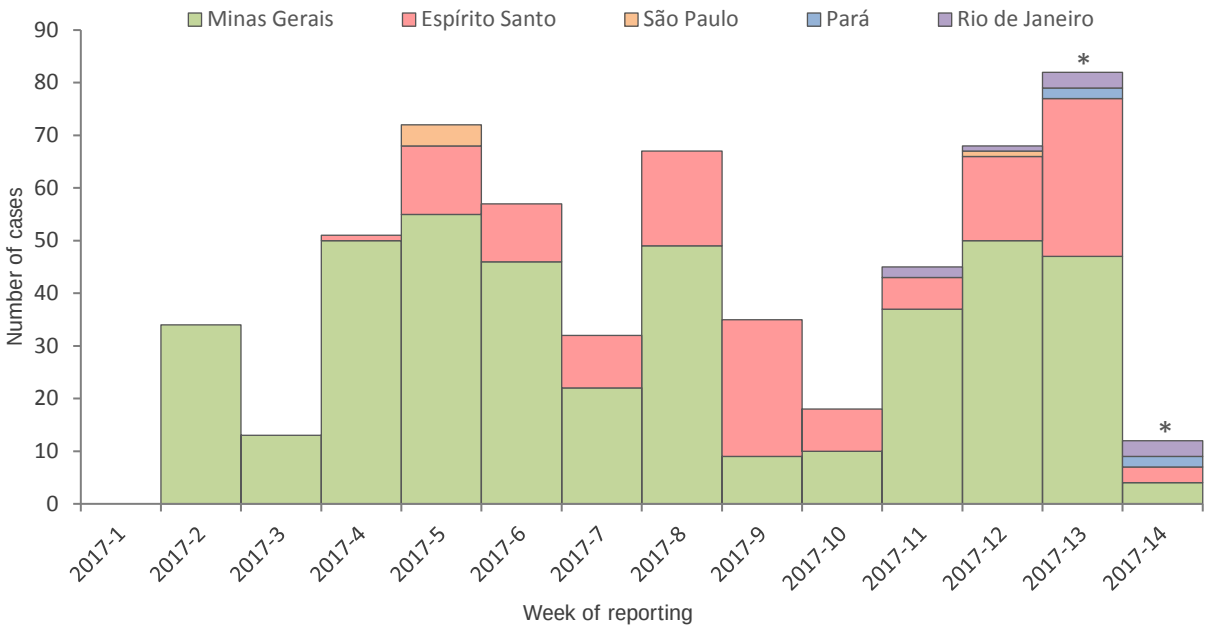
In January 2017, Brazil reported a yellow fever outbreak with two transmission foci in the western part of the State of Minas Gerais and epizootics in the neighbouring State of Espírito Santo [24]. The first laboratory-confirmed cases were reported on 19 January 2017 by Brazil's Ministry of Health. In 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. On 3 April 2017, WHO/PAHO reported six confirmed autochthonous cases in the municipality of Casimiro de Abreu in Rio de Janeiro State, which is located 136 km away from the city of Rio de Janeiro [25].

Between 6 January and 5 April 2017, Brazil reported 1 036 cases (450 suspected and 586 confirmed), including 239 deaths (49 suspected and 190 confirmed) [10]. The breakdown by States is presented in Table 1.

Table 1. Distribution of human cases of yellow fever, by State and confirmation status, Brazil, 6 January–5 April 2017

State	Cases			Deaths		
	Suspected	Confirmed	Total	Suspected	Confirmed	Total
Minas Gerais	287	426	713	38	138	176
Espírito Santo	98	142	240	6	43	49
Rio de Janeiro	19	9	28	1	1	2
São Paulo	8	5	13	1	4	5
Pará	5	4	9	1	4	5
Paraná	9	-	9	-	-	-
Bahia	8	-	8	-	-	-
Santa Catarina	6	-	6	1	-	1
Rio Grande do Sul	4	-	4	-	-	-
Amapá	1	-	1	-	-	-
Distrito Federal	1	-	1	-	-	-
Goiás	1	-	1	-	-	-
Mato Grosso	1	-	1	-	-	-
Mato Grosso do Sul	1	-	1	-	-	-
Tocantins	1	-	1	1	-	1
Total	**450**	**586**	**1036**	**49**	**190**	**239**

Figure 2. Distribution of confirmed human cases of yellow fever by week of reporting and State, Brazil, 2017, weeks 1 to 14 (N=586)



*: incomplete data

Source: Ministry of Health Brazil [10]

As of 5 April 2017, the proportion of cases with laboratory confirmation is 75% in Rio de Janeiro State (nine confirmed cases among 12 samples tested), 57% in Espírito Santo State (142 confirmed among 251 tested), 50% in Pará State (four confirmed among eight samples tested), 32% in Minas Gerais State (426 confirmed among 1 098 tested) and 6% in São Paulo State (five confirmed among 85 tested) [10].

Yellow fever vaccination in Brazil

On 5 April 2017, the Ministry of Health of Brazil started to adopt a single dose of the yellow fever vaccine for areas with vaccination recommendation throughout the country [10]. The measure is valid as of this month (April) and is in accordance with guidance from the World Health Organization (WHO). Vaccination for yellow fever is routine throughout the entire territory of 13 States (Acre, Amazonas, Amapá, Pará, Rondônia, Roraima, Tocantins, Federal District, Goiás, Mato Grosso do Sul, Mato Grosso, Maranhão and Minas Gerais) and in specific sub-areas in six States (Bahia, Piauí, São Paulo, Paraná, Rio Grande do Sul and Santa Catarina) [26]. Brazilian health authorities are recommending vaccination in rural or forested areas and for people who travel to these areas. The States of Ceará, Rio Grande do Norte, Paraiba, Pernambuco, Alagoas, Sergipe, Espírito Santo and Rio de Janeiro are outside of the area covered by the recommended routine vaccination programme [26].

In the context of the yellow fever outbreak in 2017, 21.6 million extra doses have been sent to five States since the start of 2017: Minas Gerais (7.5 million), São Paulo (4.78 million), Espírito Santo (3.65 million), Rio de Janeiro (3.7 million) and Bahia (1.9 million) [10]. In addition, 4.1 million doses have been distributed in Brazil for routine vaccination since January of this year [10]. In the next two weeks, the States of Rio de Janeiro, Bahia and São Paulo will receive one million doses each. At present, 7.5 million doses of vaccine would be needed to immunise the population of areas requiring increased vaccination coverage against yellow fever in affected municipalities in the States of São Paulo, Bahia, Rio de Janeiro, Minas Gerais and Espírito Santo [10].

Travel information

According to the International Air Transport Association (IATA), 584 000 passengers are estimated to have travelled by air between April and June 2015 from the EU/EEA to Brazil. During these three months, the main countries of departure in EU were Italy (17%), France (16%), Portugal (16%), Spain (12%), Germany (11%) and the United Kingdom (10%). Among these, an estimated 404 000 flew to the five States with confirmed autochthonous cases, namely São Paulo (59%), Rio de Janeiro (31%), Minas Gerais (7%), Espírito Santo (2%) and Pará (1%).

Vaccine recommendations

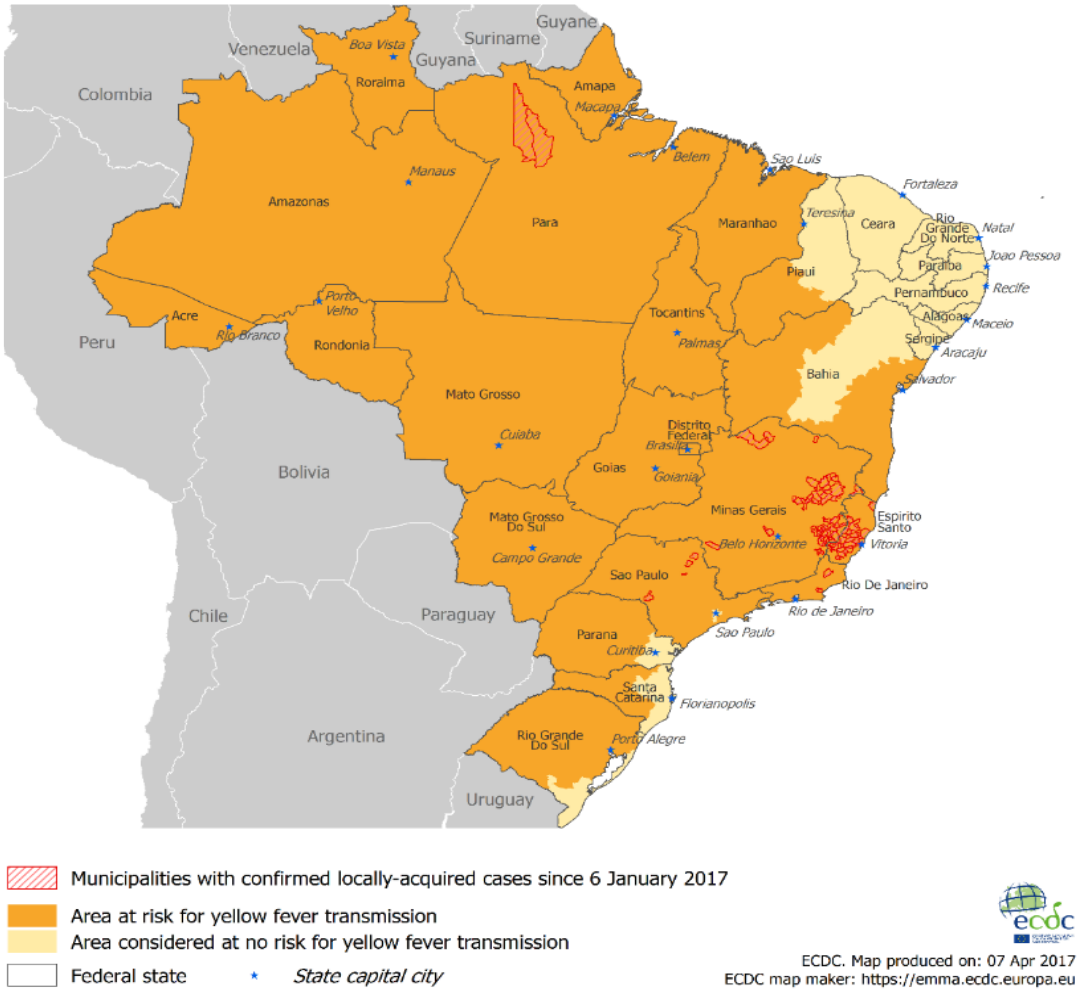
The vaccination recommendations in the six EU Member States with the highest numbers of travellers to Brazil (France, Germany, Italy, Portugal, Spain and the United Kingdom) follow current WHO recommendations [1,8]. The validity of a yellow fever vaccination certificate has now been extended from 10 years to life [27]. Vaccination against yellow fever is recommended for people aged ≥9 months who are travelling to areas considered at risk of yellow fever transmission in Brazil (last update 4 April 2017, WHO link) [1-6].

Prior to the current outbreak, neighbouring States such as Espírito Santo and Rio de Janeiro were considered to be at low risk of transmission and not included in the routine vaccination programme [7,26]. In late January 2017, WHO reconsidered its yellow fever risk assessment in order to inform national immunisation policy and recommendations for travellers, and in connection with this the areas at risk of yellow fever transmission in Brazil were revised, including municipalities in the southern part of Bahia State neighbouring Minas Gerais State, the whole State of Espírito Santo with the exception of the urban area of Vitoria, and northern areas of Rio de Janeiro State bordering Minas Gerais and Espírito Santo. WHO published several updates on the extension of the areas at risk of yellow fever transmission in February and March 2017.

As of 3 April 2017, the WHO Secretariat has determined that the following new areas should also be considered at risk of yellow fever transmission: new municipalities in the State of Bahia, the entire State of Rio de Janeiro (including the urban areas of Rio de Janeiro City and Niterói) and São Paulo, including the urban area of Campinas [25,28]. ECDC will publish and regularly update a map showing areas with a risk of yellow fever transmission, in accordance with WHO recommendations, and the distribution by State of confirmed yellow fever cases in Brazil related to the current outbreak* (Figure 3) [10][25,28].

* http://ecdc.europa.eu/en/healthtopics/yellow_fever/current-transmission/Pages/yellow-fever-map.aspx

Figure 3. Distribution of confirmed yellow fever cases by municipality, Brazil, 2017, as of 5 April 2017



Source: adapted from [1-7, 10]

Yellow fever vaccine

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 [29]. These adverse reactions have only been reported 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 [30]. 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 auto-immune diseases, immune deficiencies or other related underlying conditions, and also among the elderly.

An individual risk benefit analysis should be conducted prior to vaccination, taking into account the season (higher risk of transmission from December to July in Brazil), destination and duration of travel, and the likelihood of exposure to mosquitoes (e.g. rural areas, forests) [31].

ECDC threat assessment for the EU

The geographical extension of the outbreak from Minas Gerais to Bahia and Rio de Janeiro States is of concern since the low vaccination coverage in some areas before the current emergency immunisation campaign means there is a risk of further cases among the local population. There is a possibility of a change in the yellow fever transmission cycle, from a sylvatic cycle to peri-urban or urban cycle during this outbreak. However, to date, *Aedes aegypti* has not been reported as playing a role in transmission [25]. ECDC will closely monitor the situation as confirmed epizootics in the vicinity of large cities (Vitoria, Espírito Santo, Salvador, Bahia and Rio de Janeiro) represent a significant risk for a change in the transmission pattern. The Brazilian health authorities are preparing a strategic plan for dose fractionation of the vaccine if there is a sharp increase in cases of sylvatic yellow fever, with a risk of the disease spreading in cities with large populations.

Risk for EU travellers to and EU residents in affected areas

EU travellers to affected areas or EU residents in the affected areas who are unvaccinated 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.

According to International Health Regulations (2005) 'yellow fever is the only disease for which countries may require proof of vaccination from travellers as a condition of entry under certain circumstances and may take certain measures if an arriving traveller is not in possession of such a certificate' (Annexes 6 and 7 and Article 36) [32]. Since 2016, a single dose of yellow fever vaccine is considered sufficient to confer sustained life-long protective immunity against yellow fever disease [33]. According to WHO, vaccine should be offered to all unvaccinated travellers aged >9 months, travelling to and from at-risk areas following an individual risk-benefit analysis in order to inform the individual decision to be immunised against yellow fever, unless they belong to the group of individuals for whom yellow fever vaccination is contraindicated [34]. Yellow fever vaccination is not required for EU travellers upon entry to Brazil, but WHO recommends valid vaccination before visiting areas at risk of yellow fever transmission, as of 4 April 2017 [28]. ECDC is regularly publishing an updated map and list of States reporting confirmed cases of yellow fever in Brazil.

Risk of transmission in continental Europe

The likelihood of yellow fever virus being introduced into the EU/EEA countries by viraemic travellers returning from Brazil is considered low, as most are likely to have been immunised. However, the introduction of the virus through viraemic travellers remains possible. The likelihood could increase in the event of further geographical spread and intensity of yellow fever transmission, resulting in larger numbers of unvaccinated travellers being potentially exposed.

The risk of local yellow fever transmission in the EU/EEA following introduction by a viraemic traveller is currently considered very low as weather conditions in Europe are not favourable for vector activity. Recent studies have shown that *Aedes albopictus* mosquitoes from France can potentially transmit yellow fever virus in laboratory settings [35]. Yellow fever transmission has not been observed in nature to date through *Aedes albopictus*.

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

French Guiana

French Guiana is endemic for yellow fever. The most recent case was identified in 1998 in an individual living close to the border with Suriname [36]. Routine yellow fever immunisation has been mandatory for residents since 1967, and is compulsory for people entering the area [37]. Vaccination coverage through routine vaccination is high, as demonstrated by the most recent 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 [37].

Atlantic islands

The *Aedes aegypti* vector of yellow fever in urban settings is present in many OCTs and OMRs, particularly in the Caribbean and Madeira. In these areas, yellow fever vaccination checks could be introduced for travellers coming from Brazil in order to reduce the risk of yellow fever introduction. See Annex 1 and country list of the International Travel and Health website [1,8]. Travellers should be aware of potential requests for proof of yellow fever vaccination.

France's High Council for Public Health has published guidelines for reducing the risk of importing yellow fever into receptive areas where *Aedes aegypti* is present by recommending:

- vaccination of travellers to risk areas, applying recommendations for international travellers in accordance with international travel and health guidelines (16 February 2017);
- integrated vector management; and
- enhancement of clinicians' awareness to facilitate early detection of suspected cases [8].

Aedes aegypti is present in Madeira, Portugal, but vector activity is currently low. However, the risk may increase towards the summer months. No proof of yellow fever vaccination is required upon entry to Madeira.

Yellow fever and safety of SoHO

Risk of yellow fever transmission via substances of human origin (SoHO) is theoretical. Transfusion or transplantation-transmitted yellow fever has not been reported although a risk of infectious SoHO donation from an unvaccinated asymptomatic viraemic donor cannot be excluded. The yellow fever 17D vaccine has been transmitted through transfusion of blood donated by recently immunised donors [38]. Donation of blood is possible four weeks after vaccination with attenuated viral vaccine [39].

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