Prevention of yellow fever in travellers: an update

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For centuries, yellow fever virus infection generated substantial fear among explorers, tourist travellers, workers, military personnel, and others entering areas of transmission. Currently, there is transmission only in some areas of tropical South America and sub-Saharan Africa. When symptomatic, yellow fever infection causes severe liver dysfunction and coagulopathy with elevated mortality rates. Since there is no effective treatment, vaccination against yellow fever, available since 1937, represents an important preventive intervention in endemic areas. Every year, an increasing number of individuals are travelling to yellow fever endemic areas, many of whom have complex medical conditions. Travel health practitioners should do individualised assessments of the risks and benefits of yellow fever vaccination to identify potential contraindications. The most relevant contraindications include a history of thymoma or thymus dysfunction, AIDS, and individuals receiving immunosuppressive drugs including biological therapies or chemotherapy. We briefly review strategies to prevent yellow fever infection in travellers with the use of yellow fever vaccination and the use of personal protection measures to avoid mosquito bites.

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Introduction

Yellow fever is a viral haemorrhagic fever caused by a mosquito-borne flavivirus.[1,2] The yellow fever virus is a single-stranded RNA virus transmitted in tropical and subtropical regions of Africa, South and Central America, and Trinidad and Tobago (figure 1).[3] An effective vaccine for yellow fever has been available since the 1930s.[4] Yellow fever remains the only disease specifically designated under the 2005 International Health Regulations for which proof of vaccination or prophylaxis with an International Certificate of Vaccination or Prophylaxis (ICVP) can be required for travellers as a condition of entry to any of the 196 countries, including all WHO member states.[5,6]

An increasing number of individuals are travelling to the tropics, including yellow fever endemic areas.[7] Protecting travellers against yellow fever provides individual benefits and reduces the risk of the introduction of this disease into new settings with ecological conditions conducive for its transmission, including settings where it existed but has been eliminated.[5,8,9] In this Review, we provide an update regarding yellow fever vaccine recommendations in travellers.

Eco-epidemiology of yellow fever infection

Currently, approximately 44 countries are at risk of yellow fever transmission with intermittent sylvatic epizootics, sporadic cases, and urban outbreaks (figure 1).[8,10] Of these countries, 40 are considered the most vulnerable to yellow fever outbreaks (13 in the Americas and 27 in Africa).[10] In nature, the cycle of transmission involves non-human primates and humans who acquired the infection by mosquitoes.[11] Human infection usually occurs in forested areas, although urban outbreaks can occur.[12] This distinction is unclear with the increasing urbanisation of rural areas. In the Americas, human infection occurs in the sylvatic cycle, driven by the growing incursion of human populations into forests or jungles for activities such as housing, mining, agriculture, oil extraction, and other occupational roles.[13] The urban-dwelling *Aedes aegypti* causes transmission during urban outbreaks, being the vector for inter-human transmission from viraemic human hosts in the Americas.[14] In Africa, where the entomological inoculation rate is generally 20–30 times higher than in South America, *Aedes* spp, particularly *Aedes africanus*, causes yellow fever transmission in both the sylvatic, intermediate, and urban cycles.[15] In the hinterlands of tropical South America, *Aedes albopictus* plays a role in bridging the sylvatic and urban cycles.[16,17] As

Key messages

- Increasing global travel poses the risk of introduction of yellow fever into new areas where mosquitoes are capable of effectively transmitting the yellow fever virus
- Depending on the destination and type of travel, a detailed discussion of the risks and benefits of yellow fever vaccination is a crucial element of the pre-travel doctor's visit
- The 17D yellow fever vaccine is a live attenuated strain that generated the 17D-204 and 17DD substrains, which are used to produce yellow fever vaccine and confer lifelong protection in most individuals
- Administration of the yellow fever booster vaccination is indicated in some travellers, including in those whom initial vaccination might not have resulted in immunity. Common examples include patients with a HIV infection, those who underwent a haematopoietic stem-cell transplantation, those who were vaccinated as young children, pregnant women, and others
- Severe and life-threatening side-effects of yellow fever vaccination, such as viscerotropic or neurotropic disease, occur predominantly in those who are very young (<6 months) or very old (>60 years), and those with a history of thymoma and other forms of immunosuppression, such as AIDS and drug-induced immunosuppression (eg, with biologicals)
- Dose-sparing strategies of the yellow fever vaccine do not meet the International Health Regulations but induce similar immune responses to full doses for international travellers during periods of yellow fever vaccine shortage

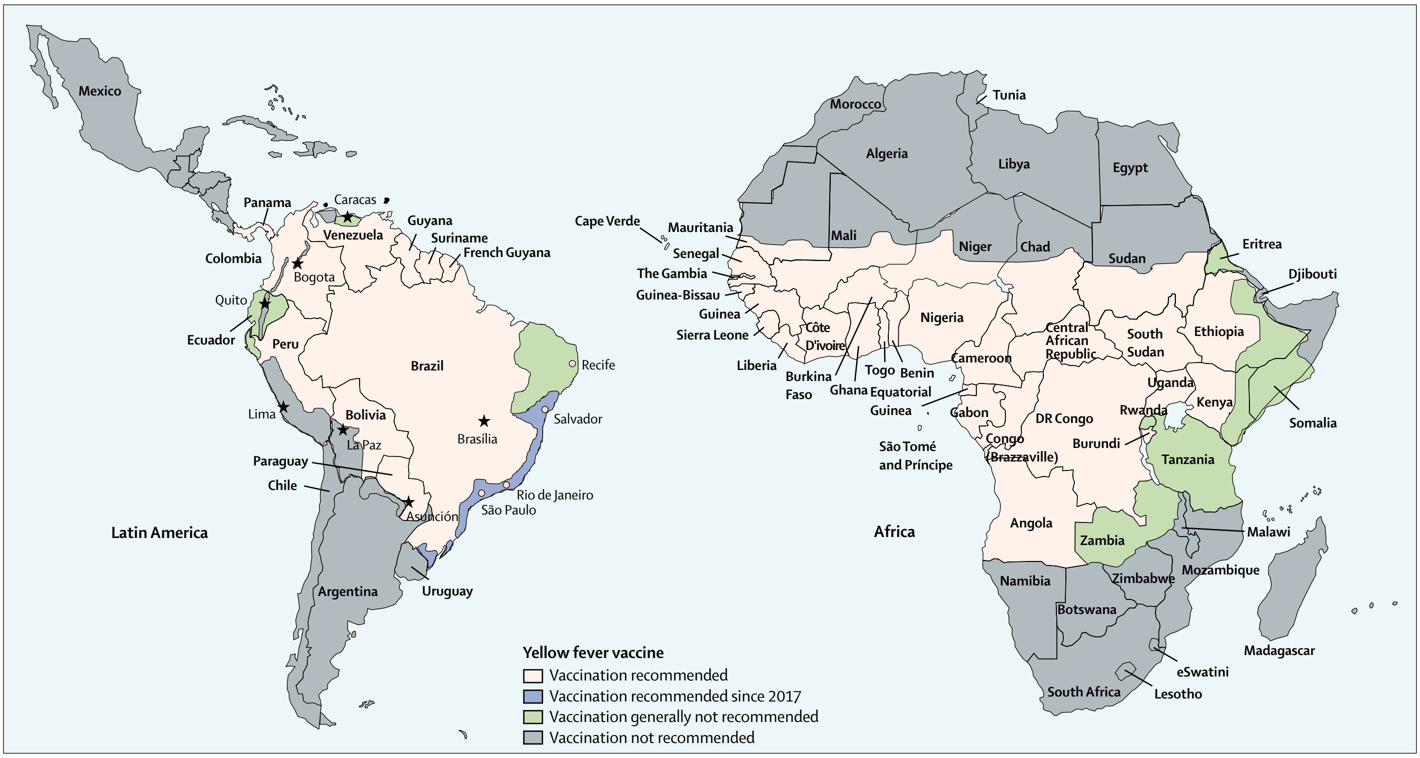

Figure 1: **Geographical areas with risk of yellow fever virus transmission in Latin America and Africa**

this flavivirus initially emerged in these African forests, non-human primates residing in these areas had a high natural immunity, and when infected, they usually developed only asymptomatic viraemia.[2]

By contrast, non-human primates in the Americas, such as howler monkeys (*Alouatta* spp), frequently develop disease with increased mortality rates because of a low baseline natural immunity.[12] During epizootics in the Americas, infection among *Alouatta* spp indicates the circulation of yellow fever and its potential spillover into the human population. Therefore, *Alouatta* spp infection is a surveillance tool used for the early warning of yellow fever transmission and prioritising vaccination efforts.[12,18] There are periodic geographical expansions and retractions of areas at risk of yellow fever transmission linked to complex interconnected ecological factors and the fluid nature of yellow fever virus activity.[19]

Similar to other arboviruses, most individuals with the infection are asymptomatic. The ratio of symptomatic to asymptomatic infection ranges from 1:7 to 1:12.[17] The number of people with the infection is four times higher in west Africa than in the Americas.[17] In South America, among symptomatic infections, the mortality rate reaches 40–60% compared with 20% in west Africa.[1] The lower mortality rate in Africa is most likely because of genetic factors that might have been selected by the co-evolution of the virus and hosts.[17] Overall, there are an estimated 200 000 clinical cases of yellow fever and 30 000 deaths per year, with more than 90% of clinical cases occurring in Africa.[16,20] These numbers rely on passive surveillance, so the true incidence is difficult to estimate, and in many cases, the under-reporting or over-reporting of cases depends on the ability to obtain laboratory confirmation. There seems to be an increase in the number of yellow fever outbreaks over the past few decades in Africa and the Americas. Substantial upsurges in yellow fever activity were noted in Africa in the 1960s, and the Americas in the late 1980s.[21,22] In Brazil, an epidemic took place from 1935 to 1940, followed by sporadic cases in the following decades in endemic areas of the Amazonian states subsequently spreading to the Brazilian states of Minas Gerais in 2002, and São Paulo, Paraná, and Rio Grande do Sul in 2007–2009.[23,24] There were also outbreaks in Argentina and Paraguay in 2007–09. The yellow fever outbreak in Brazil, from Dec 2016, to Oct 2018, highlights the overlap of the sylvatic and urban cycles of yellow fever transmission with the *Sabethes* spp mosquito playing a crucial role in the Americas.[11,15,25] This outbreak occurred mostly in the coastal areas of the states of São Paulo, Minas Gerais, and Rio de Janeiro, with cases occurring in large urban centres leading to more than 2000 cases and more than 680 deaths.[11,15,26,27] In Africa, a massive outbreak occurred in Angola during 2015–16, spreading to the Democratic Republic of the Congo and Uganda and causing more than 4000 cases of yellow fever and more than 375 deaths.[17,28] In the Americas, before the outbreak in Brazil, there was also an outbreak in Peru and Bolivia from 2016 to 2017, resulting in more than 85 cases with 32 deaths.[15]

Yellow fever infection might result in a spectrum of clinical manifestations, ranging from a non-specific viral illness to full-blown haemorrhagic fever and death.[16] People with the symptomatic disease often present with a biphasic illness. During the initial phase, patients present with fevers, chills, headache, back pain, myalgia, nausea, vomiting, and fatigue. The second phase manifests with high fever, jaundice, coagulopathy, hepatitis, and renal failure.[1] Treatment is limited to supportive medical care since no antiviral therapy is effective. In the outbreak in Brazil, patients admitted to the intensive care unit with severe manifestations of yellow fever had better outcomes when they received proton-pump inhibitors to prevent gastrointestinal bleeding, anticonvulsant therapy when their ammonia concentrations were more than 70 μmol/L, and underwent early institution of plasma exchange.[29] Despite these interventions, the in-hospital case fatality rate was 67%.[29] To reduce the effect of yellow fever in endemic areas, it is essential to raise population immunity through routine childhood immunisation activities and mass vaccination campaigns.[10,22]

Yellow fever infection in travellers

Yellow fever emerged in Africa approximately 3000 years ago.[2] Accounts of people with yellow fever date back to the end of the 15th century, with outbreaks described in west African countries among colonial populations.[2] Yellow fever arrived in the Americas through the slave trade, where it established a sylvatic cycle in the rainforests of Central America and the Amazon rainforest.[4] In the Americas, the first massive outbreak of yellow fever occurred in 1648.[30]

The construction of the Panama Canal is considered a noteworthy event in the history of yellow fever control efforts.[31] Under the leadership of President Franklin D Roosevelt, the USA commenced the canal project in 1904. In 1900, US army physician James Carroll exposed himself to an infected mosquito and succumbed to yellow fever, but this action allowed Dr Walter Reed to identify the cause for yellow fever transmission. After the confirmation of yellow fever transmission, Dr William Crawford Gorgas became the chief sanitary officer of the construction activities in the Panama Canal in 1905.[4] Gorgas orchestrated a relentless campaign to eliminate mosquito-breeding sites by using pesticides and larvicidal oil, drying out swamps, paving streets, and installing sewage systems.[31] The Panama Canal officially opened in August 1914, with a resultant increase in population movement through yellow fever endemic areas.[4] For many years, yellow fever posed a substantial threat. This infection decimated populations and human settlements with repeated epidemics in cities and coastal towns, and was exported to the Americas, the Caribbean, and Europe.[30] The development of two yellow fever vaccines in the 1930s and vector control efforts for *A aegypti* reduced its geographical range in large South American cities and resulted in a decline in the incidence outside the endemic tropical areas.[14,32] As a result of its declining effect on human populations from the 18th century to the early 20th century, yellow fever has moved down in the list of global health priorities.[16]

There continues to be sporadic cases and urban outbreaks of yellow fever in tropical areas of Africa and Latin America.[16] Additionally, an increasing number of travellers visit remote locations in tropical settings every year, and many of these individuals are unvaccinated.[32,33] The overall estimate of the risk of acquiring yellow fever among unvaccinated travellers for a 2 week stay to a high-risk area in Africa is 50 cases per 100 000 people;[8,21,34] whereas in South America, the risk is five cases per 100 000 people.[35] From 2016 to 2018, there were numerous outbreaks of suspected and confirmed cases of yellow fever resulting in many cases occurring in returning travellers.[26,27] However, there are some notable limitations to these data since the risk of acquiring yellow fever infection in travellers depends upon the destination, type of travel, season of travelling, presence of an ongoing outbreak, entomological index of transmission, and traveller vaccination status. For example, an outbreak of yellow fever took place in urban areas of Angola, spreading to neighbouring countries including the Democratic Republic of the Congo and Uganda. During this outbreak, 11 Chinese workers infected in Angola returned to China with yellow fever.[17,28,36] During the aforementioned outbreak in Brazil, there were 11 cases of yellow fever in travellers from France, Denmark, Romania, Switzerland, Germany, Argentina (three cases), and Chile (three cases). Among these travellers, there were four deaths (a case fatality rate of 36%). Most cases occurred in travellers visiting Ilha Grande, Rio de Janeiro, Brazil.[26,27]

To protect travellers and to reduce the risk of introduction (or reintroduction) of yellow fever into new geographical locations, the International Health Regulations by WHO recommended that people older than 9 months who are travelling to areas with a risk of yellow fever virus transmission should receive yellow fever vaccination, unless there is a potential contraindication.[8,21,26,35] Additionally, it is recommended that unvaccinated travellers should avoid travel.[37] Currently, there are many tropical areas globally that are free of yellow fever transmission, but where the yellow fever virus might find suitable ecological conditions for its transmission, including a high population density, environmental determinants, and vector prevalence and competence (ie, *Aedes* spp).[9] The possibility of the inter-human transmission of yellow fever in non-endemic settings by viraemic human hosts because of increasing travel to and from areas where there is a risk of yellow fever poses a severe threat, similar to what has occurred with the global spread of other arboviruses, including Zika virus and chikungunya.[17] Dispersion of yellow fever by travellers into new locations might lead to a public health emergency of international concern.[9]

Yellow fever vaccine in travellers

In 1918, the Rockefeller Foundation's International Health Commission resolved to assist in controlling yellow fever in the Americas. Initial efforts in Guayaquil, Ecuador, to develop a yellow fever vaccine resulted in many attempts that did not work.[4] After World War 1, a second yellow fever commission took place in Lagos, Nigeria, from 1925 to 1927.[4] The identification of the Asibi strain of the vaccine in 1927 was the result of this commission's efforts, whereas researchers at the Pasteur Institute in Dakar, Senegal, had previously developed the French neurotropic vaccine (Mayali strain).[10] In the 1940s, both vaccines were widely deployed. The western hemisphere and UK used the Rockefeller Foundation vaccine, whereas France and francophone African countries used the one developed at the Pasteur Institute.[16] By 1937, the Asibi strain eventually became the 17D vaccine after the 176th passage in subcultures by Max Theiler and Eugen Haagen, leading to this strain losing its viscerotropism and to some degree, its neurotropism.[4] Since the French vaccine was applied by scarification, more than 50 million Africans received this type of vaccine during mass vaccination campaigns by 1953. However, by 1983, the production of the French vaccine stopped because of substantial evidence showing the occurrence of severe neurological adverse events associated with its administration.[4] Since then, the 17D vaccine, manufactured from a defined number of seed lots, became the only one in use.[38] The yellow fever vaccine in use nowadays originates from two sub-strains of the 17D vaccine, the 17DD vaccine obtained from passage number 195 in subcultures, and 17D-204 vaccine from passage 204.[39] Both yellow fever vaccines are highly immunogenic by inducing potent cellular and humoral responses with similar safety profiles (the two vaccines have approximately 99·9% genomic similarity and similar immunogenicity and reactogenicity).[40] The reported protection of these two strains, as shown by the measurement of antibodies neutralised with the use of constant serum-varying virus (known as the log neutralisation index, the log reduction in virus titre by minimally diluted serum) and by constant virus-varying serum assays such as plaque reduction neutralisation, are 90–97% for 17D-204 and 90–98% for 17DD.[17,40] Antibodies neutralised to highly conserved conformational epitopes in the envelope glycoprotein, and possibly to the yellow fever non-structural protein NS1, are accepted as the surrogate markers of protective immunity.[1,17] These antibodies are identified in more than 90% of vaccines by day 10, which is underlying the consideration of day 10 after vaccination as the valid date for the ICVP.[17] There are currently six yellow fever vaccine producers with only four considered as prequalified by WHO: Bio-Manguinhos (Rio de Janeiro, Brazil), Sanofi Pasteur (Lyon, France), Institute Pasteur (Dakar, Senegal), and the Institute of Poliomyelitis and Virus Encephalitis (Moscow, Russia). As part of the WHO global strategy to eliminate yellow fever epidemics 2016–17, over the next decade, manufacturers of the yellow fever vaccine are planning to reach the 1·38 billion doses needed to eliminate the risk of yellow fever epidemics.[38,39]

Recommendations for yellow fever vaccination

Yellow fever vaccine should be given during childhood in endemic areas as part of routine immunisation programmes and supplemental immunisation activities, including emergency response during outbreaks and catch-up campaigns in endemic areas.[22] In many countries where there is yellow fever transmission, national immunisation programmes routinely offer yellow fever vaccine. In Africa, 22 of 27 countries with the risk of yellow fever transmission had introduced yellow fever vaccine into their childhood immunisation programme by 2017.[22] WHO expects that by the end of 2020, the remaining five African countries will have introduced yellow fever vaccine into their routine immunisation programme.[10] In the Americas, all countries with yellow fever transmission have introduced yellow fever vaccine into their routine vaccination programmes, but because of insufficient coverage, at least 11 of these countries are having catch-up campaigns to reach pockets of unvaccinated populations.[22] Increased vaccination coverage occurs during supplemental immunisation activities, such as catch-up immunisation campaigns and emergency response vaccination during outbreaks. Also, many yellow fever vaccines are given to travellers by travel health practitioners after doing a risk–benefit analysis for each patient to decide the need for the vaccine[21,26,32,37] (figure 2).

Individuals of all ages for whom vaccination is indicated (either as the initial or booster dose) should receive a subcutaneous injection of 0·5 mL of reconstituted vaccine.[21] Inactivated vaccines can be given simultaneously with the yellow fever vaccine during the pre-travel health check-up. Regarding other live viral vaccines, such as the measles, mumps, and rubella vaccine, it is recommended to give the yellow fever vaccine either simultaneously or 30 days apart from other live viral vaccines. By contrast, given the different routes of administration, the oral Ty21a typhoid vaccine can be offered simultaneously at any interval before or after receiving the yellow fever vaccine.[21]

In April, 2013, the WHO Strategic Advisory Group of Experts in Immunisation recommended that only a single primary dose of yellow fever vaccine be given, because it is sufficient to confer lifelong protection against yellow fever.[41] As a result, WHO recommended removing the 10-year booster requirement from the International Health Regulations by June, 2016, and to consider the vaccine protective for life.[22,35,42] However, this recommendation requires careful judgment by travel medicine practitioners regarding the need for booster doses.[8,41,43] Most experts recommend assessing the likelihood that the traveller remains seropositive at the

10-year mark, the specific travelling location, type of travel (as adventurous outdoor travellers are at highest risk), duration of travel, and the overall risk of exposure where an individual is travelling (if there is a current outbreak).[26,35,44] For example, a traveller who plans to spend a prolonged period during the peak transmission season in rural west Africa, or an individual travelling to Ilha Grande in Brazil, might require booster doses of the yellow fever vaccine. Boosters are needed if the traveller had an HIV infection when the last dose was given and their CD4 cell count was less than 350 cells per μL during previous administration; if they are a laboratory worker handling wild-type yellow fever and need another dose; if they were pregnant at the time when the initial dose was given; if they had a haematopoietic stem-cell transplant (HSCT) after receiving the initial dose; or if they had another form of severe immunosuppression.[35] Pregnant women have variable immune responses, which are most likely related to the trimester in which they received the yellow fever vaccine. Lower seroconversion occurs during the third trimester most likely because of alterations in cell-mediated immunity.[35,45] Boosters are also recommended for children who received yellow fever vaccine at a young age, particularly for those who received the vaccination at younger than 9 months of age.[46,47]

Additionally, considerations should be given for booster doses for those who were vaccinated during severe immunosuppression, including severe protein-deficient malnutrition. Given that the highest risk for travel-associated yellow fever occurs when travelling to west African countries or when travelling to any endemic area with an ongoing outbreak, a booster vaccination should be considered among those planning prolonged travel periods or if their occupation places them at increased risk of exposure to mosquitoes. In addition to vaccination, the use of insect repellents applied to the skin and impregnated clothing is highly recommended for travellers.[32,35,48]

Adverse effects of the yellow fever vaccine

The 17D and 17DD vaccines are live-attenuated strains that can cause serious adverse events, including vaccine-associated viscerotropic disease (YEL-AVD) or yellow fever 17D vaccine-associated neurotropic disease (YEL-AND).[40,49,50] In terms of YEL-AND, between March, 1989 and March, 2011, 113 cases of adverse neurological events, including acute meningoencephalitis syndrome, Guillain-Barré syndrome, and acute disseminated encephalomyelitis were reported worldwide following yellow fever 17D vaccination.[35] Between 1990 and 2010, 31 patients with YEL-AVD were reported in travellers from the USA, Europe, Australia, Japan, and China, whereas only six travellers had a yellow fever infection.[21] Of the 31 patients with YEL-AVD, 12 died from the infection (a case fatality rate of 39%), whereas all six of the patients with the natural yellow fever infection died (a case fatality rate of 100%).[21,26]

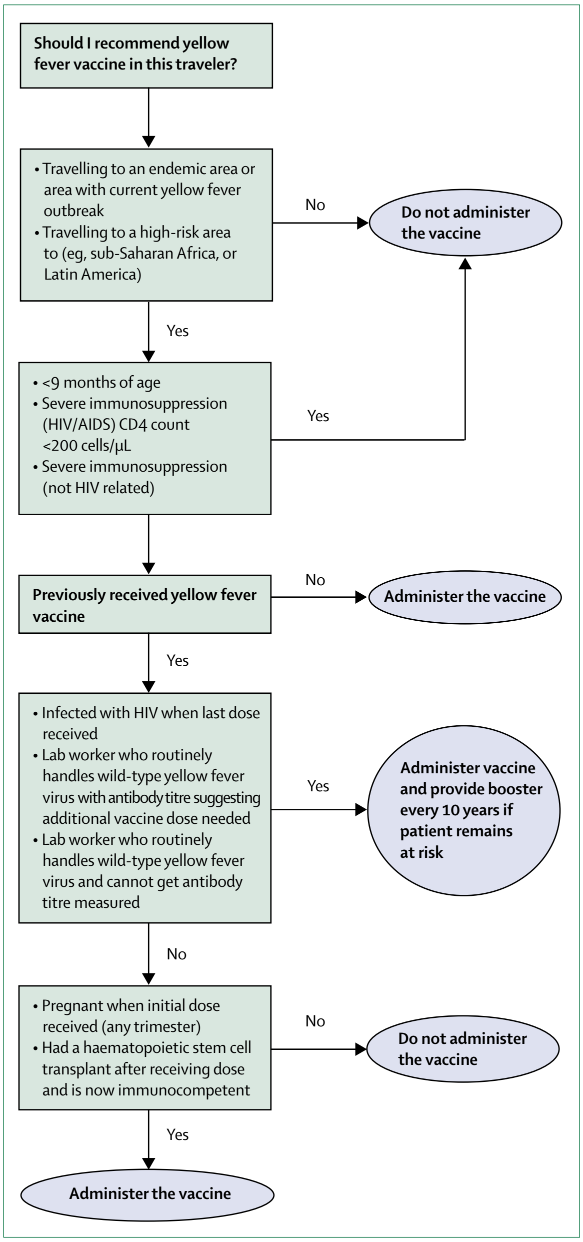

Figure 2: **YF vaccine and booster administration flow chart**

The severity of YEL-AVD is higher than any other vaccine-related adverse event with an overall case fatality rate of approximately 63%. The overall rate of serious adverse events associated with the yellow fever vaccine is three per 100 000 doses of yellow fever vaccine given to individuals younger than 60 years, and eight per 100 000 doses given to individuals 60 years or older.[38,49,51] The rate of YEL-AND, which is rarely fatal, occurs in those younger than 60 years at a rate of 0·8 per 100 000 doses but a rate of 2·2 per 100 000 doses in individuals 60 years or older.[38,49] YEL-AVD, which has a mortality risk of 30–60%, occurs at a rate of 0·3 per 100 000 doses in individuals younger than 60 years and a rate of 1·2 per 100 000 doses among those who are 60 years and older[49] (table). YEL-AVD has been reported in 72 vaccine recipients among 437 million doses distributed of the yellow fever vaccine, with only one occurring after booster vaccination.[38,49]

There have been 218 cases of YEL-AND, with only three cases occurring after receiving booster doses.[32,38] There is little information available on the safety of the yellow fever vaccine given during pregnancy. The yellow fever vaccine being given inadvertently in pregnant women has not been associated with severe adverse events, including major malformations or increased risk for fetal death.[35]

Another important safety concern is the potential serological interaction among individuals vaccinated against yellow fever, increasing the severity of dengue infections by antibody-dependent enhancement. In this regard, evidence suggests that in dengue-endemic areas there is no apparent association between having been given yellow fever vaccination and an increased risk of severe dengue fever.[52]

Fractionated dosing of yellow fever vaccination

The use of fractionated doses of the yellow fever vaccine is considered a vital vaccination strategy during vaccine shortages, mainly if this occurs during an outbreak.[8] Some studies have documented that the administration of a fifth (0·1 mL) of the regular full dose of the yellow fever vaccine induces a protective immune response that lasts for more than 10 years among otherwise healthy adults.[53,54] A dose-sparing regimen was first used in children younger than 24 months, pregnant women, and those living with HIV during the 2016 yellow fever outbreak in the Democratic Republic of the Congo.[55] A second dose-sparing alternative is the intradermal administration of the yellow fever vaccine, which offers the potential advantage of mimicking natural yellow fever inoculation by an infected mosquito and promoting infected dendritic cells to travel to regional lymph nodes, resulting in viraemia and systemic infection.[8] Two studies by Roukens and colleagues[53,54] in the Netherlands have shown the non-inferiority of the fractionated dose of Stamaril (Sanofi Pasteur, Lyon, France) compared with the full dose of yellow fever vaccine in terms of immunogenicity and duration of seroconversion. At this point, intradermal administration of the yellow fever vaccine is not considered a standard recommendation but is certainly a strategy that could be instituted in the context of an outbreak with insufficient supplies of the yellow fever vaccine.

	<60 years	≥60 years
Overall serious events	3·0/100 000	8·0/100 000
Neurotropic disease	0·8/100 000	2·2/100 000
Viscerotropic disease	0·3/100 000	1·2/100 000

Number of adverse events recorded per 100 000 vaccine administrations by disease process and age at the time of vaccination.

Table: **Adverse events associated with yellow fever vaccination**

Yellow fever vaccination in travellers with specific conditions

There are many important risk factors that should be addressed when considering the yellow fever 17D vaccine. Special consideration should be given to young children, pregnant women, individuals with HIV, patients who are immunocompromised, including those with a history of thymus disorder (thymoma or myasthenia gravis), and adults aged 60 years and older.[56] These individuals not only have a variable immune response but also have a higher rate of serious adverse events related to the 17D yellow fever vaccine.[57] Travel health practitioners should consider offering yellow fever vaccination to travellers visiting high-risk areas in sub-Saharan Africa and tropical South America if there is no previous history of receiving this vaccine, and the individual has no contraindication.[35] The immunogenicity of yellow fever vaccine among individuals who receive the vaccine by the age of 10 years old is 92%, and for those people vaccinated when they are older than 20 years is 80%. The rate of vaccine seroconversion in children aged 4–10 years is 93%.[32,58] The neutralising antibody response generated to the 17D vaccine is lower in African-American populations than in those of white European ancestry, most likely reflecting some genetic barrier of resistance in African populations.[17] Yellow fever vaccine is highly effective since there have been few cases of the vaccine not working reported among 540 million doses given.[42] Among situations where the vaccine did not work, many have occurred within 10 days of vaccination. Travellers need to obtain their vaccine at least 10 days before entering an endemic area of yellow fever transmission.[24,32,33,35]

Contraindications to yellow fever vaccine

Similar to other live-attenuated vaccines, yellow fever vaccine is contraindicated in immunocompromised individuals.[59–61] Travel-related risk in individuals living with HIV depends on the immune status of the patient.[61,62] Advanced HIV-associated immunosuppression is a contraindication for yellow fever vaccine administration, including HIV infection or $CD4^+$ T-cell count of less than 200 cells per μL (<15% of total in children aged <6 years).[61,63] Among those with a $CD4^+$ T-cell count of 200–350 cells per μL, there are some concerns of reduced immunogenicity and safety.[61] In this patient group, we recommend that the decision to give the yellow fever vaccine should be individualised, taking into account factors such as whether the patient has achieved virological suppression for more than 6 months and whether the patient has a history of adequate adherence to antiretroviral therapy. Between $CD4^+$ T-cell counts of 350–499 cells per μL yellow fever vaccine is safe, but it might have reduced immunogenicity.[61,63,64] Among those with a CD4+ T-cell count of greater than 500 cells per μL, vaccination is considered safe and immunogenic (when the antibody titres were measured at 30 days and 1 year after vaccination).[63]

The yellow fever vaccine is contraindicated in those with a CD4+ T-cell count of less than 200 cells per μL or below 15% of total lymphocytes in children younger than 6 years, because of safety and immunogenicity concerns.[35] Additionally, the yellow fever vaccine is contraindicated in patients with thymus disorders associated with abnormal immune function, including thymoma, individuals with malignant neoplasms receiving chemotherapy, immunosuppressive, and immunomodulatory therapies such as biological agents including rituximab,[65,66] individuals with primary immunodeficiencies, those with an allergy to a vaccine component, and those with a history of transplantation.[21,35] There are some additional precautions that clinicians need to consider when recommending the yellow fever vaccine, including when recommending it to pregnant women or during lactation, in individuals older than 60 years, in people living with HIV with CD4+ cell counts between 200–499 cells per μL, or children living with HIV younger than 6 years with a 15–24% total lymphocyte count.[21,35] Similar to other immunosuppressive conditions, a history of transplantation has been a contraindication for the use of live-attenuated vaccines, including the yellow fever vaccine.[48,51,58–63] However, there are reports of the use of the yellow fever vaccine in both HSCT and solid organ transplant recipients.[67,68] The most extensively reported case series of the safety and immunogenicity of the yellow fever vaccine among HSCT recipients include 21 individuals who had a withdrawal of immunosuppression (39 months after HSCT and 33 months after the discontinuation of immunosuppression) and no history of graft-versus-host disease.[69–71]

Additionally, there are more than 20 individuals included in different reports who received both yellow fever vaccine and solid organ transplantation without evidence of severe adverse events.[72] Therefore, we suggest that for individuals with a history of HSCT or solid organ transplant, practitioners should carefully weigh the risk–benefit ratio by using individualised assessments of the risk of acquiring yellow fever versus potential adverse events associated with vaccination. Selected individuals in whom immunosuppression has been discontinued for 2 years or longer, have no evidence of graft-versus-host disease, and have normal CD4+ cell counts and IgG concentrations might be potential candidates to receive yellow fever vaccination. Nevertheless, patients should be discouraged from travelling to endemic areas during the initial years after transplant.[71]

Documentation of yellow fever vaccination

Travellers should provide proof of yellow fever vaccination at international points of entry into some countries under the International Health Regulations. Many countries require proof from travellers arriving from specific countries to prevent the importation of yellow fever.[21] As proof, a completed ICVP should be stamped and signed. Travel health practitioners who issue the ICVP should note that the main difference from the old certificate is that they have to specify in writing that the disease for which the certificate is issued is yellow fever.[5] For people in whom the administration of the yellow fever vaccine is contraindicated and are still considering travelling to an endemic area of yellow fever transmission or to a country that requires proof of yellow fever vaccination, the medical contraindication section of the ICVP should be completed specifying yellow fever vaccine, the name of the traveller, and reasons for contraindication. This section of the ICVP should be signed by the health-care provider to be considered as a medical waiver to fulfil international regulations. It is also recommended that travel health practitioners provide the traveller with a signed and dated exemption letter.[21]

In January, 2019, the public health authorities of Brazil started issuing the ICVP electronically to facilitate international travel and trade. Therefore, authorities at international points of entry, on airlines, and at other conveyances operators need to be aware of this policy introduced by Brazil.[6] This certificate can be accessed electronically anywhere in the world by downloading the certificate from a designated website. This situation might lead to a paradigm change regarding the expedition of ICVP among other countries in the Americas and other continents. Finally, under the International Health Regulations, WHO does not recommend documenting fractional doses of yellow fever vaccine in the ICVP card. However, a letter or note can be written in a different vaccination record to note a fractional dose of 0·1 mL of the yellow fever vaccine being given in the context of potential vaccine shortages.[73]

Conclusions

Preventing yellow fever in travellers offers individual benefits and reduces the risk of introducing yellow fever into non-endemic areas with conducive ecologies. For most travellers, immunisation once in a lifetime might provide enough protection. However, travel medicine practitioners should assess every traveller regarding the likelihood of maintaining protective antibodies and the intensity of yellow fever transmission at the travel destination. Young children, pregnant women, individuals living with HIV, and with other forms of immunosuppression require further booster yellow fever vaccination when travelling to at-risk areas. Travellers with contraindications for receiving yellow fever vaccine and travelling to yellow fever endemic areas should be discouraged from travelling. However, if travel is urgent or inevitable, travellers should adhere to strict personal protective clothing and insect repellent use (for skin and clothes). There are essential contraindications to

Search strategy and selection criteria

We identified references through PubMed and Scopus searches (applying a restriction to English, Spanish, and Portuguese articles) using the search terms: "arbovirus", "flavivirus", "yellow fever", "America", "Africa", "yellow fever vaccination", "travellers", and "emergence", from January, 1960, to December, 2019. We included multiple spellings, truncated nomenclatures, and abbreviations in the search. We reviewed the articles resulting from these searches and the most relevant references cited in those articles.

consider when recommending yellow fever vaccine, including allergies to components of the vaccine, history of thyroid disorders such as thymoma, drug-induced immunosuppression, and advanced HIV-associated immunosuppression. Among individuals older than 60 years, the decision to recommend vaccination depends upon individualised assessments of the specific destination, type of travel, and comorbidities. The outbreak of yellow fever in Brazil leading to many cases occurring among unvaccinated travellers illustrates the importance of educating travellers regarding the risk of this infection and travel health practitioners continuously maintaining updated information regarding the epidemiology and transmission patterns of yellow fever in endemic regions.

Contributors

ER, AFH-M, and CF-P conceived the idea of the article. ER, NGQ, DBC, and CF-P did the search in bibliographical databases and the literature review. AJR-M developed the final figures. LC reviewed the literature and revised the manuscript for content. All authors read the first draft and contributed to subsequent versions. All authors approved the final version.

Declaration of interests

AFH-M reports a K12-clinical trial award and is the co-principal investigator of the Expanded Access Investigational New Drug Application Programme to provide Stamaril vaccine to people in the USA for vaccination against yellow fever. All other authors declare no competing interests.

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