



# Yellow Fever in Travelers

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## Abstract

**Purpose of Review** This decade has seen a resurgence of yellow fever (YF) that has also affected travelers with a record number of international travelers infected by YF virus including the first documented importation of YF into Asia.

**Recent Findings** The recent resurgence of YF has been attributed largely to sub-optimal vaccination coverage along with waning population-level immunity. New lessons have been learnt with regard to the clinical management of severe YF as a result of the Brazilian outbreak. With increasing YF cases in travelers, travel medicine providers need to familiarize themselves with the diagnosis and clinical management of severe YF. Prevention remains the mainstay, and all efforts need to be taken that travelers do not circumvent the International Health Regulations. More than 80 years of experience with YF vaccine reinforce the generally acceptable safety profile of YF vaccine but highlight the unique serious adverse events of viscerotropic and neurotropic disease, in particular in first-time vaccinees.

**Summary** Continued physician and traveler education regarding the risks and benefits of YF vaccination is needed, with an urgent need to better define “significant and unavoidable risk” for improved benefit-risk assessments.

**Keywords** Viscerotropic adverse events · Neurotropism · Risk-benefit assessment · Travel

## Introduction

Yellow fever is an old-age scourge and one of the arboviral diseases associated with the highest case fatalities [1]. This decade has seen a resurgence of yellow fever (YF) that has also affected travelers with a record number of international travelers infected by YF virus returning to Europe and the USA [2]. End 2015 to mid 2016, Angola experienced its biggest yellow fever outbreak for decades that rapidly spread via mobility networks within the country and to neighbouring nations [3]. Towards the end of 2016, YF outbreaks emerged in close proximity to the most populated areas of metropolitan São Paulo and Rio de Janeiro in Brazil, thus posing an all-time high risk for rapid global spread via air travel. Healthcare

professionals from non-endemic countries are therefore increasingly likely to see travelers with yellow fever. Here we review the risk of yellow fever in travelers, clinical management, as well as provide an update on the efficacy and safety yellow fever vaccines.

## Epidemiology

Yellow fever is an acute infectious disease caused by the yellow fever virus, a flavivirus transmitted in tropical or subtropical areas, mainly through the bite of infected *Aedes* spp. mosquitoes. YF is currently reported or has been reported in 34 countries in tropical Africa and 13 countries in the Americas, with sub-Saharan Africa carrying about 90% of the overall burden. Official reports of yellow fever incidence grossly underestimate the true number of cases, first of all because surveillance is based on the case definition of “fever and jaundice”, but jaundice is not frequent even in severe yellow fever cases [4]; second, in many countries, no surveillance systems exist; and third, a large proportion of yellow fever infections can be asymptomatic or mildly symptomatic and difficult to differentiate clinically from other febrile

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illnesses in countries with limited resources for laboratory confirmation.

The recent resurgence of YF has been attributed largely to sub-optimal vaccination coverage along with waning population-level immunity [5]. Overall, substantial increases in YF vaccine coverage have occurred since 1970, but notable gaps still exist in coverage within risk zones, with around 400 million people still requiring vaccination in areas with YF virus transmission to achieve the 80% population coverage threshold recommended by WHO. The resulting gaps in YF vaccination coverage affect between 43 and 52% of the population within yellow fever risk zones [5, 6]. Lack of harmonized YF maps and the changing epidemiology of YF led to a collaborative WHO and CDC initiative in 2008–2010 to develop criteria and systematically apply such criteria for the designation of risk and specific changes to the classification of areas with risk of transmission of YF virus [7]. Four levels of YF risk were outlined and geographical areas were classified into the following categories: endemic, transitional, low potential for exposure and no risk.

## Risk in Travelers

The travel volume to YF endemic areas and countries is increasing rapidly [8]. More than 9 million people from non-endemic countries in Asia, Europe and North America travelled to countries where YF is endemic in 2002, and these numbers have likely increased given the increasing travel volumes globally [9]. Unvaccinated travelers who visit areas in Africa during periods of epidemic activity have an estimated risk of 1 in 267 and risk of death of 1 in 1333, although the risks are considerably lower during inter-epidemic periods [9]. Risk of illness and death for individuals travelling to South America is thought to be about ten times lower than it is for those travelling to Africa, because of the lower rate of transmission in the jungle cycle in the Americas [9].

In recent years, the number of travelers importing yellow fever virus to non-endemic countries is at a record high [10]. Eleven unvaccinated Chinese working in Angola were infected with YF virus and exported the virus to China; the first documented exportation of yellow fever via travelers to Asia [11]. Between January 2018 and December 2018, 10 travel-related cases of yellow fever, including four deaths, were reported in unvaccinated international travelers returning from Brazil [2]. Since then, two further cases were reported through the GeoSentinel Surveillance Network (GeoSentinel Director Dr. David Hamer, personal communication). GeoSentinel is a global network of travel medicine providers that see ill returned travelers [12] and is set up to assess destination specific risks [13], risks by purpose of travel [14–17], and by diseases [18–22] and time trends [23]. Yellow fever was not reported in a descriptive analysis of life-threatening tropical

diseases among 82,825 ill western travelers reported to GeoSentinel from June 1996 to August 2011 [24]. Travelers' risk of acquiring YF is difficult to predict due to seasonal and epidemic variations, short duration of travel, ecologic determinants of virus transmission, immunity profiles and activities. Overall, however, the incidence of YF in travelers is very low, lower, in fact, than most other vaccine-preventable travel-related diseases [24–26], also because many travelers are protected through YF vaccination.

## Clinical Manifestations and Clinical Management

Clinical symptoms usually appear 3–6 days after a bite from an infected mosquito. YF virus first replicates in the site of inoculation, after which it spreads to the lymph nodes. It then travels to the liver, spleen, bone marrow, kidneys and myocardium but rarely spreads to the brain; instead, it exhibits mainly viscerotropic affinity. As for other flaviviruses such as dengue [27] and Japanese encephalitis [28], the majority of infected persons remain asymptomatic. In those who become symptomatic, typically, the disease onset is abrupt and characterized by fever, muscle pain, particularly backache, headache, shivering, loss of appetite and nausea or vomiting. Congestion of the conjunctivae and face is common, as is relative bradycardia in the presence of fever [29]. In approximately 15% of symptomatic persons, the illness recurs in more severe form after a brief remission of 2–24 h [29]. YF can be a treacherous disease as its initial clinical presentation may be quite benign and non-specific but can then take a fulminant course within a matter of a few days [30]. Clinicians need to be highly suspicious of YF, as earlier diagnosis may result in better management of this life-threatening disease.

Treatment of uncomplicated yellow fever is based on supportive clinical management. In mild disease, acetaminophen or paracetamol is used to treat the symptoms of fever, myalgia and back pain and the patient can be managed at home. Salicylates and non-steroidal anti-inflammatory drugs should be avoided because of the risk of gastrointestinal bleeding and platelet suppression, particularly during the early stages of disease when YF is clinically indistinguishable from dengue.

Risk factors for developing more severe yellow fever include older age, high AST levels [31] and high YF viral load [32]. In the experience of the intensive care of a tertiary hospital in Sao Paulo, Brazil, during the recent YF outbreak, the fatality rate was 67% [4]. Patients with diabetes mellitus had a higher case fatality rate (CFR) of 80%, although the difference was not significant due to the small sample size [4]. Leading causes of death were severe gastrointestinal bleeding, status epilepticus, severe metabolic acidosis, pancreatitis and multi-organ failure [4]. The following management lessons for severe YF were learnt from the Brazilian experience:

anticonvulsant drugs in patients with any symptoms of hepatic encephalopathy or arterial ammonia levels  $> 70 \mu\text{mol/L}$  should be commenced, and therapeutic doses of intravenous proton pump inhibitors should be administered to prevent gastrointestinal bleeding. Other new therapy recommendations include early institution of plasma exchange [4].

## Diagnosis

YF is difficult to diagnose clinically, especially during the early stages of the febrile disease. The differential diagnosis is wide and includes dengue [27], malaria, leptospirosis, viral hepatitis and other haemorrhagic fevers. Incubation time and epidemiological clues will help to raise the suspicion and request for laboratory confirmation. During the first days of illness, the diagnosis can be made by reverse transcriptase polymerase chain reaction (RT-PCR). However, laboratory diagnosis of YF is generally accomplished by testing serum to detect virus-specific IgM and neutralizing antibodies. A positive serological test for YF IgM is not sufficient to confirm a case [29]. If a person suspected of having YF tests positive for YF IgM, serology for other common flaviviruses should be carried out. Neutralizing antibody levels should be confirmed by using the plaque reduction neutralization test (PRNT), a more specific test for YF [33], though cross-reactivity with other flaviviruses can occur here as well, thereby challenging interpretation. A history of recent vaccination needs to be taken into account when interpreting the results of YF testing. On 31 July 2018, the Centers for Disease Control (CDC) and WHO launched a trial version of a new ELISA test which is simpler and faster to perform. The new kit, called ELISA YF MAC HD, developed by CDC, ensures a standardized platform for YF IgM testing, shortens the turnaround time from 2 days to just 3.5 h but does not overcome the cross-reactivity issues with other flaviviruses [34].

## Yellow Fever Vaccine

All currently available YF vaccines are live attenuated viral vaccines from the 17D lineage based on a wild-type YF virus isolated in Ghana in 1927, developed more than 80 years ago by empirical passage in tissue culture, principally chicken embryo. The attenuated vaccine virus exists in 2 sub-strains (17D-204 and 17DD) which share 99.9% sequence homology [29]. Both sub-strains are used in vaccines prepared by culturing the virus in embryonated eggs, which is the main reason why YF vaccines are not rapidly scalable during an outbreak. The vaccine contains sorbitol and/or gelatin as a stabilizer and is lyophilized, without a preservative. Lyophilized vaccine should be stored at  $2\text{--}8^\circ\text{C}$  and reconstituted immediately before use with the sterile diluent provided by the

manufacturer. After reconstitution, most YF vaccines should be kept on ice, protected from sunlight and discarded after 1–6 h. YF vaccines are given as a single dose (0.5 ml) subcutaneously.

Currently, there are several manufacturers: Sanofi Pasteur (for the North American and European market), Institut Pasteur in Senegal, Tiantan in China, Bio-Manguinhos/Fiocruz in Brasil and Chumakaov Institute in Russia, but only four manufacturers are WHO pre-qualified.

About 80–100% of vaccine recipients develop protective levels of neutralizing antibodies within 10 days and 99% do so within 30 days [29]. Interestingly, no formal human efficacy studies have been performed with YF vaccine; however, 80 years of experience with more than 600 million doses given attest to an extremely high efficacy. The systematic review that was the basis for WHO's grading table [35] showed that since the introduction of YF vaccination in the 1930s, and following the administration of  $> 540$  million doses of vaccine since then, only 12 suspected cases of YF disease post vaccination have been identified [36].

## Serious Adverse Events to Yellow Fever Vaccination

YF vaccines have been available since the 1930s and are generally considered safe and effective. Of 666 respondents in a travel medicine clinic in Germany, 370 (55.6%) reported AEs, of which 258 (38.7%) were systemic and 230 (34.5%) were local. No severe AEs associated with YF vaccination were reported. Elderly vaccinees (aged  $\geq 60$  years) reported fewer total AEs than those aged  $< 60$  years (42.9% vs 60.3%;  $P < 0.001$ ) [37]. However, reports on serious adverse reactions with severe clinical outcomes and even deaths emerged in the endemic population and travelers since 2001 [38–40]. Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) is a rare and serious adverse event with symptoms that mimic wild-type YF [38, 39]. The pathologic mechanism is poorly understood but is likely not due to the impaired magnitude of adaptive immunity but instead to anomalies in the innate immune system and a possible disruption of the CCR5-RANTES axis [41]. Age and thymus dysfunction appear to be the main risk factors for YEL-AVD. Age-related regression of the thymus is associated with a decline in naive T cell output. This is thought to contribute to the reduction in T cell diversity seen in older individuals and linked with increased susceptibility to infection [42]. Autosomal recessive, complete interferon alpha/beta receptor 1 deficiency was also shown to result in life-threatening complications of vaccination with live attenuated measles and YF viruses in previously healthy individuals [43]. Adverse events following YF vaccination reported to the U.S. Vaccine Adverse Event Reporting System (VAERS) from 2007 to 2013 including age- and sex-specific

reporting rates of all SAE, anaphylaxis, YF vaccine-associated neurologic disease (YEL-AND) and YF vaccine-associated viscerotropic disease (YEL-AVD) highlighted the following findings [44]: There were 938 adverse events following YF vaccination; of these, 84 (9%) were classified as SAEs for a rate of 3.8 per 100,000 doses distributed. Reporting rates of SAEs increased with increasing age with a rate of 6.5 per 100,000 in persons aged 60–69 years and 10.3 for those aged 70 years and above. The rate for anaphylaxis was 1.3 per 100,000 doses distributed and was highest in persons below the age of 18 years (2.7 per 100,000). Reporting rates of YEL-AND and YEL-AVD were 0.8 and 0.3 per 100,000, respectively; both rates increased with increasing age. These findings underpin the importance of continued physician and traveler education regarding the risks and benefits of YF vaccination, particularly for older travelers. YEL-AVD only occurs after primary vaccination.

Neurotropic serious adverse reactions (YEL-AND) have been recognized since the 1950s in children younger than 9 months of age, an observation which led to the age restriction. YEL-AND is considered a collective group of clinical syndromes and can be due to the following: direct viral invasion of the central nervous system resulting in encephalitis or meningitis, a peripheral autoimmune complex (resulting in Guillain-Barre syndrome, acute disseminated encephalomyelitis or myelitis) or a combination of both direct viral and autoimmune response. Risk factors are young and older age, although, unlike YEL-AVD, a greater proportion of cases have been in younger adults and those without obvious risk factors, hence, YEL-AND are more difficult to predict.

Limited data on the use of YF vaccination during pregnancy are available and are usually derived from reports where pregnant women were either inadvertently vaccinated or given the vaccine during outbreaks. Two studies found no increased risk of major malformations or fetal death [45, 46]. However, an earlier study suggested a higher rate of spontaneous abortions with a relative risk of 2.3 among 39 pregnant women who received the vaccine [47]. Persons living with HIV who have a CD4+ count > 200 cells/mm<sup>3</sup> do not have increased risk of AEs from YFV [48]. Safety of live vaccines in immunocompromised travelers by mechanisms other than HIV is of particular interest. In one Swiss study, of 197 immunocompromised travelers, 92 had received the YF vaccine, but reassuringly, the incidence of systemic and local reactions was the same as when administered in healthy controls [49]. Some argue that we are possibly erring on the side of caution and under-vaccinating travelers who would benefit from YF vaccination [50]. Egg allergy vaccination protocols seem to provide a safe way to immunize patients with egg allergy [48].

## Co-administration with Other Travel Vaccines

Compact and short pre-travel immunization schedules, which include several vaccinations in a single visit, are desirable for many travelers [51]. However, concomitant vaccination could potentially compromise immunogenicity and/or safety of the individual vaccines and, therefore, possible vaccine interferences should be carefully assessed. Interference is particularly of concern for two live vaccines. Given the current measles, resurgence [52, 53] that may necessitate offering measles vaccination to adult travelers and migrants [54–57] who may also require YF vaccine demands more guidance on whether such vaccines can be co-administered on the same day or whether 28 days interval should be observed. Geometric mean titres for YF were approximately three times higher among those who received MMR vaccinations 30 days later compared to concurrent administration of MMR and YF in a study in Brazil, suggesting that MMR and YF vaccines should not be given on the same day [58]. In a phase 4, randomized, non-inferiority trial in the Gambia, infants aged 9–10 months who were randomly assigned to receive the IPV, measles-rubella and YF vaccines, singularly or in combination showed that YF antibody titres were reduced by co-administration but the seroconversion rates achieved non-inferiority [59]. Concurrent co-administration with inactivated vaccines is less of a problem. A recent study provided evidence that MenACWY-CRM can be administered with typhoid Vi polysaccharide vaccine and live attenuated YF vaccine without compromising antibody responses stimulated by the individual vaccines (NCT01466387) [60].

## Duration of Protection and Controversies About the Need for Booster Doses

In April 2013, the Strategic Advisory Group of Experts (SAGE) on immunization stated that a single dose of YF vaccine is sufficient in the general population to confer lifelong protection against YF. As the period of validity of the International Certificate of Vaccination and Prophylaxis (ICVP) was extended to a lifetime in June 2016, no booster doses are officially needed. The rationale for this recommendation was based on a systematic review by Gotuzzo et al. which identified 6 studies indicating that a high proportion of vaccine recipients (> 90%) have detectable levels of serum neutralizing antibodies up to 20 years post YF vaccination [36]. In 2015, the Advisory Committee on Immunization Practices (ACIP) in the USA voted that a single primary dose of YF vaccine provides long-lasting protection and is adequate for most travelers [61]. ACIP also approved recommendations for at-risk laboratory personnel and certain travelers to receive additional doses of YF vaccine. However, Amanna and Slifka argued based on epidemiological data on vaccine

failures (particularly evident at > 10 years after vaccination) that current recommendations to no longer administer YFV-17D booster vaccination should be carefully re-evaluated [62]. Seroconversion rates in infants aged 9 months are clearly lower than in adults, and this fact would suggest a booster dose at least 10 years later for those who received YF vaccination at the age of 9 months [63]. Few studies have assessed the duration of humoral immunity following YF vaccination in non-endemic populations such as travelers. A recent CDC study on the persistence of neutralizing antibodies to YF among 234 US travelers showed that among the 155 individuals who were vaccinated < 10 years prior to serum collection, 146 (94%) had a positive PRNT compared with 82% (54/66) of individuals vaccinated  $\geq$  10 years prior to serum collection ( $P = 0.01$ ) [64]. Post-vaccination PRNT titers showed a time-dependent decrease. Individuals with immune-compromising conditions were less likely to have a positive PRNT (77%) compared with those who were not immune-compromised (92%;  $P = 0.04$ ) [64]. This study triggered several editorials and letters to the editor in the *Journal of Travel Medicine* arguing for two lifetime doses [65, 66] versus following the WHO recommendation for one life time dose in travelers [67]. A booster dose could be considered for certain travelers with risk factors, persons living with HIV or other immunocompromising conditions who are planning travel to high-risk areas based on immune competence and time since vaccination.

A prospective study determined the potential impact of the SAGE recommendations on the vaccination activity of travel clinics. The authors showed that among 1037 subjects seen in three travel clinics for a YF vaccination in 2013, about 32.3% went for a booster dose that is no longer useful according to the revised SAGE recommendations. A drop in vaccination activity has to be expected by travel clinics in the next years, and changes in daily exercise have to be anticipated, as YF vaccination is a large part of the regular work of many healthcare providers specializing in travel medicine [68].

## Vaccine Shortage

Vaccine shortages for YF vaccine supply that affect travelers recur on a frequent basis [69], the most recent in North America due to a change in manufacturing in the USA. Sanofi Pasteur, the manufacturer of the only YF vaccine (YF-VAX) licensed in the USA, announced that their stock of YF-VAX is totally depleted as of 24 July 2017. YF-VAX for civilian use will be unavailable for ordering from Sanofi Pasteur until the new manufacturing facility is completed. In anticipation of this temporary total depletion, in 2016, Sanofi Pasteur submitted an expanded access investigational new drug application to the Food and Drug Administration to allow for importation and use of Stamaril, the YF vaccine manufactured by Sanofi Pasteur in France [70]. Vaccine

shortages in Western countries have led to increasing uptake of fractional YF vaccines in travelers despite the fact that such use is currently only WHO-endorsed in endemic populations for outbreak use [71].

## Fractional Yellow Fever Vaccine

An expert review on fractional YF vaccine was recently published including the rationale and summary of immunogenicity data [72]. All YF vaccines are all highly potent, with average doses between 10,000 and 44,000 international units (IU), which is far above the WHO's recommended minimum of 1000 IU [73]. In principle, the quantity of vaccine virus in one-fifth of the standard dose would therefore still exceed the WHO's minimum requirement [73]. Based on this observation, WHO endorsed the use of one-fifth of the standard YF dose for outbreak situations when stockpiles have been depleted, which happened during the YF outbreak in Angola and DRC and now also in Brazil. However, the potency varies from manufacturer to manufacturer and from batch to batch and in particular varies from time since vaccine formulation, and hence, various questions need to be addressed with regard to the immunogenicity and safety at doses just below the 1000 IU. Solid immunogenicity data of fractional YF vaccines only exist for male adults in Brazil [74, 75]. The extent and duration of protection of fractional doses in populations such as children, pregnant women, persons with HIV and other comorbidities that may result in different vaccine responses are currently unknown. The first study on one-fifth dose in children 2 years of age was conducted in DRC after the emergency roll-out of fractional doses and reassuringly showed high seroconversion rates 1 month following subcutaneous administration [76]. The results of studies comparing seroconversion rates after fractional dose versus full-dose YF vaccination for each WHO-prequalified vaccine product (ClinicalTrials.gov number, NCT02991495), including in special populations such as children and persons living with HIV, are now much awaited [77]. Until those questions are addressed, fractional YF vaccination is not yet compliant with the International Health Regulations (IHR), although some countries have started to use in light of the vaccine shortage [78]. Should fractional YF vaccination be indeed equivalent to the standard dose, then the lower dose could become an antigen-sparing strategy of much broader utility in the future [77].

## International Health Regulations and Yellow Fever

YF is the only disease for which the IHR mandate proof of vaccination for travelers from countries where YF is endemic to countries vulnerable for YF, defined as the

presence of suitable vectors [79]. An ICVP (also commonly called a “yellow card”) is valid for a lifetime. Unfortunately, the 11 cases of exportation of YF via unvaccinated Chinese workers from Angola to China in 2016 show that the IHR regulations can be circumvented [80]. In fact, modelling studies show that none of the approximately 250,000 Chinese workers in Angola at the time of the YF outbreak were vaccinated [81].

Media reports of counterfeit markets abound. Yet, there is surprisingly little academic literature documenting the extent of this problem. Checks at airports and land crossing points appear to be non-systematic. In a study in Tanzania, checks were also performed in travelers who did not enter Tanzania from a YF-endemic country. No seasonal or daytime pattern could be identified; the thoroughness of checks varied widely. In the case of travel without valid YFV, an exemption certificate was always accepted [82]. It is of utmost urgency that governments turn their attention to enforcing the IHR.

## Yellow Fever Risk in Asia

For travelers not complying with the IHR, importation of the virus by a viremic traveler could initiate an enzootic transmission cycle, leading to a long-term infection risk for the local population. Although solid data on the extent of IHR circumvention is unavailable, it is likely that the 11 cases of importation from Angola to China will not remain the only cases. Why outbreaks of YF have not yet occurred in Asia is unknown. The 11 cases were imported in China’s winter; hence, vectorial capacity of *Aedes* mosquitoes was low [83]. *Aedes aegypti*, the more efficient vector than *Aedes albopictus*, does not exist in most parts of Europe, and hence, Europe and largely the USA are less at risk, but not at zero risk, as YF outbreaks did occur in the Western hemisphere in the past [84]. With changing climate conditions, such a risk may increase [85, 86], further compounded by the fact that recent outbreaks have occurred around urban centres [87]. Is Asia prepared for a YF epidemic? Competent vectors exist, but some cross-protection through Asia’s highly prevalent dengue seroprevalence exists [88]. More studies are needed to understand the vectorial capacity and vector competence of *Aedes aegypti* in Asia. Furthermore, a better risk assessment is urgently needed for YF establishment in Asia. Strengthening of laboratory-based surveillance capable of detecting imported YF, capacity to rapidly import vaccines should YF become established and training healthcare workers in clinical management of severe YF need to be urgently implemented [11, 89].

## Pre-travel Advice

YF vaccine is currently recommended for travel to 42 countries where YF is currently reported or was reported in the past and where vectors/reservoirs remain. Risk assessment for travelers is a challenge, and an evidence-based GRADE approach is needed [90], in particular for low incidence but high impact diseases such as YF. The risk of vaccine adverse reactions has to be balanced against the risk of acquiring a disease with a high case fatality rate. The most common adverse reactions are similar to other live attenuated vaccines and include localized reactions, fever, headache, asthenia, malaise and myalgia, which are very common and generally mild and occur within 1 week of vaccination. No evidence exists to suggest that the reporting rates of allergic reactions are higher compared to other egg-derived vaccines. Viscerotropic and neurotropic reactions are the unique serious risks that need to be carefully explained to all travelers. All cases have been in primary vaccinees and therefore should not occur with booster doses. Viscerotropic disease has a rapid onset, with rapid clinical deterioration within 7 days and a fatality rate in reported cases up to 50%, usually within 10 days. Risk factors include older age, autoimmune disease, thymectomy for thymoma, systemic lupus erythematosus and pernicious anaemia [91]. No clear risk factors have been recognized for neurotropic reactions, except for very young age.

It is very important to include travelers in the decision making process. Most travelers agreed they needed to understand destination-specific YF risks (82%) and vaccine risks (88%) and wanted to be involved in YF vaccine decisions (87%) [92]. The majority of registered travel agencies in Peru did not provide sufficient and accurate information regarding risk and prevention of YF to travelers [93]. Providers need effective risk communication skills and the ability to elicit and respond to travelers’ concerns to help them make informed, shared decisions. For YF vaccines, this is particularly challenging given the uncertainties of true risk at destination versus YF vaccine associated adverse events. The risk is often unpredictable and variable for an individual person and cannot be quantified with any certainty in real time given that new emergence of outbreaks can often also not be predicted. For example, the recent YF outbreak in Brazil occurred in a metropolitan area that was not really predicted and required ad hoc change in recommendations [94]. It is also important that travel medicine providers are not falsely reassured by the absence of YF case reports in certain destinations, as the absence of cases could reflect good vaccine coverage rather than absence of YF virus transmission [95]. Travel medicine practitioners need to ensure that there is indeed an indication for YF vaccination and weigh the risk of adverse events versus individual risk of acquiring YF during travel, dependent on duration, outbreak intensity and activities during travel. Travel health practitioners should be aware of the

complexities, limitations and difficulties in quantifying risk data [96], in particular for low incidence diseases such as yellow fever. There is an urgent need to better define “significant and unavoidable risk” for improved benefit-risk assessments. For persons older than 60 with immunocompromising conditions, the vaccine should be avoided, unless the risk of YF is higher than the risk of viscerotropic or neurotropic adverse events. For all persons with a history of thymus disease, a medical certificate should be issued stating that such travelers are exempt from vaccination. Travel medicine practitioners need to advise on alternative risk management measures including personal protective measures to avoid mosquito bites although compliance rates are notoriously low [97–99].

## Conclusions

With increasing YF cases in travelers, travel medicine providers need to familiarize themselves with the diagnosis and clinical management of severe YF. Prevention remains the mainstay, and all efforts need to be taken that travelers do not circumvent the International Health Regulations. More than 80 years of experience with YF vaccine reinforce the generally acceptable safety profile of YF vaccine but highlight the unique serious adverse events of viscerotropic and neurotropic disease, in particular in first-time vaccinees. Continued physician and traveler education regarding the risks and benefits of YF vaccination is needed, with an urgent need to better define significant and unavoidable risk for improved benefit-risk assessments.

## Compliance with Ethical Standards

**Conflict of Interest** Annelies Wilder-Smith declares no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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