The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever

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The changing epidemiology of yellow fever and continued reports of rare but serious adverse events associated with yellow fever vaccine have drawn attention to the need to revisit criteria for the designation of areas with risk for yellow fever virus activity, and to revise the vaccine recommendations for international travel. WHO convened a working group of international experts to review factors important for the transmission of yellow fever virus and country-specific yellow fever information, to establish criteria for additions to or removal from the list of countries with risk for yellow fever virus transmission, to update yellow fever risk maps, and to revise the recommendations for vaccination for international travel. This report details the recommendations made by the working group about criteria for the designation of risk and specific changes to the classification of areas with risk for transmission of yellow fever virus.

Introduction

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 in Africa or *Haemagogus* spp mosquitoes in South America. On both continents, both jungle (sylvatic) and urban transmission cycles exist. In the jungle cycle, the virus is transmitted between non-human primates and various mosquito species in the forest canopy. In the urban cycle, the virus is transmitted between human beings and mosquitoes (predominately *Aedes aegypti*) in urban areas. In Africa, transmission of the virus can also occur in an intermediate cycle between human beings or non-human primates and *Aedes* spp mosquitoes that breed in tree holes in savannah areas.

During the past decade, official reports of yellow fever incidence (50–120 cases a year from South America and 200–1200 cases a year from Africa) probably underestimate the true number of cases. Many cases of jaundice and fever (a surveillance definition of yellow fever) are not assessed, unexplained deaths go unreported, symptoms suggest alternative diagnoses, and, in some countries, surveillance systems for yellow fever are not in place. The case-fatality rate ranges from 20% to 50% and is partly dependent on case recognition and testing practices. Because no antiviral treatment exists for the disease, prevention through use of personal protection measures and vaccination is crucial to lower disease risk and mortality.

Yellow fever 17D (YF 17D) is a live, attenuated vaccine that has been in use for more than 70 years, with hundreds of millions of doses given during this period. Although immunity from vaccination probably lasts for a lifetime, a 10 year interval between vaccinations is stipulated in the International Health Regulations (2005) for individuals travelling to countries with a yellow fever vaccination entry requirement. The International Certificate of Vaccination or Prophylaxis is a traveller’s official documentation; it becomes valid 10 days after vaccination and remains so for 10 years.

Yellow fever vaccine is given for two reasons: to protect travellers visiting areas with risk of yellow fever virus transmission and to prevent international spread by minimising the risk of importation and translocation of the virus by viraemic travellers.

Every year, about 9 million people from Asia, Europe, and North America travel to countries where yellow fever is endemic; the number of travellers who actually visit areas within these countries where transmission of the virus occurs might exceed 3 million. Unvaccinated travellers who visit areas in Africa during periods of epidemic activity have an estimated risk of illness of one in 267 and risk of death of one in 1333, although the risks are likely to be lower during interepidemic periods. Risk of illness and death for individuals travelling to South America might be about ten times lower than it is for those travelling to Africa, because the rate of transmission in the jungle cycle is lower there. However, the risk of yellow fever for travellers visiting any area depends on the time of year, the traveller’s itinerary and activities, vector population densities, and the presence of circulating yellow fever virus. In endemic areas with high vaccination coverage, the occurrence of yellow fever outbreaks has decreased substantially. Yellow fever surveillance in human beings in these areas does not accurately show the underlying risk for exposure, especially for non-immune travellers, because the jungle cycle of the virus in non-human primates is not affected by widespread human vaccination. This hidden risk for virus exposure presents a challenge for health-care providers about whether to vaccinate patients preparing for travel.

Countries where the vectors and non-human primate hosts exist are vulnerable to the introduction of yellow fever virus, even if the disease is not endemic. Importation of the virus by an infected traveller could initiate an...
enzootic transmission cycle, leading to a long-term infection risk for the local population. This risk is probably highest in densely populated regions infested with A aegypti, such as Asia, the Caribbean, Central America, and coastal South America. The International Health Regulations state that proof of vaccination might be required from travellers entering such vulnerable countries from areas with a risk of yellow fever transmission.

Historically, YF 17D vaccine has been regarded as one of the safest vaccines. However, yellow fever vaccine-associated neurologic disease (YEL-AND) has been recognised for many years, and, since 2001, yellow fever vaccine-associated viscerotropic disease (YEL-AVD) has been reported. Clinically, YEL-AVD resembles naturally acquired yellow fever, and, in its most severe form, presents with jaundice, multiorgan failure, and distributive shock. YEL-AVD is estimated to occur in 0·4 per 100 000 doses. For people aged 60 years or older, the reported incidence is roughly four times higher. YEL-AND can develop as meningoencephalitis (direct invasion of the CNS by the yellow fever vaccine virus) or as autoimmune manifestations in which antibodies or T cells produced in response to the vaccine cross-react with neuronal epitopes and lead to central or peripheral nerve damage. YEL-AND is estimated to occur in 0·8 per 100 000 doses. In people aged 60 years or older, YEL-AND occurs at 1·8 per 100 000 doses. Because of these serious adverse events, clinicians are advised to vaccinate only those individuals truly at risk for exposure to yellow fever virus or who must be vaccinated to meet country entry requirements. Clinicians should carefully consider the risks and benefits of vaccination for every patient, and in some cases might choose to issue a letter of medical exemption from yellow fever vaccination. Contraindications and precautions to yellow fever vaccination are given in the WHO website and position paper, and are presented in the Advisory Committee on Immunization Practices’ recommendations for yellow fever vaccine.

The global yellow fever risk map
Since the mid-20th century, the global yellow fever risk map has depicted the best estimate of the distribution of the virus and has been used to guide vaccination recommendations for travellers. The first risk map was created at the end of World War 2 by the Expert Commission on Quarantine—which had been appointed by the UN Relief and Rehabilitation Administration—and relied on the results of serosurveys and expert opinion. In 1948, responsibility for maintenance of the global yellow fever risk map was assumed by the Yellow Fever Panel, which had been appointed by the newly formed WHO. However, the many subsequent changes made to the map were often done without documentation of the rationale or methods used. Historically, the US Centers for Disease Control and Prevention (CDC) used the WHO risk map in its publications. However, in 2005, CDC created a map that differed from the WHO map. The publication of different versions of the global yellow fever risk map by public health institutions was problematic for public health professionals and travel medicine clinicians.

The scarcity of well documented and consistent methods in yellow fever risk assessment and the changing global epidemiology of the disease emphasised the need to revise
and standardise the geographical risk assessment for yellow fever. For instance, in late 2007 and early 2008, the disease re-emerged in Paraguay and Argentina after more than 30 years. Furthermore, increased numbers of cases were reported from many countries in central Africa that had previously reported cases only rarely. In addition to vaccine safety concerns and the changing epidemiology of yellow fever, the International Health Regulations require WHO to regularly publish a list of countries and geographical regions in annex 1 of the ITH publication, and to revise the yellow fever risk map and recommendations for vaccination.

The 2008 consultation outlined four levels of yellow fever risk and classified geographical areas into four corresponding categories: endemic, transitional, low risk (changed to low potential for exposure in the second WHO consultation in 2010), and no risk (table 1). The factors identified in table 1 were adopted as the criteria for the addition or removal of countries and geographical regions in annex 1 of the ITH publication.

After the 2008 consultation, a working group (the Informal Working Group on Geographic Risk for Yellow Fever) was formed to systematically assess the risk for yellow fever virus transmission in South America and Africa and to ensure that risk maps and vaccination recommendations were harmonised on the basis of consistent criteria.

The working group met by teleconference regularly (roughly every month) from September, 2008, to May, 2010. The yellow fever risk profile (all available studies and reports) for every country that had risk for yellow fever virus transmission was systematically reviewed with the criteria outlined in table 1. In the absence of specific yellow fever virus data, the working group members provided expert opinion and used available data sources on vegetation and elevation of a country or region to reach a consensus. Whenever possible, the second administrative level boundaries within countries were used to describe risk areas. However, subnational data did not exist for some countries (eg, Rwanda, Uganda, and Angola). In these cases, decisions were made on a country-wide basis.

The 2010 consultation on yellow fever and international travel

In South America, the expert consensus was that areas at an elevation of 2300 m or higher are not suitable for yellow fever vectors. Furthermore, no cases of yellow fever were documented to occur above this elevation. WHO updates this list every year in annex 1 of the International Travel and Health (ITH) publication (widely referred to as the Green Book).

The 2008 consultation on yellow fever and international travel

WHO convened a consultation on yellow fever and international travel on Sept 4–5, 2008, in Geneva, Switzerland (the 2008 consultation), after recognition by travel medicine experts at WHO and CDC of the need to harmonise both the classifications of geographical risk for yellow fever and vaccine recommendations. The goals of the 2008 consultation were to discuss factors important for transmission of the virus, to establish criteria for the addition or removal of countries and geographical regions in annex 1 of the ITH publication, and to revise the yellow fever risk map and recommendations for vaccination.

In South America, the expert consensus was that areas at an elevation of 2300 m or higher are not suitable for yellow fever vectors. Furthermore, no cases of yellow fever were documented to occur above this elevation. WHO updates this list every year in annex 1 of the International Travel and Health (ITH) publication (widely referred to as the Green Book).

In Africa, the barren or sparsely vegetated lands of the Sahara desert are not suitable for the development of immature mosquitoes and were, therefore, not thought to harbour a risk for virus transmission. By use of the normalised difference vegetation index, a conservative vegetation line was used to separate barren or sparsely vegetated zones (eg, Sahara desert) from others, including shrubland zones, which might be conducive to the development of immature mosquitoes (figure 2).
Although this line could be readily established west to east from Mauritania to Eritrea along the southern edge of the Sahara desert, the separation of vegetation zones was more complicated in eastern and southern Africa, where the mixture of zones is more complex. In such areas, vegetation data were used in conjunction with expert opinion and historical information about virus circulation. Insufficient data were available to allow an estimation of an elevation limit for yellow fever risk in Africa.

Initial working group decisions based on yellow fever case data, serological evidence, vegetation zones, and elevation boundaries were used to produce an interim harmonised global map published in WHO’s 2009 ITH publication and CDC’s Health Information for International Travel 2010 (widely referred to as the Yellow Book).1,2 The working group’s review of all countries in South America and Africa continued after the aforementioned publications were issued.

WHO convened the second consultation on yellow fever and international travel in March, 2010 (the 2010 consultation), to review country-specific risk designations and vaccine recommendations, criteria for the addition or removal of countries and geographical regions in annex I of the ITH publication, and the implications of these criteria for the ITH. Future steps for yellow fever risk mapping were also proposed.

This consultation resulted in three major outcomes. First, the consultation adopted a new term—low potential for exposure (table 1). Potential exposure to yellow fever virus in these areas is expected in only rare circumstances—eg, prolonged travel, heavy exposure to mosquitoes, and inability to avoid mosquito bites. Vaccine recommendations for travel to these areas should be based on an assessment of travellers’ potential for increased exposure to the virus on the basis of their specific travel plans.

Second, the 2010 consultation suggested changing the harmonised map published in WHO’s ITH publication and CDC’s Health Information for International Travel from a risk map to a vaccination map. The yellow fever risk maps for South America (including Panama and Trinidad and Tobago; figure 3) and Africa (figure 4) will be published online and will be used by the working group to periodically reassess the four classifications of risk. However, vaccination maps (published in WHO’s ITH [one for Africa and one for the Americas] and CDC’s Health Information for International Travel) will provide more clarity and ease of use for clinicians by designating where vaccination is always recommended (endemic and transitional areas), generally not recommended except in specific circumstances (areas with low potential for exposure), and never recommended (areas with no risk; table 1).

Third, the 2010 consultation endorsed the working group’s proposal that a transit time of 12 h or less in an international airport be considered to pose no risk for yellow fever virus transmission, irrespective of the yellow fever risk classification of the country in which the airport is located. Although data for vectors infected with yellow fever virus in airports are scarce, the working group judged the risk to passengers transiting airports for 12 h or less to be negligible.

Country-specific outcomes of the working group

The following countries in Africa and South America had no change to their holoendemic classification and are not discussed in more detail in this paper: Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Congo (Brazzaville), Côte d’Ivoire, Equatorial Guinea, French Guiana, Gabon, Ghana, Guinea, Guinea-Bissau, Guyana, Liberia, Nigeria, Rwanda, Senegal, Sierra Leone, Suriname, The Gambia, Togo, and Uganda. These countries either repeatedly reported yellow fever infection in human beings or non-human primates, had insufficient subnational data or inadequate surveillance systems to establish whether the virus was circulating at low levels in specific areas, or were ecologically similar to adjacent countries with risk for yellow fever virus transmission. Cape Verde and Djibouti were also reviewed, and no change was recommended to their classification of no risk.

The working group proposed changes to the risk classifications of the countries outlined in table 2. Selected countries with the most substantial changes to their risk classification are described below to show the process and complexity of assigning risk. A full

Figure 2: Use of vegetation to define yellow fever risk areas on the southern border of the Sahara desert

Niger is used as an example here, but the same method was used to delineate the barren or sparsely vegetated zones from other vegetation zones on the southern border of the Sahara desert.
description of the rationale for changes to risk classifications for all countries is beyond the scope of this report, but is included in the webappendix (pp 1–2).

South America

After reporting of yellow fever was instituted in 1927, the first official notification of human cases in Argentina occurred in 1966. However, during the extensive 1948 epizootic in Brazil, the virus was detected in the Misiones Province in Argentina, and one person with yellow fever was identified in Campos de Taranco. In 1965–66, another epizootic was detected in southern Brazil and northern Argentina, with 54 cases of yellow fever in human beings reported from Misiones and Corrientes provinces during 1965–67; suspected cases and the presence of yellow fever vectors and non-human primate hosts were recorded in surrounding provinces. In 2001, an epizootic occurred in border areas of Brazil, but no human cases were reported in Argentina. In 2007–08, a similar epizootic expansion occurred in border areas of Brazil (Paraná) and Paraguay. Yellow fever was widely detected in non-human primates in the districts of Misiones and Corrientes, and at least five human cases were confirmed in Misiones in areas affected in 1966. In view of these periodic expansions of epizootic activity and subsequent human cases, all departments of Misiones and selected departments of Corrientes were classified as transitional; selected departments of Chaco, Jujuy, Formosa, and Salta were classified as having low potential for exposure. All other areas of the country were classified as posing no risk.

In Brazil, the Amazon region is holoendemic for yellow fever, as are areas bordering this region (eg, Maranhão, Tocantins, western Bahia State, and the Distrito Federal [Brasília])—all these areas are regarded as endemic. Regions in the south, including Santa Catarina and Rio Grande do Sul, have intermittent yellow fever virus activity when there is southward expansion of the virus. These areas were classified as transitional. In the endemic areas in Brazil, routine immunisation has been practised for many years and most infections are in unvaccinated migrants. Several yellow fever cases have been reported in unvaccinated tourists entering the endemic region from the Europe or USA.34–36

Areas of Colombia east of the Andes and lower than 2300 m were classified as endemic for yellow fever, except for the arid Uribia municipality in the Guajira Peninsula, which is probably unsuitable for Haemagogus spp mosquitoes. The municipalities bordering Panama (Acandi, Unquia, Jurado, and Riosucio) in Chocó Department were reclassified as transitional because during the late 1940s outbreaks occurred in the Antioquia Department in Colombia, and in eastern Panama, suggesting that conditions in these municipalities could support the transmission of yellow fever virus.37 The Pacific coastal region has had no reports of human cases, and no serological data exist from which to establish past presence of the virus. However, surveillance has been restricted or absent in this highly forested area, which is ecologically suitable for yellow fever virus transmission. Because this region is positioned between the transitional and endemic areas in the north of Colombia and the area with low potential for exposure in the south in Ecuador (figure 3), the entire departments of Narino, Cauca, and Valle de Cauca, and all municipalities of the Chocó Department, except for those bordering Panama, were classified as having low potential for exposure. The cities of Barranquilla, Cartagena, Cali, and Medellin were classified as areas of low potential for exposure because they are large urban areas with good surveillance and restricted potential for Haemagogus spp activity.

In Ecuador, areas east of the Andes below 2300 m were included in the endemic areas, on the basis of ecology (Amazonian forest) and the repeated notification of human cases of yellow fever. Much like in Colombia, the coastal areas were classified as areas with low potential
for exposure. The cities of Guayaquil and Quito and the Galápagos Islands were thought to have no risk, either because of elevation or distance from an endemic or transitional zone.

Previously, the region of Panama to the east of the Canal Zone was classified as an endemic area. Cases of yellow fever in human beings (sporadic individual cases or clusters of cases) have been reported at long intervals during expansions of virus transmission from bordering endemic areas. Yellow fever outbreaks were recorded in Panama in 1948, 1956–57, and 1974. Epizootics in 1948 affected the entire country, whereas the outbreak in 1956–57 was confined to eastern Panama. Similarly, a third epizootic wave with four associated human cases in Darién Province in 1974 did not reach the Panama Canal. Whether the virus is permanently present in Panama or is periodically introduced during infrequent epizootic waves from South America is unclear. However, yellow fever vectors and non-human primates are present in this area, the ecological setting in which the virus is transmitted has not changed, and surveillance of infections in human beings, although improving, inherently lacks sensitivity. Additionally, routine vaccination of infants—implemented in the eastern part of the country since 1974—has led to high levels of immunity in the population, eliminating the disease in people who live in the area. However, the virus presumably still circulates in forests and is capable of causing disease in unvaccinated people such as travellers. Therefore, despite the absence of reported human cases since 1974, travellers to eastern Panama could risk yellow fever virus infection, especially during extensive outdoor activity. Consequently, areas east of the canal were classified as transitional.

Southeastern Paraguay, northern Argentina, and southern states of Brazil have a history of intermittent epizootic yellow fever, which often result in infections in human beings. From 1927 to 2007, the only year in which human cases of yellow fever were reported in Paraguay was 1974, when nine cases of were reported from Amambay Department, which borders Brazil. In 2008, 24 individuals from the departments of San Pedro and Caaguazú, and the urban area of Laurelty, near Asunción, were reported as having yellow fever, eight of whom died. Both the 1974 and 2008 outbreaks resulted from epizootics that began in Brazil. Unrecognised sporadic cases might have occurred in Paraguay in other years. Furthermore, whether or not enzootic transmission continues after recognised outbreaks is not clear. Although cases of human disease have not been reported in northern Paraguay, this region is bordered by endemic areas in Bolivia and Brazil. Because of these reports of yellow fever virus in Paraguay and in

Figure 4: Areas with risk of yellow fever virus transmission in Africa, 2010

*São Tomé and Príncipe was classified as low potential for exposure.
neighbouring countries during the past 3 years, all of Paraguay was classified as transitional. The city of Asunción was regarded as an area with low potential for exposure because the outbreak in Asunción in 2008 was a result of epizootic expansion into the northern part of the country and subsequent translocation of the virus into the city.

**Africa**

Most of the Democratic Republic of the Congo is regarded as endemic, because many outbreaks have been reported in the country since 1912.4 The only controversial area is Katanga Province in the south of the country, which has been included and excluded from various yellow fever risk maps as an endemic area. No human cases have been reported from Katanga Province. Although yellow fever antibodies were absent in one location (Elizabethtown) in 1934,42 such antibodies were detected in 2–15% of adults at six of 14 locations in Katanga Province in 1951–53.43 Without more up-to-date data for yellow fever virus activity and because this region is contiguous with endemic areas of the country to the north and the western region of Zambia (an area of low potential for exposure) to the southeast, it is viewed as an area with low potential for exposure.

In the past, Eritrea has been both included and excluded from yellow fever risk maps. Although no cases have been reported in Eritrea, serosurveys in 1942–43 detected neutralising antibodies in children and adults from seven of 15 locations, with an overall seroprevalence of 4·9% in children younger than 15 years.43,44 These findings were confirmed during the 1953–54 serosurvey,43,45 when 6% of children were seropositive. Yellow fever vectors and non-human primate hosts are present in Eritrea, and the western districts are characterised by savannahs conductive to transmission of yellow fever virus by *Aedes* spp mosquitoes that breed in tree holes. Therefore, the working group classified the western region as having a low potential for exposure, and the rest of the country—where for ecological reason, yellow fever vectors are not expected to be supported—as having no risk.

Somalia had previously been classified as endemic in the southern part of the country (WHO) or the entire country (CDC), despite the absence of reported human cases. A low prevalence of yellow fever antibodies (3·7%) was recorded in adults in southeastern Somalia (Middle Shabelle District) in 1942,46 and a 1966–67 serosurvey showed neutralising antibodies (with a prevalence of 8·5%) also in Middle Shabelle District (near Mogadishu).46 Furthermore, south and south-central Somalia probably have enough rainfall and vegetation to support transmission of the virus. Therefore, the working group designated districts in the south of Somalia (figure 4; table 2) as areas with low potential for exposure. The northern areas of Somalia are ecologically unfavourable for transmission of yellow fever virus and therefore have no risk. This view is supported by the absence of serological evidence for human infection in adjacent Djibouti.41

Tanzania was previously classified as endemic. However, no cases of yellow fever in human beings or in non-human primates have been reported. The only evidence for virus activity comes from serological surveys done in the 1940s, which showed a low prevalence of seropositivity in children and adults (<5%).43 The only controversial area is the southern part of the country (Maryania and Pemba) as areas with low potential for exposure, and the rest of the country—where for ecological reason, yellow fever vectors are not expected to be supported—as having no risk.

<table>
<thead>
<tr>
<th>Previous classification</th>
<th>2010 consultation on yellow fever and international travel revised classifications</th>
<th>Listed in revised annex 1 (2011) of International Travel and Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Democratic Republic of the Congo</td>
<td>Endemic (whole country)</td>
<td>Endemic: all areas except as mentioned below</td>
</tr>
<tr>
<td></td>
<td>Low potential for exposure: Katanga Province</td>
<td>Yes</td>
</tr>
<tr>
<td>Eritrea</td>
<td>No risk (whole country)</td>
<td>Low potential for exposure: Asseba, Debub, Gash Barka, Mae Kel, and Semenawi Keih Bahri states</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>Endemic (whole country)</td>
<td>Endemic: all areas except as mentioned below</td>
</tr>
<tr>
<td></td>
<td>Low potential for exposure: Afar and Somali provinces</td>
<td>Yes</td>
</tr>
<tr>
<td>Kenya</td>
<td>Endemic (whole country)</td>
<td>Endemic: all areas except as mentioned below</td>
</tr>
<tr>
<td></td>
<td>Low potential for exposure: the entire North Eastern Province; states of Kilifi, Kwale, Lamu, Malindi, and Tana River, in the Coast Province, and the cities of Nairobi and Mombasa</td>
<td>Yes</td>
</tr>
<tr>
<td>São Tomé and Príncipe</td>
<td>Endemic (whole country)</td>
<td>Low potential for exposure: whole country</td>
</tr>
<tr>
<td>Somalia</td>
<td>Endemic (whole country)</td>
<td>Low potential for exposure: Bakool, Banaadir, Bay, Galgudud, Gedo, Hiraan, Lower Juba, Middle Juba, Middle Shabelle, and Lower Shabelle regions</td>
</tr>
<tr>
<td></td>
<td>No risk: all other areas not listed above</td>
<td>No</td>
</tr>
<tr>
<td>Tanzania</td>
<td>Endemic (whole country)</td>
<td>Low potential for exposure: whole country</td>
</tr>
<tr>
<td>Zambia</td>
<td>No risk (whole country)</td>
<td>Low potential for exposure: North-Western and Western provinces</td>
</tr>
<tr>
<td></td>
<td>No risk: all other areas not listed above</td>
<td>No</td>
</tr>
</tbody>
</table>

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confirmed cases have been officially reported from the for transmission of yellow fever virus. Although no was removed from the lists of areas or countries with risk and CDC maps until 2005, when for unclear reasons, it potential for exposure.
in serosurveys, Tanzania was classified as having low of human cases and low prevalence of antibodies detected
history of travel to the mainland. Because of the absence of human cases and low prevalence of antibodies detected in serosurveys, Tanzania was classified as having low potential for exposure. Western Zambia was designated as endemic on WHO and CDC maps until 2005, when for unclear reasons, it was removed from the lists of areas or countries with risk for transmission of yellow fever virus. Although no confirmed cases have been officially reported from the country, a suspected case was described from the North-Western Province in 1943. Many locations in the western part of Zambia in the Zambezi River basin were surveyed in 1944, and again in 1951–53; neutralising antibodies were detected with a seroprevalence up to 18%. In view of this information and the fact that neighbouring areas in Angola and the Democratic Republic of the Congo are designated as having yellow fever risk, the working group reclassified the North

Table 2: Classifications for selected areas with risk for transmission of yellow fever virus

<table>
<thead>
<tr>
<th>South America</th>
<th>Previous classification</th>
<th>2010 consultation on yellow fever and international travel revised classifications</th>
<th>Listed in revised annex 1 (2011) of International Travel and Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>Transitional (specific regions only)</td>
<td>Transitional: all departments of Misiones (including Iguaçu Falls), and Departments of Roros and Astraprada, Capital, General Alvear, General Paz, Ituzaingó, Itá, Paso de los Libres, San Cosme, San Miguel, San Martín and Santo Tomé in Corrientes Province. Low potential for exposure: all departments of Formosa Province; Department of Bermejo in Chaco Province; Departments of Lede, Santa Róbla, San Pedro, and Valle Grande in Jujuy Province; and Departments of Anta, General José de San Martín, Ñan, and Rivadavia in Salta Province.</td>
<td>Yes</td>
</tr>
<tr>
<td>Brazil</td>
<td>Endemic (specific regions only)</td>
<td>Endemic: entire states of Acre, Amazónas, Amazonas, Distrito Federal (including the capital city of Brasilia), Goiás, Maranhão, Mato Grosso, Mato Grosso do Sul, Minas Gerais, Pará, Rondônia, Roraima, and Tocantins; and designated areas of Bahia, Paraná, Piauí, and São Paulo states. Transitional: designated areas of Santa Catarina and Rio Grande do Sul states. No risk: all areas not listed above.</td>
<td>Yes</td>
</tr>
<tr>
<td>Colombia</td>
<td>Endemic (whole country)</td>
<td>Endemic: all areas except as mentioned below. Transitional: Acandi, Uninga, Jurado, and Rio Jucu municipalities in the Choco department. Low potential for exposure: areas below 2300 m in the departments of Nariño, Cauca, and Valle de Cauca; the Alto Baudó, Atrato, Bagadó, Bahía Solano, Bajo Baudó, Belén de Bajirá, Bojayá, Carmen del Darién, Céreugue, Condoto, El Canton de San Pablo, El Carmen de Atrato, Istmina, Litoral del San Juan, Llano, Medio Atrato, Medio Baudó, Medio San Juan, Nivelita, Niqui, Quibío, Río Itú, Río Quito, San José del Palmar, Sipí, Tado, and Unión Panamericana municipalities of the Choco Department; and the cities of Barranquilla, Cartagena, Cali, and Medellín. No risk: areas above 2300 m, Unía municipality in the La Guajira department, and the city of Bogotá.</td>
<td>Yes</td>
</tr>
<tr>
<td>Ecuador</td>
<td>Endemic (specific regions only)</td>
<td>Endemic: areas below 2300 m in the provinces of Morona-Santiago, Orellana, Pastaza, Napo, Sucumbíos, and Zamora-Chinchipe. Low potential for exposure: entire provinces of Esmeraldas, Guayas, Manabi, and Los Ríos, and designated areas of the provinces of Azuay, Bolívar, Canar, Carchi, Chimborazo, Cotopaxi, El Oro, Imbabura, Loja, Pichincha, and Tungurahua. No risk: Areas above 2300 m, the cities of Guayaquil and Quito, the Galápagos Islands, and all areas not listed above.</td>
<td>Yes</td>
</tr>
<tr>
<td>Panama</td>
<td>Endemic (specific regions only)</td>
<td>Endemic: entire comarcas (autonomous territories) of Emberré and Kuna Yala, the entire province of Darién, and areas of the provinces of Colón and Panamá that are east of the Canal Zone. No risk: city of Panama, the Canal Zone, San Blas Islands, Balboa Islands, and all areas not listed above.</td>
<td>Yes</td>
</tr>
<tr>
<td>Paraguay</td>
<td>Endemic (specific regions only)</td>
<td>Endemic: whole country except as mentioned below. Low potential for exposure: city of Asunción.</td>
<td>Yes</td>
</tr>
<tr>
<td>Peru</td>
<td>Endemic (specific regions only)</td>
<td>Endemic: areas below 2300 m in the regions of Amazonas, Loreto, Madre de Dios, San Martín, and Ucayali and designated areas of the following regions: Ancash, Apurimac, Ayacucho, Cajamarca, Cusco, Huancavelica, Huanuco, Junín, La Libertad, Pasco, and Puno. Transitional: designated areas of Puna region. Low potential for exposure: entire regions of Tumbes and Lambayeque, and designated areas of Cajamarca and Pura regions. No risk: areas above 2300 m, the cities of Cusco and Lima, Machu Picchu, and the Inca Trail; and all areas not listed above.</td>
<td>Yes</td>
</tr>
<tr>
<td>Trinidad and Tobago</td>
<td>Endemic (whole country)</td>
<td>Endemic: all areas except as mentioned below. Low potential for exposure: city of Port of Spain. No risk: Tobago.</td>
<td>Yes</td>
</tr>
<tr>
<td>Venezuela</td>
<td>Endemic (specific regions only)</td>
<td>Endemic: all areas except as mentioned below. Low potential for exposure: Aragua, Carabobo, Miranda, Vargas, and Yaracuy, and the Distrito Federal. No risk: entire states of Falcon and Lara, the peninsular section of the Paez municipality of Zulia Province; Margarita Island; and cities of Caracas and Valencia.</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Vaccination is recommended for travellers visiting endemic or transitional areas. In general, vaccination is not recommended for travellers whose itineraries are restricted to areas with low potential for exposure. Although not generally recommended for travellers to areas with low potential for exposure, vaccination might be considered for a small subset of travellers whose itinerary would place them at increased risk of exposure to yellow fever virus, such as prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites—risk of exposure should be weighed against individual risk factors for vaccine-associated adverse events (eg, age, immune status) when deciding to vaccinate. Vaccination is not recommended for travellers whose itineraries are restricted to areas regarded as having no risk.
Western and Western provinces as areas with low potential for exposure.

Because serological evidence from surveys done 60–75 years ago was the principal rationale for the designation of all or parts of São Tomé and Príncipe, Tanzania, Zambia, Somalia, and Eritrea as areas with a low potential for exposure, the relevance of such historical data should be considered. During this time, ecological changes such as land use changes, reduced availability of breeding sites in tree holes, reduced populations of specific non-human primates, and climate change could have altered the dynamics of yellow fever virus transmission. However, no available evidence suggest that such changes have occurred or affected virus transmission. Another limitation of the remote serological data is that they were derived by use of undiluted or minimally diluted (a 1:10 dilution) human serum samples tested against only yellow fever virus in a mouse neutralisation test, raising the possibility that detected antibodies could have been caused by cross-reactions with heterologous flaviviruses. These concerns are most relevant for areas of uncertain risk at the borders of endemic zones. However, in the absence of more up-to-date serosurvey data, including results from tests for multiple flaviviruses, no evidence refutes the data from 60–75 years ago.

Special situations outlined by the working group

Although Central America and western Panama have reported yellow fever cases in the past, they have been classified by the working group as having no risk, on the basis of the following considerations. First, no yellow fever virus activity (ie, in human beings, non-human primates, or mosquitoes) has been reported for an extended period of time (five to eight times the typical cycle of re-emergence of epizootic yellow fever in tropical America). The interval between epizootics in South America varies, but is generally 7–10 years. Second, after the elimination of yellow fever in urban areas in this region by 1925, the virus was not detected until its introduction from Panama in 1948, with an ensuing spread into Central America that ended in 1954. Third, natural barriers prevent the introduction of the virus across the Canal Zone, with the disease disappearing from Central America west of the Canal Zone shortly after the last event was reported in 1956. Several groups of researchers with active field and surveillance programmes, including the Gorgas Memorial Laboratories and the Middle America Research Unit, have not detected the virus west of the Canal Zone, suggesting that persistent virus activity in an enzootic cycle has not occurred since.

Cities with no risk or low potential for exposure

The working group identified specific cities (table 2), some of which are major tourist destinations, as posing little to no risk for yellow fever virus transmission. Although Aedes aegypti might be present, posing a theoretical risk for urban transmission, the disease has not been detected in these cities, and surveillance would be expected to promptly identify cases. Therefore, they were designated as no risk or low potential for exposure.

Implications for the ITH and national immunisation policies

The working group agreed that countries with areas with only low potential for exposure be excluded from the list of countries with risk in annex 1 of the ITH publication. Such exemptions apply to Eritrea, São Tomé and Príncipe, Somalia, Tanzania, and Zambia (table 2). Yellow fever vaccination will generally not be recommended for travel to these countries, unless travellers’ itineraries indicate potentially increased risk of exposure and the benefit of vaccination outweighs the risk of vaccine-associated adverse events (eg, age, altered immune status).

This change to annex 1 of the ITH publication has implications for vaccine entry requirements for travellers from São Tomé and Príncipe, Somalia, and Tanzania who are travelling outside their countries (Eritrea and Zambia were not previously listed). The working group recommends that travellers arriving from these countries do not need to provide evidence of vaccination. However, according to the International Health Regulations, countries with vulnerable populations and susceptible vector species can define their own yellow fever vaccine entry requirements.

The findings of the working group regarding the geographical risk for yellow fever might also affect countries’ national immunisation policies. Priority setting for vaccination campaigns and introduction of yellow fever vaccine in infant immunisation schedules have always relied on the official WHO maps, and the new classification will need to be taken into account during formulation of national vaccination policies. Additionally, when gaps in information exist, countries are encouraged to pursue field research such as serological surveys and detection of the virus in vectors and non-human primates to guide the development of risk maps and immunisation policies in the future.

Concluding remarks

The working group knows of no other systematic review of all countries considered to have risk for yellow fever virus transmission. Through the WHO consultations and the Informal Working Group on Geographic Risk for Yellow Fever, criteria were developed for risk of virus transmission, countries and geographical regions with risk for virus transmission were reassessed with these criteria, and vaccine recommendations for travellers were made on the basis of yellow fever risk. This process provides transparent decision-making and clear descriptions of areas with risk for yellow fever virus transmission. These data provide the framework underlying the yellow fever vaccination maps that will be published in CDC’s Health Information for International Travel and WHO’s ITH publications. By
Review

Search strategy and selection criteria

The working group identified studies and reports that contained potentially useful data about the transmission of yellow fever virus by searching PubMed, reviewing relevant bibliographies, consulting subject matter experts, assessing unpublished data (including serosurvey, entomological, and disease incidence data), and examining official case reports from national or international health organisations (eg, WHO). To capture all historical data, we searched PubMed up to May, 2010, with the search term “yellow fever”. There were no language restrictions on the PubMed search. Additional references were sought from those papers’ bibliographies, from subject matter experts, and from the personal collections of the members of the working group.

Contributors

ESJ contributed to the primary writing of the report, the data search, figure creation, data analysis, data interpretation, and editing of the final paper. GP, MDG, DRH, JL, RFL, JES, OT, and AW-S contributed equally to the writing of the report, figure creation, data analysis, data interpretation, and editing of the final paper. TPM contributed to the writing of the report, research, data review, and data analysis.

Conflicts of interest

WHO provided travel support for ESJ, MDG, DRH, JES, OT, AW-S, and TPM. DRH declares that his institution (the National Travel Health Network and Centre) receives a registration fee from yellow fever vaccination centres in England, Wales, and Northern Ireland as part of a programme of registration, training, and audit for yellow fever centres. RFL declares that WHO receives funding from the Global Alliance for Vaccines and Immunization for the Yellow Fever Initiative. AW-S has been sponsored to attend conferences and has received speaker’s fees from Sanofi Pasteur, Novartis, and GlaxoSmithKline. TPM declares board membership, patents, and stock options for Xcellerex. GP and JL declare that they have no conflict of interests.

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The epidemiology of this vector-borne disease is dynamic and subject to changes resulting from climate change, including cyclical events affecting rainfall patterns, and human factors, such as migration and air travel. Many areas in the Americas, Africa, and Asia are susceptible to the introduction and spread of yellow fever; the establishment of dengue fever and chikungunya, transmitted by A aegypti, in these areas shows that they are also at risk for urban yellow fever. The monitoring of countries or geographical regions with risk for transmission is important. WHO continues to document findings of case reports, outbreaks, and scientific research on yellow fever, and updates on disease activity in South America and Africa are published regularly in the Weekly Epidemiological Record.” Yellow fever outbreaks are also reported in the WHO Disease Outbreak News. The working group will continue to incorporate this information and use input from WHO member states to make updates to yellow fever risk maps and to assess vaccine recommendations for travellers. The working group is also developing guidance for countries that want to change their yellow fever risk classification. Finally, the working group endorses efforts to strengthen disease surveillance in affected regions and strongly encourages countries to undertake surveillance research and surveys to improve the knowledge base and subsequent analysis of yellow fever risk.