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SCIENTIFIC AND TECHNICAL ADVISORY GROUP ON GEOGRAPHICAL YELLOW FEVER RISK MAPPING (GRYF)[1]

TERMS OF REFERENCE

This document is for the information of WHO (Headquarters and Regional Offices), GRYF members and advisers.

World Health Organization

[1] See resolution WHA68.4 on *Yellow fever risk mapping and recommended vaccination for travellers, available at* http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R4-en.pdf.

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I. Background and rationale

"The Sixty-eighth World Health Assembly, in resolution WHA68.4[2] requested the Director-General to establish a formal scientific and technical advisory group on geographical yellow fever risk mapping, with the participation of countries with areas at risk of yellow fever, to: (i) maintain up-to-date yellow fever risk mapping; and (ii) provide guidance on yellow fever vaccination for travellers in ways that facilitate international travel."

This document describes background and rationale for establishment of this group as well as scope of work, functions and procedures.

Yellow Fever risk trends

Yellow Fever (YF) was originally imported into the Americas from Africa, and became widely established there. There are nowadays an estimated 200,000 cases of YF, causing 30,000 deaths[3] worldwide each year, with 90% occurring in Africa[4]. Although most infections present few symptoms, some lead to an acute illness.

Unvaccinated travellers who visit areas in Africa during periods of epidemic activity have a 1 in 267 risk of illness and a 1 in 1,333 risk of death due to YF; the risks are likely to be lower between epidemic periods. The risk of illness and death for individuals travelling to South America is considered to be 10 times lower than it is for those travelling to Africa because viral transmission occurs in the forest canopy away from human contact, and because vaccine coverage is higher. However, travellers' risk of acquiring YF is difficult to predict due to variations in the ecologic determinants of virus transmission and in protective behaviours, immunity profiles, and activities[5].

The density and habitats of the most common mosquito vector Aedes *aegypti* has recently expanded both in urban and rural areas. This mosquito is now again infesting regions from which it was previously eradicated. YF has never been reported from Asia, but, should it be accidentally imported, the potential for outbreaks exists because the appropriate mosquito vector is present[6]. Most countries in Asia with high Aedes *aegypti* mosquito density are considered "receptive" for YF transmission.

There is no specific treatment for YF. Vaccination is highly recommended as a preventive measure for travellers to, and people living in, endemic countries. A single dose of YF vaccine is sufficient to confer sustained immunity and life-long protection against YF disease and a booster dose of YF vaccine is not needed[7]. The introduction of the YF 17D vaccine in the 1930s provided an effective preventive measure

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[2] See resolution WHA68.4 on *Yellow fever risk mapping and recommended vaccination for travellers, available at http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R4-en.pdf.*

[3] WHO: Expanded Programme on Immunization. The resurgence of deadly yellow fever. EPI UPDATE 21, March 1992.

[4] Monath TP et al. Chapter 38, Yellow fever vaccine. In Plotkin SA, Orenstein WA, eds. Vaccines, 6th edition. Elsevier Saunders, 2013:2903–3156.

[5] Monath TP, Cetron MS. Prevention of yellow fever in persons traveling to the tropics. Clinical Infectious Diseases, 2002, 34: 1369–1378.

[6] Yellow fever : a current threat, http://www.who.int/csr/disease/yellowfev/impact1/en/

[7] Position paper Yellow Fever vaccination Weekly Epidemiological Report No. 20, 2013, 88, 201–216, http://www.who.int/entity/wer/2013/wer8820.pdf?ua=1

resulting in a significant decline of the disease. However, more recently, there has been a resurgence of YF due to changes in population dynamics, urbanization, deforestation coupled with other agricultural and developmental activities, climate changes and a decline in population immunity[8].

Yellow Fever risk assessment

The scarcity of well documented and consistent methods in YF risk assessment and the changing global epidemiology of the disease emphasised the need to revise classification and standardise the geographical risk assessment for YF. 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.

WHO convened an Informal Working Group on Geographic Risk for Yellow Fever 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[9]. The working group met by teleconference regularly (roughly every month) from September, 2008, to May, 2010 and then on an ad hoc basis. This working group outlined four levels of yellow fever risk and classified geographical areas into four corresponding categories: endemic, transitional, low risk, 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 International Travel and Health (ITH) publication.

The risk of YF was determined on the basis of the virus circulation in humans, non-human primates and vectors; the distribution of YF vectors and animal reservoirs; and the ecological factors[10]. Within certain countries, and where data exist, it is possible to stratify areas according to the epidemiological risk of YF virus transmission.

The factors identified by the group which can provide useful information on risk of YF virus transmission were:

- Periodicity of reported human or animal YF cases (active or passive surveillance);
- Presence and distribution of mosquito vectors and non-human primate hosts involved in the YF virus transmission cycle (field research);
- Ecological factors (proxy indicators for presence, abundance, and activity of vectors and primates): Vegetation, rainfall, elevation, temperature (satellite imagery);
- Historical serological surveys of the human population;
- Detection of YF virus or antibodies in non-human primates and in vector mosquitoes (field studies).

[8] WHO Yellow Fever fact sheet web page, http://www.who.int/mediacentre/factsheets/fs100/en/

[9] 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, Lancet Infect Dis 2011; 11: 622–32, http://www.sciencedirect.com/science/article/pii/S1473309911701475

[10] Background for the Consultation on Yellow Fever and International Travel, 2010, http://www.who.int/ith/YFrisk.pdf

	Classification criteria	Risk for infection	Vaccination
Endemic	Areas with persistence of enzootic yellow fever virus transmission for long periods of time, where yellow fever vectors and non-human primate hosts are present, and where yellow fever infections are repeatedly reported in human beings, non-human primates, or both, where yellow fever cases in human beings were reported regularly before high yellow fever immunisation coverage was achieved, or where serosurveys (prevaccination era) show evidence of high levels of yellow fever virus infection	High	Vaccination recommended for all travellers aged 9 months or older
Transitional	Areas bordering zones that are endemic for yellow fever with periodic evidence of virus transmission during epizootic or epidemic expansions, where yellow fever vectors and non-human primate hosts are present, and where yellow fever infections are reported in human beings, non-human primate hosts, or both (sporadic or epidemic) at long intervals and during yellow fever epizootic cases or epidemic expansions from bordering endemic areas, or where serosurveys (pre-vaccination era) show evidence of yellow fever virus infection in individuals born before the previous yellow fever virus expansion	Moderate to high	Vaccination recommended for all travellers aged 9 months or older
Low potential for exposure	Areas bordering zones where yellow fever is endemic or transitional, where yellow fever vectors and non-human primate hosts are present, where no yellow fever infections have been reported in either human beings or non-human primates, and where serological or other evidence of low levels of yellow fever viral transmission in the past might exist	Low	Vaccination generally not recommended for travellers to areas with low potential for exposure; however, vaccination might be considered for a small subset of travellers whose itineraries would place them at an increased risk for exposure to yellow fever virus (eg, prolonged travel, heavy exposure to mosquitoes, inability to avoid mosquito bites)
No risk	Areas where no past or present evidence of virus circulation exists or environmental conditions are not conducive to yellow fever virus transmission	None	Vaccination not recommended

Criteria were defined at the 2008 and 2010 WHO consultations on yellow fever—some criteria include elements for which there is no scientific basis for definition (eg, high levels, long intervals) and which will need interpretation by experts with experience in this disease area. Decisions regarding the use of yellow fever vaccine for travellers must consider several factors, such as a patient's risk of infection, country entry requirements, and the potential for serious adverse events after vaccination—in the absence of such information, a conservative approach to vaccination is justified.

Table 1: Classifications of geographical areas, according to risk of transmission of yellow fever virus

Other WHO Groups contributing to the YF work are:

- *The Strategic Advisory Group of Experts (SAGE)*[11] on Immunization established by the Director-General of the World Health Organization in 1999 provides guidance on the work of WHO. SAGE is the principal advisory group to WHO for vaccines and immunization. It is charged with advising WHO on overall global policies and strategies, ranging from vaccines and technology, research and development, to delivery of immunization and its linkages with other health interventions. SAGE recommendations guide the technical content of the ITH publication.

- *The Global Advisory Committee on Vaccine Safety (GACVS)*[12], an expert clinical and scientific advisory body, established in 1999 by WHO provides independent, scientifically rigorous advice on vaccine-safety issues of potential global importance. Recommendations from this group regarding yellow fever vaccination will be brought to the attention of the Scientific and Technical Advisory Group on Geographical Yellow Fever Risk Mapping (GRYF) for its consideration and included in the ITH publication [13].

- *The technical unit in charge of yellow fever control*. This unit convened a group of YF experts and developed a multidisciplinary risk assessment methodology for field investigations which includes serological surveys in human an non-human primate, and assessment of vector density and infectivity [14]. The field investigation methodology proposed aims at supporting a more systematic approach for data collection and analysis to assess YF risk in an area, and to determine appropriate vaccination strategies at national level (e.g. the need for either preventive or reactive campaigns, or the use of the vaccine in the childhood expanded programme on immunizations). This unit will work closely with the GRYF secretariat and appropriate results from field investigations and data available for vaccination coverage will be shared with the GRYF members to document the YF risk classification status and determine appropriate protective measures for travellers.

The GRYF will work in close collaboration with the technical units[15] responsible for the Yellow Fever Initiative and for immunization and vaccine safety.

International Health Regulations

YF is the only disease expressly listed in the International Health Regulations (IHR) for which countries can require proof of vaccination from travellers as a condition of entry into a country[16]. The IHR stipulate that vaccination with a WHO approved YF

[11] See SAGE web pages, http://www.who.int/immunization/sage/en
[12] GACVS http://www.who.int/vaccine_safety/committee/en/ *and Yellow fever vaccine safety web page, http://www.who.int/vaccine_safety/committee/topics/yellow_fever/en/*
[13] International Travel and Health web page, http://www.who.int/ith/en/
[14] Yellow Fever in Africa: Estimating the Burden of Disease and Impact of Mass Vaccination from Outbreak and Serological Data, http://apps.who.int/iris/bitstream/10665/158260/1/PMC4011853.pdf?ua=1
[14] Risk assessment on yellow fever virus circulation in endemic countries, http://apps.who.int/iris/bitstream/10665/112751/1/WHO_HSE_PED_CED_2014.2_eng.pdf
[15] *Yellow fever technical unit publications http://www.who.int/csr/resources/publications/yellowfever/en/*
[16] International Health Regulations, http://www.who.int/topics/international_health_regulations/en/

vaccine[17] provides protection against infection for 10 years, and that the certificate of vaccination or re-vaccination is accordingly valid for 10 years. The WHO World Health Assembly in May 2014 adopted an amendment to Annex 7 of IHR[18], which stipulates that the period of protection afforded by YF vaccination, and the term of validity of the certificate will change from 10 years to the duration of the life of the person vaccinated. This change will enter into force legally in July 2016.

The requirement of a proof of vaccination from travellers as a condition of entry into a country shall not be more restrictive of international traffic and not more invasive or intrusive to persons than reasonably available alternatives that would achieve the appropriate level of health protection. In determining whether to implement the requirement of a proof of vaccination from travellers, countries shall base their determinations upon scientific principles, available scientific evidence of a risk to human health, or where such evidence is insufficient, the available information including from WHO and other relevant intergovernmental organizations and international bodies; and any available specific guidance or advice from WHO. A country implementing a requirement of a proof of vaccination which significantly interferes with international traffic shall provide to WHO the public health rationale and relevant scientific information for it. WHO shall share this information with other countries and may, where appropriate, request that the country concerned reconsider the application of the measures.

International Travel and Health

The WHO International Travel and Health (ITH) publication provides guidance on the full range of significant health issues associated with travel. Updated chapters and annexes are available from the WHO web site[19]. The ITH country list includes YF vaccination certificate country's requirements and WHO recommendations to travellers. Every year WHO sends a questionnaire to Member States to update this list.

ITH Annex 1 is a table listing countries with risk of YF transmission and countries requiring YF vaccination. The terms "country" and "countries" cover countries, territories and areas.

Risk of YF transmission is defined as YF being currently reported or having been reported in the past and presence of vectors and animal reservoirs representing a potential risk of infection and transmission. Annex 1 also includes yellow fever vaccination requirement for travellers having transited through the airport of a country