

BELGIAN CONSENSUS MEETING ON TRAVEL MEDICINE

25-05-2012

The consensus meeting was chaired by A. Van Gompel. Secretary of the meeting was W. Peetermans.

A PowerPoint presentation was prepared by A. Van Gompel; topics for change or discussion were examined and discussed by the Belgian scientific study group on travel medicine. Additional decisions made during the consensus meeting will be included in the final PowerPoint presentation, that will be sent to all participants for additional remarks and approval. The final presentation will be available on the website of the Institute of Tropical Medicine, Antwerp.

<http://www.itg.be/itg/GeneralSite/Default.aspx?WPID=293&L=N> or

<http://www.itg.be/itg/GeneralSite/Default.aspx?WPID=293&L=F>

The PowerPoint presentation will also serve as a basis for presentation and approval by the High Council for Public Health (meeting of 20-09-2012).

Hand-outs (“consensus brochure” in Dutch and French) with highlighted changes will be distributed electronically after the meeting of the High Council for Public Health and can be found on the ITM website. All illustrative documents such as WHO maps can also be consulted on the ITM website. The updated Medasso Guide will be published on this website from 15 July on.

The sources for the 2012 recommendations were:

- International Travel and Health WHO / Voyages Internationaux et Santé OMS (WHO edition 2012, partly freely available on the website (http://www.who.int/ith/chapters/ith2012en_countrylist.pdf) or to buy as a pdf-file or as a printed book).
- Health Information for International Travel (CDC: edition 2012, freely available on the website or as a printed book).
- international literature and ISTM congress; discussion forum ISTM.
- electronic version of Medasso-travel advice 2012-2013 (on the website of the ITM).

The chairman insisted that only the last version of these documents should be consulted; not the earlier editions.

Yellow fever

WHO-CDC maps and recommendations

The advice for yellow fever vaccination has changed considerably in 2011.

WHO installed an informal working group that prepared a background document

(www.who.int/ith/YFrisk.pdf). This document described new risk categories for yellow fever transmission (endemic; transitional; low risk; no risk). These areas (within a country) were determined based upon diagnosis of cases of yellow fever in humans and/or animals; results of serological surveys and the presence of vectors and animal reservoirs.

In the WHO edition “**International Travel and Health**” there is a list of

- countries with yellow fever transmission risk
- countries requiring yellow fever vaccination certificate for travelers arriving from countries with risk of yellow fever transmission
- countries requiring yellow fever vaccination certificate for all travelers.

The countries / regions on the **2011 WHO “yellow fever vaccine recommendations” maps**

are either white (vaccination "not recommended"); red (vaccination "recommended" i.e. "strongly recommended or obligatory" - for details see

http://www.who.int/ith/chapters/ith2012en_countrylist.pdf) or shaded with crossed lines (vaccination "generally not recommended"). This latter zone is for areas where there is a low potential for yellow fever virus exposure.

Most difficulties arise for shaded / crossed areas where vaccination is “generally not recommended”.

- WHO says “vaccination might be considered for a subset of travelers who are at increased risk of exposure to mosquito bites because of prolonged travel (some experts define this risk starting from more than one week travel in rural areas), heavy exposure to mosquitoes, or inability to avoid mosquito bites. Consideration of vaccination of any traveler must take into account the traveler’s risk of being infected with yellow fever virus, country entry requirements and individual risk factors for serious vaccine associated adverse event (e.g. age, immune status)”.

- The Belgian Scientific Study Group for Travel Medicine (as well as in The Netherlands) reformulates this advice as follows: **“low risk area, but yellow fever vaccination is recommended unless there is a (relative) contra-indication for vaccination”**.

Contraindications and **Precautions** (“**relative contraindications**”) to yellow fever vaccine administration are well summarized in Table 3-23 from the CDC Yellow Book 2012 (<http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/yellow-fever.htm>) (original reference MMWR August 30, 2010).

- **Contraindications** are: allergy, age less than 6 months; symptomatic HIV infection or CD4-T lymphocyte count <200 per ml; thymus disorder associated with abnormal immune function; primary immune deficiencies; malignant neoplasms; transplantation; immunosuppression or immunomodulatory therapies.
- **Precautions** (“**relative contraindications**”) to yellow fever vaccine administration are: age 6 to 8 months; age more than 60 years; asymptomatic HIV infection and CD4-T lymphocyte 200-499 per ml; pregnancy and breastfeeding.

It might be prudent to include "relapsing remitting multiple sclerosis" (MS)

One of the difficulties is the notion that countries requiring a yellow fever vaccination certificate do not consider the area of the itinerary but the country as a whole. So it is safe to vaccinate **travelers who cross borders** coming from countries that are either red or shaded with crossed lines. Furthermore, there are countries that more explicitly demand yellow fever vaccination certificates (e.g. South Africa, Tanzania & Zanzibar, North Sudan and South Sudan; etc) when arriving from neighboring countries.

Another problem is the **definition of transit in airports**. In principle yellow fever vaccination is not required if the traveler stays in the transit zone of the airport for maximum 12 hours with an entry and exit record of the same day. A vaccination certificate is required if the duration of a transit in the airport of a country with risk of yellow fever transmission is more than 12 hours. Many countries, however, require a vaccination certificate for any transit in an endemic country, irrespective of the duration (list in PowerPoint-presentation and hand-out). The recommendation for yellow fever vaccination must also take into consideration that flight itineraries can change unannounced (e.g. stopover in Ethiopia or Senegal).

One can use the red and shaded / crossed areas for giving individual advice to travelers with relative contraindications for yellow fever vaccination. When these travelers stay in the shaded / crossed areas and use mosquito repellants during the day, they can engage the trip. They must be instructed not to change their travel destination during their stay (e.g. travel to coastal cities in Brazil, without going to the countryside or Iguassu waterfalls). The same is true when these travelers with relative contraindications for yellow fever vaccination go to the Sahara desert areas of countries such as Mali, Niger or Chad.

Finally, it was noticed that countries (Eritrea, Zambia) or regions within countries (parts of Argentina, Ecuador, Peru, Venezuela) that were considered yellow fever free on previous maps are now partly shaded with crossed lines. When crossing borders leaving these countries, the neighboring country may then ask for a vaccination certificate.

The final remark made by the chairman was that yellow fever vaccination is a **onetime investment** with a very low risk of complications (versus continuous /cumulative risk because of future travels) to be taken at an earlier age, for instance when travelling to countries with risk or low risk for yellow fever transmission. The risk for adverse events is associated with the primo-vaccination, not with later doses.

The chairman refers to a document that is prepared for the High Council for Public Health concerning vaccination in children and adults that are immunocompromised or suffer from chronic diseases. This document is in its final stages of preparation and will be published on the website of the High Council and presented during a symposium November 23, 2012 .

Additional remarks concerning yellow fever vaccination were made:

- Maps remained unchanged except for Brasil, where the area further expands towards the coast.
- Risk must be assessed in detail for mixed travel itineraries and cruises.
- Interference of simultaneous vaccination of YF and Measles-Mumps-Rubella. There is somewhat lower seroconversion rate for YF, mumps and rubella, not for measles. Therefore both vaccines should preferentially be separated by 1 month.
- There is a relative contraindication / precaution for using live-virus vaccines in patients with an exacerbation of relapsing remitting multiple sclerosis. MMR is safe if administered several weeks in advance or after immunosuppressive therapy. Inactivated vaccines are considered safe for MS patients.
- Age-based risk assessment for possible adverse reactions towards YF vaccination (neurotropic or viscerotropic disease) has not changed.
- YF vaccine is contraindicated for persons with a thymus disorder that is associated with abnormal immune function (e.g. thymoma, myasthenia gravis). YF vaccine can be administered (if indicated) in persons who underwent incidental surgical removal of the thymus or have a remote history of radiation therapy to the thymus.

II. Malaria

- The WHO guidelines for malaria have not fundamentally changed.
- WHO Map has minor changes (Venezuela & Turkey).
- For zone C (called WHO type 3 and type 4) a prescription of Malarone®, doxycycline or mefloquine should be considered on case by case basis.
- For many countries in Asia and South America the risk is highly variable depending on area; season and way of traveling. Strict anti-mosquito measures only (plus an emergency self treatment in many cases) can be discussed with the individual traveler as a valid alternative.
 - For Zanzibar and central & south Madagascar this has become an option too.
 - Several countries (e.g. Dar es Salaam; Zanzibar) have a labile situation where the eradication programs seem to be successful but reintroduction can occur suddenly and unexpectedly
- India is a paradox for malaria as well: it has the highest absolute number of malaria cases but an extreme low risk for travelers (most often *P. vivax*, but *P. falciparum* is possible). The advice remains either use **chemoprophylaxis** or emergency self treatment.
- *P. knowlesi* infections now have been described without direct rainforest exposition (e.g. in Thailand).
- Pregnancy remains problematic for malaria prophylaxis advice.

Doxycycline is contraindicated. In Scandinavia, however, they consider doxycycline taken during the first trimester as no risk because dental formation has not yet occurred. Malarone® is contraindicated during pregnancy but seems to be safe based upon large registries. Therefore several countries such as France are rather permissive for Malarone® use during pregnancy. It remains FDA class C.

Mefloquine is relatively contraindicated during the first trimester but can be used safely according to product insert, CDC and many national authorities.
- A new drug for malaria treatment became available besides Malarone and Riamet : Eurartesim®, another combination of dihydroartemisinin and piperaquine. Adult dose is 4 tablets per day for 3 days (without food). Dose adjustment according to weight.

III. Other vaccines

1. Tetanus-Diphtheria

There is a temporary stock-break for Tedivax PA®. It can be replaced by Boostrix® (including pertussis) or Revaxis® (including polio).

2. Polio

No new outbreaks / cases have been described in India ; India has been declared poliofree

But the situation is not solved yet in Nigeria, Pakistan, and several countries with re-established or imported cases in Africa and Central-Asia.

Advice for liberal vaccination (one booster after adolescence provides life-long protection) remains active.

3. Measles

Travelers born after **1-1-1970** (*formerly 1960*) who had no proven clinical measles or received no or only one vaccine shot require measles vaccination. Two doses are needed for protection.

Early vaccination – from the age of 6 months on - is actually advised even for many some European destinations because of measles outbreaks. The dose given before the age of 12 months will not count for the final complete series of “2 doses”.

4. Rabies

Rabies import cases have been reported from several European countries. Awareness must be stressed during travel medicine consultation concerning risks and need for postexposure prophylaxis.

Prophylactic rabies vaccine is no longer available via IPH/ WIV/ISP. Rabies vaccine is now commercially available in Belgium. (either Mérieux or Novartis). Rabies vaccine Mérieux® is reimbursed, but not Rabipur® (request still pending). The two vaccines are interchangeable and can be used for subsequent vaccination.

The vaccination scheme is 3 shots within one month. This is the basis whereafter the patient remains for decades (probably lifelong) boostable. So the only once needed booster dose can be given after one year or later. Every shot counts, so even if a

second or third dose is delayed, it can be considered as an individual determinative dose. It is safe to measure the rabies antibody titre after the third shot if delayed doses were given (e.g. more than 12 months).

The postexposure rabies management remains the responsibility of the WIV/IPH/ISP. Insurance agencies can be contacted for shipping the rabies immunoglobulin dose. After the postexposure rabies vaccination series, the same longterm boostability is present.

5. Cholera

The vaccine has very limited indications. No change in the approach.

6. Meningococcal vaccine: polysaccharide or conjugated vaccine?

Since 2011 we have two meningococcal vaccines commercially available: the polysaccharide vaccine Mencevax® (33 euro) and the new conjugated vaccine Menveo® (52,6 euro). A second conjugated vaccine (Nimenrix®) will be launched in September 2012.

Conjugated vaccines have the advantage (1) that antibody titers decline more slowly so that protection can last longer. Furthermore (2) immune memory is installed and (3) carriership is prevented. It is not clear at this point at which time point a booster dose for the conjugated vaccine has to be given (3 (as advised in the US) or 5 or 10 years ?). The risk for carriership after Hajj is very low because every pilgrim coming from endemic countries receives eradicating antibiotic treatment on arrival in Saudi Arabia. For these reasons, the consensus conference expresses no priority for either vaccine for Hajj pilgrims. Mencevax can be used when the travelers says that he only need the vaccine once (for Hajj). Conjugated vaccine is preferred for repetitive exposition within a few years such as expats and frequent travelers to countries of the meningitis belt. Several cases of invasive meningococcal disease in "travelers" coming from the meningitis belt have been reported in Europe (Eurosurveillance 21 May 2012 - but yet no details known - VFR's ? - no secondary cases), indicating the usefulness of preventing carriership by a conjugated vaccine. Menveo® is registered for children from the age of 2 years (studies in children of 2 months are done, the request for EMA is prepared); Nimenrix® will be registered for children from the age of 1 year.

7. Japanese encephalitis (Ixiaro®)

- The full dose has to be used for children and adults between 3 and 18 years of age. Between the age of 1 and 3 half dose is indicated. The standard scheme requires 2 injections, separated by one month (can be reduced to 21 days if time is lacking). Afterwards, the traveler remains boostable which means that a booster dose can be given after 12-24 months. Timing for subsequent boosters remains to be decided. Difficulties to study booster requirements in endemic countries is due to repetitive exposure to other flavivirus that may generate partial cross-immunogenicity.
- When the patient was vaccinated with JEvax® previously the consensus meeting gives the advice to use two doses of Ixiaro® when JEvax® dates from five years back or more. If less than 5 years since JEvax®, one shot with Ixiaro® is advised (supported by data in Vaccine 2012 & an oral communication ESCTM Dublin 2012 (and published in Clinical Infectious Diseases).

I. Varia

1. Hajj : the legal requirements of Saudi Arabia remain unchanged (influenza strongly advised and meningococcal vaccine obligatory). The embassy prefers that the vaccines are declared in the yellow booklet, but a WHO stamp is not required. Whether other ways of documentation (e.g. attestation by the general practitioner) can suffice, is unclear and will be checked.
2. Traveler's diarrhea : Rifaximin is not yet commercially available. It is not recommended for invasive diarrhea or prophylaxis. It is also very expensive. Even with raising antibiotic resistance, the consensus meeting still recommends fluoroquinolones or azithromycin for early treatment. A study estimated an enhanced risk for cardiovascular death when using azithromycin during 5 days. It is unclear if other risk factors have influenced this result such as indication for azithromycin, underlying disorders, previous medication, etc. For traveler's diarrhea a single dose is enough in the large majority of cases. Therefore the consensus meeting has not changed its advice.
3. Mass gatherings and "close distance" holidays: there is a need for checking the vaccination status if travelers want to visit large gatherings such as Euro-football or Olympic Games. A check for the "2-dose" vaccination of MMR is imperative. Travelers and doctors must also be aware of the epidemiological situation in other European countries that may require additional measures (such as Tick-bite

encephalitis in Central Europe). Hepatitis A is also recommended for intermediate endemicity countries.

Symposium : the High Council for Public Health organizes a national symposium to present its new guidelines : “Vaccination of immunocompromised patients and patients with chronic disorders” on Friday, November 23 (whole day programme).

13th CISTM : the 13th CISTM conference will be held in Maastricht from 19 – 23 May 2013. Four members of the Belgian study group serve in the local organizing committee.