

CONSENSUS TRAVEL June 24th 2016**Venue: WIV/ISP****INTRODUCTION**

The purpose of this consensus meeting is to discuss some selected domains in travel medicine. In particular changes with clinical impact will be highlighted. Preparatory work has been done by Ula Maniewski, Patrick Soentjens and Yves Van Laethem. The summary report highlights the major points of discussion. The full powerpoint presentation will be available on the website of the Institute for Tropical Medicine Antwerp (ITMA).

In the future, a consensus meeting will be held every 2 years, alternating with the national seminar on travel medicine.

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TOPICS

The domains selected for this consensus meeting are

- Yellow fever (YF)
- Traveller's diarrhea (TD)
- Zika virus
- Malaria (new maps)
- Vaccine overview

YELLOW FEVER

by Ula

A WHO consensus states that "as of July 11th 2016, for both existing or new certificates, revaccination or a booster dose of yellow fever vaccine cannot be required of international travellers as a condition of entry into a State Party, regardless of the date their international certificate of vaccination was initially issued". In practice, this means that we do not have to renew the YF certificate for travelers that have been vaccinated in the past. But: this statement does not provide any recommendation concerning the need for booster vaccination in individual persons. This means that each country has to decide for itself which recommendations will be used regarding YF vaccine boosters, in particular in 'special populations', such as immune compromised or pregnant travelers.

At this moment, it is not very clear whether booster vaccination is indicated in selected travelers. What is the policy in other countries? There is a list of recommendations per country, available on the website of WHO. Some countries accept YF vaccination 'for life'.

A look at the 'yellow fever map' shows us that nothing has changed since 2014 concerning the 'risk areas' and the recommendation for vaccination (or against).

Belgian guidelines can be summarized as follow:

- one YF vaccine provides lifelong protection for individuals with normal immune function
- in this case, no boosters are needed and on the certificate, it is written that **'the certificate [is] valid from: .../.../... until: lifelong'**

- in case there is doubt about the durability of the vaccine response, one can decide to
 - give a booster (with a 10 years interval)
 - measure the level of serum neutralizing antibodies

A key question is: who is **not** considered to be lifelong protected after one YF vaccination?

The following proposal is made:

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- healthy people with a special condition
 - < 9 months old
 - pregnant women
 - interval < 28 days after vaccination with another live attenuated vaccine

⇒R/ give one booster before next travel and indicate validity on the certificate until 'first day of validity + 1 year'
- people with immune suppression (hiv, other disease, treatment ...) or people living in a 'high risk situation' (lab, region with YF outbreak ...)
- ⇒R/ test for neutralizing antibodies and give a boost if necessary OR give a boost after 10 years
- people submitted to stem cell transplantation after having received a YF vaccine
- ⇒R/ give a booster at least once OR test for antibodies before travel

The slides show how the certificate can be completed in practice

What about Angola?

An epidemic started in December 2015, and it is still ongoing. YF vaccination is thus strongly recommended, according to the updated maps, available with the slides.

Are there indications to use a reduced dose of YF vaccine, e.g. in emergencies?

A WHO Strategic Advisory Group of Experts (SAGE) states that "using a fifth of a standard vaccine dose would still provide protection against the disease for at least 12 months and possibly much longer. But "a yellow fever vaccine given at a fractional dose would not qualify for a yellow fever certificate under the IHR requirements. Travellers will need to obtain the full dose of the vaccine to be eligible for the yellow fever certificate."

What to do if adverse effects are suspected?

There is a special procedure to be followed, outlined on the slides. Blood samples can be sent to the Robert Koch Institute in Berlin. Please keep also the ITMA informed.

In conclusion, it is clear that, before administering the YF vaccine, contraindications and possible precautions should be checked for, as usual. Concerning concomitant medications, recommendations are available as published by the Hoge Gezondheidsraad/Conseil Supérieur de la Santé (see slides).

As a reminder: do not forget other mandatory vaccines, such as poliomyelitis or meningitis for pilgrimage travelers.

Questions and discussion

-already filled in YF certificates will not have to be adapted according to the new WHO directives
-a date for a booster is not "officially required" on the YF certificate; it is only there to remind the traveler

-it is proposed to revaccinate travelers to countries that will not follow the new WHO guidelines according to the "classical 10 years rule" but only until July 11th, 2016

-when it is indicated (see list) and in case of doubt, it can be decided to measure neutralizing YF antibodies; a serum sample can be sent to the ITMA; it takes about 3 weeks to have the result; there is no extra cost, but please add the indication for the test (for example: 'immunosuppression' or 'immunosuppressive drugs').

TRAVELLERS' DIARRHEA

by Patrick

Should self treatment with antibiotics by travelers be advocated? This was already discussed in the past by Belgian infectiologists. More information on the slides.

There are arguments supporting self treatment: you might prevent the trip from being ruined, you may shorten clinical disease with a few days, you may avoid hospitalization abroad with extra costs and risk of wrong antibiotic use, et cetera. On the other hand, more liberal antibiotic use increases the risk of selection of multiresistant germs with possible effects on public health. Many questions remain and more studies are needed.

The recommendations found in the literature differ from country to country. E.g., the Germans are less inclined to antibiotics as compared to the US and Canada.

A US study on a (small) military population showed no difference in symptoms at 48h in the treatment vs no treatment arm. TD turned out to be independently associated with incorrect use of antibiotics (due to suboptimal self treatment).

In a Dutch study by the group of Leo Visser (Leiden) Asia and Africa emerged as "risk continents" according to the number of TD cases. It was found that the expected degree of subjective inconvenience due to TD before travel exceeded the degree of inconvenience estimated after travel, in those who developed TD and judged it to be a "large problem" before travel. This can make us believe that TD is not always that severe from the traveler's perspective.

So it seems that still useful data could be gathered, e.g. by a prospective study that would look at the effect of antibiotic treatment on the degree of inconvenience in a randomized way, where the decision to use antibiotics or not would be taken before departure. In the Jessa Ziekenhuis, they are already doing a prospective evaluation with a questionnaire (see slides).

Another aspect of TD is its association with intestinal carriage of resistant bacteria after travel. It is a fact that carriage of multiresistant bugs is on the rise. Traveling seems to be an important element of spread. Sometimes, more colonization can lead to multiresistant organ infection.

The study of Anu Kantele (Finland) looked at the colonization rate of travelers with ESBL-producing *Enterobacteriaceae*. Independent risk factors were: the geographic region of travel, the occurrence of TD, age, and the use of antibiotics for TD. The effect of loperamide use was also evaluated: the risk for ESBL carriage increased with concomitant use of loperamide. Data such as these led to a call to be careful and to restrict the prescription of antibiotics for TD. We should not forget that the number of travelers is huge and increasing, so that the background prevalence of multidrug resistant organisms in the home country might increase. Furthermore, other studies pointed towards an increased risk of subsequent infection with *Salmonella* and *Campylobacter* after exposure to fluoroquinolones.

So in summary, we should be aware of the problems linked to antibiotic use for TD, inform travellers about it, try to act restrictively and select those persons that would benefit most from antibiotic treatment, and adapt the choice of antibiotics according to the geographic location.

The BE Studygroup for Travel Medicine would like to change the algorithm for antibiotic treatment of TD. Antibiotic prescriptions are only necessary for trips to Asia and Africa with a duration of at least 16 days or more. The preferred antibiotic regimen is 1g QD azithromycin (two pills of 500 mg at once). For children, azithromycin 10mg/kg once a day during three days is recommended.

Antibiotics can be prescribed in the following exceptions, making it always a patient tailored decision:

- adventurous travel (longterm travel, high altitude and jungle trekking)
- all travel to the Indian subcontinent
- immunocompromised patients (hypo- or agammaglobulinemia, immunosuppressive treatment, hematological malignancies, HIV, et cetera)
- patients with underlying disorders at risk for complications (diabetes, renal insufficiency, heart failure, et cetera)
- children (until the age of 12 years)
- pregnancy

PPI use need to be decreased or if possible avoided during travels to tropical countries; you don't always need to prescribe antibiotics for this medical condition of hypo- or achlorhydria.

Questions and discussion

-for travellers to Latin America, symptomatic treatment should be preferred, with the recommendation to seek local healthcare advice if necessary; "jungle travel" can however be considered an exception

-what should be the preferred choice for persons with a long QT syndrome? macrolides nor fluoroquinolones are an optimal choice; maybe rifaximine (not registered in Belgium) could be considered?

ZIKA VIRUS

by Ula

Zika still is a problem for Central- and South-America. However, also Cabo Verde and some other islands in the Pacific Ocean are involved (see maps on the slides). It is recommended to check recent information (website of ITM, CDC, WHO ...) when giving advice to individual travelers.

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Guidelines are available (see slides) laying emphasis on the pregnant woman.

What about the woman with childwish? How long after travel will she have to wait to get pregnant, and what about the duration of the risk of getting infected by semen of an infected male traveler?

CDC and WHO give the advice to postpone conception for at least 8 weeks after the start of Zika symptoms in the female, and at least 6 months after the start of Zika symptoms in the male. If there were no Zika symptoms, a waiting period of 8 weeks after visiting a risk area is recommended. Does this period suffice? We cannot be really sure about it because it is based on a few case reports, but we can test

A schedule for applying diagnostic serology/PCR in pregnant women (blood,urine) at risk is proposed by the Hoge Gezondheidsraad/Conseil Supérieur de la Santé (see slides).

What to tell to pregnant women who want to travel to risk areas (including malaria)?

If possible, they should postpone the journey (or change the destination). Potential risk and prevention issues concerning should of course be discussed.

As far as concerns malaria chemoprophylaxis, all authorities agree that mefloquine is OK at all stages of pregnancy. There are only sparse data on atovaquone-proguanil, but it can be used in pregnancy. For doxycycline, recommendations differ according to the source, but we agree with the English and Scandinavian guidelines that it can be used until week 15 of pregnancy. An artemisinin based treatment can be safely used in the 2nd and 3^d trimester. But during the first trimester it can only be used if no other options are available (teratogenic in mice in early pregnancy)

YF vaccine can be given to pregnant women traveling to endemic areas where exposure will be likely. But, it can be assumed that the seroconversion rate will be less when vaccinated later in pregnancy. Lactation is no contra-indication for YF vaccine, but the child should preferably be older than 6 months. If not, then it is better to stop lactation during a 2 weeks period after vaccination.

Genital mutilation? Please dare to talk about it when it is judged that there could be a risk for the child (see country map of genital mutilation in the slide presentation).

Questions and discussion

-so, do we prescribe atovaquone-proguanil to pregnant women? yes, but it should be discussed with the woman

-revaccination of a lactating woman: does she have to interrupt lactation? there is no clear answer; probably not, but we do not know it

MALARIA

Yves comments on the new malaria maps.

Globally, there are not many changes.

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Travellers at risk should of course respect the "ABCDE of prevention".

Should or can we impregnate our mosquito nets? Chemical kits are not allowed to be freely sold any more. So it is difficult to do it yourself. We can buy impregnated nets, but the question is whether "they are as they should be".

DEET remains a good repellent. The percentage plays a role. Recommend DEET of $\pm 30\%$ for children and pregnant women, although it is not clear if there is a risk when using higher percentages. DEET cannot be found everywhere, especially the high percentages; this should be taken into account. Stand by emergency therapy still is an option in low risk regions.

The "malaria 2016 map" differs somewhat from the "malaria 2015 map", but the differences are small. There is now an "orange zone" of "moderate risk" (e.g. in South-America and in Asia). In the Amazon region, there is still risk, but lower than before. See also the slide presentation on malaria risks in Ecuador. In Africa, there are some small zones with less risk (see map).

In India, the risk is also limited (except Assam and Orissa region; preventive measures remain important but chemoprophylaxis is not necessary for most travellers (see map: <http://www.itg.be/ITG/Uploads/MedServ/India2015.jpg>).

There is now less risk in Myanmar and the Philippines (see the slide presentation).

Concerning chemoprophylaxis with atovaquone-proguanil, there is not enough evidence to recommend a twice a week schedule.

Questions and discussion

-should atovaquone-proguanil always be taken until 7 days after return? maybe 5 days can suffice, but there are no clear data

-in case of a switch from mefloquine to atovaquone-proguanil during chemoprophylaxis, for how long should the treatment be continued? there are no clear data on this, so in theory you should continue until 4 weeks after stopping mefloquine

VACCINES

by Patrick

An overview is summarized on the slides.

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Tetanus-diphtheria

- ✓ in case diphtheria-antitoxin should be needed urgently, there are ways of rapid communication within Europe, via the WIV/ISP

MMR

HepA

HepB

- ✓ test for antibodies only in special conditions, and once in a lifetime

Polio

- ✓ an extra vaccine is mandatory after a stay for at least 4 weeks in a country where wild polio virus is circulating (Pakistan and Afghanistan) and is strongly recommended for those leaving countries where vaccine derived polio virus is circulating (Ukraine, Madagascar, Nigeria, Guinea, Myanmar, Laos); give it between 4 weeks and 12 months before leaving the country; administration should be noted in the certificate

Typhoid fever

- ✓ maybe we use it too often? vaccination is recommended in case of travel longer than 3 weeks to "the Indian subcontinent"; this involves "all countries situated around India", so probably including Sri Lanka, but in fact not S-E Asia (although *not according to the WHO map*)
- ✓ consider the vaccine for adventurous travel in subtropical countries

Meningococcus

- ✓ vaccine Menveo® - Nimenrix®: 3 years validity for Hajj pilgrims following the regulator of Saudi Arabia
- ✓ WHO guideline (WHO Weekly Epidemiological Report July 2016): 8 years validity for a conjugate vaccine, but not yet accepted by Saudi Arabia, so not yet applicable for this Hajj 2016-

Influenza

- ✓ maybe already give the vaccine in spring? we do not have it in summer.

TBE

- ✓ there are fast schedules now; vaccination can be done in 14 days, with a boost 1 year later (see slides)

Japanese encephalitis

- ✓ two injections, with a boost at 1 or 2 years
- ✓ is a second booster needed after 6 years? we need more data
- ✓ half the dose should be used by the pediatricians
- ✓ there also is a fast one week schedule, already accepted in France (with Ixiaro)
- ✓ there are alternative vaccines available in Asia (eg IMOJEV MD)

Rabies

- ✓ we are probably undervaccinating
- ✓ prevention remains important!
- ✓ the vaccination schedules are difficult and painful; one can use intradermal schedules
- ✓ there is an accelerated one week (D0-D7) IM schedule (see slides)
- ✓ are 3 injections once in a lifetime enough? the idea is that boostability will remain so that 2 injections will suffice after a bite
- ✓ which PEP regimen after a bite is recommended (when pre-exposure schedule was performed before travel)? 4 intradermal injections on one day or 2 injections IM at the same time will suffice, but always given as soon as possible after the bite
- ✓ PEP needs to be started ASAP after the bite, and certainly within 5 days; but, in exceptional cases where PEP has not been started within this delay, it should be started regardless of the time that has elapsed (so when there has been a risk, one has to start PEP, "too late" is not a good reason not to start any more)
- ✓ the WHO SAGE group will publish recommendations on Rabies PrEP/PEP schedules in 2017

Dengue

- ✓ a vaccine is implemented in a few endemic countries, , not indicated for travelers.

Malaria

- ✓ vaccine is studied in a few pilot studies in endemic countries, but a vaccine not indicated for travelers.

Mers-CoV

- ✓ do not forget it!

Closing remarks

-as already stated, the Consensus Meeting will be held every 2 years, in October, in alteration with the Belgian travel medicine seminar

-a new Medasso guide is available, published on the website of ITGA

-there was a mail from Dominique Wagner from SANIPORT, saying that they will not deliver the YF certificates any more; you can order the certificates

- by mail= via bookorders@who.int
- address= WHO PRESS / EDITIONS OMS / EDICIONES DE LA OMS
CH-1211 GENEVA 27, SWITZERLAND
WHO Press: Direct Tel. +41 22 791.32.64
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-how do we deal with the fact that the demand for travel advice exceeds the capacity of the centers, during the busy season? **a call is done to all centers to try to increase capacity temporarily during the summer months.**