Expertenkomitee für Reisemedizin
Comité d'experts pour la médecine des voyages
Comitato di esperti per la medicina di viaggio
Expert committee for travel medicine

Zika Virus
Information and recommendations of the Swiss Expert Committee for Travel Medicine (ECTM)*
(Update December 2018)

*members listed below

Background: In 2015 an explosive spread of the Zika Virus occurred in Central and South America, and the Caribbean. Zika virus infection during pregnancy can cause birth defects such as microcephaly and/or other neurological disorders.

Pathogen: The Zika virus (ZIKV) belongs to the virus family Flaviviridae, which includes the viruses that cause dengue fever, yellow fever, tick-borne encephalitis (TBE), Japanese encephalitis, and West Nile fever.

Reservoir: Monkeys, humans

Vectors: Mosquitoes (*Aedes* genus, subgenus *stegomyia*, mainly *Aedes aegypti*)

Geographical distribution: ZIKV was first isolated in 1947 from a rhesus monkey in the Zika Forest in Entebbe, Uganda. Until 2007, only isolated cases or small clusters had been diagnosed in Africa and in Southeast Asia. In 2007, the island Yap (Federated States of Micronesia), Western Pacific, reported a first ZIKV outbreak that was followed by a large outbreak in French Polynesia and other territories in the Pacific in 2013-2014. Between 2013 and 2015 the Zika virus was probably introduced from the Pacific to Brazil leading to an outbreak from 2015 onwards that further spread to almost all countries of the Americas and the Caribbean. In 2016 - 2017 there were also ZIKV outbreaks reported in the Pacific islands Cap Verde, Singapore and Florida. The current distribution of ZIKV can be seen at:
https://wwwnc.cdc.gov/travel/page/world-map-areas-with-zika
The current standard classification of ZIKV epidemiology per country can be found at WHO:
http://www.who.int/emergencies/zika-virus/classification-tables/en/

Transmission:
a) Vector borne (main transmission route): ZIKV is transmitted through *Aedes* (subgenous *stegomyia*) *aegypti / albopictus* mosquitoes in tropical and subtropical regions. These mosquitoes are mainly active during the day and early evening hours. *Aedes* mosquitoes are quite aggressive and prefer to bite humans. They are mainly found in cities. Zika cases transmitted by mosquitoes are the predominant way of infection in humans.

b) Sexual: ZIKV can be transmitted by sexual intercourse. This is possible from both asymptomatic and symptomatic persons through genital, and anal intercourse. Sexual transmission is possible from male to female, male to male, and female to male (Moreira et al., 2017, Baud et al., 2017). Up to date, the maximal documented time of sexual transmission is 44 days after symptom onset, most reports indicate shorter intervals (Moreira et al., 2017, Baud et al., 2017, CDC, 2018). Infectious ZIKV particles have been detected through semen up to 69 days after symptom onset (Arsuaga et al., 2016), and in the female genital tract up to 2 days after symptom onset. ZIKV RNA detection has been reported in semen for more than 12 months; however, most cohorts report a shorter interval with an estimated mean time to ZIKV RNA clearance of 54 days (Mead et al., 2018). In the female genital tract, ZIKV RNA was detected up to 14 days after onset of symptoms (Nicastri et al., 2016). However, the presence of ZIKV RNA in genital fluids is not necessarily associated with infectivity; hence, the exact duration of possible sexual transmission remains unknown.

c) Transfusion: Transmission via a blood transfusion is possible.

d) Materno-fetal: Perinatal transmission was first reported in 2013 during the French Polynesian outbreak and has since been confirmed in the Brazilian outbreak and elsewhere from 2015 onwards, including in pregnant travellers upon return.
As of current knowledge, vertical transmission occurs in around 30% all ZIKV infected pregnant women, and around 50% of all infected foetuses will have symptomatic congenital infections (Pomar, BMJ 2018). The risk of birth defects is similar for symptomatic and asymptomatic infections (Honein, JAMA 2017), and there was a higher risk of birth defects in women who were infected around the preconception period or during the first pregnancy (Hoen, NEJM 2018). Consequently, clinically relevant damages to the child were found in around 5 to 13% of ZIKV positive mothers (Honein, JAMA 2017; Hoen, NEJM 2018, Pomar, BMJ 2018), which is comparable to other congenital diseases such as CMV. Prolonged detection of viral RNA in pregnant women might be the result of viral replication in the foetus or placenta. Infectious ZIKV particles have been detected in breast milk, but no transmission to neonates by breastfeeding has been reported to date.

Risk assessment of ZIKV infection for travellers: ZIKV infection is possible where the ZIKV is endemic. Because of the reported congenital infections during the ZIKV outbreaks in the Pacific and Americas, risk of ZIKV infection with risk of birth defects has to be considered and should be discussed during pre-travel consultation.

Clear risk of ZIKV infection is difficult to assess as several factors (seasonality, other flavivirus cross-immunity, herd immunity, traveller's behaviour…) are most probably involved, and the epidemiological situation of ZIKV has been assessed differently depending on the consulted source (ECDC, CDC). Moreover, since the peak of the outbreak in 2016, the epidemiological surveillance has decreased and reliable updates are lacking. The Swiss Expert Committee for Travel Medicine (ECTM) assumes the risk to be low to get infected by ZIKV during travel in confirmed or probable endemic countries (category 2-4 of the WHO ZIKV classification). The justification of this assumption is based on the epidemiology observed in Asia and Africa. ZIKV has probably been endemic in Asia and Africa for many decades without revealing an epidemic spread, as it has been the case in 2015-2016 in the Americas/Caribbean or in 2013 in Oceania.
Therefore, for pregnant women or women planning to get pregnant, the Swiss ECTM considers the risk to be low for acquiring a ZIKV infection leading to foetal malformation in countries of category 2-4 of the WHO ZIKV classification.

Based on this background, the Swiss ECTM defines the ZIKV infection risk for travellers as follows:
Increased risk for congenital infection = all category 1 countries of the WHO ZIKV classification
Low risk for congenital infection = all other countries in tropical and subtropical regions (category 2-4 of the WHO ZIKV classification).

Incubation Period: Not exactly known, probably 3-14 days.

Disease: Only one out of five infected people fall ill with usually mild symptoms of generally short duration (2-7 days). The main symptoms are a maculopapular rash that is often itchy and spreads from the face to the body, fever (however often missing), conjunctivitis, joint pain in the small joints of the hands and feet, muscle pain, and headache. More rarely, neurological complications are observed (meningitis; or ascending, usually temporary paralysis, the Guillain-Barré-Syndrome). There is evidence that ZIKV infection during pregnancy causes microcephaly in the unborn child along with other possible neurological damage to the brain, eye (blindness) and ear (hearing loss). In addition, miscarriage, premature delivery, and impaired intrauterine growth may occur.

Diagnosis and treatment: Since the recent outbreak in Latin America, ZIKV has been recognized as a possible aetiology of fever or neurological symptoms after travel. Like other diseases, diagnostic tools and management are under the responsibility of the medical doctor in charge. The decision to

perform one or several ZIKV diagnostics tests (RT-PCR and/or serology)
should be discussed in the routine diagnostic evaluation of all fever patients returning from a sub- or tropical country. However, due to the risks of congenital malformation, irrespective of the clinical presentation, and due to its sexual transmission, particular attention should be given to pregnant women. Specific diagnostic guidelines take into account the exposure risk, the period of asymptomatic carriage either in the female genital tract or in the semen and the diagnostic specificity of the respective test.

In clinical management, medication containing acetylsalicylic acid (e.g. Aspirin®) or non-steroidal anti-inflammatory drugs (such as ibuprofen) should not be used before exclusion of (concomitant) dengue infection. A specific antiviral therapy and/or a vaccination against ZIKV do not exist.

Laboratory Diagnostics of ZIKV (PCR plus serology) can be performed in:
Switzerland:

- Hôpitaux Universitaires de Genève (reference laboratory): http://www.hug-ge.ch/laboratoire-virologie
- Labor Spiez: http://www.laborspiez.ch/de/the/bs/pdf/Diagnostik_von_Zikavirus_Infektionen.pdf
- University Hospitals and some private laboratories will also offer ZIKV testing

Germany:

- Bernhard Nocht Institut: https://www.bnitm.de/aktuelles/mitteilungen/954-empfehlungen-zurdiagnostik-der-zika-virus-infektion/
- Robert Koch Institut in Berlin

Mandatory reporting: Since March 5th 2016, reporting of ZIKV infections in Switzerland is mandatory.

*members of the Swiss ECTM: head or representative of the travel clinics of Basel (Swiss TPH), Bern (Dep.of Infectious Diseases), Geneva (Dep. of Tropical and Travel Medicine), Lausanne, (unit of Tropical and Travel Medicine), Ticino, St. Gallen, Zürich (Dep. of Public Health), representative of the Swiss Society of Infectious Diseases, and Swiss Society of General Medecine.

Recommendations of the Expert Committee of Travel Medicine (ECTM) of Switzerland for congenital ZIKV infection evaluation:

After ZIKV potential exposure:

Testing for ZIKV after travelling to a ZIVK endemic region **should not be done on a routine basis** after possible ZIKV exposure. Indeed, ZIKV infection is generally a mild and self-limited infection.

WHO should be tested?
Screening for ZIKV can be considered in the following situations:

- **Pregnant women:** All pregnant (symptomatic/asymptomatic) women with potential exposure to ZIKV* should further be assessed by specialists in gynaecology and medical specialities with experience in ZIKV testing (tropical medicine or infectious disease specialists).

HOW to test:
the following investigations for ZIKV may be considered:
A: Laboratory testing:

1. **Symptomatic** pregnant women **AND last ZIKV exposure* < 4 weeks :**
    - RT-PCR in serum (up to 4 days) and/or in urine (up to 39 days)
    - Serological testing if > 4 days after onset of symptoms
    - Serum storage at first consultation
    - Consider TORSCH (Toxoplasmosis, Rubella, Syphilis, CMV, HSV) and VZV
    - If ZIKV serology and RT-PCR are negative: repeat serology 4 weeks after the first test

2. **Symptomatic AND last ZIKV exposure* > 4 weeks** OR **asymptomatic** pregnant women
    a) **low risk**** : no intervention
    b) **increased risk**** : Serological testing (IgM and IgG for ZIKV) and serum storage

B. Ultrasound diagnostics (US): After **increased ZIKV congenital risk infection exposure**** of the pregnant women OR **symptomatic pregnant women**, ultrasound (US) investigation in short intervals should be considered to assess the risk of developing microcephaly or other neurological disorders in the unborn. In addition to the routine US evaluation performed in Switzerland, a morphological US e.g. 28 weeks of gestation and at least 4 weeks after maternal exposition is recommended. According to the results follow up ultrasound investigations in short intervals (every 4 weeks) and checking potentially prolonged viremia by PCR on plasma/serum could be considered (see reference David Baud, Driggers et. al, 2016).

Of note:

- If pregnancy is uncertain, a pregnancy test should be performed
- The sensitivity, specificity and positive predictive value of ZIKV laboratory diagnostic tests are not conclusively defined. Therefore, a negative laboratory test (ZIKV PCR and/or serology) does not exclude a ZIKV infection, but one might estimate the risk of infection in a better way by repeated tests
- Detection of ZIKV in blood, urine and amniotic fluid can be negative despite proven foetal infection
- ZIKV can be detected in pregnant mothers or amniotic fluids without foetal infection

***Definition of a potential ZIKV exposure:** a) history of travel/residence in an area with ZIKA transmission (category 1 - 4 of the WHO ZIKV classification) and/or b) unprotected sexual contact with a man within 2 months after ZIKV symptoms AND/ or upon his return from a possible ZIKV transmission area, irrespective of ZIKV clinical presentation.

****Definition of the ZIKV congenital infection risk:** increased risk = potential ZIKV exposure* to all category 1 countries of the WHO ZIKV classification OR IgM+ ZIKV partner; low risk = potential ZIKV exposure* all other countries in tropical and subtropical regions (category 2-4 of the WHO ZIKV classification).

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Prevention for travellers:

The Expert Committee of Travel Medicine (ECTM) of Switzerland recommends the following:

- **All travellers** with potential ZIKV exposure* should be informed about the risk of the congenital infection and its sexual transmission. Counselling on safer sex practice and on contraceptive methods is recommended. Protection against mosquito bites (indoors and outdoors) during daytime, evening and early night time hours (especially in the mid-morning and late afternoon to dusk) by using repellents (DEET), wearing long-sleeved shirts and long pants of light colours that could be impregnated or sprayed with an insecticide.

- Due to congenital complications, **pregnant women** (regardless of pregnancy trimester) or women who cannot rule out a pregnancy should be advised to not travel to areas with **increased** ZIKV congenital infection risk**.
  If travel cannot be avoided, special pre-travel advice is necessary including advice of strict protection against mosquito bites and pre-departure serology. A follow-up after travel is recommended.
  If the partner had increased** ZIKV exposure, safer sex practice is recommended at least for 2 months* (during all pregnancy according to CDC). A serology afterwards may also be proposed.

- **Couples and women who are planning a pregnancy** should avoid becoming pregnant (safer sex) while travelling and, due to carriage in semen, should wait at least 2 months (Baud, 2018) after symptoms onset (if symptomatic) OR (if asymptomatic) after ZIKV **increased**** risk exposure*.
  A period of at least 3 months (CDC 2018) is recommended in case of medical assisted procreation.
  In certain case, when delaying conception is not possible (continuous travelling), a serological testing (> 4 weeks after ZIKV increased** exposure*) before conception might be proposed.

Of note:

- In case of travel to/ or stay in a ZIKV endemic area during pregnancy, women (asymptomatic or symptomatic) should inform their gynaecologist for further follow up.
- Pregnant women should discuss their sex partner's possible history of having been in areas with ZIKV transmission and history of illness consistent with ZIKV disease.

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