



## Zika Virus

### Information and recommendations of the Swiss Expert Committee of Travel Medicine (ECTM)

#### Background:

Since 2015 there has been an explosive spread of the *Zika* Virus in Central and South America and the Caribbean. *Zika* virus infection during pregnancy can cause birth defects such as microcephaly 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. ZIKV was first isolated in 1947 from a rhesus monkey in the Zika Forest in Entebbe, Uganda. Until 2007, only isolated cases had been diagnosed in Africa and in Southeast Asia.

#### Reservoir:

Monkey, humans

#### Vectors:

Mosquitoes.

#### Incidence/risk areas:

ZIKV Transmission patterns can change rapidly; for the current status see the following links of the European Centers for Disease Control and Prevention ([ECDC](#)) and for US the Center of Disease Control and Prevention ([CDC](#), USA).

With regard to the ZIKV transmission risk for travellers, ECDC classifies countries as follows:

**High risk:** red and red-hatched countries

**Moderate risk:** yellow marked countries

**Low or very low risk:** gray/bleu marked countries

As of 27.7.2017, in the past three months ZIKV transmission **with high risk** to travellers (see [ECDC](#) map) is currently occurring in **Central** and **South America**, the **Caribbean**, in **Africa\*** in Angola, Guinea Bissau, Cape Verde, in **Asia\*** in Singapore, Maldives, **Thailand**, Vietnam, and in **Oceania** in Samoa, Solomon Islands, Marshall Islands, Fiji, Micronesia, Papua New Guinea, Palau, and Tonga, **USA** in Texas (Cameron county).

\*For some countries in Asia and Africa the epidemiological situation of ZIKV has been assessed differently depending on the consulted source (ECDC, CDC). For most countries in Asia ECDC has estimated the risk of ZIKV transmission to be moderate (yellow countries) or low/ very low (grey/blue countries), see ECDC map Link. The Swiss Expert Committee of Travel Medicine (ECMT) assumes for countries in Asia and Africa, the risk to get infected and to get ill by ZIKV is lower than in Americas/Caribbean. ZIKV has been endemic in Asia and Africa probably already for many years without identifying an epidemic spread as it is the case since 2015 in the Americas/Caribbean. For women **trying** to get pregnant, the risk for acquiring a ZIKV infection in countries of Asia or Africa not mentioned under "high risk" leading to fetal malformation is considered by ECTM as to be very low.

Areas with ZIKV transmission following previous ZIKV circulation has been reported for several other countries; a detailed and weekly updated list can be found at [ECDC](#).

Prior to 2015, there were several small outbreaks in Africa, Southeast Asia, and the Pacific Islands (Yap/Micronesia, French Polynesia, Vanuatu, and the Cook Islands).

#### Transmission:

*Zika* virus is transmitted through *Aedes aegypti* / *albopictus* mosquitoes. 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.

There have been several documented cases of sexual transmission (man to woman, woman to man, man to man, even after the acute phase of the disease). Up to date, the maximum documented time of ZIKV RNA detection in semen after onset of symptoms is 188 days. According to ECDC, intermittent detection in semen has been documented for more than 12 months. In one asymptomatic case ZIKV RNA was detected in semen 39 days following departure from ZIKV- affected area. It is unknown for how long ZIKV is infectious in semen. So far, infectious virus particles were detected through semen culture at 69 after onset of symptoms. ZIKV might be also transmitted by oral sex, vaginal secretions or menstrual blood (ZIKV RNA has been detected in vaginal fluids up to 14 days after onset of

symptoms). However, as per current knowledge, the extent and the duration of the risk of sexual transmission cannot be predicted.

Transmission via a blood transfusion is also possible. The detection of ZIKV in saliva alone does not confer conclusive evidence for this mode of transmission.

**Incubation Period:**

Not exactly known, probably 3-14 days.

**Disease:**

Only one out of five infected people get sick. In symptomatic patients, symptoms are usually mild and 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 (redness of the eyes), 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 scientific consensus that ZIKV infection during pregnancy causes microcephaly (too small brain and head) in the unborn child, along with other possible neurological damage to the brain, eye and ear. In addition, miscarriage, premature delivery, and impaired intrauterine growth may occur. Up to now, it is unclear how many infected pregnant women will have vertical transmission to the fetus and in how many cases of fetal/intrauterine infection this will result in clinically relevant damage of the child. A recent study in US pregnant women with confirmed ZIKV transmission during pregnancy showed that 1 in 10 pregnancies had an adverse outcome. A report of the US Zika Pregnancy Register showed that the risk of birth defects was similar for symptomatic and asymptomatic infections. There was a higher risk of birth defects in women who were infected around the preconception period or during the first pregnancy. A Brazilian study showed that ZIKV positive pregnancies with symptomatic ZIKV symptoms presented 46% of adverse pregnancy outcomes compared to 11.5% for ZIKV negative pregnancies (Brasil et al., 2016).

**Diagnosis:**

**General comment:** The recommendations for ZIKV diagnostics and prevention vary by country, and updates are done very frequently. This causes a lot of uncertainties. In addition, ZIKV diagnostic tests are not yet validated and the sensitivity/specificity are still unknown. The following recommendations of the Swiss Expert Committee of Travel Medicine (ECTM) are consensus orientated and take into account the published recommendations (see references).

**RT-PCR:** during acute infection. Of note, in blood, positive PCR results can only be expected up to 4 days after onset of symptom, in urine the virus can be detected by PCR up to 3 weeks, in sperm potentially longer. Pregnant women may have longer lasting viraemia than non-pregnant women. ZIKV RNA could be detected with RT-PCR in serum for up to 46 days after symptom onset for symptomatic pregnant cases and 53 days after exposure for asymptomatic pregnant women.

**Serology:** Zika IgM/IgG antibodies occur 5 days after onset of symptoms. Cross reactions with other flaviviruses (e.g. dengue) are possible. Detection of dengue NS-1-antigen however is specific for dengue but negative for Zika (although exceptions have been described).

**Recommendations of the Expert Committee of Travel Medicine (ECTM) of Switzerland:**

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

WHO should be tested? Testing and 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).
- **Symptomatic patients,** after travelling to a ZIKV epidemic/endemic area/potential ZIKV exposure\*

HOW to test: the following investigations might be considered:

#### **A: Laboratory testing:**

1. **Symptomatic traveler:** rule out malaria, dengue and other febrile illnesses according to travel destination and exposure. With regard to ZIKV:
  - a. **< 7 days after onset of symptoms:** RT-PCR on serum or plasma plus RT-PCR in urine (5-10 ml), and serology after min. 4 days of symptoms
  - b. **7-28 days after onset of symptoms:** serology (serum IgM and IgG) plus RT-PCR in urine
    - If serology is negative, repeat after 28d.
    - If serology is positive for IgM only, repeat after at least 7d for detection of IgG seroconversion and RT-PCR in urine.
  - c. **> 28 days after onset of symptoms:** serology only.
  
2. **Pregnant women with or without symptoms :**
  - a) **Last ZIKV exposure\* < 28 days :**
    - RT-PCR in serum or plasma
    - RT-PCR in urine
    - Serological testing if > 4 days after onset of symptoms.
    - Serum storage at first consultation.
    - Discuss TORSCH (**T**oxoplasmosis, **R**ubella, **S**yphilis, **CMV**, **H**SV) and VZV.

→ If ZIKV serology and RT-PCR are negative: repeat serology and RT-PCR (on plasma and urine 28d after the first test
  
  - b) **Last ZIKV exposure\* >28 days:**
    - RT-PCR (plasma/serum for possible prolonged viremia, and urine) and
    - Serology (IgM and IgG for ZIKV and Dengue) and serum storage

#### **B. Ultrasound diagnostics (US):**

After potential ZIKV exposure\* of the 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. Early morphological US e.g. 16-18 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 3-4 weeks) and checking potentially prolonged viremia by PCR on plasma/serum should be considered (see reference David Baud, Driggers et. al, 2016).

#### **Of note:**

- If pregnancy is uncertain, a pregnancy test should be performed.
- The sensitivity and specificity 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.
- **\*Definition of a ZIKV exposure:** a) History of travel/residence in an area with ZIKA transmission (if symptomatic) or in high risk areas of ZIKV transmission (if asymptomatic) and/or b) unprotected sexual contact (without a condom) with a **woman within 8 weeks** and/or with a **man within 6 months** after their return from an area with high risk areas of ZIKV transmission, irrespective of whether she/he had ZIKV symptoms or not.

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

##### Switzerland:

- Hôpitaux Universitaires de Genève: <http://www.hug-ge.ch/laboratoire-virologie>
- Labor Spiez: [http://www.laborspiez.ch/de/the/bs/pdf/Diagnostik\\_von\\_Zikavirus\\_Infektionen.pdf](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-zur-diagnostik-der-zika-virus-infektion/>
- Robert Koch Institut in Berlin: <http://www.hug-ge.ch/laboratoire-virologie>

**Treatment:**

Symptomatic: Paracetamol, fluid, rest. No medication that contains acetylsalicylic acid (e.g. Aspirin) or nonsteroidal anti-inflammatory drugs (such as Ibuprofen) as these may enhance bleeding in case of (concomitant) dengue infection.

A specific antiviral therapy and/or a vaccination against ZIKV do not exist.

**Prevention:**

Information of the population living in ZIKV endemic areas on breeding habitats or mosquitos, elimination of water containing facilities around houses/living areas.

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

- **For all travellers:** Travellers visiting countries with risk of ZIKV transmission should be informed about the ongoing outbreak, the possibility of sexual ZIKV transmission and the risk of ZIKV infection of the foetus during pregnancy. 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 should be impregnated or sprayed with an insecticide, sleeping under mosquito bed nets or in air conditioned rooms.
- **Pregnant Women:** For the risk assessment of possible neonatal malformation while infected by ZIKV during pregnancy
  - **All pregnant women** (regardless of pregnancy trimester) or women who cannot rule out a pregnancy should be advised not to travel to areas with ZIKV transmission. If travel cannot be avoided, special pre-travel advice is necessary including advice of strict protection against mosquito bites.
  - **Safer sex practice** for the **whole duration of pregnancy**, if the partner had a ZIKV exposure\*
- **Couples and women who are planning a pregnancy** should avoid becoming pregnant while travelling in an area with high risk of ZIKV transmission. As per current knowledge, to avoid sexual transmission following timeframes\*\* after potential ZIKV exposure\* are advised before trying to conceive (safer sex practice during these timeframes):
  - **Women:** at least **8 weeks** after symptoms onset (if symptomatic) or after last ZIKV exposure\* (if asymptomatic)
  - **Men:** at least 6 months after symptoms onset (if symptomatic) or after last ZIKV exposure\* (if asymptomatic)
  - Discuss with their healthcare provider the period for deferring conception/pregnancy in relation to individual exposure characteristics and availability of test results.
- **Patients with underlying immune disease and/or severe chronic diseases** should take maximal protection against mosquitos.

**Of note:**

- **\*Definition of a ZIKV exposure:** a) History of travel/residence in an area with high risk of ZIKV transmission and/or b) unprotected sexual contact (without a condom) with a woman within 8 weeks and/or with a man within 6 months after their return from an area with high risk of ZIKV transmission, irrespectively whether she/he had ZIKV symptoms or not.
- \*\* as proposed by WHO it can be considered to prolong the timeframes up to 6 months for both women and men after potential ZIKV exposure.
- With regard to testing after ZIKV exposure, please see above section on ZIKV diagnostics.
- Travel to areas with moderate or low risk reported\_ZIKV transmission: women who are planning to get pregnant should consider postponing travel. To the current knowledge, in countries of Asia and Africa not mentioned under “high risk ZIKV transmission areas” (see section “incidence” or areas with sporadic ZIKV transmission, the risk of an infection or even damage to the unborn child cannot be excluded but is estimated to be very low. Pregnant women are advised not to travel to any ZIKV endemic countries.

- How long to wait with reproduction after potential exposure? Is it possible to shorten the time from 6 months to a shorter interval after last ZIKV exposure? Some experts consider serology testing after a minimum of 4 weeks after return (potential last exposure\*). In a review on 25 symptomatic patients with exact dates of exposure and symptom onset, all infected persons had a positive serology by 28 days (Lessler et al). Negative tests would then allow to proceed with having unprotected (condom) sex. However, serological data are best known for symptomatic patients, data on asymptomatic ZIKV infections are scarce. In addition, data on sensitivity and specificity are only available from small series. If a traveller is demanding a serological examination for ZIKV infection, he/she should be informed on the currently limited data available and a second serological test should be offered about one month later. Until all serology results are available however, use of condoms or abstinence from sex is recommended.
- Travellers with clinical suspicion of ZIKV infection within 3 weeks of their return from a ZIKV endemic area should seek a physician and should mention their travel destination.
- 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

#### **Obligation to report:**

Since March 5th 2016, the Swiss Federal Office of Public Health has made reporting of ZIKV infections in Switzerland mandatory.

#### **References, Literature und Websites:**

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Last update: 18.8.2016