

Zika Virus Infection and Pregnancy

Information for Healthcare Professionals

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Zika virus is considered endemic in the Americas and Caribbean following the 2015-16 outbreak as well as in much of Africa and Asia.¹ The majority of people infected with Zika virus have minimal symptoms. For those with significant symptoms, Zika virus tends to cause a mild, short-lived (2 to 7 days) illness.²

Based on events and subsequent study, the WHO have concluded that Zika virus infection during pregnancy is a cause of Congenital Zika Syndrome, which encompasses congenital brain abnormalities, including microcephaly.³ Zika virus has also been recognised as a trigger of Guillain-Barré syndrome.⁴

Epidemiology

The Zika virus was first discovered in a Rhesus monkey in Uganda in 1947 and in humans a few years later.¹ The first outbreak reported outside of Africa and Asia occurred in Micronesia in 2007. This was followed by an outbreak of the same strain in French Polynesia in 2013 and subsequent outbreaks in other parts of the Pacific.¹

Brazil confirmed its first case of local Zika virus transmission in May 2015. The virus then spread rapidly throughout South America, Central America, and the Caribbean.¹ This rapid spread over the last year is mainly due to an immunologically naïve population and the distribution of *Aedes aegypti* mosquitoes, the primary vector for transmission.⁵ The epidemic in the region largely subsided by early 2017, but the infection is believed to remain widely endemic.

Countries with current or past Zika virus transmission have been given one of two risk ratings (risk or very low risk), based on the reporting of Zika cases and the likelihood of infection to UK travellers. A list of countries with Zika virus risk and very low risk can be found on Public Health England's (PHE) website (<https://www.gov.uk/guidance/zika-virus-country-specific-risk>).

Imported infections have been detected in travellers returning to the UK; further information is available on the PHE website (<https://www.gov.uk/guidance/zika-virus>).¹

Transmission

Zika virus is predominantly transmitted by the bite of an infected female *Aedes* mosquito, most commonly *Aedes aegypti*. Other species of *Aedes* mosquito also have the potential to transmit this virus.⁶ After an infected mosquito bites a human, the first symptoms can develop in 3 to 12 days but it can be shorter or longer in some people.

The *Aedes aegypti* mosquito is not present in the UK and is unlikely to establish in the near future as the UK temperature is not consistently high enough for it to breed.

Cases of maternal fetal transmission have been confirmed¹²⁻¹⁵. Viable virus has been detected in breast milk and possible Zika virus infections have been identified in breastfeeding babies but Zika virus transmission through breast milk has not been confirmed.⁶ Therefore, the benefits of breastfeeding are likely to outweigh the risks of Zika virus infection in infants.²⁵

Almost all cases of Zika virus are acquired via mosquito bites. However, a small number of cases of sexual transmission have been reported. Most cases have been male-to-female, but male-to-male and female to male transmission has occurred²⁷. Potential routes of transmission include vaginal, anal, oral sex and the sharing of sex toys.²⁸ Case reports suggest that sexual transmission can occur shortly before, during, and after symptoms but also when the individual did not recall symptoms.⁷⁻⁹ The virus has been shown to be present in semen, vaginal secretions and menstrual blood.^{9-11,27,29} Zika virus has been detected in semen up to 188 days after symptom onset¹⁰, but infectious virus has only been reported up to 69 days.¹¹ The risk of sexual transmission of Zika virus is considered to be low.

Zika virus can be transmitted by blood transfusion. In the UK, standard precautions for ensuring safe blood donations and transfusions are in place to prevent this (<https://www.transfusionguidelines.org/dsg/wb/guidelines/tropical-viruses>).

Symptoms

The majority of people infected with Zika virus have minimal symptoms. For those with significant symptoms, it tends to cause a mild, short-lived (2 to 7 days) illness.^{16,17} Signs and symptoms suggestive of Zika virus infection may include a combination of the following: rash; itching/pruritus; fever; headache; arthralgia/arthritis; myalgia; conjunctivitis; lower back pain; retro-orbital pain.

The symptoms of Zika virus infection may be similar to those of dengue fever (caused by a related flavivirus) and chikungunya (an alphavirus). These two infections are also transmitted by the *Aedes aegypti* mosquito and are found in the same geographical areas. Differential diagnosis requires laboratory testing (see Diagnosis below).¹⁸

There is no evidence that pregnant women are more vulnerable to acquiring Zika virus infection or that this infection causes a more serious illness in pregnant women.

Serious complications from Zika virus infection are rare. WHO has concluded that Zika virus infection during pregnancy is a cause of congenital brain abnormalities, including microcephaly; and that Zika virus is a trigger of Guillain-Barré syndrome.³

Congenital Zika Virus Syndrome

Congenital Zika Virus Syndrome is used to refer to the range of manifestations, in addition to congenital microcephaly, that have been reported following exposure to Zika virus in utero¹⁹ (see Table 1).

The risk of birth defects in some studies appears low compared with other viral infections such as CMV and rubella; however, the incidence of Zika virus infection can be comparatively very high during outbreaks. There have been differing reports of the rates of adverse outcomes in offspring of women who test positive for Zika virus during pregnancy.^{21,22}

The period of gestation at which the infection is acquired may be important. A fetus infected in early gestation is more likely to be affected compared to infection later in pregnancy.^{22,23}

Table 1: Fetal abnormalities reported in pregnancies complicated with Zika virus infection.^{14,23,25}

Cranial abnormalities	Extra-cranial abnormalities
Microcephaly	Fetal growth restriction
Cerebral and/or ocular calcifications	Oligohydramnios
Ventriculomegaly	Talipes
Periventricular cysts	
Callosal abnormalities	
Microphthalmia	
Cerebellar atrophy (transverse diameter <5th percentile)	
Vermian agenesis	
Blake’s cyst	
Mega cisterna magna (>95th percentile)	
Choroid plexus cyst	
Brain atrophy leading to micrencephaly (abnormally small brain)	
Cortical and white matter abnormalities (e.g. agyria)	

Prevention

There is currently no vaccine or drug available to prevent Zika virus infection. The *Aedes aegypti* mosquito, the primary vector for Zika virus, is active predominantly during daylight hours; bites are most common during mid-morning and late afternoon to dusk, when the mosquito is most active. This is in contrast to the *Anopheles* mosquito which transmits malaria and which is more active by night. Travellers to areas with risk for Zika virus transmission should take all possible measures to minimise the chances of mosquito bites. This includes wearing light-coloured, loose-fitting clothes that cover as much exposed skin as possible, for example long trousers and long sleeves. Because the *Aedes* mosquito is active during daylight hours, it is important that travellers to these areas cover up during the daytime as much as possible. Clothing can be treated with an insecticide (e.g. permethrin) which kills insects, including mosquitoes, on contact.²²

N, N-diethyl meta toluamide (DEET) based repellents are the most effective available insect repellents, and have been widely used for over 50 years. Preparations with concentrations of DEET up to 50% are commonly available and are safe in pregnant and breastfeeding women (and in infants and children over the age of 2 months).^{22,26} Care should be taken to ensure that insect repellents are not ingested, and that they do not come in contact with the eyes or mouth.

Insect repellents should be used as per the manufacturer's instructions and re-applied regularly, particularly after swimming or washing and in hot humid conditions when they may be removed by perspiration. When both sunscreen and insect repellents are required, the insect repellent should be applied over the sunscreen. DEET based repellents can reduce the sun protection factor (SPF) of sunscreen so a higher factor sun cream (SPF 30-50) should be used when also using DEET based repellents.²²

The following cannot be recommended as insect repellents: citronella oil-based repellents (these have a very short duration of action); vitamin B12 complex; vitamin B1; tea tree oil.²⁶

Travellers staying in accommodation without screening should sleep under a mosquito net, particularly in malaria risk areas. Those sleeping or resting during the day in an area with Zika virus should do so either in a well screened room, air conditioned room or under a mosquito net. Ideally, nets should be impregnated with permethrin or other contact insecticide. Retreatment after six months of use is necessary.²⁶ A Leaflet entitled, "Mosquito Bite Avoidance for Travellers" is available on the PHE Website (<https://www.gov.uk/government/publications/mosquito-bite-avoidance-for-travellers>).

Travel Advice for Pregnant Women and Couples Considering Pregnancy

In the UK, the National Travel Health Network and Centre (NaTHNaC), and Health Protection Scotland (via TRAVAX and FitforTravel) provide advice for pregnant women regarding potential travel to areas with risk for Zika virus transmission. For further information see: NaTHNaC (<http://travelhealthpro.org.uk/zika-virus-update-and-advice-for-pregnant-women/>), TRAVAX (www.travax.nhs.uk) and FitforTravel (www.fitfortravel.nhs.uk). Healthcare providers should ask all pregnant women and their partners about recent and forthcoming travel

It is recommended that:

- in some countries where there is evidence of a current outbreak of Zika virus with significant transmission, **pregnant women should postpone non-essential travel** until after the pregnancy.
- In other countries where there have been reported recent outbreaks, re-introduction of Zika virus or endemic transmission but not current outbreak, pregnant women are advised to **consider postponing non-essential travel until after the pregnancy**.

Specific recommendations for the affected countries can be found in the 'other risks' section of the NaTHNaC country information pages (<https://travelhealthpro.org.uk/countries>).

Pregnant women who must travel (or choose to travel) to an area with risk for Zika virus transmission should take all necessary precautions to minimise the chances of a mosquito bite, as described above.

Pregnant women and their partners should consistently use barrier methods for vaginal, anal and oral sex during and after travel to reduce the risk of the developing fetus being exposed to Zika virus. Barrier methods should be continued for the duration of the pregnancy, and should be used even in the absence of Zika symptoms.

Pregnant women recently returned to the UK from areas with risk for Zika virus transmission should inform their obstetrician, midwife or GP that they may have been exposed to the virus so that they can be monitored and/or tested.

It is recommended that couples considering pregnancy should check the Zika risk for their intended destination before travel and consider any travel advisories. As screening of asymptomatic travellers for Zika virus infection is not available in the NHS, such couples should consider whether to avoid travel to a country or area with risk for Zika virus transmission, rather than delay conception for the recommended period (see below) after travel. This particularly includes couples in assisted conception programmes.

Diagnosis

The diagnosis of Zika virus infection should be considered in individuals who experience symptoms suggestive of acute Zika virus infection within 2 weeks of leaving an area with risk for Zika virus transmission OR within 2 weeks of sexual contact with a male sexual partner who has recently travelled within the previous three months to an area with high or moderate risk of Zika virus transmission.

Pregnant women presenting to their healthcare provider with current or previous symptoms of Zika virus that began within 2 weeks of return to the UK, should be tested. The algorithm for assessing pregnant women with a history of travel can be accessed here: <https://www.gov.uk/government/publications/zika-virus-interim-algorithm-for-assessing-pregnant-women-with-a-history-of-travel>.

If a health professional suspects Zika virus infection, advice can be sought from their local Infectious Disease, Microbiology or Virology Consultant in the first instance.

Zika virus testing is not available for individuals who do not have symptoms consistent with Zika virus infection.

Diagnostic laboratory testing is available from PHE's Rare and Imported Pathogens Laboratory (RIPL), a specialist centre for advice and diagnosis for a wide range of unusual viral and bacterial infections including Zika virus. The recommended sample types for testing will depend on whether the patient has current symptoms or previous symptoms that have now resolved. Clinicians should refer to PHE's sample testing advice webpage for information on sample types required and the tests available for different patient groups. Sample testing advice will be regularly reviewed and updated accordingly. <https://www.gov.uk/guidance/zika-virus-sample-testing-advice>

In the UK, samples for testing for Zika virus should be sent to RIPL, accompanied by the appropriate RIPL request form clearly stating symptoms, date of symptom onset, areas visited, dates of travel and the stage of pregnancy (weeks of gestation).

Zika virus PCR can also be performed on amniotic fluid although it is currently not known how sensitive this test is for congenital infection or the likelihood of an infected fetus being affected, i.e. subsequently developing a fetal abnormality.¹²

RIPL is a specialist centre for advice and diagnosis for a wide range of unusual viral and bacterial infections including Zika virus.

Treatment

There is no specific antiviral treatment available. However, Zika virus infection is usually mild and short-lived, and requires no treatment. Supportive nursing care and relief of symptoms are the standard treatment.

Symptomatic pregnant woman should be advised to get plenty of rest, drink adequate fluids and manage pain and fever with regular paracetamol and other cooling measures. In the unlikely event that symptoms become severe, she should seek medical advice.

Recommendations for pregnant women and those considering pregnancy

The following scenarios outline the appropriate management for women **CONSIDERING** pregnancy, for pregnant women with a partner who has travelled to a country or area with risk for Zika virus transmission, for pregnant women with **CURRENT** symptoms, **PREVIOUS** symptoms or **NO** symptoms at all.

Couples considering pregnancy:

It is recommended that women should avoid becoming pregnant while travelling in a country or area with risk for of Zika virus transmission.

If a couple is considering pregnancy, consistent use of effective contraception is advised to prevent pregnancy and barrier methods (e.g. condom use) are advised during vaginal, anal and oral sex to reduce the risk of conception and the developing fetus being exposed to Zika virus. These measures should be followed while travelling and for:

- three months after return from an area with risk for Zika virus transmission, or last possible Zika virus exposure, if both partners travelled
- three months after return from an area with risk for of Zika virus transmission, or last possible Zika virus exposure, if just the male partner travelled
- two months after return from an area with risk for Zika virus transmission, or last possible Zika virus exposure if only the female partner travelled

Last possible Zika virus exposure is defined as the later of either the date of leaving an area / country with risk of Zika virus transmission, or the date on which last unprotected sexual contact with a potentially infectious partner took place.

If a woman considering pregnancy develops symptoms compatible with Zika infection on her return to the UK, it is recommended that she avoids becoming pregnant for 2 months following recovery.

The Faculty of Sexual and Reproductive Healthcare's (FSRH) advice is that effective contraception should commence in advance of travel to a country or area with risk for Zika virus transmission. The FSRH's statement on the different contraceptive methods available to women can be found here:

<https://www.fsrh.org/documents/contraception-advice-for-women-and-the-female-partners-of-men/>.

Pregnant women whose partner has been to an area with risk for Zika virus transmission:

If a pregnant woman's partner has been to an area with risk of Zika virus transmission, barrier methods (e.g. condoms) are advised during vaginal, anal and oral sex for the duration of the pregnancy to reduce the risk of sexual transmission and the fetus being exposed to Zika virus.

Note: testing of returning travellers who had *previous* Zika-like symptoms and whose partners are currently pregnant should be discussed individually with a local infection specialist. Please refer to the Zika virus sample testing advice web page which will be kept updated with test availability (<https://www.gov.uk/guidance/zika-virus-sample-testing-advice>).

Pregnant women reporting CURRENT or PREVIOUS symptoms suggestive of Zika virus disease:

Pregnant women with a history of travel to a country or area with risk for Zika virus transmission and who have or have had symptoms consistent with Zika virus disease during or within 2 weeks of travel OR within 2 weeks of sexual contact with a male partner who has recently travelled to a country or area with risk for Zika virus transmission (regardless of her own travel history due to the possibility of sexual transmission) should be tested for Zika virus infection by submitting appropriate samples to RIPL (<https://www.gov.uk/guidance/zika-virus-sample-testing-advice>).

If they are significantly unwell, and particularly if they require hospitalisation, other travel associated infections, including malaria, must also be considered. For pregnant women with a rash, clinicians should also consider other causes of rash in pregnancy (<https://www.gov.uk/government/publications/viral-rash-in-pregnancy>).

If laboratory testing shows evidence of Zika virus infection, the woman should receive a baseline fetal ultrasound, if this has not already been performed, and be referred to a fetal medicine service for further assessment.

If Zika virus antibodies are NOT detected in a serum sample collected 4 or more weeks after the last possible travel-associated or sexual exposure, then recent Zika virus infection can be excluded. Pregnant women with negative antibody results for such samples do not require further extra fetal ultrasound follow-up, unless there are additional concerns.

Pregnant women who have visited a country or area with risk for Zika virus transmission but had NO symptoms of Zika Virus:

Routine testing of asymptomatic pregnant women (those who remained asymptomatic while travelling and for two weeks after their return from areas with risk for Zika virus transmission) is not available on the NHS. However, as many people with Zika virus do not have symptoms, baseline fetal ultrasound should be offered and repeated at 18-20 weeks and a repeat considered at 28-30 weeks in line with WHO guidance.³²

Any pregnant woman with possible exposure to Zika virus, presenting with fetal ultrasound findings consistent with microcephaly:

Any pregnant woman in whom a small fetal head (head circumference more than 2 Standard Deviations below the mean for gestational age, i.e. below the 2.5th centile) or brain abnormality (such as intracranial calcifications) is diagnosed on ultrasound, and who has previously visited during pregnancy an area with risk for Zika virus transmission, should be referred to a maternal fetal medicine service for further assessment. Although the majority of babies with a head circumference more than 2 SD below the mean will be normal and will not have microcephaly, referral to a specialist fetal medicine service is recommended. Microcephaly is usually diagnosed when the baby's Head Circumference is even smaller than this, and usually together with structural abnormalities of the brain that can be diagnosed with specialist imaging (Table 1). Women with a diagnosis of fetal microcephaly or intracranial calcifications but who have not travelled, and do not have a partner who travelled, to a country or area with risk for Zika virus transmission during pregnancy do not need to be assessed for Zika virus infection.

If fetal microcephaly or brain abnormality, such as intracranial calcification (see table), is diagnosed, consideration should be given to performing an amniocentesis to test for the virus using RT-PCR. This decision should be taken only after careful counselling. Amniocentesis is associated with a small risk of miscarriage or preterm birth and in general should not be performed before 15 weeks of gestation. However, for the purpose of identifying Zika virus, amniocentesis should not usually be performed before 20 weeks of gestation as fetal urination is not well-established until then (and this is the source of the virus in the amniotic fluid). Even if positive, it is not known how sensitive this test is for congenital infection, nor the likelihood of an infected fetus being affected. Nevertheless, if there is fetal abnormality on ultrasound and Zika virus PCR on amniocentesis is positive, then it is highly likely that the abnormality is Zika virus associated and that the outcome is likely to be poor. When brain abnormalities are identified on ultrasound scan, consideration should be given to performing fetal brain MRI which may detect further abnormalities that have not been detected on ultrasound. When a significant brain abnormality or microcephaly is confirmed in the presence of Zika virus infection, the option of termination of pregnancy should be discussed with the woman, regardless of gestation.

Perinatal outcome

Women with laboratory diagnosed Zika virus infection:

Any pregnant woman with positive laboratory diagnosis, spontaneous abortion/stillbirth or anticipated TOP or livebirth should be discussed with a local Infection Specialist and then with RIPL *before* sending samples (<https://www.gov.uk/guidance/zika-virus-sample-testing-advice>).

An anticipated live birth must be discussed with a local neonatologist; interim guidance for neonatologists and paediatricians details the appropriate management and follow-up of these babies (<https://www.gov.uk/government/publications/zika-virus-congenital-infection-algorithm-and-interim-guidance-for-neonatologists-and-paediatricians>).

Pregnancy advice leaflet

An advice leaflet for pregnant women who have travelled to a country or area with risk for Zika virus transmission is available at: <https://www.gov.uk/government/publications/zika-virus-advice-for-women-returning-from-areas-with-active-zika-virus-transmission>

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