# Zika virus infection and pregnancy:
# Interim clinical guidance for healthcare professionals

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Zika virus infection is a **notifiable disease** in Ireland under the Infectious Diseases (Amendment) Regulations 2016 (S.I. No. 276 of 2016). All medical practitioners and laboratories are required to notify it to the Medical Officer of Health.

Information on the process of notifying infectious diseases including the case definition of Zika infection is available at: http://www.hpsc.ie/NotifiableDiseases/.

Zika virus is a viral infection that is currently circulating most prominently in tropical and sub-tropical areas. Zika virus is transmitted to humans by *Aedes* mosquitoes, especially by the *Aedes aegypti* species. Up to 80% of people who become infected by zika virus have no symptoms. Symptomatic infections are characterised by a mild self-limiting illness that usually lasts about 2 to 7 days and may be accompanied by fever, an itchy maculopapular rash, conjunctivitis, headache and myalgia/arthralgia. There is currently no evidence that pregnant women are more susceptible to zika virus infection than non-pregnant women.

There is evidence that infection with zika virus is the cause of a serious birth condition called microcephaly, seen in a high proportion of women infected with zika virus, in which the baby is born with an abnormally small head. In these cases, the baby's brain may not have formed properly during pregnancy.

This guidance summarises key advice for those working in Obstetrics and Gynaecology, since they may be consulted by pregnant women, who plan on travelling to or are returning from countries with active zika virus transmission.

The HPSC website also provides the following zika virus resources:

- Zika virus infection: Interim Clinical Guidance for Primary Care
- Laboratory investigation of zika virus infection
- Frequently asked questions for the general public
- Frequently asked questions for pregnant women and women who are planning a pregnancy
- A list of countries reporting local transmission of confirmed zika virus infection.

## Epidemiology

Prior to the 2016 epidemic of zika virus infection, the first outbreaks to be recorded outside of Africa and Asia occurred in 2007 (Micronesia) and in 2013 (French Polynesia). Since then, rapid spread of the disease through the Americas has occurred and there are currently over 80 countries affected worldwide. France reported three cases of locally acquired zika virus infection during 2019. These cases represent the first known vector-borne transmission of zika virus by *Aedes albopictus* in Europe. The Health Protection Surveillance Centre (HPSC) of the HSE maintains a list of affected countries on their website based on information from WHO.

Rapid transmission of the disease is attributed to exposure of the virus in a population with no prior exposure and the extensive and burgeoning distribution of the *Aedes* mosquito as the vector of transmission.(- This type of mosquito is unlikely to establish in Ireland in the near future as the mean ambient Irish temperature is not consistently high enough for it to breed. To date, Ireland has reported a small number of imported cases of zika virus infection.

## Transmission

Currently, zika virus is primarily transmitted by the more tropical form of the *Aedes* mosquito, *Aedes aegypti*. *Aedes* mosquitoes are a tropical and subtropical genus of biting mosquito and carry a range of diseases (mainly flaviviral): dengue fever, yellow fever, West Nile fever, eastern equine encephalitis and more recently, chikungunya (an alphavirus) and zika virus. *Aedes* mosquitoes tend only to be active and to bite during the day time (unlike most other mosquito species). They are especially active in the morning and later afternoon. There are two major (and several minor) *Aedes* species: *A. albopictus* (the 'Asian Tiger' mosquito) and *A. aegypti* (the 'yellow fever' mosquito). )

Transmission of zika virus infection occurs primarily from the bite of an infected mosquito, after which the first symptoms can develop in 3 to 12 days. Sexual transmission of zika virus has also been documented. This is more likely if the man had symptoms of zika virus infection. For this reason, it is important to practice safe sex (by wearing a condom during vaginal, anal and oral sex) with a partner who has recently returned from, or is living in, an affected area.

For advice on how to prevent sexual transmission see information in on HPSC website

Zika virus can be transmitted through blood, but this is not a common occurrence. However, the application of standard precautions for safe blood donations should prevent this eventuality. The European Centre for Disease Prevention and Control (ECDC) have recommended that blood safety authorities should consider the deferral of donors with a relevant travel history to areas of active zika virus transmission.

To date, there are no reports of infants getting zika virus through breastfeeding. Because of the benefits of breastfeeding, mothers are encouraged to breastfeed even in areas where zika virus is found.

## Symptoms

An estimated three out of four people infected with zika virus do not have symptoms at all. For those who have symptoms, zika virus generally causes a mild illness that lasts for 2 to 7 days. The incubation period (the interval between being infected by a mosquito bite and developing symptoms) is usually between 3 and 12 days.

The most common symptoms include:

- itchy rash (very common)
- mild fever (in only a minority of cases)
- muscle or joint pains (quite common)
- headache (in about half of cases)
- non-purulent conjunctivitis

Serious complications from zika virus infection are uncommon. However, there is evidence that infection with zika virus is the cause of a serious birth condition called microcephaly, seen in a high proportion of women infected with zika virus, in which the baby is born with an abnormally small head. In these cases, the baby's brain may not have formed properly during pregnancy.

## Microcephaly

Microcephaly is a rare neurological condition in which an infant's head is significantly smaller than expected. Microcephaly is defined as a condition at birth in which the baby's head measurement is less than expected for age and sex. Microcephaly can present as an isolated condition or may be associated with other symptoms such as seizures, developmental delay, learning difficulties, hearing loss or feeding difficulties or problems with ocular development. These symptoms have varying degrees of severity and in some cases may be life-threatening. It is very difficult to predict the consequences of microcephaly at the time of birth, so close follow-up is needed through check-ups to monitor and evaluate affected babies. There is no specific treatment for microcephaly. Care is centred on follow-up, health promotion and maximization of the child's abilities.

## Diagnosis

Zika virus infection should be considered in all:

- symptomatic individuals returning from an area with active transmission of virus and who develop symptoms within 10 days of return, consistent with a zika like illness.
- symptomatic individuals who have had unprotected sex with a recently* returned traveller from an affected area

Currently, the tests available in Ireland are zika virus RNA nucleic acid testing (NAT) and serological testing (antibody detection). Antibody testing is less reliable due to cross-reactivity with other flaviviruses (e.g. dengue, yellow fever) making interpretation of test results difficult.
In Ireland, samples for testing are sent to the National Virus Reference Laboratory (NVRL) which is a specialist centre for a wide range of viral infections. Further information on laboratory testing is available on the HPSC website.

* Within 6 months of return from an affected area

## Treatment

There is currently no vaccine or specific treatment for zika virus infection. Treatment for everyone, including pregnant women, consists of relieving pain, fever and any other symptoms. To prevent dehydration, it is advised to control the fever, rest and drink plenty of water.

## Infection prevention

There is currently no vaccine or drug available to prevent zika virus infection. The most important thing is to avoid mosquito bites to prevent infection with zika virus or other infections transmitted by mosquitoes. The mosquito that spreads zika virus is active during the day as well as at night so it is important to protect yourself from mosquito bites at all times.

### *Prevention of sexual transmission*

Sexual transmission has been reported in several countries. Condoms should be used for duration of stay in an affected area by all travellers and as follows upon return from an affected area. For detailed advice on prevention of sexual transmission see HPSC website. This precautionary approach is being adopted to minimise the threat to the unborn baby while also minimising inconvenience for the couple. The above intervals are based on the currently available evidence and may be subject to change as further research is published.

### *General and travel advice*

Women who are pregnant (or women trying to become pregnant) should consult their doctor or seek advice from a travel clinic before travelling to a country affected by zika virus. Pregnant women planning to travel to a zika-affected area are advised to postpone non-essential travel until after delivery. If travel is unavoidable, the woman should consult her antenatal healthcare provider or seek advice from a travel clinic two months in advance of travelling to a country affected by zika virus. She should ensure scrupulous mosquito bite avoidance measures, both during daytime and night time hours but especially during mid-morning and late afternoon to dusk, when Aedes mosquitoes are most active. In addition, they should follow the same recommendations as for all travellers:

- Use condoms for the duration of stay in zika affected area
- Protect skin from exposure to mosquitoes by wearing long sleeves, long trousers and hats
- Use mosquito repellent as indicated by health authorities and according to instructions on the label
- N-diethyl metatoluamide (DEET) is safe to use during pregnancy and while breastfeeding (and in infants and children over the age of 2 months) but only in concentrations less than 50%. The risk to a pregnant woman's unborn baby from zika virus would outweigh any potential risk from DEET.
- If using sunscreen, mosquito repellent should be applied after sunscreen
- If you sleep during the day, protect yourself with insecticide-treated mosquito netting
- Identify and eliminate possible mosquito breeding sites, such as standing collections of water

- Pregnant women who travel to areas where zika virus is circulating should inform their obstetrician, midwife or GP during their prenatal check-ups as they may have been exposed to zika virus. See appendix 1 for clinical assessment algorithm for pregnant women who have a history of travel to a zika affected area.

### Pregnant women with symptoms

Healthcare providers should ask **all pregnant women** about recent travel history.
Testing for zika virus infection should be considered in:

- Pregnant women who report symptoms compatible with zika virus infection, within 10 days of returning from an affected area
- Symptomatic pregnant women who have had unprotected vaginal, anal or oral sex with a recently returned traveller from an affected area
- Testing may also be considered for pregnant women with acute onset of symptoms NOT consistent with zika virus infection but who are within 10 days of return from an affected area and IF the symptoms are not explained by other common infectious causes (e.g. URTI, UTI)

If they are symptomatic at the time of assessment, blood (EDTA tube) and urine sample should be requested. The National Virus Reference Laboratory will test for zika virus RNA using nucleic acid testing (NAT). Further information on laboratory investigation of zika virus infection is available on the HPSC website. If test results are:

- **Positive or inconclusive zika virus RNA**: Request a baseline ultrasound scan at 18-20 weeks gestation followed by serial ultrasound scans (at four weekly intervals) to monitor fetal growth and anatomy. It is recommended that these scans should be performed by a Fetal Medicine Unit. Appropriate psychosocial care should also be initiated by referral to relevant counselling services. Time of baseline scan and subsequent ultrasound has been recommended because fetal ultrasound might not detect microcephaly or intracranial calcifications until the late second or early third trimester of pregnancy.

- **Negative zika virus RNA**: Baseline fetal ultrasound scan at 18-20 weeks gestation should be performed by the Fetal Medicine Unit. If no evidence of microcephaly or intracranial calcification on scanning, continue with prenatal care and consideration may be given to perform serial ultrasound scans at local antenatal services (up to four weekly) to monitor fetal growth and anatomy. Even with negative testing at this stage appropriate psychosocial care should be offered.

  If in doubt about the requirements for testing the NVRL can be contacted for further advice.

### *Additional testing notes:*

- Zika virus RNA can be detected by nucleic acid testing (NAT) in blood within 0-7 days post onset of symptoms and in urine within 0-10 days post onset of symptoms. The following samples should be taken:
  - Clotted blood (plain tube or serum separator tube)
  - a small volume of urine without preservative. These should be sent to the local microbiology/virology laboratory.
- Taking and storing a clotted blood sample locally, without immediate testing is recommended. This sample can then be tested for zika IgG in the event that there is a later concern about fetal development.
- Clinicians should consider other travel-associated infections including dengue and chikungunya virus infections, malaria, common infections and non-infectious diseases in the differential diagnosis.
- Clinicians should consider other causes of rash in pregnancy in the differential diagnosis, as appropriate.
- Request forms must clearly indicate that the patient is pregnant, including the number of week's gestation, the travel history (countries visited and the dates of the outward and return journeys) and the clinical details (patient's symptoms, date of illness onset).
- If in doubt about the eligibility or requirements for testing the NVRL can be contacted for further advice.

### Pregnant women NO symptoms

- Pregnant women with a history of travel to an area with active zika transmission but who do NOT report clinical illness consistent with zika virus infection within 10 days of returning from an affected area, are not routinely recommended to be tested for zika virus RNA or other serology testing. This is because it is unclear as to when the viraemic phase of the illness took place and because of the risks of misinterpretation of serology results due to cross reactivity with other flaviviruses (e.g. dengue, yellow fever). Taking and storing a clotted blood sample locally, without immediate testing is recommended. This sample will be available for retrospective testing, in the event that there is concern at a later date about fetal development.
- If in doubt about the requirements for testing the NVRL can be contacted for further advice.

A baseline fetal ultrasound scan performed at a Fetal Medicine Unit should be offered and consideration given to follow-up with serial scans at local antenatal services (up to four weekly). Appropriate psychosocial care can also be offered at this stage.

If their male partner also travelled to an affected area, condom use during vaginal, anal and oral sex, for the duration of pregnancy is recommended.

## After delivery

### *Live births*

Following a live birth with a laboratory confirmation of maternal zika virus infection, it is recommended to:

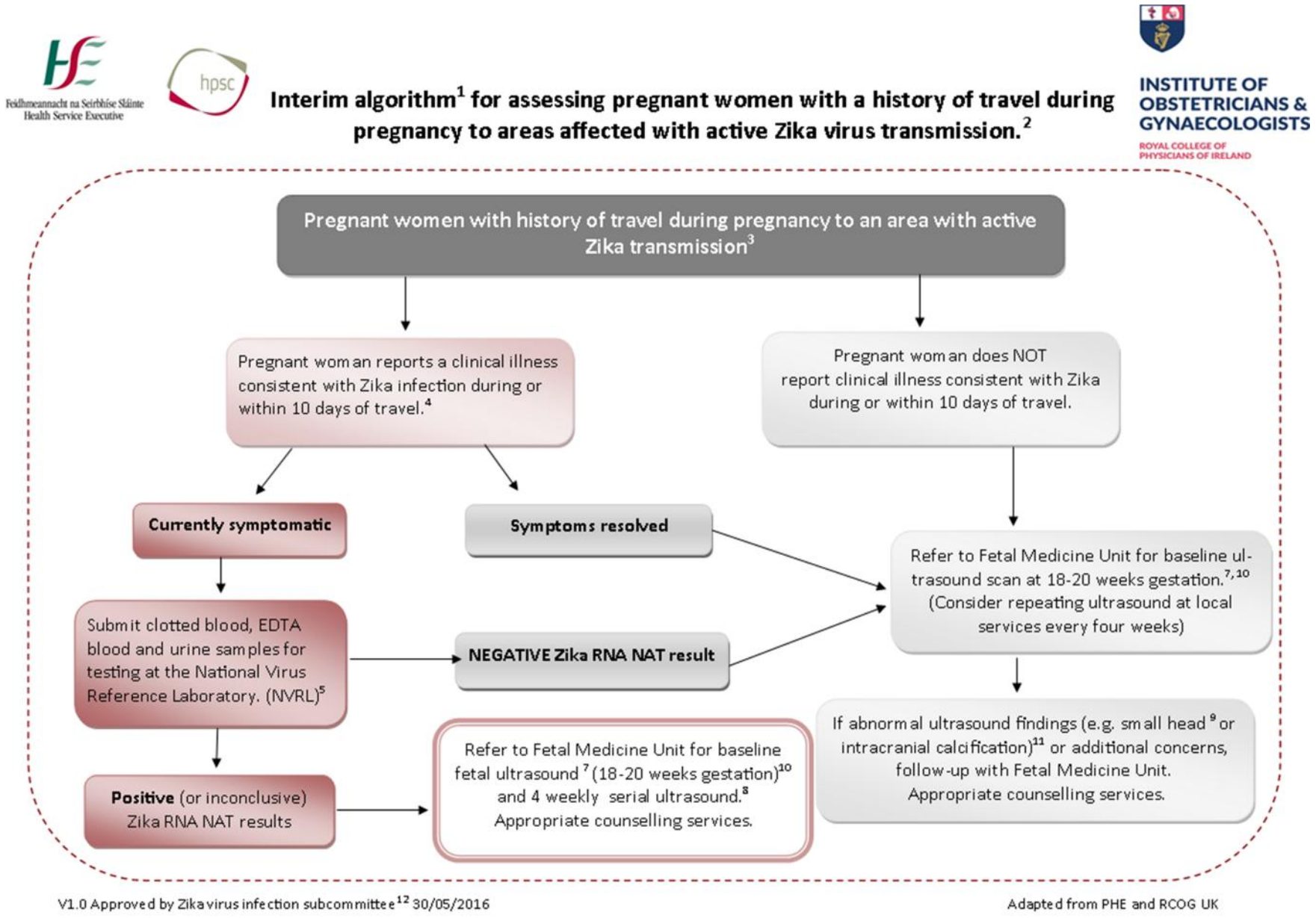
- Test placental and umbilical cord histopathology
- Test placental tissue and cord tissue for zika virus RNA nucleic acid testing (NAT)
- Test umbilical cord blood for zika and Dengue virus

Appropriate care and follow-up of these babies should occur into childhood to determine the adverse effects of congenital zika virus infection.

### *Fetal loss*

In the case of fetal loss, some testing may be requested to help gain some further understanding of the pathophysiology of zika virus and to assist in the counselling of women after their loss. These tests might include umbilical cord and placental zika virus RNA nucleic acid testing (NAT).

## Appendix 1


Interim algorithm[1] for assessing pregnant women with a history of travel during pregnancy to areas affected with active Zika virus transmission.[2]
INSTITUTE OF OBSTETRICIANS & GYNAECOLOGISTS
ROYAL COLLEGE OF PHYSICIANS OF IRELAND
Pregnant women with history of travel during pregnancy to an area with active Zika transmission[3]
Pregnant woman reports a clinical illness consistent with Zika infection during or within 10 days of travel.[4]
Pregnant woman does NOT report clinical illness consistent with Zika during or within 10 days of travel.
Currently symptomatic
Symptoms resolved
Submit clotted blood, EDTA blood and urine samples for testing at the National Virus Reference Laboratory. (NVRL)[5]
NEGATIVE Zika RNA NAT result
Refer to Fetal Medicine Unit for baseline ultrasound scan at 18-20 weeks gestation.[7,10] (Consider repeating ultrasound at local services every four weeks)
Positive (or inconclusive) Zika RNA NAT results
Refer to Fetal Medicine Unit for baseline fetal ultrasound [7] (18-20 weeks gestation)[10] and 4 weekly serial ultrasound.[8] Appropriate counselling services.
If abnormal ultrasound findings (e.g. small head [9] or intracranial calcification)[11] or additional concerns, follow-up with Fetal Medicine Unit. Appropriate counselling services.
V1.0 Approved by Zika virus infection subcommittee [12] 30/05/2016
Adapted from PHE and RCOG UK

**Interim algorithm for assessing pregnant women with a history of travel during pregnancy for areas affected with active Zika virus transmission**

**ADDITIONAL NOTES**

1. Interim guidance will be updated as more information becomes available. Currently this algorithm applies to women in all stages of pregnancy although based on information available from Brazil and experience from other congenital infections (such as CMV, rubella and toxoplasmosis), infection in early pregnancy is likely to be the greatest risk.
2. Laboratory testing is performed by the National Virus Reference Laboratory (NVRL). Zika virus testing will be performed using Zika virus RNA NAT testing or serology.
3. Assessment of pregnant women should be based on a history of travel to countries and territories reporting active ZIKV transmission in the last 9 months. See the most up to date list at www.hpsc.ie. This is in contrast to pre travel advice where countries or overseas territories are classified as having **current active** ZIKV transmission if confirmed autochthonous cases have been reported in the last 3 months.
4. Clinical illness is consistent with Zika virus disease if two or more symptoms (acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) are present. However, testing can also be considered for pregnant women with acute onset of symptoms within 10 days of travel to an area with Zika virus transmission that are not explained by other common infectious causes (e.g. URTI, UTI).
5. The samples required are a clotted blood (plain tube or serum separator tube) for serology, or EDTA blood and a small volume of urine without preservative for Zika virus RNA testing The sample form must clearly state both the travel history (i.e. which countries visited and the dates of the outward and return journeys) and the clinical details (i. e .the patient's symptoms and the date of illness onset). This is so that the appropriate investigations can be performed and their results correctly interpreted.
6. If an alternative diagnosis is made there is no need for further Zika virus-specific follow up.
7. For women without current symptoms, taking and storing a clotted blood sample locally, without immediate testing, is recommended. In the event that there is a later concern about fetal development, this sample will be available for retrospective testing, including detection of Zika antibodies.
8. This evaluation and follow-up is likely to include repeat fetal ultrasound at four weekly intervals and consideration of fetal MRI. Abnormal fetal findings will prompt appropriate investigation including, for example, submission of booking and current serum samples for toxoplasma, rubella, parvovirus and CMV serology.
9. In this context, 'small fetal head' is defined as: Head Circumference more than 2 Standard Deviations below the mean for gestational age, i.e. below the 25th centile.
10. Time of first scan and subsequent ultrasound has been recommended because fetal ultrasound might not detect microcephaly or intracranial calcifications until the late second or early third trimester of pregnancy.
11. Apart from microcephaly and intracranial calcifications, other brain abnormalities that have been reported in association with Zika virus infection are ventriculomealy, cell migration abnormalities (e.g. lissencephaly, pachygyria), arthyrogryposis (congenital contractures) secondary to central or peripheral nervous system involvement.
12. This interim algorithm for assessing pregnant women with a history of travel during pregnancy for areas affected with active Zika virus transmission has been adapted from the Public Health England and UK Royal College of Obstetrics with due consideration given to the Irish context.