

Zika virus infection and pregnancy: Interim clinical guidance for healthcare professionals Version 1.0 Date 30/05/2016

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 an emerging viral threat that is currently circulating most prominently in the Americas and the Caribbean.⁽¹⁾ 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.⁽²⁾ 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/arthritis.⁽³⁾ 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.^(4,5)

Epidemiology

Prior to this current 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). Brazil reported their first case of Zika virus disease in May 2015.⁽¹⁾ Since then, rapid spread of the disease through the Americas has occurred and there are currently over 30 countries affected. The Health Protection Surveillance Centre (HPSC) of the HSE maintains a regularly updated [list of affected countries on their website](#). 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.⁽³⁾ 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.⁽⁶⁾

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).^(7;8)

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. In general, direct human to human transmission does not occur however, it has been shown that **sexual transmission of virus** can occur due to persistence of the virus in semen for extended periods of time.⁽⁹⁾ 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. To date no cases of sexual transmission from females to males have been reported.

For advice on how to prevent sexual transmission see information in **Figure 1**.

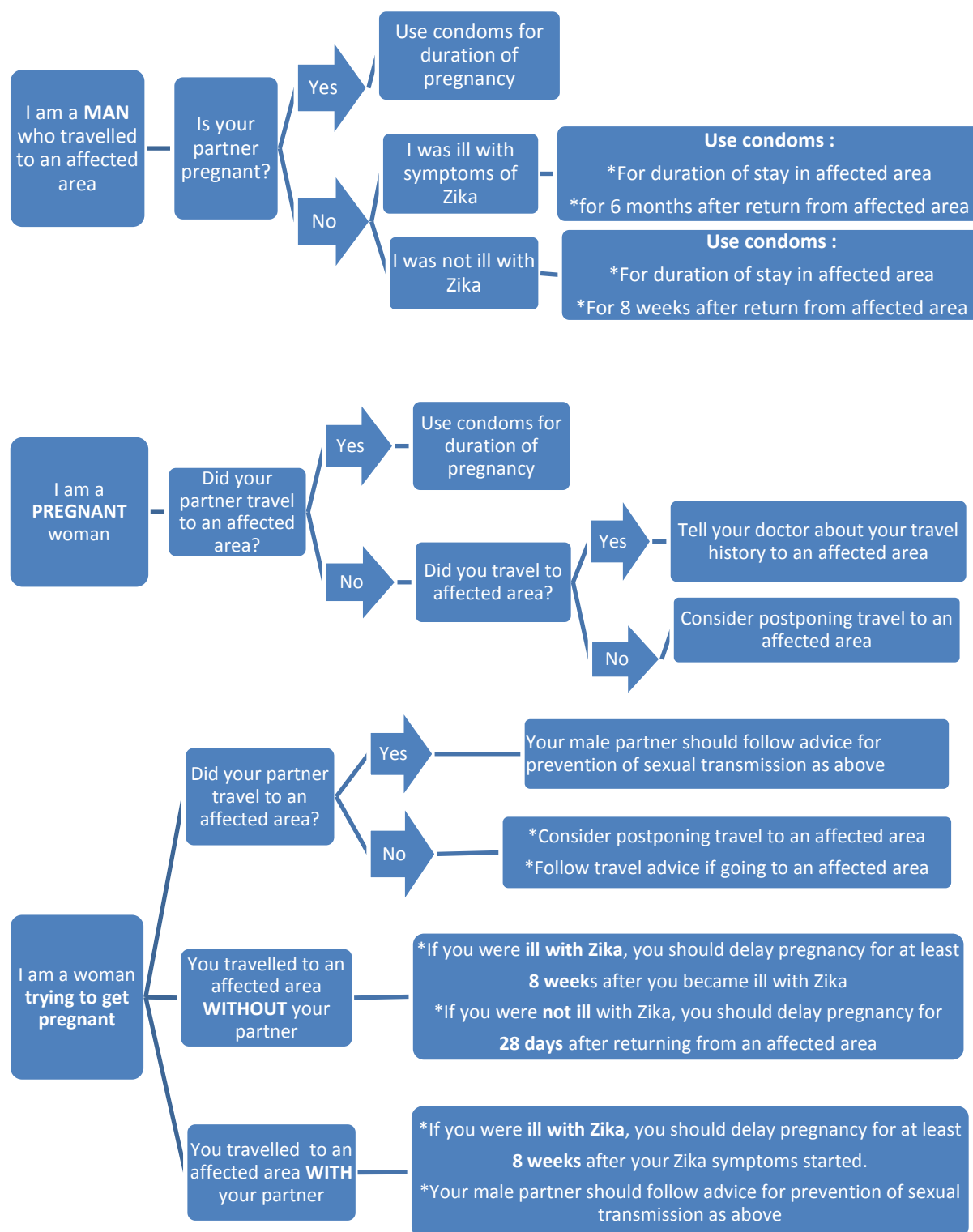


Figure 1: Advice for prevention of sexual transmission of Zika virus infection

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.⁽⁵⁾

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.⁽¹⁰⁾

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.⁽¹¹⁾

The most common symptoms include:⁽¹¹⁾

- 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. Increases in cases of microcephaly and Guillian Barré Disease (GBS) have been reported in areas where Zika virus is widely circulating. Although the association between Zika virus infection and both of these neurological conditions has yet to be shown to be indisputably causal, there is growing evidence to support the association.⁽⁵⁾

Microcephaly

A temporal association has been shown with microcephaly and Zika virus infection. In October 2015, the Brazilian Ministry of Health reported a rapid increase in the number of babies born with microcephaly in the nine month outbreak period of Zika virus in Brazil.^(5;12) Zika virus has been demonstrated to cross the placental barrier. In addition, the time of gestation when the infection is acquired appears to be important with findings from one Brazilian study of 35 cases of microcephaly, showed that Zika infection in early pregnancy appears to pose the greatest risk⁽¹³⁾ which appears to be similar to other congenital infections such as rubella, cytomegalovirus and toxoplasmosis. Recent research strongly supports a causal link between Zika virus infection and microcephaly.^(4;5)

Microcephaly is a rare neurological condition in which an infant's head is significantly smaller than expected. Microcephaly can lead to seizures, developmental delay or feeding difficulties.

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.^(5;12;14)

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.⁽¹⁴⁾

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 two weeks of return, consistent with a Zika like illness.
- symptomatic individuals who have had unprotected sex with a recently¹ returned traveller from an affected area

Currently, the test available in Ireland for Zika virus is reverse transcriptase polymerase chain reaction (RT-PCR). Antibody testing is less reliable due to cross-reactivity with other flaviviruses (e.g. dengue, yellow fever) making interpretation of test results difficult.⁽¹³⁾

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.

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.⁽¹⁵⁾

Prevention of sexual transmission

Although, the risk of sexual transmission of Zika virus is thought to be low, a number of instances of male-to-female sexual transmission have been reported in several countries. To date no cases of sexual transmission from females to males have been reported.

For **females** it is also important to prevent sexual transmission of Zika by:

¹ Within 6 months of return from an affected area

- **Using condoms** during vaginal, anal and oral sex for the **duration of their stay in an affected area**.
- **Using condoms** during vaginal, anal and oral sex for the **duration of their pregnancy with a male partner who travelled to an affected area**.
- By delaying pregnancy for at **least 28 days** after return to Ireland, if the woman travelled to the affected area without her partner or **8 weeks** if her partner has also returned from an affected area and remains well.
- If symptomatic with Zika, by delaying pregnancy for **8 weeks after onset of symptoms**.

If the **male partner** travelled to an affected area, prevention of sexual transmission by using condoms during vaginal, anal and oral sex and delaying pregnancy as follows:

- Couples whose male partner was **ill with Zika** should delay pregnancy for **6 months**.
- Couples whose male partner travelled to an affected area but was **not ill** with Zika should delay pregnancy for **8 weeks**.
- Couples whose male partner travelled to an affected area should use condoms for oral, anal and vaginal sex for the duration of pregnancy.

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 calculated to incorporate the duration of both incubation and viraemic periods.

The suggested six month period of condom use for men who had suspected or confirmed Zika virus infection reflects a precautionary approach that is based on the prolonged presence of the virus in semen (21 to 62 days – ECDC March 2016).

For further advice on prevention of sexual transmission see [Figure 1](#)

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.⁽¹⁶⁾
- 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 two weeks 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 two weeks 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, a serum, EDTA plasma and urine sample should be requested. The National Virus Reference Laboratory will test for Zika virus using RT-PCR. If test results are:

- **Positive or inconclusive Zika RT-PCR test:** 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.⁽¹³⁾

- **Negative Zika RT-PCR test:** 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:

- Symptomatic women who present more than 2 weeks after onset of symptoms are NOT recommended to have a PCR test for Zika virus infection for the following reasons:
 - the incubation period is between 3 to 12 days, so their illness is unlikely to be caused by Zika virus,
 - Zika virus RNA is not usually detectable in blood after this period.
- Zika virus can be detected by PCR testing of blood during the period when the patient is symptomatic; therefore, PCR testing should only be undertaken when symptoms are present at the time of clinical assessment. The following samples should be taken:
 - clotted 'red top' (plain) or 'yellow top' (serum separator) blood,
 - EDTA 'purple top' blood, and
 - a small volume of urine without preservative. These should be sent to the local microbiology/virology laboratory.
- Taking and storing a clotted serum sample locally, without immediate testing is recommended. This sample can then be tested retrospectively 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 weeks 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 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 two weeks of returning from an affected area travel, Zika RT-PCR or other serology testing is currently not routinely recommended 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).⁽¹³⁾ Taking and storing a clotted serum 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.

Women whose partners have been to an affected area

Zika virus can be passed between sexual partners in the man's semen. This is especially likely if the male partner developed symptoms of Zika virus disease. As Zika virus can be passed in a man's semen, it is important to practice safe sex with a partner who has recently returned from an [affected area](#) as described below:

- Pregnant women should use condoms during vaginal, anal and oral sex for the duration of their pregnancy with a male partner who travelled to an affected area.
- For further advice on prevention of sexual transmission in women who are not pregnant see [Figure 1](#)

This is a precaution and may be revised as more information becomes available.

After delivery

Live births

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

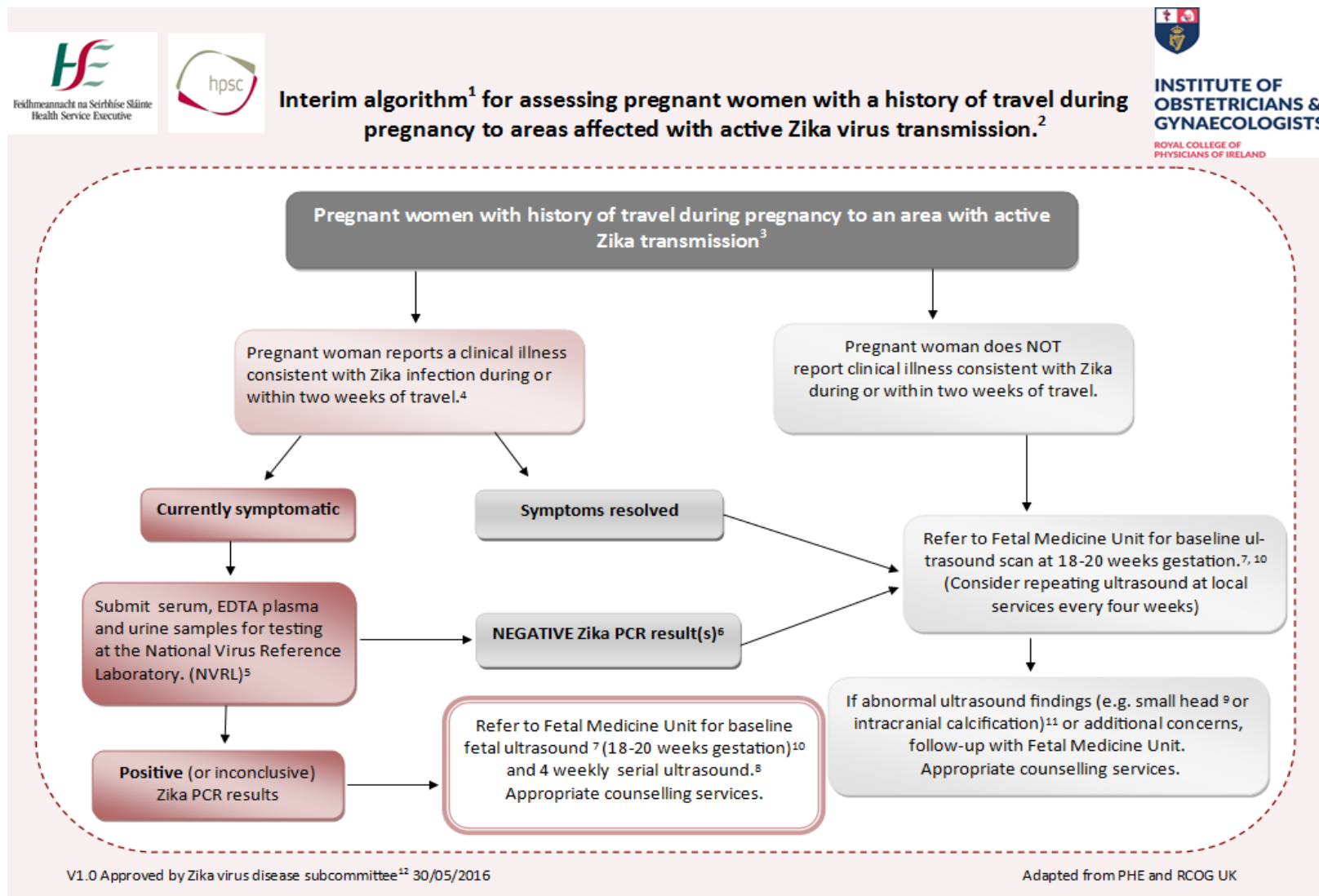
- Test placental and umbilical cord histopathology
- Test placental tissue and cord tissue for Zika virus RT-PCR
- Test umbilical cord blood for Zika and Dengue virus

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 RT-PCR.

Appendix 1



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). ZIKV testing will be performed exclusively using real-time PCR rather than any serology test.
3. Active Zika transmission is defined as an area where there is an on-going outbreak of Zika virus transmission, i.e. locally acquired cases reported in the last 6 months. Countries currently reporting Zika outbreaks: www.hpsc.ie
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 two weeks of travel to an area with ZIKV transmission that are not explained by other common infectious causes (e.g. URTI, UTI).
5. The samples required are a clotted blood (or serum), an EDTA 'purple top' blood (or plasma) and a small volume of urine without preservative. 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 ZIKV-specific follow up.
7. For women without current symptoms, taking and storing a clotted serum 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 ZIKV infection are ventriculomegaly, cell migration abnormalities (e.g. lissencephaly, pachygyria), arthrogryposis (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.

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