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Zika virus congenital infection: Interim guidance for neonatologists and paediatricians

This guidance is intended for neonatologists and paediatricians in England. It has been produced by PHE and a Zika virus neonatal working group.

Introduction and background information

There is an ongoing outbreak of Zika virus infection, mostly focussed in South and Central America and the Caribbean. Based on a growing body of research, there is scientific consensus that Zika virus is a cause of microcephaly and other congenital anomalies (also referred to as congenital Zika syndrome) and Guillain-Barré syndrome[1]. Symptomatic Zika virus infection is typically mild and short-lived in most individuals, but particular attention is required for women who are pregnant or who are planning a pregnancy due to the risks to the developing fetus associated with Zika virus infection in pregnancy.

Almost all cases of Zika virus are acquired via mosquito bites. However a small number of cases of sexual transmission have been reported [2-4]. Zika virus has been shown to be present in semen, although it is not yet known how long the virus can persist[5] or how transmissible it is in semen. The risk of sexual transmission of Zika virus is thought to be low, but the number of reports is increasing. Therefore, if available, the travel history of the partner should also be considered in the evaluation of a case.

Whilst viable virus has been detected in breast milk there is currently no evidence that Zika virus can be transmitted to babies through breast milk [6]. Therefore, breastfeeding is encouraged as the benefits of breastfeeding appear to outweigh the risks of Zika virus infection [7].

Diagnostic laboratory testing is available from PHE's Rare and Imported Pathogens Laboratory (RIPL) https://www.gov.uk/government/collections/rare-and-imported-pathogenslaboratory-ripl.

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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

Zika Virus and Congenital Zika Syndrome

Cases of maternal-fetal transmission of Zika virus have been confirmed [8-11] and a number of congenital abnormalities potentially associated with maternal Zika virus infection during pregnancy have been described [10, 12-18] (see table 1).

Imaging	**On examination**
Cerebral and cerebellar atrophy	Microcephaly
Cerebral calcifications	Craniofacial disproportion
Cortical and white matter abnormalities (eg agyria, pachygyria, lissencephaly)	Redundant scalp skin
Ventriculomegaly	Closed anterior fontanelle
Internal hydrocephalus	Exuberant external occipital protuberance
Periventricular cysts	Intrauterine growth restriction
Choroid plexus cyst	Contractures
Blakes's cyst	Talipes
Mega cisterna magna	Umbilical hernia
Vermian dys/agenesis	Hypertonia or spasticity
Callosal abnormalities	Hyperreflexia
Brain stem/spinal cord degeneration	Irritability
Ocular abnormalities (intraocular calcifications, cataracts, microphthalmia, macular alterations, optic nerve abnormalities	Convulsions, tremors
	Hearing and visual abnormalities

Table 1 Reported fetal and neonatal abnormalities potentially associated with Zika virus infection

Surveillance for congenital anomalies potentially associated with Zika virus infection has been established in the UK. Further information is available on the PHE website [https://www.gov.uk/guidance/zika-virus#surveillance-for-congenital-zika-syndrome].

Paediatricians should work closely with obstetric colleagues to identify confirmed and potentially infected infants born to parents who had travelled to areas with active Zika virus transmission. Evidence of fetal infection should be sought as detailed below.

Recommendations for the management of neonates of mothers with possible exposure to Zika virus during pregnancy or within 4 weeks before conception

Confirm that there has been active Zika virus transmission in the past nine months in the country visited using this link http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/Zika-transmission-past-9-months.aspx

Establish if the mother developed an illness compatible with Zika during pregnancy (including a combination of the following symptoms: rash; itching/pruritus; fever; headache; arthralgia/arthritis; myalgia; conjunctivitis; lower back pain; retro-orbital pain) and confirm if Zika virus testing and/or an antenatal USS have been done.

In cases where maternal Zika virus infection, with or without fetal abnormality, was diagnosed prenatally OR where fetal abnormalities were diagnosed prenatally, please follow the prenatally agreed plan.

Perform a clinical assessment including:

- physical examination: check for lymphadenopathy, hepatosplenomegaly, dysmorphic features, rash or other skin abnormalities, perform a complete neurological examination
- measure: head circumference, length, weight, assessment of gestational age
- if septic, follow local sepsis guidelines & consider testing for Zika virus
- ensure screening for hearing has been done before discharge

Following live birth of:

A. a normal baby, but maternal Zika serology or PCR tests were positive

Or

B. a baby with abnormalities (regardless of maternal Zika virus test results, or presence or absence of maternal symptoms consistent with Zika virus infection) of mothers with possible exposure to Zika virus during pregnancy or within 4 weeks of conception.

In the UK, any samples for testing for Zika virus should be sent to RIPL. Cases MUST be discussed with RIPL (usually by the local Infection specialist) prior to sample submission.

<u>Investigations at birth:</u>

- histopathological examination of the placenta and umbilical cord
- check that placental tissue and umbilical cord tissue have been obtained for Zika Virus PCR

Investigations at birth or within 48 hours of birth

1. ascertain whether there is a prenatally agreed Zika virus testing plan. If so, collect the neonatal samples for Zika virus testing according to the prenatally agreed plan. Confirm with the relevant local Infection specialist that they are liaising with RIPL to arrange testing of all the appropriate maternal and neonatal samples.
2. there may not be a prenatally agreed Zika virus testing plan if a neonatal abnormality has been identified only on *postnatal* examination of a baby born to a mother who, despite potential exposure, has had no Zika virus testing during pregnancy. If so, the case should be discussed urgently with the local Infection specialist in order to ensure that the appropriate neonatal and maternal samples are obtained and sent to RIPL for Zika virus testing.
3. in a baby with abnormalities, collect samples for testing for syphilis, toxoplasma, rubella, cytomegalovirus and herpes simplex virus infections
4. collect samples for full blood count, clotting, urea & electrolytes, liver function tests, C- reactive protein
5. perform cranial ultrasound; if microcephaly or intracranial abnormalities are present perform an MRI of the brain
6. perform ophthalmologic evaluation, including examination of the retina. If abnormal, repeat (as per ophthalmological decision)
7. refer for more targeted hearing screening as outpatient if indicated
8. consider other evaluations specific to the infant's clinical presentation
9. consider investigations for differential diagnosis of microcephaly (eg chromosomal, genetic, metabolic, environmental exposure to toxins, radiation)
10. consider consultation with paediatric geneticist, infectious disease specialist, neurologist, endocrinologist according to test results
11. if abnormalities are present, please complete the BPSU reporting card

Follow up of a baby with abnormalities where Zika virus cannot be excluded OR a normal baby with laboratory evidence of Zika virus infection

- Note that a normal baby whose mother tested positive for Zika virus by PCR or serology is likely to test positive for Zika IgG because of placental transfer. Follow up should therefore be tailored individually after discussion with the local infection specialist and RIPL

In all other cases:

- follow up at 3 months, then 3 monthly up to 12 months if clinically stable, more frequently if symptomatic (eg seizures)

- perform hearing test at 3-6 months if initially normal, refer to audiologist for further evaluation if abnormal
- perform ophthalmology review at 6 months if initially normal, liaise with ophthalmologist about further follow-up if abnormal
- discuss with local neurologists on best imaging and frequency of intracranial imaging
- consider performing an EEG if clinically indicated
- arrange early referral to community paediatric team for neuro-developmental assessment and long-term support
- follow up should be continued into childhood in order to detect adverse sequelae

Follow up of a normal baby whose mother had symptoms compatible with Zika virus infection whilst travelling or within 2 weeks of return but no Zika antibody test was performed four weeks or more after last possible exposure to Zika virus.

- appropriate samples for diagnostic testing will be advised by RIPL on a case-by-case basis**.**
- If maternal Zika virus infection could not be excluded, review at 3 months
- if any issues become apparent, tailor follow up accordingly
- if the baby remains well, refer to primary care/health visitor with advice to refer back to secondary care early if any concerns arise
- review at 12 months by a neonatologist or paediatrician
- Further guidance will follow as more evidence becomes available

Follow up of a normal baby whose mother was symptomatic whilst travelling and for 2 weeks after return but maternal Zika antibody testing was negative 4 weeks or more after her last possible exposure to Zika virus or whose mother was previously asymptomatic.

- record and inform primary care provider of maternal history
- provide routine care
- if concerns during routine investigation (eg hearing test), follow up accordingly

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