Screening, assessment and management of neonates and infants with complications associated with Zika virus exposure in utero

Rapid Advice Guideline

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1. Introduction

1.1 Background

On 1 February 2016, the World Health Organization (WHO), following a meeting of the International Health Regulations (IHR) Emergency Committee on Zika virus, declared the clustering of microcephaly cases, Guillain-Barré syndrome and other neurological conditions reported in some areas affected by Zika virus transmission, a Public Health Emergency of International Concern. (1), (2), (3)

Increased rates of congenital microcephaly - as high as 20-fold - have been reported in north eastern Brazil since late 2015. (4) As of 18 August, 2016, a total of 17 countries or territories have reported microcephaly and/or other central nervous system malformations potentially associated with Zika virus infection or suggestive of congenital infection. Three of these countries reported microcephaly cases among neonates born to mothers in countries with no endemic Zika virus transmission but who reported recent travel history to Zika-affected countries in the WHO Region of the Americas. Since 2015, 67 countries and territories have reported evidence of mosquito-borne Zika virus transmission. Before this, evidence of local mosquito-borne Zika infections had been reported in 13 countries and territories.

1.2 Objectives

The aim of this document is to provide guidance on the screening, clinical assessment, neuroimaging and laboratory investigations of neonates and infants born to women residing in areas of Zika virus transmission. This document updates the WHO interim guidance *Assessment of infants with microcephaly in the context of Zika virus* published on 4 March 2016. Recommendations are provided regarding the management and follow-up of neonates and infants known or suspected to have had Zika virus exposure in utero. A range of congenital abnormalities (not limited to microcephaly) has been reported (see 2.1 and 2.2) in association with Zika virus exposure in utero. This update also includes narrative summaries of recent evidence underpinning the recommendations, as well as operational considerations for implementation.

This guidance is intended to inform the development of national and local clinical protocols and health policies that relate to neonatal and infant care in the context of Zika virus transmission. It is not intended to provide a comprehensive practical guide for the management of Zika virus infections or neonatal neurological conditions including microcephaly.

1.3 Scope

This guidance is relevant to all neonates and infants born to women residing in areas of active Zika virus transmission, particularly those women with suspected or confirmed Zika virus infection during pregnancy. WHO guidance on pregnancy management in the context of Zika virus infection is provided in a separate document. (5)

1.4 Target audience

The primary audience for this guidance is health professionals directly providing care to neonates and infants and their families including paediatricians, general practitioners, midwives and nurses. This guidance is also intended to be used by those responsible for developing national and local health protocols and policies, as well as managers of maternal, newborn and child health programmes in regions affected by Zika virus.

2. Complications related to Zika virus infection in infants

2.1 Microcephaly

Microcephaly is a condition where a baby has a head that is smaller when compared with other babies of the same sex and age. An infant is considered to have microcephaly when the head circumference (also known as occipito-frontal circumference) is less than a specific cut-off value compared with head circumference reference standards for boys or girls of equivalent gestational or postnatal age. Head circumference reflects intracranial volume and is an important measurement to monitor a child's brain growth.

Microcephaly can be caused by numerous genetic factors including chromosomal and metabolic disorders, and also non-genetic etiologies (6) including congenital infections, intrauterine exposure to teratogens, perinatal injuries to the developing brain and severe malnutrition. Depending on the timing of insult, microcephaly may be present at birth (congenital) or may develop postnatally (acquired).

While microcephaly is a clinical sign and not a disease, congenital microcephaly (i.e. microcephaly present at birth) often indicates an underlying pathology in the brain and has been associated with a range of neurological sequelae including developmental delay, intellectual impairment, hearing and visual impairment and epilepsy. [(6), (7), (8), (9)]

There are limited reliable data on the prevalence of congenital microcephaly. Worldwide, birth defect registries report rates of congenital microcephaly ranging from 0.5 per 10 000 births (0.005%) to 10-20 per 10 000 births (0.1 - 0.2%), based on a cut-off of more than three standard deviations (SD) below the median for age and sex adjusted standards and including stillbirths and terminated pregnancies (but excluding microcephaly associated with anencephaly or encephalocoele). (Michelle Griffin, personal communication, 2016) While different causes of congenital microcephaly may account for some regional variability, methods for evaluating and measuring head circumference in fetuses and neonates may also account for some differences in case ascertainment. The combined birth prevalence of microcephaly from the European Surveillance of Congenital Anomalies (EUROCAT) from 2008 to 2012 was 2.85 per 10 000 births (including live births, fetal deaths and termination of pregnancies following prenatal diagnosis) [(10)] while the Latin American Collaborative Study of Congenital Malformations (ECLAMC) estimated the prevalence of congenital microcephaly (<-3SD) to be 1.98 per 10 000 births. [(11)]

Investigation of infants with congenital microcephaly in settings of Zika virus transmission has detected transplacental transmission of Zika virus and, where the pregnancy has been terminated or resulted in a stillbirth, Zika virus has been recovered from fetal brain tissue. [(12), (13)] An autopsy study of a fetus with a history of Zika virus exposure in utero showed evidence of activated microglia and macrophages in the brain, suggesting that host immune responses may contribute to the pathogenesis of microcephaly. [(12)] Zika virus is known to be highly neurotropic [(14)] and may therefore adversely affect fetal development by directly infecting the brain or indirectly, by infecting the placenta. In vitro and animal studies have shown that Zika virus can infect neural progenitor cells and may affect their cell cycle regulation and survival. [(15), (16)]

2.2 Congenital Zika virus syndrome

In addition to congenital microcephaly, a range of manifestations including craniofacial disproportion, spasticity, seizures, irritability, brainstem dysfunction such as swallowing problems, limb contractures, hearing and ocular abnormalities, and brain anomalies detected by neuroimaging have been reported among neonates where there has been in utero exposure to Zika virus.[(17), (18), (19), (20), (21)] Reported neuroimaging findings include cortical/subcortical calcifications, cortical malformations, simplified gyral pattern/migrational abnormalities, brainstem/cerebellar hypoplasia, and ventriculomegaly. While congenital microcephaly was the sign that first raised attention to the effect of Zika virus on the developing fetus, in up to one in 5 cases, some of these neurological abnormalities have occurred without associated microcephaly and have become evident only following birth.[(22)] The abnormalities consistently reported in these infants, including abnormal neuroimaging findings, suggest that a congenital syndrome, akin to congenital rubella or cytomegalovirus (CMV) infection, is attributable to in utero Zika virus infection.

Based on a review of observational, cohort, and case control studies, there is now strong scientific consensus that Zika virus is a cause of microcephaly and other neurological complications that together constitute a congenital Zika virus syndrome. [(23)]

Longer term clinical follow-up of infants born to women with a history of confirmed Zika virus infection at different times during pregnancy is needed. As additional evidence accumulates, WHO will update the clinical profile associated with congenital Zika virus syndrome.

3. Evidence and recommendations

3.1 Screening infants for congenital Zika virus syndrome

3.1.1 Initial history taking, clinical and anthropometric assessment

Microcephaly is defined as a head circumference of more than two standard deviations below the median for age and sex. [(24)] **Severe microcephaly** is present when the head circumference is more than three standard deviations below the median for age and sex.

Increased rates of congenital microcephaly have been reported in settings of Zika virus transmission in Brazil beginning in late 2015 [(2), (4)] and French Polynesia from 2013-2015. [(25), (26)] However, not all children with congenital Zika virus syndrome present with microcephaly. Some of these children with normal birth head circumference have appeared to have a disproportionately small head relative to the face (craniofacial disproportion), which may suggest relatively poor brain growth. [(18)] Among 602 cases of definite or probable congenital Zika virus syndrome, about one in five presented with head circumferences at birth in the normal range (above −2 SD for age and sex of the median INTERGROWTH-21 standard. [(22)]

Given the association between congenital microcephaly and other neurological morbidities such as cognitive delay, intellectual disability, cerebral palsy and epilepsy, [6] a small head circumference is an important clinical sign requiring further evaluation and follow-up. However, screening at birth for complications resulting from in utero Zika infection is presently hampered by diagnostic methods for determining Zika virus infection. Molecular methods can detect active infection in adults, but diagnostic technologies to establish prior infection, such as one occurring during pregnancy, are not available. Furthermore, it is estimated that up to 80% of Zika virus infections may be asymptomatic. [27] Hence, routine measurement of head circumference of all infants born to mothers in areas of Zika virus transmission, in addition to evaluation for other possible signs or symptoms, is essential to screen for congenital Zika virus syndrome.

3.1.2 Head circumference cut-off values to determine microcephaly

Different head circumference cut-off values (i.e. the measurement used to determine if an infant has a small head or not) have been used for defining microcephaly. These have included: <-2 SD (i.e. more than 2 SD below the median); < 3rd percentile (i.e. less than the 3rd percentile; and <-3 SD (i.e. more than 3 SD below the median). Head circumference cut-offs of either <-2 SD or < 3rd percentile will therefore designate more infants as having microcephaly, whereas using a cut-off of <-3 SD will designate fewer infants having microcephaly, though these infants will have more severe microcephaly and will be more likely to have neurological or developmental abnormalities. A consistent agreed case definition for congenital microcephaly is therefore important in order to standardize data.

3.1.3 Choice of growth standards for head circumference measurements

The WHO Child Growth Standards (WHO CGS), [28] derived from the WHO Multicentre Growth Reference Study (MGRS) describe optimal growth trajectories of infants and children from birth for whom there are no apparent barriers to growth. [29] The WHO CGS provide mean and median values for weight, length/height and head circumference by sex and age, and describe their distributions according to either percentiles or standard deviations. However, measurements less than the 1st percentile cannot be further classified to indicate the severity of microcephaly. For example, head circumferences of 31.0 cm and 30.4 cm in a term boy are both less than the 1st percentile; but 31.0 cm is between -2 SD and -3 SD, and 30.4 cm is below -3 SD. Standard deviation measurements can also be aggregated to provide a mean Z score for a specific population, whereas head circumference values based on percentiles cannot be summarized in the same way. However, the WHO CGS only provides values for term infants (i.e. from 37-42 weeks gestation) and were not disaggregated within this range. A single head circumference standard is therefore applied for all neonates considered term from 37 weeks to 41 weeks and 6 days (37^{+0} to 41^{+6}).

The INTERGROWTH-21 project (IG-21) adopted a similar methodology to the WHO MGRS to describe normal fetal growth and birth anthropometric measurements for weight, length and head circumference.[30] However, the IG-21 Size at Birth Standards are disaggregated by sex and gestational age (including between 37-42 weeks), and also provide standards for very preterm infants.

The choice of standard used – WHO CGS or IG-21 – should also reflect the availability and reliability of gestational age assessments. Accurate gestational age is difficult to ascertain unless an ultrasound assessment has been performed early in the first trimester. Dates of last menstrual period are commonly unreliable and estimated dates of delivery may vary widely when these are used to determine 'term' for any pregnancy.

The WHO CGS provides an appropriate reference standard for term neonates where gestational age is not reliably known. However, when the gestational age is accurately known it is preferable to use a standard appropriate for that gestational age. Otherwise, it is possible that microcephaly will be over-diagnosed. For example, an infant boy born at 37 weeks gestation with a head circumference of 31.0 cm (between -1 SD and -2 SD based on IG-21 standards) will be considered to have microcephaly based on -2 SD WHO CGS for boys (i.e. 31.9 cm). Similarly, an infant girl at 38 weeks gestation with a head circumference of 31.0 cm (between -1 SD and -2 SD based on IG-21 standards) will also be considered to have microcephaly based on -2 SD WHO CGS for girls (i.e. 31.5 cm).

In some regions, large numbers of women experience unfavourable conditions before and during pregnancy and their offspring are therefore at greater risk of fetal growth restriction. In these populations, using either WHO CGS or IG-21 standards, more neonates may be identified as having microcephaly. For example, in parts of Kenya up to 8.5% of neonates may have head circumference less than -2 SD of median for age (Charles Newton, personal communication, 2016).

Table 1. Comparison of head circumference standards – WHO CGS and IG-21 by sex and gestational age

	Gestational age (weeks)	Standard deviation	IG-21 size at birth (cm)	WHO Child Growth Standards
BOYS	37	0	33.02	*WHO CGS provides a single set of head circumference values from 37 weeks to 41 weeks and 6 days gestational age* 0 SD = 34.5 cm -2 SD = 31.9 cm -3 SD = 30.7 cm 3rd percentile = 32.1 cm 1st percentile = 31.5 cm
		-2 SD	30.54	
		-3 SD	29.12	
	38	0	33.47	
		-2 SD	31.05	
		-3 SD	29.67	
	39	0	33.90	
		-2 SD	31.54	
		-3 SD	30.19	
	40	0	34.31	
		-2 SD	32.00	
		-3 SD	30.68	
	41	0	34.70	
		-2 SD	32.44	
		-3 SD	31.14	
GIRLS	37	0	32.61	*WHO CGS provides a single set of head circumference values from 37 weeks to 41 weeks and 6 days gestational age* 0 SD = 33.9 cm -2 SD = 31.5 cm -3 SD = 30.3 cm 3rd percentile = 31.7 cm 1st percentile = 31.1 cm
		-2 SD	30.24	
		-3 SD	28.85	
	38	0	33.03	
		-2 SD	30.73	
		-3 SD	29.37	
	39	0	33.41	
		-2 SD	31.17	
		-3 SD	29.85	
	40	0	33.76	
		-2 SD	31.57	
		-3 SD	30.29	
	41	0	34.08	
		-2 SD	31.94	
		-3 SD	30.68	

3.1.4 When to measure the head circumference

In order to obtain the most accurate comparison with either WHO CGS or IG-21 standards, head circumference measurements should be taken within the first 24 hours to be compatible with the time intervals used in the respective studies. [29], [30]

No matter which standard is used and when it is measured, it is essential to meticulously follow recommended methods to avoid measurement errors. [31]

3.1.5 Recommendations

1. Neonates should have their head circumference measured in the first 24 hours of life:
   a. For term neonates (37-42 weeks), WHO Child Growth Standards for size at birth should be used to interpret measurements. If accurate gestational age is known, INTERGROWTH-21 Size at Birth Standards are preferred.
   b. For preterm neonates, INTERGROWTH-21 Size at Birth Standards for gestational age and sex should be used to interpret measurements.
2. All mothers should be asked about clinical signs and symptoms suggestive of Zika virus infection and/or laboratory confirmation of Zika virus infection during pregnancy, including when the possible infection occurred (first, mid or final trimester).
3. Neonates should be examined to assess whether the head appears disproportionately small relative to the face (craniofacial disproportion).

Operational considerations

- If head circumference cannot be measured during the first 24 hours, it should be measured within the first 72 hours.
- Health practitioners should be trained in the correct method for head circumference measurement and the use of these growth standards in areas where they are not in routine use.

3.2 Clinical assessment of neonates for congenital Zika virus syndrome

3.2.1 Etiology of congenital microcephaly

Microcephaly is associated with numerous genetic etiologies, including chromosomal and metabolic disorders and also non-genetic causes. (6) Non-genetic causes include congenital infections notably the TORCH infections (toxoplasmosis, rubella, cytomegalovirus and herpes), syphilis, varicella–zoster, parvovirus B19 and human immunodeficiency virus (HIV). Other non-genetic causes include intrauterine exposure to teratogens such as alcohol and ionizing radiation, pre- and perinatal injuries to the developing brain (hypoxia-ischaemia, trauma), and severe malnutrition.

3.2.2 Congenital microcephaly and neurodevelopmental outcomes

When all forms of microcephaly are considered, there appears to be general correlation between the degree of microcephaly and the likelihood of neurological impairment. (32), (33) A study based on the National Institute of Neurological Disorders and Stroke Collaborative Perinatal Project found that among children with birth head circumference between -2 SD and -3 SD, about 11% had an intellectual quotient (IQ) less than 70; and among children with birth head circumference -3 SD or below, 51% had IQ <70 at seven years of age. (8) Thus, a substantial proportion of children with head circumference between -2 SD and -3 SD will still have normal development.

Studies of children with congenital infections report frequent microcephaly in children with symptomatic congenital CMV (34) and congenital rubella syndrome. (35), (36) However, children with congenital CMV without microcephaly may still have cerebral cortical malformations that lead to neurological impairments such as intellectual disability and epilepsy. (37) In the context of a congenital infection, microcephaly is often predictive of worse neurodevelopmental outcomes. (38), (39)

Congenital infections may also be associated with other neurological consequences ranging from isolated sensorineural hearing loss to severe destructive brain lesions. Congenital infections, particularly CMV, are among the most common causes of hearing impairment. Postnatal onset of hearing impairment and a progressive course are also common. (40) Children with congenital microcephaly of unspecified etiologies also demonstrate an increased incidence of sensorineural hearing loss. (41) Microcephaly may similarly be associated with eye and vision abnormalities. One large study found that 30% of children with microcephaly of heterogeneous etiologies had disorders of the eyes. (9) Chorioretinitis and other ocular abnormalities are frequently reported in children with congenital CMV. (42), (43)

3.2.3 Zika virus exposure in utero and neurological consequences

Reports from areas with Zika virus transmission note that children with congenital Zika virus syndrome commonly, but not always, have congenital microcephaly. Autopsy studies have found the presence of Zika virus in affected fetuses and infants supporting the conclusion that Zika virus can have a major deleterious effect on the developing brain. (12), (44) Early reports suggest that children with congenital Zika virus syndrome may also have sensorineural hearing loss; however, due to the limited duration of follow-up among index cases to date, the prevalence and clinical course are not yet fully known. (17) Ocular findings such as focal pigment mottling of the macula, loss of foveal reflex, macular atrophy, chorioretinal atrophy, optic nerve abnormalities (including hypoplasia) have also been reported in children with congenital Zika virus syndrome. (45), (46), (47) Other clinical signs and symptoms commonly noted in neonates with congenital microcephaly where maternal Zika virus infection in pregnancy was either suspected or confirmed include arthrogryposis, early-onset spasticity, hyperirritability, swallowing difficulties and seizures. (17), (20)

3.2.4 Assessing a neonate with congenital microcephaly

Identifying the underlying cause of microcephaly has implications for the child's prognosis, and is also important to monitor and manage potential complications and to counsel future pregnancies. Some causes of microcephaly may be suspected or diagnosed by history (e.g. fetal alcohol syndrome or maternal malnutrition), physical and neurological examination (e.g. syndromes with dysmorphic features) or a combination of both (e.g. congenital infections). Ancillary tests including neuroradiological and laboratory investigations often aid etiological diagnosis (see 3.3 and 3.4).

3.2.5 Recommendation

4. In neonates with congenital microcephaly or in whom the head appears disproportionately small relative to the face, a full history and physical and neurological examination, including assessment of hearing and vision, should be performed in order to detect additional abnormalities potentially associated with Zika virus infection.

Operational considerations

- The clinical history and full physical and neurological examinations may help to differentiate congenital infections from environmental causes of congenital microcephaly or genetic disorders.
- It is essential that all neonates, especially those born in areas with active Zika virus transmission, are screened for hearing loss at the earliest possible opportunity, preferably before they are discharged from hospital.
- Hearing screening should be performed according to the WHO guiding principles for newborn and infant hearing screening. [48] Screening can be performed using automated auditory brainstem responses (ABR) or otoacoustic emissions (OAE) screening procedures. In places where it is not possible to undertake physiological tests to identify hearing loss, assessment can be undertaken using behavioural measures;
- Accurate assessment of vision by clinical examination during the newborn period may be difficult. Where possible an ophthalmologist should perform an ocular examination.

3.3 Neuroimaging of neonates for congenital Zika virus syndrome

3.3.1 Neuroimaging and microcephaly

Neuroimaging abnormalities are common in children with congenital microcephaly, especially where there are associated neurological signs or symptoms. These findings may help to determine the underlying cause of microcephaly. In settings without Zika virus, neuroimaging abnormalities have been noted in 80% of children with head circumference <-3 SD by computed tomography (CT) or magnetic resonance imaging (MRI); [49] in a separate study, 88% of such children had abnormal neuroimaging findings when examined by MRI alone. [50] Most of the children had neurological signs or symptoms, though these were not always present at birth.

Neuroimaging data of infants with congenital microcephaly in settings of Zika virus transmission is limited; cerebral calcification has commonly been detected in such children and is often subcortical in location. [18], [51], [52] Other reported findings include brain atrophy and ventriculomegaly, cerebellar and brainstem anomalies, cortical gyral abnormalities and callosal abnormalities. [12], [18], [19], [51], [52], [53], [54] Gyral abnormalities are described as polymicrogyria, pachygyria or lissencephaly. [18], [51], [52] However, high resolution images often suggest polymicrogyria which are most commonly diffuse but may be frontal predominant. The presence and pattern of these gyral abnormalities suggest that Zika virus directly interferes with brain development, as opposed to destroying the brain later in development. [12]

These neuroimaging abnormalities can also be found in infants with other congenital infections such as CMV syndrome. For example, intracranial calcifications have been identified in about half of children with symptomatic congenital CMV [34], [38], [55] though these calcifications tend to be subependymal rather than subcortical. [56] Congenital CMV infection can also cause brain malformations such as polymicrogyria, pachygyria, atrophy and other anomalies [37], [56] similar to those described in infants with congenital Zika virus syndrome. However, emerging evidence suggests that the neuroimaging findings in congenital Zika virus syndrome may be more striking than those with other congenital infections.

3.3.2 Magnetic resonance imaging, computerized axial tomography or ultrasound examination

Cerebral calcification may be more readily identified by CT compared to MRI. However MRI has a higher resolution and better ability to delineate abnormalities such as those of the cerebral cortex and posterior fossa. The available literature and limited clinical experience suggest that either CT or MRI is sufficient to identify typical radiological features of congenital Zika virus syndrome.

The utility of postnatal cranial ultrasound in congenital Zika virus syndrome is unknown. In congenital CMV infection, cranial ultrasound is often useful to detect pathological findings including calcification, ventriculomegaly and cystic changes. [57], [58] However, the distribution of brain calcification in congenital Zika virus syndrome appears to be more peripheral, making it potentially difficult to detect by postnatal cranial ultrasound. Furthermore, the quality of postnatal cranial ultrasound depends on the size of the anterior fontanelle. Experience from Brazil indicates that many neonates with suspected congenital Zika virus syndrome have a very small or closed anterior fontanelle at birth [18] and cranial ultrasound may not be feasible or reliable for providing useful clinical information in these cases.

3.3.3 Recommendations

5. In neonates with head circumference < -2 SD **and** ≥ -3 SD, or where the head is disproportionately small relative to the face, (and no strong indication from clinical examination of a genetic or environmental cause of microcephaly) neuroimaging should be performed if:
   a. Zika virus infection is suspected in the mother during pregnancy; or
   b. Any neurological signs or symptoms are present;
6. In neonates with head circumference < -3 SD neuroimaging should be performed if there is no strong indication from clinical examination of a genetic or environmental cause of microcephaly.
7. When neuroimaging is indicated:
   a. Either CT or MRI can be used.
      – CT is satisfactory to identify neuroimaging findings suggestive of congenital Zika virus syndrome.
      – MRI is satisfactory to identify neuroimaging findings suggestive of congenital Zika virus syndrome, and may also provide further detail and detect other conditions.
   b. If CT or MRI are not available, cranial ultrasound can be performed if the anterior fontanelle is of adequate size.

Remarks

- Currently there are no known pathognomonic neurological findings for congenital Zika virus syndrome. Findings reported in neonates with congenital Zika virus syndrome include: cerebral calcification, brain atrophy and ventriculomegaly, cerebellar and brainstem anomalies, cortical gyral abnormalities and callosal abnormalities.
- Cerebral calcification is commonly seen in congenital infections. Some genetic disorders, such as Aicardi–Goutières syndrome, [59] are also associated with cerebral calcification.

Operational considerations

- In addition to availability, radiation exposure in CT, higher cost and potential need for sedation in MRI should be considered when selecting an imaging modality.
- Neuroradiological findings should be interpreted in the context of other clinical and laboratory information.
- When indicated, cranial ultrasound should be performed by an ultrasonographer experienced in neonatal cranial ultrasound.

3.4 Laboratory investigations of neonates for congenital Zika virus syndrome

3.4.1 Identifying other causes of microcephaly including congenital infections

The clinical and neuroimaging findings of neonates born with microcephaly due to congenital infections or some genetic disorders can be similar. In order to provide the most appropriate care and to counsel families of children with congenital microcephaly, it is important to establish the underlying etiology. A clinical history, including immunization status, past and recent infections, and exposures, can ascertain risk factors or characteristics of one etiology or another. A careful physical examination of the neonate may also identify signs that point toward a specific diagnosis.

Additional laboratory testing can help to make a diagnosis of other congenital infections such as CMV or rule out genetic disorders such as Aicardi-Goutières syndrome [59] and mutations in the *OCLN* gene, [60] whose brain manifestations may mimic congenital infections.

In order to attribute microcephaly or other neurological findings to in utero Zika virus exposure, other causes of congenital abnormalities must be excluded.

However, there is currently no validated laboratory diagnostic test or commercial assay to confirm congenital Zika virus infection or exposure in neonates. Zika virus ribonucleic acid (RNA) has been detected by reverse transcription polymerase chain reaction (RT-PCR) from the serum of neonates with perinatal transmission of Zika virus from the mother. [61] Zika virus IgM has also been detected from the CSF of infants with congenital Zika virus syndrome. [62] As the sensitivity and specificity of RT-PCR and serological testing for Zika virus in neonates with suspected congenital Zika virus infection is being established, it is recommended that both RT-PCR and serology be performed to determine congenital infection.

3.4.2 Recommendations

8. Serological testing for TORCH infections should be performed (unless excluded in the mother in pregnancy):
   a. in neonates with congenital microcephaly; or
   b. where the head is disproportionately small relative to the face;

   And

   c. where Zika virus infection is suspected in the mother during pregnancy; or
   d. any neurological signs or symptoms are present
9. The role of serological and virological testing for Zika virus in neonates should be assessed based on further data on sensitivity and specificity and understanding of cross-reactivity with other flaviviruses.

Operational considerations

- Positive CMV serology in a neonate is not a reliable indicator of in utero CMV infection. Diagnosis requires detection of CMV in urine, saliva, blood or other tissues within 2-3 weeks of birth.

3.5 Management of neonates with congenital Zika virus syndrome

3.5.1 Early complications

Clinical data available from Brazil show that infants with congenital Zika virus syndrome are at high risk for a spectrum of complications including developmental delay, seizures, hearing and visual impairment, excessive irritability, early-onset spasticity, swallowing difficulties, arthrogryposis and hip dysplasia. [17], [20] Due to limited follow up to date, the course of congenital Zika virus syndrome is yet to be fully understood. However, children with congenital infections and/or microcephaly are at high risk for developmental delays and auditory and visual impairment and the risk of these are higher in the setting of

3.5.2 Recommendations

10. Families of neonates with congenital Zika virus syndrome should be informed about the diagnosis and advised regarding management and prognosis.
11. Psychosocial support and advice should be provided to families of neonates with congenital Zika virus syndrome as described in WHO interim guidance on 'Psychosocial support for pregnant women and for families with microcephaly and other neurological complications in the context of Zika virus'. [67]
12. Infants with congenital Zika syndrome should receive a comprehensive neurodevelopmental assessment, and supportive therapy should be put in place for any difficulties noted including irritability, seizures, swallowing difficulties, early onset spasticity and hip dysplasia.
13. Multidisciplinary approaches should be adopted to provide early interventions and support to promote neurodevelopment, prevent contractures and manage early complications as outlined in WHO mhGAP and community-based rehabilitation guidelines. [65], [66]

Operational considerations

- Health care practitioners need to be trained and provided with resources to recognize and manage the reported neurological complications associated with congenital Zika virus syndrome.
- Parents and families should be educated to recognize the presence of seizures
- Community-based rehabilitation and support may be relevant especially in resource limited settings.

3.6 Follow-up of children in areas of Zika virus transmission

3.6.1 Short and long term follow-up

Limited follow-up data are available regarding children affected by congenital Zika virus syndrome, the description