Version 1.0, 8/21/2016

Zika Pregnancy outcome reporting of brain abnormalities and other adverse outcomes

The following box details the inclusion criteria for brain abnormalities and other adverse outcomes potentially related to Zika virus infection during pregnancy. All pregnancy outcomes are monitored, but weekly reporting of adverse outcomes is limited to those meeting the below criteria. All prenatal and postnatal adverse outcomes are reported for both Zika Pregnancy Registries (US Zika Pregnancy Registry, Zika Active Pregnancy Surveillance System) and Active Birth Defects Surveillance; however, case finding methods dictate some differences in specific case definitions.

Brain abnormalities with and without microcephaly

- Confirmed or possible congenital microcephaly[#]
- Intracranial calcifications
- Cerebral atrophy
- Abnormal cortical formation (e.g., polymicrogyria, lissencephaly, pachygyria, schizencephaly, gray matter heterotopia)
- Corpus callosum abnormalities
- Cerebellar abnormalities
- Porencephaly
- Hydranencephaly
- Ventriculomegaly / hydrocephaly (excluding "mild" ventriculomegaly without other brain abnormalities)
- Fetal brain disruption sequence (collapsed skull, overlapping sutures, prominent occipital bone, scalp rugae)
- Other major brain abnormalities, including intraventricular hemorrhage *in utero* (excluding post-natal IVH)

Early brain malformations, eye abnormalities, or consequences of central nervous system (CNS) dysfunction

- Neural tube defects (NTD)
    - Anencephaly / Acrania
    - Encephalocele
    - Spina bifida
- Holoprosencephaly / Arhinencephaly
- Structural eye abnormalities
    - Microphthalmia / Anophthalmia
    - Coloboma
    - Cataract
    - Intraocular calcifications
    - Chorioretinal anomalies involving the macula (e.g., chorioretinal atrophy and scarring, macular pallor, gross pigmentary mottling and retinal hemorrhage); excluding retinopathy of prematurity
    - Optic nerve atrophy, pallor, and other optic nerve abnormalities
- Congenital contractures (e.g., arthrogryposis, club foot, congenital hip dysplasia) with associated brain abnormalities
- Congenital deafness documented by postnatal testing

[#]Live births: measured head circumference (HC) adjusted for gestational age and sex <3rd percentile at birth, or if not measured at birth, within first 2 weeks of life; pregnancy loss: prenatal HC* more than 3 SD below the mean based on ultrasound or postnatal HC <3rd percentile. Birth measurements based on intergrowth21 standards (http://intergrowth21.ndog.ox.ac.uk/) which are based on measurements within 24 hours of birth, and therefore measurements within 24 hours of birth are appropriate for this assessment.

Table 1. Case Definitions for Birth Defects Reported Weekly by Zika Pregnancy Registries and Monitored and Reported Weekly by Active Birth Defects Surveillance

Adverse Outcomes	Case Definitions	
	Zika Pregnancy Registries Pregnancies with laboratory evidence of Zika virus infection	**Active Birth Defects Surveillance**[#] All birth defects of interest as part of the Zika response (with codes noted for case-finding purposes) Unless otherwise specified, the same defect descriptions and exclusion criteria for the Pregnancy Registries also apply to the Active Birth Defects Surveillance
Laboratory evidence of possible Zika virus infection in mother, fetus, infant, or placenta†	Required	Not required, but travel history and assessment of Zika virus exposure or symptoms including codes for arboviral disease noted in medical record should be abstracted
Brain abnormalities with and without microcephaly		
Confirmed or possible congenital microcephaly[¶]	1) Live births: measured head circumference (HC) adjusted for gestational age and sex <3rd percentile at birth[¶], or if not measured at birth, within first 2 weeks of life 2) Pregnancy loss: prenatal HC*,‡ more than 3 SD below the mean on prenatal ultrasound OR postnatal HC[¶] <3rd percentile	1) Diagnosis of microcephaly or mention of microcephaly or small head in the medical record **AND** 2a) Live births: measured head circumference (HC) adjusted for gestational age and sex <3rd percentile at birth[¶], or if not measured at birth, within first 2 weeks of life OR 2b) Pregnancy loss: prenatal HC*,‡ more than 3 SD below the mean on prenatal ultrasound OR postnatal HC[¶] <3rd percentile ICD-10-CM: Q02 CDC/BPA: 742.10, 742.486
Intracranial calcifications	Intracranial (within the brain) calcifications, calcium deposits, or brightly echogenic foci Seen on prenatal or postnatal cranial imaging‡ (ultrasound, CT, or MRI)	*Intracranial calcifications* ICD-10-CM: No specific code; may be included under Q04.8, Q04.9 CDC/BPA: 742.48
Cerebral / cortical atrophy	Atrophy or hypoplasia of cerebral structures Seen on prenatal or postnatal cranial imaging‡ (ultrasound, CT, or MRI)	*Cerebral atrophy* ICD-10-CM: No specific code; may be included under Q04.3 CDC/BPA: 742.48
Abnormal cortical gyral patterns: Agyria, lissencephaly, microgyria, polymicrogyria, pachygyria, schizencephaly, gray matter heterotopia	Pachygyria is a simplified and unusually thick gyral pattern and is considered a subset of lissencephaly by some. Microgyria and polymicrogyria are too many small folds in the cortical surface. Schizencephaly is	*Agyria and lissencephaly, microgyria, polymicrogyria, schizencephaly and gray matter heterotopia* ICD-10-CM: Q04.3, Q04.6, Q04.8

	the presence of abnormal clefts in the cerebral hemispheres. Gray matter heterotopia are clumps of gray matter located in the wrong place. Look for terms such as agyria, lissencephaly, microgyria, polymicrogyria, simplified gyral pattern, pachygyria, schizencephaly, heterotopia,cortical dysplasia, neuronal migration disorder Seen on prenatal or postnatal cranial imaging‡ (ultrasound, CT, or MRI)	CDC/BPA: 742.24, 742.25, 742.28
Corpus callosum abnormalities	Agenesis, hypoplasia, thin, partial, or absent corpus callosum Seen on prenatal or postnatal cranial imaging‡ (ultrasound, CT, or MRI)	*Corpus callosum abnormalities* ICD-10-CM: Q04.0 CDC/BPA: 742.21
Cerebellar abnormalities	Atrophy or hypoplasia of the cerebellum or cerebellar vermis Seen on prenatal or postnatal cranial imaging‡ (ultrasound, CT, or MRI)	*Cerebellar abnormalities* ICD-10-CM: No specific code; may be included under Q04.3 CDC/BPA: 742.23, 742.31
Porencephaly	Porencephaly describes a cavity or cyst within the cerebral hemisphere. Look for porencephaly or porencephalic cyst. EXCLUDE: isolated choroid plexus cyst Seen on prenatal or postnatal cranial imaging‡ (ultrasound, CT, or MRI)	*Porencephaly* EXCLUDE: isolated choroid plexus cyst ICD-10-CM: Q04.6 CDC/BPA: 742.41, 742.42
Hydranencephaly	In hydranencephaly, all or part of the cerebral hemispheres are replaced by fluid-filled sacs. Look for hydranencephaly. Seen on prenatal or postnatal cranial imaging‡ (ultrasound, CT, or MRI)	*Hydranencephaly* ICD-10-CM: No specific code; should be included in Q04.3 CDC/BPA: 742.32
Ventriculomegaly / hydrocephaly	Large, enlarged, or dilated cerebral ventricles (which may be specified as lateral, third or fourth ventricles), or hydrocephalus or ventriculomegaly EXCLUDE: isolated “mild” ventriculomegaly without other brain abnormalities Seen on prenatal or postnatal cranial imaging‡ (ultrasound, CT, or MRI)	*Ventriculomegaly / hydrocephaly* EXCLUDE: isolated “mild” ventriculomegaly without other brain abnormalities ICD-10-CM: Q03.0–Q03.9 CDC/BPA: 742.30, 742.38, 742.39
Fetal brain disruption sequence	Fetal brain disruption sequence components include: collapsed skull, overlapping sutures, prominent occipital bone, scalp rugae	Fetal brain disruption sequence No specific code. This might be coded as a single brain malformation or as the individual components. ICD-10-CM: Q04.8, Q04.9, Q76.4, Q75.8, Q75.9, Q82.8 CDC/BPA: 742.48, 754.08, 754.09, 756.08, 756.09, 757.39, 757.80

Other major brain abnormalities	Any major brain abnormality not previously listed elsewhere including intraventricular hemorrhage (IVH) that clearly occurred in utero Note: Exclude IVH acquired postnatally	*Other major brain abnormalities* ICD-10-CM: Q04.0–Q04.9, Q07.00–Q07.03 CDC/BPA: 742.20, 742.22, 742.29, 742.48, 742.90
Early brain malformations, eye abnormalities, or consequences of CNS dysfunction		
Neural tube defects (NTDs) and holoprosencephaly		
Anencephaly / Acrania	Failure of the brain and skull to form. Includes prenatal* or postnatal diagnosis of anencephaly	*Anencephaly* ICD-10-CM: Q00.0–Q00.2 CDC/BPA: 740.0–740.2
Encephalocele	Sac-like protrusion or projection of the brain and the membranes that cover it through an opening in the skull, resulting in an opening in the midline of the upper part of the skull, the area between the forehead and nose, or the back of the skull.	*Encephalocele* ICD-10-CM: Q01.0–Q01.9 CDC/BPA: 742.00–742.09
Spina bifida	An opening in the spine through which nerve tissue and/or meninges protrude. It can result in herniation of the brain into the foramen magnum (Arnold-Chiari malformation) Prenatal or postnatal diagnosis of spina bifida or Arnold-Chiari malformation‡	*Spina bifida* ICD-10-CM: Q05.0–Q05.9, Q07.01, Q07.03 CDC/BPA: 741.00–741.99
Holoprosencephaly / Arhinencephaly	Failure of the forebrain to develop into two cerebral hemispheres, typically causing defects of the face and brain Seen on prenatal or postnatal cranial imaging‡ (ultrasound, CT, or MRI)	*Holoprosencephaly / Arhinencephaly* ICD-10-CM: Q04.1, Q04.2 CDC/BPA: 742.26, 742.27
Structural eye abnormalities		
Microphthalmia / Anophthalmia	Small or absent eye or eyes	*Microphthalmia / Anophthalmia* ICD-10-CM: Q11.0–Q11.2 CDC/BPA: 7443.00, 743.10
Coloboma	A gap, notch or area of missing tissue in part of the eye, including the iris, choroid, lens, retina, or optic disc	*Coloboma* ICD-10-CM: Q12.2, Q13.0, Q14.1–Q14.8 CDC/BPA: 743.34, 743.43, 743.48, 743.49, 743.51, 743.52, 743.535, 743.58, 743.59
Cataract	Clouding of the lens of the eye diagnosed postnatally	*Cataract* ICD-10-CM: Q12.0 CDC/BPA: 743.32
Intraocular calcifications	Intraocular calcifications diagnosed postnatally	*Intraocular calcifications* No specific code. This might be coded under the affected part of the eye. ICD-10-CM: Q13.8, Q13.9, Q14.1–Q14.9 CDC/BPA: 743.48, 743.49, 743.51, 743.51, 743.58,

		743.59
Chorioretinal anomalies involving the macula including chorioretinal atrophy and scarring, macular pallor, gross pigmentary mottling and retinal hemorrhage	Changes in the posterior segment of the eye in particular involving the macula EXCLUDE: retinopathy of prematurity	*Chorioretinal atropy and scarring, macular pallor, gross pigmentary mottling and retinal hemorrhage.* No specific code. This might be coded under the affected part of the eye. ICD-10-CM: Q14.1–Q14.9 CDC/BPA: 743.51, 743.52, 743.53, 743.58, 743.59
Optic nerve atrophy, pallor, and other optic nerve abnormalities	Optic nerve hypoplasia, optic nerve abnormalities, optic nerve pallor, double-ring sign, increased cup-to-disc ratio	*Optic nerve atrophy, pallor, and other optic nerve abnormalities* *ICD-10-CM:* Q14.2 CDC/BPA: 743.52
Congenital contractures and joint abnormalities (arthrogryposis, club foot with associated brain abnormalities, congenital hip dislocation with associated brain abnormalities)	Arthrogryposis, joint contractures, decreased flexibility of the joints; talipes equinovarus or clubfoot with associated brain abnormalities; congenital hip dislocation or developmental dysplasia of the hip with associated with brain abnormalities	*All infants with arthrogryposis/multiple joint contractures.* *Only include if associated with brain abnormalities: club foot, talipes equinovarus, congenital hip dislocation or developmental dysplasia of the hip* ICD-10-CM: Q65.0–Q65.9, Q66.0–Q66.9, Q74.3 CDC/BPA: 754.30, 754.31, 755.80
Congenital deafness	Deafness documented by postnatal testing	*Congenital deafness* ICD-10-CM: H90.0–H91.9, Q16.0–Q16.9 CDC/BPA: 744.09

[¶]Birth measurements based on intergrowth21 standards; http://intergrowth21.ndog.ox.ac.uk/Standard charts are based on measurements within 24 hours of birth, and therefore measurements within 24 hours of birth are appropriate for this assessment.

[#]ICD-10-CM codes included are for case-finding only. All potential diagnoses must be verified by record review and abstraction. CDC/BPA codes are listed for birth defects surveillance programs that use CDC/BPA codes for coding of birth defects (http://www.cdc.gov/ncbddd/birthdefects/documents/macdpcode0807.pdf).

†Laboratory evidence of possible Zika virus infection in mother, fetus, infant, placenta, or umbilical cord: rRT-PCR or immunohistochemical staining positive for Zika virus in any clinical specimen, **OR** Zika virus IgM positive or equivocal and Zika virus plaque reduction neutralization testing (PRNT) of 10 or greater in serum or cerebrospinal fluid (CSF). If PRNT is not performed due to local health department practices, laboratory evidence of possible Zika virus infection includes Zika virus IgM positive, PRNT not performed. For information on laboratory testing of infant samples and interpretation of the results, please see Table 2 below.

*****Prenatal ultrasound measurements based on the Society for Maternal Fetal Medicine Standards, http://www.ajog.org/pb/assets/raw/Health%20Advance/journals/ymob/SMFM%20Statement_Fetal%20microcephaly.pdf

[‡]Prenatal findings should be confirmed by postnatal evaluation when possible. A suspected brain abnormality noted on prenatal evaluation that is clearly not present on postnatal evaluation should not be included.

Reporting notes:

- Reporting should make clear that reported selected birth defects are not necessarily caused by Zika virus infection
- Reported numbers may increase or decrease as preliminary information is clarified

Plan for routine review of birth defects in both systems:

- Preliminary data will be reported on a weekly basis
- Every month: Infants with select birth defects will be reviewed to determine whether important information is missing
- Every 3 months, summary data on all defects (combined from all reporting jurisdictions) will be reviewed by clinical geneticist(s) to determine if a pattern is emerging

Table 2: Interpretation of results of laboratory testing of infant's blood, urine and/or cerebrospinal fluid for evidence of congenital Zika virus infection

Infant test results*		
rRT-PCR	**IgM**	**Interpretation**
Positive	Positive or Negative	Confirmed congenital Zika virus infection
Negative	Positive	Probable congenital Zika virus infection[+]
Negative	Negative	Negative for congenital Zika virus infection[+]

Abbreviations: rRT-PCR = real-time reverse transcription-polymerase chain reaction; IgM = Immunoglobulin M

*Infant serum, urine or cerebrospinal fluid.

[+]Laboratory results should be interpreted in the context of timing of infection during pregnancy, maternal serology or clinical findings consistent with Zika virus disease in infants, and any confirmatory testing with plaque reduction neutralization testing (PRNT).

Testing recommended for:

1. Infants born to mothers with laboratory evidence of Zika virus infection during pregnancy

2. Infants who have abnormal clinical or neuroimaging findings suggestive of congenital Zika syndrome and a maternal epidemiologic link suggesting possible transmission, regardless of maternal Zika virus test results.

Recommended infant laboratory evaluation:

Zika virus rRT-PCR testing should be performed on both infant serum and urine, and Zika virus IgM enzyme-linked immunosorbent assay (ELISA) should concurrently be performed on infant serum. If CSF is obtained for other studies, rRT-PCR testing for Zika virus RNA and Zika virus IgM should be performed on CSF

Infant laboratory testing for Zika virus should be performed within two days after birth; if testing is performed later, distinguishing between congenital, perinatal, and postnatal infection will be difficult.

Diagnostic Classifications of Congenital Zika Virus Infection:

1. **Congenital Zika virus infection in infant**: Zika virus PCR positive in an infant specimen

2. **Probable congenital Zika virus infection in infant:** Zika virus IgM detected in an infant, without detectable Zika virus RNA. If the infant's initial sample is IgM-positive, but PRNT was not performed on the mother's sample, PRNT should be performed on the infant's initial sample. PRNT should be performed on a sample collected from a child aged ≥18 months whose initial sample was IgM positive if Zika-specific neutralizing antibodies were detected by PRNT on either the infant's or mother's sample. If the infant's initial sample is negative by both IgM ELISA and RT-PCR, but clinical concerns remain (e.g., microcephaly with negative evaluation for other known causes), PRNT at age 18 months can be considered. If PRNT results at 18 months are negative, the child is considered to not have congenital Zika virus infection.

   a. If PRNT results at 18 months are positive, congenital infection is presumed, but postnatal infection cannot be excluded, especially for children living in an area with active Zika virus transmission.

3. **Negative for congenital Zika virus in infant**: Zika virus PCR and IgM negative. However, results should be interpreted in the context of timing of infection during pregnancy, maternal serology or clinical findings consistent with Zika virus disease in infants, and any confirmatory testing with PRNT.