Surveillance for Microcephaly

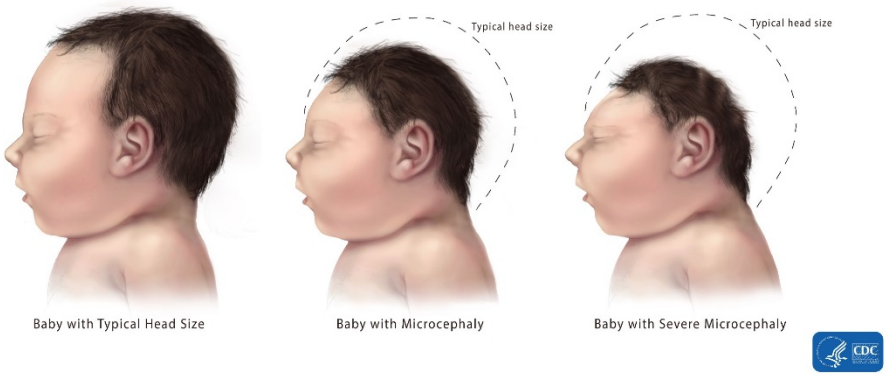
Janet D. Cragan, MD, MPH
Birth Defects Branch, NCBDDD, CDC
February 18, 2016

Outline

- What is microcephaly?
- Surveillance definition
- Causes of microcephaly
- Case ascertainment
- What information to collect
- Estimation of prevalence, monitoring for changes

Microcephaly

- Microcephaly is the clinical finding of a small head compared with infants of the same sex and age, or gestational age if measured at birth
- Head circumference is considered a reliable assessment of the volume of the underlying brain
  - Head circumference (HC) is also known as occipital-frontal circumference (OFC)



Congenital Microcephaly

- Congenital microcephaly is present prenatally or at the time of birth/delivery
  - Abnormal development of the brain (often genetic)
  - Arrest or destruction of normally-forming brain (e.g., infection, vascular disruption)
- Acquired microcephaly develops after birth due to a delivery complication or postnatal insult, trauma or infection
  - HC is normal at birth
  - As the baby grows in length, the head becomes comparatively smaller

AP Photo/Felipe Dana

Types of Microcephaly

- Disproportionate - Head is small out of proportion to the weight and length, which may be normal for age and sex
- Proportionate - Head size, weight and length all are small for age and sex but proportional to each other
- "Relative" microcephaly - Head size measures within the normal range for age and sex, but is small out of proportion to the weight and length
- Prenatal diagnosis of microcephaly
  - Can be detected on mid-pregnancy anomaly scan (ultrasound) at 18-20 weeks
  - May not be evident until the late 2nd or into the 3rd trimester
  - Usually present by 36 weeks gestation
  - Serial prenatal ultrasounds may be needed to detect the development of microcephaly *in utero*.

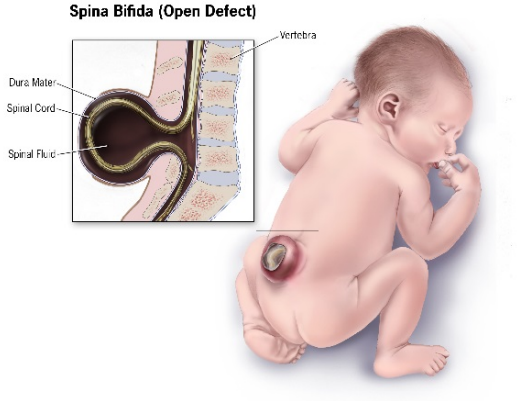
Other Birth Defects with Abnormal Head Size

Anencephaly

- Failure of the neural tube to close resulting in failure of the brain and skull to form

Spina bifida

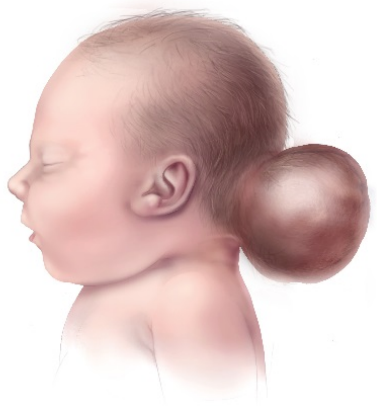
- Failure of neural tube closure resulting in an opening in the spine
- Can occur anywhere along the spine



Other Birth Defects with Abnormal Head Size

Encephalocele

- A sac-like protrusion of the brain and membranes that cover it through an opening in the skull
- Can have other brain and face defects

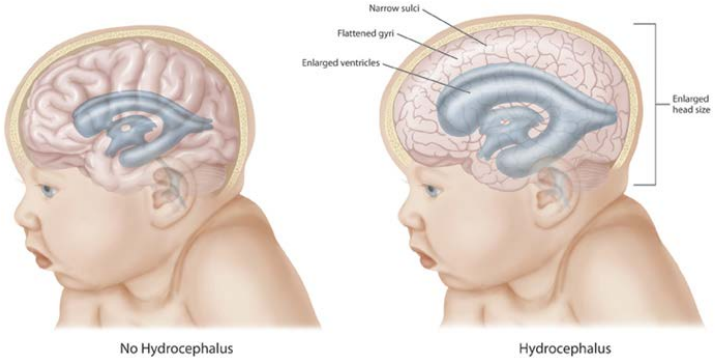


Holoprosencephaly/Arrhinencephaly

- Failure of the brain to fully divide into two cerebral hemispheres and other parts

Hydrocephalus

- Accumulation of fluid in the brain
- Enlarged ventricles and skull

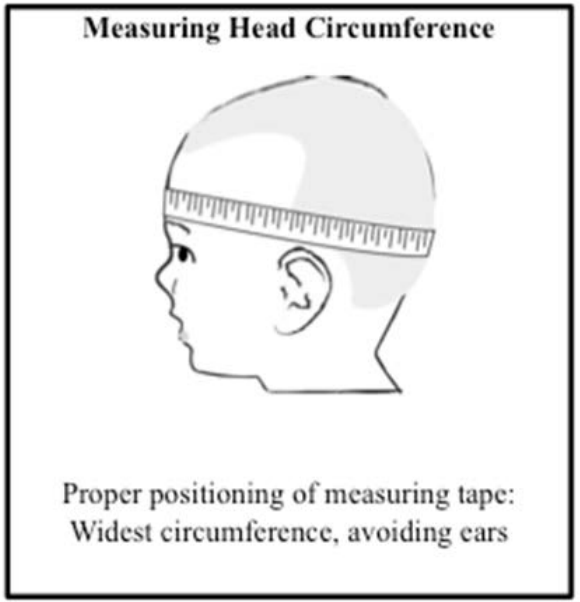


Brain Abnormalities That Can Occur with Congenital Microcephaly

- Intracranial calcifications
- Hydrocephalus ex-vacuo
  - Damaged brain matter shrinks and is surrounded by fluid
- Hydranencephaly
  - Damaged brain matter replaced by pockets of fluid
- Pachygyria, lissencephaly
  - Abnormal ridges and folds (gyri) in the brain

Measuring Head Circumference (WHO*)

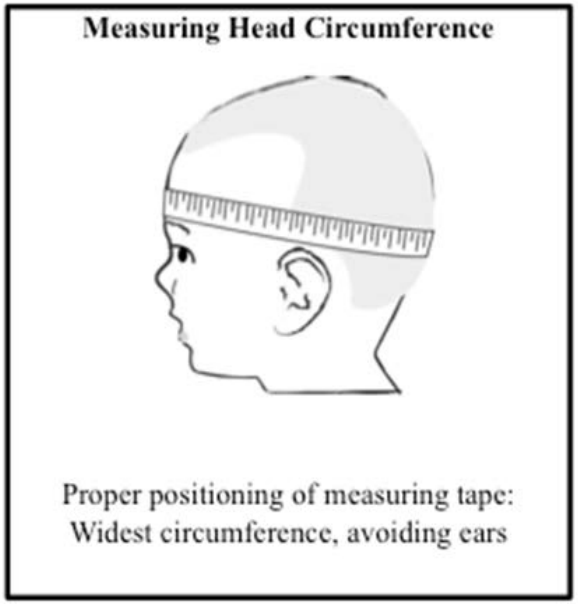
- Use a measuring tape that cannot be stretched
- Securely wrap the tape around the widest possible circumference of the head
  - 1-2 finger-widths above the eyebrow on the forehead
  - At the most prominent part of the back of the head
- Take the measurement three times and select the largest measurement to the nearest 0.1 cm



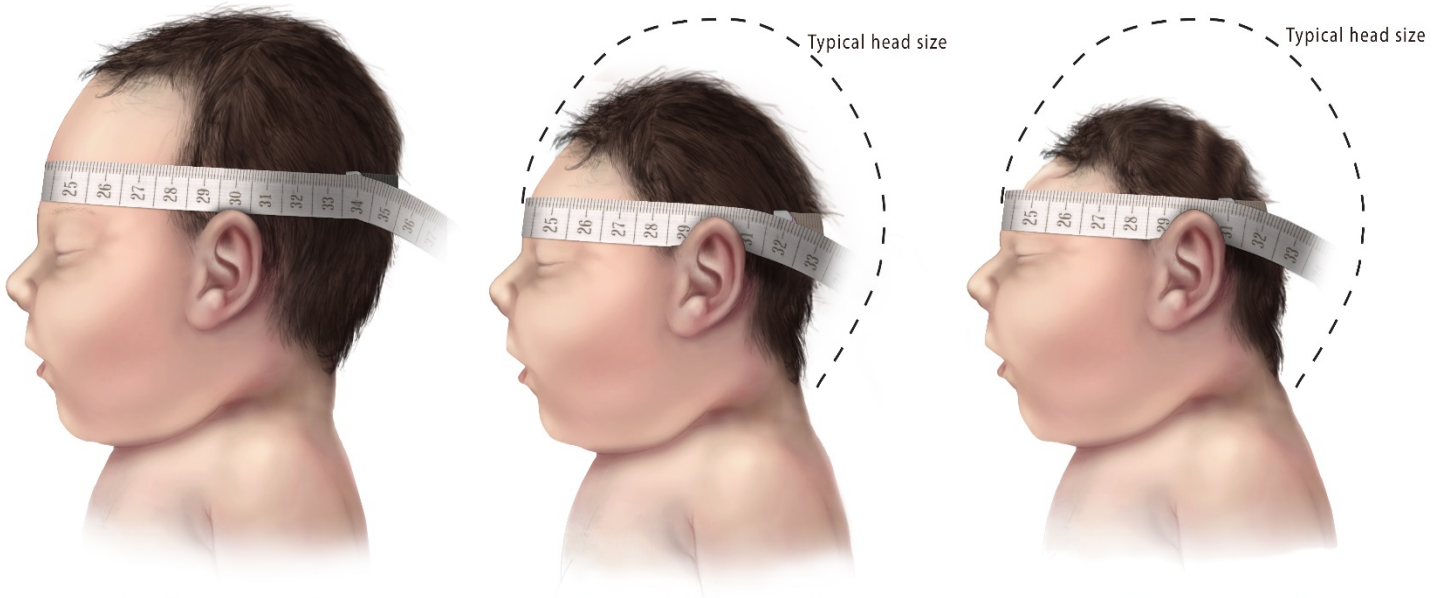
* World Health Organization

When to Measure Head Circumference

- Although HC measurements may be influenced by molding and other factors related to delivery, most commonly-used HC reference charts by age and sex are based on measurements taken before 24 hours of life.
  - If measurement within the first 24 hours of life is not done, the HC should be measured as soon as possible after birth.



Measuring Head Circumference



Baby with Typical Head Size

Baby with Microcephaly

Baby with Severe Microcephaly

Definition of Congenital Microcephaly

Definite

- Live Births
  - HC at birth < 3rd percentile for gestational age and sex, OR
  - If HC at birth is not available, HC <3rd percentile for age and sex within the first 6 weeks of life, adjusted for gestational age if preterm
- Stillbirths and Elective Terminations
  - HC at delivery < 3rd percentile for gestational age and sex

Possible

- Live Births
  - If an earlier HC is not available, HC < 3rd centile for age and sex beyond 6 weeks of life
- All Pregnancy Outcomes
  - Microcephaly diagnosed or suspected on prenatal ultrasound in the absence of available postnatal HC measurements

Definition of Congenital Microcephaly

- These is no single universally accepted definition of congenital microcephaly
  - Some clinicians use different cut-points
    - E.g., less than 5th or less than 10th percentile for age and sex
  - Include these children in surveillance data, along with relevant HC measurements, if the medical record states they have congenital microcephaly
- Children for whom no HC measurement is available but the medical record states they have congenital microcephaly should be included in surveillance data
- Surveillance staff should not assign a diagnosis of microcephaly based only on the HC value in the medical record without mention of the diagnosis

Suggested Reference Charts for Head Circumference at Birth by Gestational Age

Gestational Age at Birth	Reference Chart	Web Link
33 to 43 Weeks	INTERGROWTH-21st Newborn Size at Birth Chart	https://intergrowth21.tghn.org/articles/intergrowth-21st-newborn-size-birth-chart/ A tool for calculating percentiles for head circumference for infants 33-42 weeks is available at: https://intergrowth21.tghn.org/global-perinatal-package/intergrowth-21st-comparison-application/
24 to 32 Weeks	INTERGROWTH-21st Very Preterm Size at Birth References	https://intergrowth21.tghn.org/articles/intergrowth-21st-very-preterm-size-birth-references-and-z-scores-standard-deviations/ A tool for calculating percentiles for head circumference for infants 24-32 weeks is also available from this site.
< 24 Weeks	INTERGROWTH-21st Fetal Growth Standards	https://intergrowth21.tghn.org/articles/intergrowth-21st-fetal-growth-standards/ A tool for calculating z-scores for fetal growth standards is also available from this site.

Intergrowth-21st Fetal Growth Standards are based on measurements *in utero* only. International standards for birth measurements in infants less than 24 weeks gestation are not available. For most elective pregnancy terminations and many stillbirths, accurate postnatal head circumference measurements are not possible.

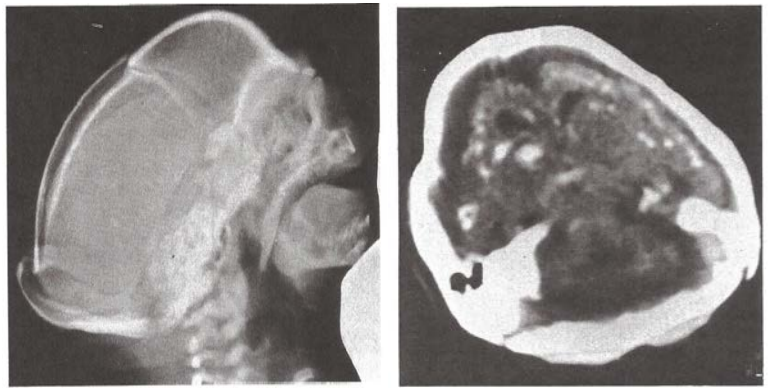
For a study comparing head circumference measurements in utero to those obtained after birth, see: Melamed N, Yogev Y, Danon D, et al. Sonographic estimation of fetal head circumference: how accurate are we? Ultrasound Obstet Gynecol 2011

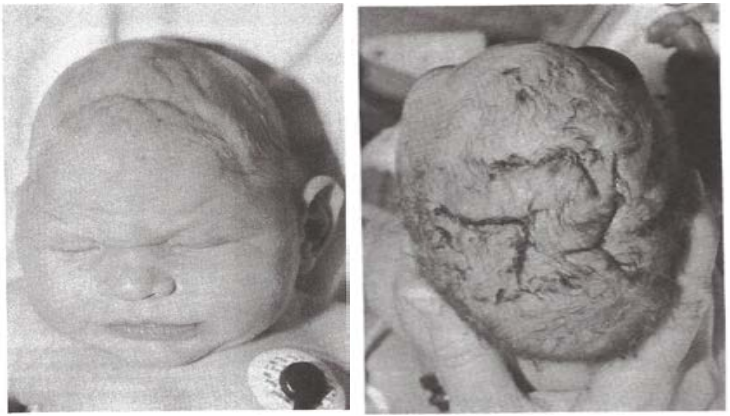
Additional Resources for Growth Charts

- Fenton TR and Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatrics* 2013;13:59-72.
- Olsen IE, Groveman SA, Lawson L, et al. New Intrauterine Growth Curves Based on United States Data. *Pediatrics* 2010;125:e214-e224.
- Villar J, Giuliani F, Bhutta ZA, et al. Postnatal growth standards for preterm infants: the preterm postnatal follow-up study of the INTERGROWTH-21st Project. *Lancet Glob Health* 2015;3:e681-691. Charts available at: https://intergrowth21.tghn.org/articles/new-intergrowth-21st-international-postnatal-growth-standards-charts-available/
- World Health Organization Child Growth Standards for birth to 5 years are available at: http://www.who.int/childgrowth/standards/en/
- Tools to calculate percentiles for weight, length, and head circumference by sex and gestational age or postnatal age based on several of these data are available at: http://peditools.org/

Fetal Brain Disruption Sequence

- First described in 1984 but noted in earlier literature
- Brain destruction resulting in collapse of the fetal skull, microcephaly, scalp rugae and neurologic impairment
- Photos and x-ray from 1990 series*; phenotype appears to be present in affected babies in Brazil





*Moore, et al. J Pediatr 1990;116:383-386.

Causes of Microcephaly That Are Present at Birth

- *In utero* infection
  - Toxoplasmosis
  - Rubella
  - Cytomegalovirus (CMV)
  - Herpes
  - Human Immunodeficiency Virus (HIV)
  - Syphilis
  - Zika?

Causes of Microcephaly That Are Present at Birth

- Genetic causes
  - Single gene disorders (syndromes)
  - Chromosomal abnormalities, microdeletions, microduplications
  - Mitochondrial mutations
- *In utero* ischemia/hypoxia (e.g., placental insufficiency or abruption)
- Teratogens (e.g., maternal alcohol, hydantoin)
- Radiation
- Mercury (e.g., fish and seafood)
- Maternal conditions (e.g., poorly controlled diabetes, hyperphenylalaninemia)

Goals of Microcephaly Surveillance

- Identify all infants in the population diagnosed with congenital microcephaly that is present at birth/delivery
- Estimate the prevalence of congenital microcephaly over recent years (baseline)
- Monitor the frequency of congenital microcephaly going forward to assess for increases that might reflect Zika virus infection during pregnancy

Ascertainment Sources

- Where deliveries occur
  - Birth hospitals, birthing centers/midwifery practices, home births
  - Where elective terminations are performed after prenatal diagnosis of defects
- Information available on vital records (HC, microcephaly)?
- Where children with microcephaly are seen and evaluated
  - Pediatricians, family practitioners
  - Subspecialty clinics (neurology, genetics)
  - Developmental clinics, early intervention programs
- Reporting by health care providers and programs
  - May need to revise reporting forms to include information specific to microcephaly

Ascertainment Sources

- Will data sources be able to retrospectively identify children with microcephaly born in recent years?
  - ICD-9-CM code 742.1; ICD-10-CM code Q02
- Need to educate the healthcare community about microcephaly and why reporting is important
  - Need to measure and record HC for every child born regardless of the setting
  - Increased awareness and reporting alone might increase the observed prevalence
- Provide feedback and ongoing updates to maintain reporting and ascertainment going forward

Information to Collect

- Identifying information (child, parents, physicians)
  - Follow up affected children over time, assess where cases are occurring
- Maternal information
  - Date of last menstrual period (LMP) and estimated date of delivery (EDD) for gestational age estimate
  - Chronic and acute conditions during pregnancy (e.g., diabetes, epilepsy, infections)
  - Timing and results of prenatal testing (e.g., ultrasound, amniocentesis)
    - Earliest dating ultrasound (for gestational age estimate)
    - Normal results are informative
  - Pregnancy complications (e.g., placental abruption)
  - Maternal exposures
    - Medications
    - Mercury

Information to Collect

- Infant/fetal information
  - Outcome - live birth, fetal death, elective termination after prenatal diagnosis
  - Measurement of weight, length, and HC at delivery and at later ages
    - Include date and child's age with each measurement
  - Gestational age assigned at delivery, infant sex
  - Any birth complications (e.g., respiratory distress, sepsis, meningitis)
  - Findings on physical exam, including all major and minor defects
  - Evaluations performed for microcephaly – date, results
    - E.g., cranial ultrasound, CT or MRI scan (intracranial calcifications)
  - Results of newborn hearing screening
  - Subspecialty evaluations – date, results
    - E.g., neurology, ophthalmology, genetics, audiology
  - Results of genetic testing (e.g., karyotype, microarray, FISH)

Information to Collect

- Results of any Zika virus testing
  - Zika virus testing may be done at CDC or at a state health laboratory, and results may not be available in the medical record
  - Testing of maternal serum during pregnancy or after delivery, amniotic fluid, cord blood, infant serum, and cerebrospinal fluid after birth
    - Zika virus RNA by reverse transcriptase-polymerase chain reaction (RT-PCR)
    - Zika virus-specific immunoglobulin (Ig) M and neutralizing antibodies
  - Histopathologic evaluation of fixed and frozen tissue from the placenta and umbilical cord
    - Zika virus immunohistochemical staining
    - Zika virus RNA by RT-PCR

Information to Collect

- Results of testing for other *in utero* virus infections
  - Testing of maternal serum during pregnancy or after delivery for virus-specific IgM and IgG antibodies
  - Testing of cord blood and/or infant serum for virus-specific IgM and IgG antibodies
  - Infant urine culture for cytomegalovirus (CMV)

Assessing Prevalence

- Numerator: Number of live births, stillbirths >= 20 weeks, and elective terminations at any gestational age with congenital microcephaly
- Denominator: Total number of live births in the population
- Usually estimated per 10,000 live births
- Year-to-year variation in prevalence due to limited size of total population
  - Data from 2013-2015 or earlier years can provide an indication of the yearly variation to be expected
  - Prevalence of microcephaly in U.S. varies from 2 to 12 cases per 10,000 live births among state-based birth defects programs
- Goal of the surveillance is to identify a large increase in prevalence (e.g., 3- to 5-fold or more) that might reflect an increase in Zika virus infection *in utero*

Metropolitan Atlanta Congenital Defects Program

Year	# Microcephaly Cases	# Live Births	Prevalence per 10,000
Year 1	18	38779	4.6
Year 2	20	38243	5.2
Year 3	18	38215	4.7
Year 4	17	39088	4.3
Year 5	24	39837	6.0
Year 6	30	40259	7.5
Year 7	38	40900	9.3
Year 8	37	42903	8.6
Year 9	46	44933	10.2
Year 10	38	47015	8.1
Year 11	32	50019	6.4
Year 12	36	50746	7.1
Year 13	39	50543	7.7
Year 14	23	51676	4.5
Year 15	27	51808	5.2
Year 16	45	53276	8.4
Year 17	26	56070	4.6

Metropolitan Atlanta Congenital Defects Program

Microcephaly

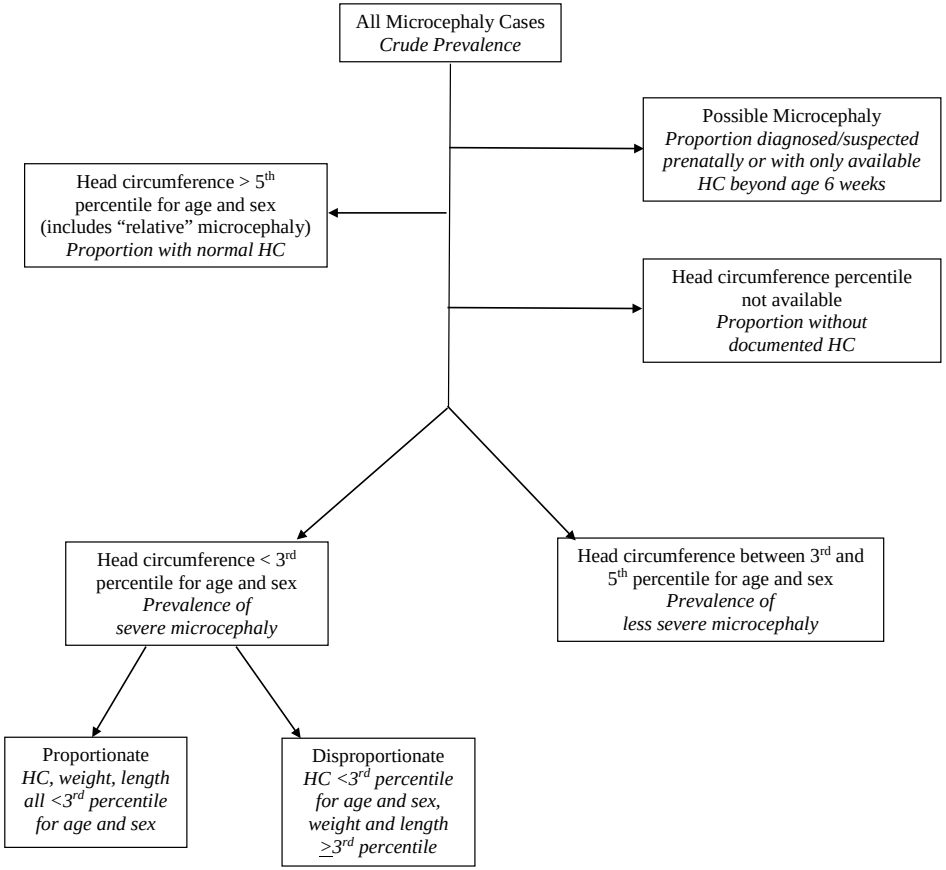
Year	# Live Births	All Cases with Microcephaly	Prevalence per 10,000	Microcephaly without Identified Cause*	Prevalence per 10,000
2007	56466	20	3.5	11	1.9
2008	54234	33	6.1	22	4.1
2009	51936	32	6.2	21	4.0
2010	48994	47	9.6	25	5.1
2011	49220	45	9.1	29	5.9
2012	34945	23	6.6	11	3.1
2013	35014	27	7.7	17	4.9
Total	330809	227	6.9	136	4.1

*Excludes cases with microcephaly and any neural tube defect; holoprosencephaly; craniosynostosis; bilateral renal agenesis; skeletal dysplasia; congenital cytomegalovirus infection (suspected or proven); any chromosomal abnormality; fetal alcohol syndrome (suspected or proven); or any clinical syndrome (suspected or proven)

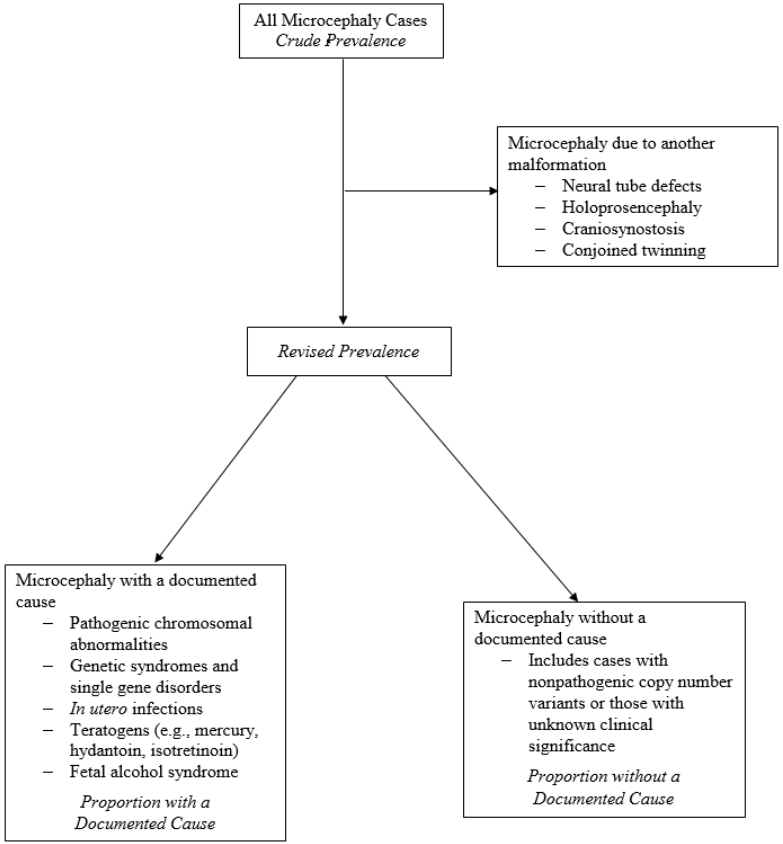
Assessing Prevalence

- Subdivide the cases of microcephaly into groups
  - Severity of microcephaly
    - HC < 3rd percentile for age and sex
    - HC between 3rd and 5th percentiles for age and sex
    - HC > 5th percentile for age and sex
    - HC values missing
  - Known (documented) causes
    - Chromosomal or genetic abnormalities
    - Syndromes (diagnosed or suspected)
    - *In utero* infections and types (positive culture or antibody titers)
    - Exposure to a known teratogen (e.g., alcohol, hydantoin)
  - No documented cause
- Monitor the relative proportion of each group over time

Prevalence of Congenital Microcephaly By Severity



Prevalence of Microcephaly By Documented Cause



Microcephaly and Zika

What we know

- Small number of positive test results for Zika virus infection in infants with microcephaly
- Microcephaly pattern consistent with Fetal Brain Disruption Sequence
  - Based on photos/scans of a small number of affected infants from Brazil
  - Retrospective investigation in French Polynesia outbreak in 2013-2014
  - Infants with other intrauterine infections such as cytomegalovirus (CMV)

What we don't know

- Causal relation between Zika virus and microcephaly or other adverse pregnancy outcomes
- Full spectrum of phenotypes in affected infants
- Impact of timing of infection during pregnancy
- Impact of severity of maternal infection
- Magnitude of the possible risk of microcephaly and other adverse pregnancy outcomes

Acknowledgments

Pamela Costa
Suzanne Gilboa
Margaret Honein
Cara Mai
Cynthia Moore
Jennita Reefhuis
Diana Valencia

National Birth Defects Prevention Network: http://nbdpn.org/
CDC Zika website: http://www.cdc.gov/zika/index.html