Editorial
Brain Malformation Surveillance in the Zika Era

The current surveillance systems for congenital microcephaly are necessary to monitor the impact of Zika virus (ZIKV) on the developing human brain, as well as the ZIKV prevention efforts. However, these congenital microcephaly surveillance systems are insufficient. Abnormalities of neuronal differentiation, development and migration may occur among infants with normal head circumference who have intrauterine exposure to ZIKV. Therefore, surveillance for congenital microcephaly does not ascertain many of the infants seriously impacted by congenital ZIKV infection. Furthermore, many infants with normal head circumference and with malformations of the brain cortex do not have clinical manifestations of their congenital malformations until several months to many years after birth, when they present with clinical manifestations such as seizures/epilepsy, developmental delays with or without developmental regression, and/or motor impairment. In response to the ZIKV threat, public health surveillance systems must be enhanced to ascertain a wide variety of congenital brain malformations, as well as their clinical manifestations that lead to diagnostic brain imaging.

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ZIKV poses a threat to the developing human brain (Johansson et al., 2016; Reefhuis et al., 2016), the spectrum and significance of which may be greater than any such threat in the United States for several generations. This is not the first time that surveillance systems were inadequate and required an upgrade to address a major public health concern. In fact, great public health surveillance programs often develop in response to public health crises. For example, the Metropolitan Atlanta Congenital Defects Program (MACDP) was established in 1967 to provide an early warning system for changes in the birth prevalence of congenital malformations, largely in response to the epidemic of thalidomide-associated birth defects (Correa et al., 2007).

MACDP, and birth defects surveillance programs from multiple states, provided surveillance data for the National Birth Defects Prevention Study (CDC, 2015), monitored major prevention efforts including rubella immunization, identified new risk factors for Down syndrome, congenital heart malformations and numerous other birth defects, and provided baseline birth prevalence data on neural tube defects essential for monitoring the effects of mandatory fortification of enriched grains with folic acid (Correa et al., 2007). The MACDP model of birth defects surveillance in states throughout the United States also provided a platform for establishing the Metropolitan Atlanta Developmental Disabilities Study (MADDS)—the first major surveillance system for developmental disabilities (Yeargin-Allsopp et al., 1992), which in turn provided a foundation for establishing the Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP) (Yeargin-Allsopp et al., 2003), and later the national Autism and Developmental Disabilities Monitoring Network (ADDM) (Christensen et al., 2016). Surveillance systems designed to monitor congenital brain malformations are needed to monitor the impact of congenital ZIKV infection and the congenital ZIKV response, as well as other potentially unrecognized threats to the developing human brain.

In utero Zika virus Infection, Congenital Microcephaly, and Brain Malformations

Since the epidemic of ZIKV-associated microcephaly was recognized in Brazil in 2015, ZIKV has spread by means of mosquito- and sexual-transmission throughout South America, Central America, and the Caribbean. Some experts anticipate that the probable near-future spread of

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ZIKV will be within areas where there is current local transmission of dengue and/or of chikungunya, viruses also spread by the *Aedes* mosquito. Yet the longer-term geographic range of congenital ZIKV infection may be significantly greater, given the extensive range of the *Aedes* mosquito and the combined mosquito- and sexual transmission of ZIKV (Petersen et al., 2016). The known combined range of *Aedes aegypti* and *Aedes albopictus* includes much of the eastern and southwestern regions of the United States (Hahn et al., 2016). As of September, 2016 local mosquito transmission of ZIKV has been documented in several areas of Florida (Boeuf et al., 2016), local sexual transmission of ZIKV has been verified in Maryland (Brooks et al., 2016), and other states throughout the southeastern United States are preparing for local spread of ZIKV. Given that an estimated 80% of adults with ZIKV infection are asymptomatic (Meaney-Delman et al., 2016), and that pregnant women are not currently being systematically screened for ZIKV, the current estimates of the numbers of ZIKV-infected pregnant women are probably under-estimates.

The spatial-temporal relationship between the congenital microcephaly outbreak in Brazil and ZIKV infection of the developing fetus supports a causal association (Cauchemez et al., 2016; Reefhuis et al., 2016; Johansson et al., 2016). ZIKV has been isolated from the placentas of mothers who had clinical ZIKV infections during pregnancy, and from the brains of newborns with congenital microcephaly in the ZIKV outbreak areas in Brazil (Mlakar et al., 2016; Driggers et al., 2016; Martines et al., 2016). A causal relationship between *in utero* ZIKV infection and congenital microcephaly is now widely accepted (Rasmussen et al., 2016).

ZIKV invades fetal neural progenitor cells and causes brain abnormalities by at least two general mechanisms: (1) direct destruction of neuronal progenitor cells and developing neurons, and (2) disruption of the differentiation, development, and migration of neurons in the developing brain (Garcez et al., 2016; Qian et al., 2016; Sarno et al., 2016; Tang et al., 2016; Cugola et al., 2016; Li et al., 2016). Both the Brazilian ZIKV strain and the Asian ZIKV strain cause abnormal cortical development in mice (Cugola et al., 2016; Li et al., 2016) that would be consistent with multiple different types of cortical malformations in human infants exposed *in utero* to ZIKV among both those with congenital microcephaly and those with normal head circumferences at birth. Therefore, it was not surprising when several different types of brain malformations were recently reported among infants exposed *in utero* to ZIKV, including polymicrogyria with schizencephalic clefts, areas of thickened cortex, areas of thinning cortex, and focal cortical dysplasia, often with asymmetry and with different types of malformations and/or brain injury in the same infant, and occurring among infants with congenital microcephaly as well as among some infants with normal head circumference at birth (de Oliveria-Szejnfeld et al., 2016).

TABLE 1. *Predicted Clinical Neurological Manifestations of Congenital Zika Infection*

Neonates with congenital microcephaly
• Profound motor and cognitive impairment
• Profound intellectual disability
• Some with cerebral palsy
• Cortical visual impairment
• Cortical auditory impairment
• Oral-motor impairment
• May worsen during first few months
• Feeding problems and aspiration
• High risk of seizures and epilepsy
• Myoclonic seizures
• Infantile spasms
Neonates with normal head circumference
• Deceleration of head growth with “acquired microcephaly”
• Less severely affected children may retain normal head size
• Developmental delay
• One or more domains
• Consistent with localization of lesion(s)
• High risk of seizures and epilepsy during first two years of life
• Neonatal seizures
• Myoclonic seizures and infantile spasms
• Onset of epilepsy later in childhood and adolescence

Yet despite reports of brain malformations without congenital microcephaly causally-associated with *in utero* ZIKV infection (Ventura et al., 2016; de Oliveria-Szejnfeld et al., 2016), the diagnostic criteria for congenital Zika syndrome currently includes congenital microcephaly (Franca et al., 2016). A systematic search for brain malformations among infants with *in utero* exposure to ZIKV and with normal head circumference at birth has not been reported; we do not know the birth prevalence of congenital brain malformations due to ZIKV. Monitoring the birth prevalence of congenital microcephaly will not be a sufficient measure of the burden of ZIKV brain abnormalities in the general population of children and adolescents.

The anticipated clinical manifestations of ZIKV-associated congenital brain malformations may be predicted from the prior experience with these types of malformations (Table 1). Newborns with congenital microcephaly will tend to have profound motor and cognitive impairment; most will suffer from profound intellectual disability, and many will meet diagnostic criteria for cerebral palsy. In addition, these infants with congenital

microcephaly will have a high risk of cortical visual impairment, cortical auditory impairment, oral-motor dysfunction with a high risk of aspiration and pneumonia, and a very high risk of seizures and epilepsy.

Among newborns with congenital ZIKV infection and with normal head circumferences, pathological processes that disrupt neuronal differentiation and migration may cause abnormalities of brain development (e.g., cortical dysplasia, polymicrogyria) that may clinically manifest only after several months to years of postnatal brain development and maturation (Table 1). For example, infants with normal head circumferences at birth may have congenital brain malformations such as focal cortical dysplasia that are typically undiagnosed until they develop seizures, intellectual disability, or other neurological symptoms of their brain malformations, and are referred to pediatric neurologists or other specialists during the first few years of life, adolescence, or young adulthood (Guerrini and Barba 2010; Gaitanis and Donahue 2013).

Current State of Congenital Brain Malformation Surveillance

Because current birth defects surveillance systems, and the subsequent epidemiology studies, do not include sufficient brain anatomical details to classify any brain malformations (other than anencephaly, hydranencephaly, and some types of hydrocephalus), the epidemiology of congenital brain malformations is in its infancy, and many of the causes of congenital brain malformations likely remain undiscovered. We do not have reasonable birth prevalence estimates, or trends in these birth prevalence estimates, for any of the major congenital brain malformations caused by *in utero* exposure to ZIKV, even though these types of congenital brain malformations may be seen with other types of congenital infections, such as congenital cytomegalovirus (White et al., 2014).

The lack of robust data collected in brain malformation surveillance is largely due to the lack of neuroimaging technology available when MACDP was started in 1967, a time when the neonatal brain was still largely unexplored, other than limited neuropathology postmortem studies (Chi et al., 1977), and a time when modern neuroimaging was not routinely used in clinical practice. Throughout the United States we are now able to visualize basic neonatal brain structures at the bedside with ultrasound. Computed tomography (CT) scans and MRI scans are available in many neonatal clinical care settings. MRI is the preferred neuroimaging technique for visualizing brain malformations in most clinical situations. Over the past 40 to 50 years the field of neuroimaging has expanded dramatically, and brain malformations surveillance has not kept up with the clinical technology.

In contrast to the surveillance of congenital brain malformations, congenital heart defects surveillance has provided trends in specific heart malformations, and has enriched the epidemiologic research of congenital heart disease, for decades. The basic diagnostic tools for differentiating the various congenital heart defects were routinely used in clinical practice in the early years of MACDP and other population-based birth defects surveillance systems, and these anatomical details have been incorporated into congenital heart defects epidemiology. Congenital heart defects surveillance has provided trends in the birth prevalence of over twenty specific defects such as Tetralogy of Fallot, hypoplastic left heart, pulmonary atresia, ventricular septal defects, and transposition of the great arteries (Mai et al., 2012). Data from birth defects surveillance systems in the United States have also allowed for etiologic studies of congenital heart defects (Malik et al., 2008; Gilboa et al., 2010; Hartman et al., 2011), and provided a basis for long-term follow-up studies (Marelli et al., 2014).

Arguably congenital brain malformations are much more complex and varied than are congenital heart defects, and yet the surveillance data collected on congenital brain malformations represents a dramatic oversimplification of the biological and clinical reality. There are many different types of brain malformations (Table 2), each with different clinical manifestations that typically vary based upon the localization and lateralization of the specific malformations. Yet surveillance of brain malformations has only followed trends in anencephaly,

TABLE 2. *Basic Classification Congenital Cortical Malformations (Barkovich et al. 2012)*

Group 1. Malformations secondary to abnormal neuronal and glial proliferation or apoptosis
I.A. Microcephaly
I.B. Megalencephalies
I.C. Cortical dysgenesis with abnormal cell proliferation
Group 2. Malformations due to abnormal neuronal migration
II.A. Heterotopia
II.B. Lissencephaly
II.C. Subcortical heterotopia and sublobar dysplasia
II.D. Cobblestone malformations
Group III. Malformations secondary to abnormal postmigrational development
III.A. Polymicrogyria and schizencephaly
III.B. Polymicrogyria without schizencephalic clefts
III.C. Focal cortical dysplasias
III.D. Postmigrational microcephaly

microcephaly, and hydrocephalus (Correa et al., 2007) – all abnormalities that can be diagnosed at birth with 1960's technology. Although surveillance of neural tube defects (NTDs), including anencephaly, has played an important role in the reduction of folic acid responsive NTDs (Agopian et al., 2012), the overall impact of public health surveillance of congenital brain malformations has been quite modest. Simply stated, surveillance of the frequency of major types of congenital brain malformations based upon modern classifications of brain malformations and routine diagnostic technology is nonexistent in the United States and around the world.

Development of Congenital Brain Malformations Surveillance

The development of congenital brain malformation surveillance will require a major departure from typical birth defects surveillance methods, and has two major challenges that must be independently addressed. First, the level of complexity of the developing brain, and a shortage of neuroradiology expertise at the community level, makes it currently impossible to consistently receive reliable and accurate reports of brain imaging from multiple different clinical care sites in communities. Clinical trials of pediatric stroke, pediatric epilepsy, and other childhood neurological disorders have used neuroimaging experts within a central coordinating center or diagnostic core to review actual brain imaging data to properly classify brain anatomical details in a consistent and systematic manner across study sites (DeBaun et al., 2014). Such a central reading of brain images for congenital brain malformation surveillance will likely be essential, and it will be necessary for surveillance systems to obtain digital copies of neuroimaging data as a component of medical record abstraction.

Second, epidemiologists typically consider birth defects to be those congenital disorders whose diagnoses and/or clinical symptoms are manifest at birth, or soon thereafter. However, congenital brain malformations, especially among those who have a normal head circumference at birth, are often not manifest for many months or years after birth (Table 1). Brain imaging is then performed when the child presents with clinical symptoms of the malformation(s), leading to the first diagnosis of a birth defect typically several months to years of life. Therefore, surveillance of brain malformations must include those developmental brain abnormalities that are diagnosed as a cause of epilepsy (e.g., infantile spasms, focal epilepsies) and other types of neurodevelopmental disorders (e.g., intellectual disabilities, learning disabilities, motor impairment, autism) at several months to years of life.

Clinical practice today should allow us to conduct population-based surveillance of major brain malformation categories that can be identified with clinically available neuroimaging (Table 2). Although fetal MRI is not able to ascertain all subtle cortical malformations identified later in childhood and adolescence, fetal MRI is now able to detect many malformations late in gestation, including polymicrogyria with schizencephalic clefts (Glenn et al., 2012), which is one of the malformations reported in association with ZIKV (de Fatima Vasco Aragao et al., 2016). Neonatal brain ultrasound and CT scan can reliably detect agenesis of the corpus callosum, thinning of the corpus callosum (often a marker for other abnormalities of cortical migration not easily seen on routine neuroimaging), and large cortical abnormalities such as schizencephaly. MRI is required to detect abnormalities such as polymicrogyria, heterotopia, and focal cortical dysplasias in newborns, infants, and children (Gupta et al., 2016). The CDC is now recommending neuroimaging of all newborns who are thought to have been exposed to ZIKV during pregnancy (Russell et al., 2016). Major clinical societies will almost certainly develop their own practice guidelines for the proper specialty evaluation, including neuroimaging, of neonates, infants and children suspected of *in utero* exposure to ZIKV.

The genetics of brain malformations is a field itself, and is quite complex (Barkovich et al., 2012). Once limited to research centers, now extensive genetic testing in children with brain malformations is part of routine clinical pediatric neurology practice. Planning neuroimaging data collection with genetic testing data, and ideally epigenetic data, is advised to position surveillance for brain malformations for the future.

CDC guidance regarding ZIKV and the care of pregnant women and infants is under constant review, and will likely undergo future updates. Approximately eighty percent of adults infected with ZIKV are asymptomatic (Boeuf et al., 2016). However, at the time of this writing, CDC does not recommend screening of all pregnant women for ZIKV (CDC, 2016). Therefore, newborns infected with ZIKV *in utero* and with normal head circumference at birth, whose mothers were asymptomatic, may present with neurological manifestations of brain malformations such as developmental delays or seizures during the first year of life (e.g., infantile spasms) or later in childhood (e.g., focal epilepsy); linking their congenital brain malformations to their prior congenital ZIKV infection will be difficult.

Therefore, a relatively complete determination of the burden of *in utero* ZIKV infection should include ascertainment of children with seizures and developmental delays throughout the first few years of life, and then linking these data with ZIKV infection data, perhaps eventually with ZIKV screening data from pregnant women. The U.S. Zika Pregnancy Registry will follow infants to 12 months of age, and could connect seizures and developmental delays to knowledge of ZIKV infection, an important start, but follow-up of these children is needed for several years to ascertain the manifestations of ZIKV-associated brain malformations among children with normal head

circumferences at birth. Changes in clinical practice guidelines regarding screening of pregnant women and infants for ZIKV will likely impact decisions regarding the appropriate surveillance system needs for monitoring congenital brain malformations.

The methods for brain malformation surveillance need to be refined, without assuming that the same system sufficient for collecting (the relatively simple) echocardiogram data will suffice for collecting complex brain imaging data. While brain malformations surveillance systems can be built upon the existing platforms of birth defects surveillance, significant additional funding will be required, including funding for pilot projects.

Data collection for brain malformation surveillance systems must include clinical manifestations of brain malformations during the first several years of life (e.g., developmental delays, developmental regression, and seizures/epilepsy). These surveillance systems will need to ascertain the incident (newly diagnosed) cases of developmental delay, regression or/and seizures over a period of years among the birth cohort(s) of children exposed to *in utero* ZIKV. The current surveillance systems (e.g., the ADDM sites) for determining the prevalence of developmental delays and autism among 8-year-old children within a birth cohort using a cross-sectional methodology (Van Naarden Braun et al., 2008) will not be sufficient for the needs of monitoring for ZIKV-associated neurodevelopmental outcomes.

CONCLUSIONS

Now is the time to develop methods for congenital brain malformation surveillance systems using state-of-the art diagnostic neuroimaging data to monitor the occurrence of new cases of congenital brain malformations. These surveillance systems, built upon the platform of current birth defects surveillance systems, will be an essential component of the fight against congenital ZIKV, and other potential environmental and infectious causes of brain malformations. There are significant logistical, financial, technical, ethical, and political challenges to developing these types of surveillance systems. In addition, clinical and scientific experts in the clinical neuroscience fields will need to join the public health surveillance efforts. These new surveillance systems born out of the current ZIKV public health crisis will both help protect the brains of future generations from ZIKV, and will also likely identify other future potential modifiable risk factors for childhood neurological disability and death.

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