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Prevalence of individual brain and eye defects potentially related to Zika virus in pregnancy in 22 U.S. states and territories, January 2016 to June 2017

Augustina Delaney[1,2], **Samantha M. Olson**[2,3], **Nicole M. Roth**[2], **Janet D. Cragan**[2], **Shana Godfred-Cato**[2], **Ashley N. Smoots**[4], **Jane Fornoff**[5], **Eirini Nestoridi**[6], **Valorie Eckert**[7], **Allison Forkner**[8], **Amanda Stolz**[9], **Katherine Crawford**[10], **Sook Ja Cho**[11], **Amanda Elmore**[12], **Peter Langlois**[13], **Amy Nance**[14], **Lindsay Denson**[15], **Nina Forestieri**[16], **Vinita O. Leedom**[17], **Tri Tran**[18], **Miguel Valencia-Prado**[19], **Paul Romitti**[20], **Jerusha E. Barton**[21], **Kristen St. John**[22], **Sylvia Mann**[23], **Lucia Orantes**[24], **Leah DeWilde**[25], **Van T. Tong**[2], **Suzanne M. Gilboa**[2], **Cynthia A. Moore**[2], **Margaret A. Honein**[2]

[1]Eagle Global Scientific, LLC, San Antonio, Texas, USA

[2]Division of Birth Defects and Infant Disorders, National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, Georgia, USA

[3]G_2S Corporation, San Antonio, Texas, USA

[4]Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, CDC, Atlanta, Georgia, USA

[5]Illinois Department of Public Health, Springfield, Illinois, USA

[6]Massachusetts Department of Public Health, Boston, Massachusetts, USA

[7]California Department of Public Health, Sacramento, California, USA

[8]Indiana State Department of Health, Indianapolis, Indiana, USA

[9]New York State Department of Health, Albany, New York, USA

[10]Virginia Department of Health, Richmond, Virginia, USA

[11]Minnesota Department of Health, St. Paul, Minnesota, USA

[12]Florida Department of Health, Tallahassee, Florida, USA

[13]University of Texas School of Public Health, Austin, Texas, USA

Correspondence: Nicole M. Roth, Division of Birth Defects and Infant Disorders, National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, GA, USA. yhw9@cdc.gov.

AUTHOR CONTRIBUTIONS

Dr Augustina Delaney had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Augustina Delaney, Samantha M. Olson, Nicole M. Roth, Janet D. Cragan, Van T. Tong, Suzanne M. Gilboa, and Cynthia A. Moore. Acquisition, analysis, or interpretation of data: All authors. Drafting of the article: Augustina Delaney, Samantha M. Olson, Nicole M. Roth, Janet D. Cragan, Van T. Tong, and Cynthia A. Moore. Critical revision of the article for important intellectual content: All authors. Statistical analysis: Augustina Delaney and Nicole M. Roth. Administrative, technical, or material support: Shana Godfred-Cato and Ashley N. Smoots. Study supervision: Van T. Tong, Suzanne M. Gilboa, and Suzanne M. Honein.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

[14]Utah Department of Health, Salt Lake City, Utah, USA

[15]Oklahoma State Department of Health, Oklahoma City, Oklahoma, USA

[16]North Carolina Department of Health and Human Services, Raleigh, North Carolina, USA

[17]South Carolina Department of Health and Environmental Control, Columbia, South Carolina, USA

[18]Louisiana Department of Health, Baton Rouge, Louisiana, USA

[19]Puerto Rico Department of Health, San Juan, Puerto Rico, USA

[20]University of Iowa, Iowa City, Iowa, USA

[21]Georgia Department of Public Health, Atlanta, Georgia, USA

[22]Rhode Island Department of Health, Providence, Rhode Island, USA

[23]Hawaii Department of Health, Honolulu, Hawaii, USA

[24]Vermont Department of Health, Burlington, Vermont, USA

[25]U.S. Virgin Islands Department of Health, Charlotte Amalie, Virgin Islands, USA

Abstract

During the Centers for Disease Control and Prevention's Zika Virus Response, birth defects surveillance programs adapted to monitor birth defects potentially related to Zika virus (ZIKV) infection during pregnancy. Pregnancy outcomes occurring during January 2016 to June 2017 in 22 U.S. states and territories were used to estimate the prevalence of those brain and eye defects potentially related to ZIKV. Jurisdictions were divided into three groups: areas with widespread ZIKV transmission, areas with limited local ZIKV transmission, and areas without local ZIKV transmission. Prevalence estimates for selected brain and eye defects and microcephaly per 10,000 live births were estimated. Prevalence ratios (PRs) and 95% confidence intervals (CIs) were estimated using Poisson regression for areas with widespread and limited ZIKV transmission compared with areas without local ZIKV transmission. Defects with significantly higher prevalence in areas of widespread transmission were pooled, and PRs were calculated by quarter, comparing subsequent quarters to the first quarter (January–March 2016). Nine defects had significantly higher prevalence in areas of widespread transmission. The highest PRs were seen in intracranial calcifications (PR = 12.6, 95% CI [7.4, 21.3]), chorioretinal abnormalities (12.5 [7.1, 22.3]), brainstem abnormalities (9.3 [4.7, 18.4]), and cerebral/cortical atrophy (6.7 [4.2, 10.8]). The PR of the nine pooled defects was significantly higher in three quarters in areas with widespread transmission. The largest difference in prevalence was observed for defects consistently reported in infants with congenital ZIKV infection. Birth defects surveillance programs could consider monitoring a subset of birth defects potentially related to ZIKV in pregnancy.

Keywords

birth defects; Zika virus infection; pregnancy; congenital Zika syndrome; population surveillance

1 | INTRODUCTION

Zika virus (ZIKV) was first recognized as a cause of birth defects in 2016 (Rasmussen, Jamieson, Honein, & Petersen, 2016). Subsequently, evidence linking in-utero ZIKV exposure with a unique pattern of brain and eye defects and neurodevelopmental abnormalities has strengthened (Moore et al., 2017). In 2018, additional evidence suggested that neural tube defects and other early brain malformations were not associated with ZIKV infection in pregnancy, and the definition of birth defects potentially related to ZIKV was updated (Delaney et al., 2018; Olson et al., 2019). In addition to microcephaly, structural defects described in infants exposed in-utero to ZIKV include, but are not limited to, intracranial calcifications, cortical/cerebral atrophy, chorioretinal abnormalities, and optic nerve abnormalities (Moore et al., 2017). Much of what is known about specific defects associated with in-utero ZIKV exposure comes from cohort studies and case reports.

Previous analyses of birth defects surveillance data showed a four-fold population-level increase in the prevalence of structural brain and eye defects and microcephaly in areas with widespread ZIKV transmission occurring 6 months after the peak of the outbreak (Smoots et al., 2020). In areas with limited local transmission, prevalence of these defects increased but the increase was not statistically significant. To date, population-level changes in individual structural brain and eye defects have not been described relative to level of community ZIKV transmission in areas with widespread, limited, or without local transmission of ZIKV.

The purpose of this analysis was to evaluate population-based birth defects surveillance data for changes in prevalence of individual defects by levels of ZIKV transmission and examine trends over time. These findings could be used to more accurately capture the spectrum of birth defects associated with in-utero ZIKV exposure during future ZIKV outbreaks and help inform resource allocations for birth defects surveillance.

2 | METHODS

During the Centers for Disease Control and Prevention's (CDC) ZIKV Response, health departments were supported to adapt existing or establish new birth defects surveillance programs to monitor 25 birth defects potentially related to ZIKV infection during pregnancy. Methods have been previously described (Delaney et al., 2018; Smoots et al., 2020) and reviewed by CDC human subjects coordinators and determined to be a nonresearch, public health surveillance activity exempt from institutional review board evaluation. Birth defects included brain defects and microcephaly, eye defects, neural tube defects and early brain malformations, and consequences of central nervous system dysfunction, such as joint contractures and hearing loss. Data were abstracted from maternal and infant medical records and other surveillance sources and submitted to the CDC. Submitted data included birth defects of interst, pregnancy outcome, birth measurements, other cooccurring defects, congenital infections, and any maternal or infant/fetal ZIKV laboratory test results. CDC clinicians reviewed submitted data to determine if brain or eye defects met the revised CDC case definition (Olson et al., 2019). Brainstem abnormalities were categorized as "other brain abnormalities" in the original case definition (Honein, 2017). However, additional evidence has suggested a stronger association between brainstem abnormalities

and in-utero ZIKV exposure (Pool et al., 2019). Submitted records were re-reviewed to identify if brainstem abnormalities including atrophy, calcifications, dysgenesis, or any other abnormality of the brainstem were present and are included in this analysis. All other pregnancy outcomes which only had a defect categorized as meeting the definition for "other brain abnormalities" were excluded from this analysis, as they were not specific enough to be meaningful for surveillance efforts. Finally, information on toxoplasmosis, other infections including syphilis, rubella, cytomegalovirus, herpes simplex, and HIV (TORCH)[1] testing was reviewed, if available, to determine if any congenital infections known to cause birth defects were likely present.

Pregnancy outcomes with defects meeting the revised CDC definition occurring January 1, 2016 to June 30, 2017 reported from 22 U.S. states and territories were included in this analysis. These jurisdictions were included because case ascertainment and review of all cases was complete at the time of analysis. Jurisdictions were divided into three groups based on the level of ZIKV transmission: areas with widespread local ZIKV transmission, areas with limited local ZIKV transmission, and areas without local ZIKV transmission during the study period (Smoots et al., 2020).

Prevalence per 10,000 live births of selected brain and eye defects and microcephaly were calculated. Brain defects included intracranial calcifications, cerebral or cortical atrophy, abnormal cortical gyral patterns, corpus callosum abnormalities, porencephaly, hydranencephaly, ventriculomegaly/hydrocephaly, cerebellar abnormalities, and brainstem abnormalities. Eye defects included microphthalmia, coloboma, congenital cataract, intraocular calcifications, optic nerve abnormalities (e.g., optic nerve atrophy, pallor, and other optic nerve abnormalities), and chorioretinal abnormalities (e.g., atrophy and scarring, gross pigmentary changes, excluding retinopathy of prematurity). Prevalence ratios (PRs) and 95% confidence intervals (CIs) were calculated using Poisson regression to compare the prevalence of defects in areas with widespread local ZIKV transmission and limited local ZIKV transmission to areas without local ZIKV transmission for the entire study period.

The study period was categorized into three-month quarters (January–March 2016, April–June 2016, etc.) to assess whether the prevalence of defects changed or remained stable over time. Because many of the individual birth defects are rare, we pooled birth defects into two groups: Group A and Group B. Group A were birth defects observed to have a significantly different prevalence, based on 95% CIs, in areas of widespread local ZIKV transmission compared with areas without local transmission; Group B were birth defects with comparable prevalence in areas of widespread local ZIKV transmission to areas without local transmission. Prevalence per 10,000 live births was calculated per quarter for each group. PR and 95% CI were calculated for the two groups using the quarter January 1 to March 31, 2016 as the reference quarter for each transmission group.

[1]TORCH testing is set of tests for infectious diseases in pregnant people including toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, HIV, syphilis, hepatitis B, varicella-zoster virus, and parvovirus B19.

3 | RESULTS

Overall, 2,004,630 live births occurred during January 2016 to June 2017 in the 22 U.S. states and territories; of these, 3,221 infants and fetuses had any brain or eye defect or microcephaly identified meeting the case definition. The percentages of pregnancy loss[2] were 3.5% (96/2,781), 4.2% (13/313), and 8.7% (11/127) in areas without transmission, limited transmission, and widespread transmission, respectively. The number of infants/fetuses with evidence of a congenital infection other than ZIKV was 63 (2.3%) in areas without widespread local transmission, 7 (2.2%) in areas with limited local transmission, and none in areas of widespread local transmission of ZIKV (data not shown).

PRs in areas of widespread local transmission compared with areas without local transmission were statistically significant for nine of 16 defects analyzed (Table 1). Prevalence of intracranial calcifications (PR = 12.6, 95% CI [7.4, 21.3]); chorioretinal atrophy, scarring, and pigmentary changes (12.5 [7.1, 22.3]); brainstem abnormalities (9.3 [4.7, 18.4]); cerebral/cortical atrophy (6.7 [4.2, 10.8]); optic nerve abnormalities (3.6 [2.3, 5.6]); abnormal cortical gyral patterns (3.2 [2.2, 4.8]); ventriculomegaly/hydrocephaly (3.0 [2.2, 4.1]); microcephaly (2.9 [2.2, 3.8]); and corpus callosum abnormalities (2.1 [1.6, 3.0]) were higher in areas of widespread local transmission than those without local transmission. Prevalence of ventriculomegaly/hydrocephaly (1.5 [1.2, 1.9]) and corpus callosum abnormalities (1.4 [1.1, 1.8]) was also significantly higher in areas with limited local ZIKV transmission than those without local transmission. Prevalence of porencephaly (2.4 [1.1, 5.1]) and microphthalmia (1.6 [1.1, 2.4]) were significantly higher in areas of limited but not widespread local ZIKV transmission.

The prevalence of Group A defects was significantly higher in three quarters, July–September 2016 (3.0 [1.3, 7.0]), October–December 2016 (3.5 [1.5, 8.1]), and January–March 2017 (5.4 [2.4, 12.3]) in areas of widespread local ZIKV transmission compared with the reference quarter but remained stable in other ZIKV transmission areas (Table 2). No significant change in prevalence over time was observed for Group B defects in any of the three ZIKV transmission areas.

4 | DISCUSSION

Most individual brain and eye defects examined had significantly higher prevalence in areas with widespread ZIKV transmission compared with areas without local transmission. When these defects were pooled together (i.e., Group A), significantly higher prevalence was found in three of five quarters. A similar pattern was observed by Smoots et al. (2020), which examined all 16 brain and eye defects together and found an increase in prevalence in the same time periods. For Group B birth defects, those defects without significant differences between areas with and without widespread local ZIKV transmission, the prevalence over the study period remained relatively stable. This suggests that the nine pooled brain and eye defects (i.e., intracranial calcifications, chorioretinal abnormalities,

[2]Pregnancy losses included miscarriages, fetal deaths, and terminations. Not all birth defects surveillance programs were able to ascertain pregnancy losses.

brainstem abnormalities, cerebral cortical atrophy, optic nerve abnormalities, abnormal cortical gyral patterns, ventriculomegaly/hydrocephaly, microcephaly, and corpus callosum abnormalities) are primarily responsible for the almost four-fold increase in prevalence of brain and eye defects that occurred 6 months after the outbreak peak. The brain and eye defects observed to have a significantly higher prevalence in areas of widespread local transmission have all consistently been described in infants with congenital Zika syndrome (Moore et al., 2017).

The prevalence of microcephaly was almost three times higher in areas with widespread local ZIKV transmission. Interestingly, the prevalence of intracranial calcifications, cortical/cerebral atrophy, brainstem abnormalities, and chorioretinal abnormalities were ~7–12 times higher, a much larger increase in prevalence than observed for microcephaly. These defects could be more specific for in-utero ZIKV exposure than microcephaly, which is a very heterogeneous condition (Freitas et al., 2020). Only the prevalence of porencephaly, cerebellar abnormalities, microphthalmia, coloboma, and congenital cataracts were similar between areas with and without widespread local transmission. For some birth defects, this could indicate that these particular defects are not related to ZIKV infection or be due in part to the rarity of the outcome (i.e., intraocular calcifications and hydranencephaly). Further, while eye defects such as microphthalmia, coloboma, and congenital cataracts have been described in infants with congenital Zika syndrome, optic nerve abnormalities and chorioretinal abnormalities are more commonly observed (de Oliveira Dias, 2018).

This analysis is subject to several limitations. First, our analysis was underpowered to detect small changes in prevalence over time because many of the individual birth defects are rare events. Second, heightened awareness of birth defects in areas with known transmission of ZIKV could have contributed to a larger portion of infants receiving recommended evaluations and identification of birth defects. This might partially explain the significantly higher prevalence of birth defects in areas of limited and widespread local ZIKV transmission. For example, milder forms of birth defects such as corpus callosum abnormalities or microcephaly might be more likely to be identified. Additional limitations of the surveillance data overall, specific to population demographics, case finding methodology, and laboratory testing, have been previously described (Smoots et al., 2020).

It is unlikely that heightened awareness fully explains the differences in prevalence observed. Birth defects such as cortical/cerebral atrophy, abnormal cortical gyral patterns, brainstem abnormalities, and optic nerve abnormalities often have noticeable clinical neurodevelopmental manifestations that make them more likely to be identified in the first year of life. Further, the defects observed to have the largest difference in prevalence in areas of widespread transmission (i.e., intracranial calcifications, cerebral/cortical atrophy, brainstem abnormalities, and chorioretinal abnormalities) are uncommon defects that have consistently been described in infants with congenital Zika syndrome (de Oliveira Dias, 2018; Del Campo et al., 2017).

Based on our findings, birth defects surveillance programs, especially those with limited capacity, could consider monitoring a smaller subset of birth defects potentially related to ZIKV in pregnancy. Birth defects surveillance programs with limited capacity or resources

could opt to monitor rarer defects that showed larger increases in prevalence such as intracranial calcifications and chorioretinal abnormalities to monitor for outbreaks and expand to monitor all 16 defects in the event of a known or suspected outbreak of ZIKV. This approach must be balanced because less severe presentations or more common defects may not be identified when ascertaining a more limited set of birth defects. For those jurisdictions that have the resources, continued surveillance of all 16 brain and eye defects is important for continuing to understand these defects in the context of ZIKV.

This study highlights the importance of population-based birth defects surveillance for understanding the full impact of new and re-emerging teratogens. In the United States, timing of testing and the high percentage of asymptomatic cases made it difficult to identify all ZIKV exposed pregnancies. Birth defects surveillance programs were able to capture defects of interest, regardless of Zika laboratory testing status, and these data have helped strengthen our understanding of the specific birth defects that are potentially the most influenced by congenital ZIKV exposure.

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Disclaimer:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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TABLE 1

Prevalence per 10,000 live births and PRs for individual brain and eye defects by transmission area

	Areas without local transmission (n = 2,781)[a]	Areas with limited local transmission (n = 313)[b]		Areas with widespread local transmission (n = 127)[c]	
	Prevalence (n)	**Prevalence (n)**	**PR**	**Prevalence (n)**	**PR**
Brain abnormalities and/or microcephaly					
Microcephaly	4.33 (781)	5.56 (87)	1.3 (1.0, 1.6)	12.51 (53)	2.9 (2.2, 3.8)
Intracranial calcifications	0.34 (61)	0.64 (10)	1.9 (1.0, 3.7)	4.25 (18)	12.6 (7.4, 21.3)
Cerebral/cortical atrophy	0.70 (127)	1.02 (16)	1.5 (0.9, 2.4)	4.72 (20)	6.7 (4.2, 10.8)
Abnormal cortical gyral patterns	1.97 (354)	1.92 (48)	1.0 (0.7, 1.4)	6.37 (27)	3.3 (2.2,4.8)
Corpus callosum abnormalities	4.18 (754)	5.94 (93)	1.4 (1.1, 1.8)	8.97 (38)	2.1 (1.6, 3.0)
Cerebellar abnormalities	2.46 (445)	2.75 (43)	1.1 (0.8, 1.5)	4.01 (17)	1.6 (1.0, 2.6)
Porencephaly	0.22 (39)	0.51 (8)	2.4 (1.1, 5.1)	0.24 (1)	1.1 (0.2, 8.0)
Hydranencephaly	0.17 (31)	0.19 (3)	Not calculated	0.00 (0)	Not calculated
Brainstem abnormalities	0.25 (46)	0.26 (4)	1.0 (0.4, 2.8)	2.36 (10)	9.3 (4.7, 18.4)
Ventriculomegaly/hydrocephaly	3.24 (585)	4.79 (75)	1.5 (1.2, 1.9)	9.68 (41)	3.0 (2.2, 4.1)
Eye abnormalities					
Microphthalmia	1.00 (180)	1.6 (25)	1.6 (1.1, 2.4)	1.89 (8)	1.9 (0.9, 3.8)
Coloboma	0.82 (148)	0.89 (14)	1.1 (0.6, 1.9)	1.18 (5)	1.4 (0.6, 3.5)
Congenital cataract	1.39 (251)	1.53 (24)	1.1 (0.7, 1.7)	0.71 (3)	0.5 (0.2, 1.6)
Intraocular calcifications	0.01 (1)	0.0 (0)	Not calculated	0.0 (0)	Not calculated
Optic nerve atrophy, pallor, and other optic nerve abnormalities	1.32 (239)	1.66 (26)	1.3 (0.8, 1.9)	4.72 (20)	3.6 (2.3, 5.6)
Chorioretinal atrophy, scarring, and pigmentary changes	0.28 (51)	0.45 (7)	1.6 (0.7, 3.5)	3.54 (15)	12.5 (7.1, 22.3)

[a] This is the reference category. Jurisdictions without local transmission of Zika virus during 2016–2017 included California (selected counties), Georgia (selected metropolitan Atlanta counties), Hawaii, Illinois, Indiana, Iowa, Louisiana, Massachusetts, Minnesota, New Jersey, New York (excluding New York City residents), North Carolina (selected regions), Oklahoma, Rhode Island, South Carolina, Texas Public Health Region 10, Utah, Vermont, and Virginia. Total live births for areas without local transmission = 1,805,659.

[b] Jurisdictions with limited local transmission of Zika virus during 2016–2017 included southern Florida counties and Texas Public Health Region 11. Total live births for areas with limited local transmission = 156,613.

[c] Jurisdictions with widespread local transmission of Zika virus during 2016–2017 included Puerto Rico and the U.S. Virgin Islands. Total live births for areas with widespread local transmission = 42,358.

TABLE 2

Prevalence per 10,000 live births and PRs of pooled birth defects by period for all transmission groups

	Areas with no local transmission (*n* = 2,781)		Areas with limited local transmission (*n* = 313)		Areas with widespread local transmission (*n* = 127)	
	Prevalence (*n*)	**PR**	**Prevalence (*n*)**	**PR**	**Prevalence (*n*)**	**PR**
Group A: PRs for pooled significant defects[a]						
January–March 2016	12.9 (380)	Reference	15.0 (39)	Reference	9.4 (7)	Reference
April–June 2016	12.7 (387)	1 (0.9, 1.1)	16.5 (42)	1.1 (0.7, 1.7)	22.2 (16)	2.4 (1.0, 5.8)
July–September 2016	12.6 (408)	1 (0.8, 1.1)	14.6 (41)	0.9 (0.6, 1.5)	27.8 (21)	3.0 (1.3, 7.0)
October–December 2016	11.1 (334)	0.9 (0.7, 1.0)	21.1 (58)	1.4 (0.9, 2.1)	32.8 (24)	3.5 (1.5, 8.1)
January–Mar 2017	11.9 (341)	0.9 (0.8, 1.1)	11.8 (30)	0.8 (0.5, 1.3)	50.9 (33)	5.4 (2.4, 12.3)
April–June 2017	11.1 (329)	0.8 (0.7, 1.0)	17.4 (42)	1.2 (0.7, 1.8)	18.9 (12)	2.0 (0.8, 5.1)
Group B: PRs pooled all other defects[b]						
January–March 2016	4.1 (121)	Reference	7.3 (19)	Reference	4.0 (3)	Reference
April–June 2016	4.0 (122)	1.0 (0.8, 1.3)	3.9 (10)	0.5 (0.3, 1.2)	2.8 (2)	0.7 (0.1, 4.1)
July–September 2016	4.2 (138)	1.0 (0.8, 1.3)	5.3 (15)	0.7 (0.4, 1.4)	2.6 (2)	0.7 (0.1, 3.9)
October–December 2016	3.7 (111)	0.9 (0.7, 1.2)	5.8 (16)	0.8 (0.4, 1.5)	6.8 (5)	1.7 (0.4, 7.1)
January–March 2017	3.6 (102)	0.9 (0.7, 1.1)	7.1 (18)	1.0 (0.5, 1.8)	4.6 (3)	1.2 (0.2, 5.7)
April–June 2017	3.9 (117)	1.0 (0.7, 1.2)	4.1 (10)	1.0 (0.3, 1.2)	1.6 (1)	0.4 (0.0, 3.8)

[a] Defects included in this group: intracranial calcifications; chorioretinal atrophy, scarring, and pigmentary changes; brainstem abnormalities; cerebral/cortical atrophy; optic nerve atrophy, pallor, and other optic nerve abnormalities; abnormal cortical gyral patterns; ventriculomegaly/hydrocephaly; microcephaly; and corpus callosum abnormalities.

[b] Defects included in this group: cerebellar abnormalities, porencephaly, hydranencephaly, microphthalmia, coloboma, congenital cataract, and intraocular calcifications.