

Zika-related Birth Defects: 2016-2017

Bureau of
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Introduction

Birth defects are structural differences that are present at birth, and they may affect the way the body appears, functions, or both. The Centers for Disease Control and Prevention (CDC) highlights that birth defects are common, costly, and critical, and that they affect approximately 1 out of every 33 infants born in the United States.¹ One study found that, in 2013, hospital stays related to any birth defect cost the US health care system \$23 billion.² Birth defect hospitalizations accounted for 3% of all hospitalizations in the same year, but totaled 5% of total hospital costs.² Depending on the severity of the birth defect, a baby's lifespan may be shortened.



Zika-related birth defects are birth defects that have been associated with prenatal Zika virus exposure. Zika virus is transmitted primarily through the bite of mosquitoes and generally causes mild illness.³ However, it can cause pregnancy complications for women, including miscarriage and stillbirth, and it has been associated with specific birth defects in infants exposed to Zika prenatally.⁴ The most widely publicized and commonly recognized birth defect associated with Zika is microcephaly, which is a smaller-than-expected head size. Although Zika virus was historically present in other parts of the world, the United States saw its first outbreak of Zika virus cases in 2016.⁵ The CDC established the US Zika Pregnancy and Infant Registry (USZPIR) for Zika surveillance and worked with states for tracking the national scope of virus transmission.

As a part of the effort to learn more about Zika, the CDC requested states to collect information on Zika-related birth defects (ZrBDs) beginning in 2016. Because the data collection was focused on learning more about these birth defects overall, surveillance was focused on the birth defect outcome and did not require Zika exposure for inclusion. An additional consideration was that the CDC was aware that not all pregnant women with Zika would be tested during pregnancy, increasing the chance that Zika-related birth defects would be missed if a diagnosis during pregnancy was the critical component of classification. At the time, 44 out of 50 US states already had a birth defects surveillance program that could be used or enhanced to include this data collection.⁶ Pennsylvania was one of 6 states that did not have an existing program. After being awarded CDC funding for tracking of ZrBDs in 2016, the state was able to implement surveillance of birth defects for the first time. Surveillance was limited to only those birth defects potentially related to Zika virus because authority to collect these

surveillance data was based upon the birth defect outcome being related to an emerging infectious disease.

This report summarizes the data collected for infants and pregnancy losses with ZrBDs that were born in 2016-2017 to Pennsylvania residents.

Methods

The birth defects for surveillance inclusion were defined by CDC. The case criteria included infants from birth to one year of life or fetal deaths that had an ICD-10-CM discharge code consistent with a Zika-related birth defect. Pennsylvania cases were additionally defined as being born in state to a Pennsylvania resident between January 1, 2016, to December 31, 2017. Live births and fetal deaths of Philadelphia county residents were excluded due to tracking of resident cases by the Philadelphia Department of Public Health (PDPH).

Infants with ZrBDs were identified using a blend of passive and active surveillance. For the passive surveillance portion, the bureau identified 120 birthing facilities and pediatric hospitals for consideration. Outreach was prioritized to facilities with the highest numbers of annual live births. Letters were sent on a rolling basis to facility CEOs and Health Information Management (HIM) managers to provide information regarding the surveillance effort. Letters to HIM managers contained the relevant diagnostic discharge codes, including any Zika-related birth defect code or stillbirth code, as well as a request for a facility case list of infants with ZrBD codes or mothers with stillbirth codes meeting the surveillance criteria. See Appendix A for the list of discharge codes and corresponding descriptions provided to facilities for patient inclusion. Fetal deaths did not require a Zika-related birth defect code to be included in a list of potential cases because they are historically not coded for anomalies as systematically and effectively as live births.⁷ Therefore, all pregnancy losses were eligible for review for a ZrBD. The bureau then processed the facility case lists received to verify that cases met the surveillance inclusion criteria. A final list of medical records being requested by the bureau was provided to facilities.

Patient data from each facility case list was entered into the REDCap Cloud electronic Zika-related Birth Defects Surveillance (ZBDS) database for those infants on the final abstraction inclusion list. Full abstraction with data collection was performed only on those infants determined to be cases. Records were reviewed onsite at the facility, reviewed via paper or electronic records mailed to the Department of Health, or reviewed using remote access to the facility's electronic medical records system. A portion of infants were identified as cases at a hospital admission occurring after the birth admission. If birth information was not available in the subsequent admission, records were requested from the birthing facility to obtain the data necessary to complete the infant's ZBDS record.

After a brief abstraction period, the bureau limited fetal death abstraction to losses occurring at 18 weeks or greater if gestational age was noted in the facilities' case lists. This reduced fetal death case review to those in which ZrBD brain anomalies would be evident in terms of fetal development, as some malformations would not be evident at an earlier gestation. If gestational

age could not be determined prior to abstraction, the record was reviewed for case classification regardless of gestational age.

All ZBDS records, including cases and non-cases, were linked to vital statistics birth certificates, fetal death certificates, and infant death certificates for further analysis. Infant death certificates were reviewed for deaths occurring within one year of life. Additionally, vital statistics records were analyzed for ZrBDs to compare case ascertainment to surveillance case ascertainment. Birth certificates and fetal death records allow reporting of only specific birth defects, so ZrBD case finding was limited to only spina bifida and anencephaly as the reportable ZrBDs on these records. The infant death certificates were reviewed for any ICD-10-CM code pertaining to a ZrBD.

Additionally, a data request was provided to the Pennsylvania Healthcare Cost Containment Council (PHC4) to link inpatient hospitalization and outpatient visit (often specialty clinics including neurology, genetics, eye specialists, etc.) data to ZBDS cases. This linkage allowed for analysis of hospital readmissions for cases up to 1 year of age, total number of hospital days, facility charges, and infant deaths.

Resulting ZBDS data and linked data were analyzed in various ways depending on the outcome of interest: by total live birth and fetal death cases, by total live births, and by birth defect category. These categories are based upon a 2017 Zika-related birth defects Morbidity and Mortality Weekly Report (MMWR) article that used a hierarchical system to provide a mutually exclusive classification for each infant: brain abnormalities with or without microcephaly, followed by neural tube defects, eye anomalies, and lastly other central nervous system (CNS) dysfunction.⁸ For hierarchical category analyses within this report, neural tube defects (NTDs) are the priority classification, followed by brain abnormalities with or without microcephaly (“brain abnormalities”), and, lastly, eye abnormalities. The “other” CNS birth defects category was ultimately excluded from states’ case criteria inclusion by CDC. Using this hierarchical system, infants with multiple birth defects that span more than one category are classified only with the highest priority category, so that each infant is represented only once in the resulting data. In comparisons to statewide demographic data, the data in this report may be presented as all live birth and fetal death cases in comparison to statewide live births, similar to the MMWR ZrBD article, or it may be presented as only live birth cases in comparison to statewide live births. The details for each analysis are outlined before presenting the relevant data. For consistency, where the same data elements exist in both ZBDS and vital statistics, the data from vital statistics was used for comparative analyses.

A “derived statewide” population value (n=227 488) was obtained from vital statistics data that aligns with the catchment area defined in the case definition. This “derived statewide” population represents all live births and fetal deaths occurring in Pennsylvania between 2016-2017 to Pennsylvania residents, including births occurring outside of a hospital setting (e.g., home births, birthing centers, etc.). The derived value excludes outcomes of Philadelphia residents and outcomes occurring out of state. The derived statewide fetal death population includes miscarriages (less than 20 weeks of pregnancy) and stillbirths (20 or more weeks of pregnancy) and is defined as pregnancy losses occurring at a gestational age of 16 weeks or more, which is consistent with vital statistics criteria for fetal death records.⁹ Any references to a different derivation of statewide data will be explicitly noted.

The first letters to facilities requesting case lists were sent in June 2017. The first data abstraction was performed in a hospital beginning September 2017, and the first upload of case data to CDC occurred in October 2017. Abstraction was completed in April 2019. Data quality review, data linkage, and subsequent analyses were performed in the following months.

Findings

In total, the bureau received 2459 potential reported cases from 70 facilities, including 1167 live births and 1292 fetal deaths. After removing 49 infants born to non-residents, there were a total of 2410 live births and fetal deaths in the final ZBDS database for which records were reviewed. After medical record abstraction and application of the CDC case classification criteria, there were 541 (22%) confirmed cases, and the remaining 1869 were determined to be non-cases. Live births comprised approximately 91% (n=491) of total identified ZBDS cases. See Tables 1 and 2 for details of records received and case status.

Table 1 – Total Counts of Live Birth and Fetal Death Medical Records Reviewed, with Case Status

	Total potential cases identified via surveillance and vital statistics		Total ZBDS records reviewed after removing non-residents		Cases		Non-cases	
	N	%	N	%	N	%	N	%
Live births	1167	47	1129	47	491	91	638	34
Fetal deaths	1292	53	1281	53	50	9	1231	66
Total	2459		2410		541		1869	

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017)

Table 2 – Percent of Live Birth and Fetal Death Cases out of Total Reported, Respectively

	Live births	Fetal deaths
Total ZBDS records	1129	1281
Total cases	491	50
% cases	43%	4%

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017)

Vital Statistics Record Linkage

Live birth and fetal death cases and non-cases were matched and linked to vital statistics (VS) data using birth certificates, fetal death certificates, and infant death certificates. Live birth and fetal death certificates used in matching pertained to pregnancy outcomes occurring in Pennsylvania to state residents within years 2016-2017, excluding Philadelphia residents. Infant death certificates included were those pertaining to infants less than 1 year of age that were born in Pennsylvania to state residents in years 2016-2017, excluding infants born to Philadelphia residents. Table 3 below shows counts of ZBDS cases that were successfully matched to VS records. In total, 2076 (86 percent) of ZBDS records were matched and linked. Of all 541 live birth and fetal death cases, all live birth cases were matched and 41 (82%) of 50 fetal death cases were matched to VS records.

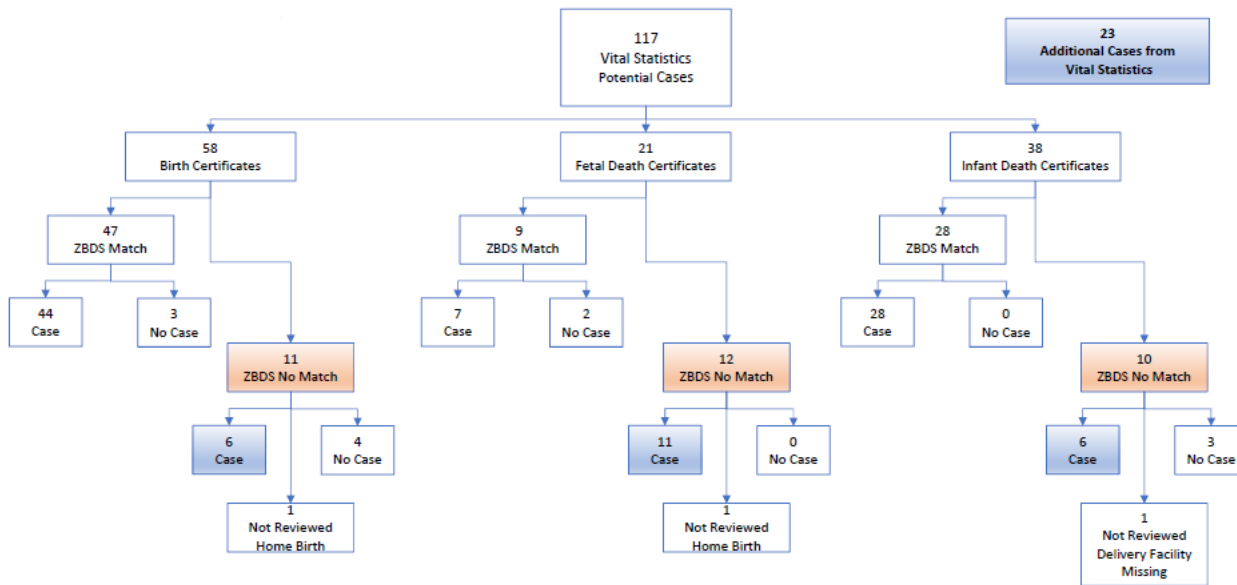
Table 3 – Percentage of Live Birth and Fetal Death Cases out of Total Reported

	Total ZBDS records			Total ZBDS cases		
	Total number	Total VS-matched	Percent VS-matched (%)	Total number	Total VS-matched	Percent VS-matched (%)
Live births	1129	1129	100	491	491	100
Fetal deaths	1281	947	74	50	41	82
Total	2410	2076	86	541	532	98

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017)

Birth certificate data, fetal death data, and infant death data were reviewed for indication of a ZrBD. For live birth and fetal deaths, this included review of the two variables “Anencephaly” and “Meningomyelocele/Spina Bifida” in the Congenital Anomalies section, as these are the only two ZrBDs currently collected on the Pennsylvania live birth and fetal death records. On infant death certificates, fields “Axis,” “Cause of Death” and “Significant Factor” ICD Codes were reviewed for any codes related to ZrBDs. There were 117 potential ZrBD cases identified via this VS record review. Of these, 84 (70%) were matched to existing records in the ZrBD data base. Seventy-nine (94%) of the 84 matched records were classified as cases in ZBDS. The remaining 33 of 117 potential records did not have matches identified in the ZBDS database. Twenty-three (70%) of the unmatched records were determined to be cases after data review and comparison to CDC criteria. These 23 cases are included in the total surveillance case counts provided above, and they accounted for approximately 4% of all identified ZrBD cases. Figure 1 below shows the numbers of potential cases identified by type of record, the numbers of unmatched for each, and the confirmed cases.

Figure 1 – Zika-related Birth Defects Cases Identified via Vital Statistics Records



SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017)

Vital statistics-linked ZBDS data was used to compare the 532 matched live birth and fetal deaths cases to the derived statewide 2016 and 2017 live births (n=227 488). These 532 cases represent the 541 matched live births and fetal death cases minus the 9 fetal deaths that did not match vital records, See Table 4 below for details.

Select variables were evaluated by type of anomaly using the mutually exclusive hierarchy described in the Methods section, with NTD given priority, followed by brain anomaly and, lastly, eye anomaly. Table 5 below provides a comparison of each category to the derived statewide populations. The fetal mortality rate of a birth defect category is obtained as fetal deaths per 1000 live birth cases within the category. The derived statewide fetal death rates are reported as fetal deaths at 16 or more weeks gestational age per 1000 live births. The derived fetal death rate in the table cannot be directly compared to Pennsylvania’s published Healthy People 2020 fetal death rate because the populations differ in gestational age criteria and geographical catchment area.¹⁰

When comparing across hierarchical birth defect categories, the highest fetal death rate occurred in infants with NTDs (242.7 fetal deaths per 1000 NTD live birth cases), followed by brain anomaly (49.5 fetal deaths per 1000 brain anomaly cases) and, lastly, eye anomaly (0 fetal deaths per 1000 eye anomaly cases), with an overall rate of 83.5 fetal deaths per 1000 ZrBD cases. It’s important to note that other comorbidities may have existed in fetal death outcomes. The data below does not attempt to attribute cause of fetal death to a ZrBD but instead shows presence of a ZrBD upon examination after the fetal death.

Table 4 – Demographics of Live Births and Fetal Deaths with Zika-related Birth Defects versus Statewide Live Births

		ZrBD cases		Statewide population	
		N	%	N	%
		532	100	227 488	100
Maternal age at delivery	<25	162	31	51 287	23
	25-34	283	53	138 021	61
	35+	86	16	38 138	17
Sex	Male	287	54	116 830	51
Birthweight	Normal (2500+ g)	303	59	208 335	92
	Low (1500-2499g)	133	26	14 735	7
	Very low (<1500g)	79	15	3 104	1
Smoking status	Smoker	87	17	27 737	12
Gestational age	Very Premature (<32 weeks)	75	14	3 425	2
	Premature (32-36 weeks)	112	21	17 384	8
	Early to Full Term (37-41 weeks)	342	65	204 918	90
	Post Term (41+ weeks)	0	0	834	<1
Race	White	383	74	176 977	78
	Black	77	15	22 326	10
	Asian	20	4	9 274	4
	Other	36	7	11 696	5
Hispanic	Hispanic	53	10	22 726	10
Payment	Private	272	51	137 607	60
	Medicaid	200	38	65 380	29
	Other or Unknown	60	11	24 501	11
BMI	Obese	227	43	76 717	34

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017)

Table 5 – Pregnancy Outcomes by Hierarchical Zika-related Birth Defect Category Compared to Derived Statewide Populations

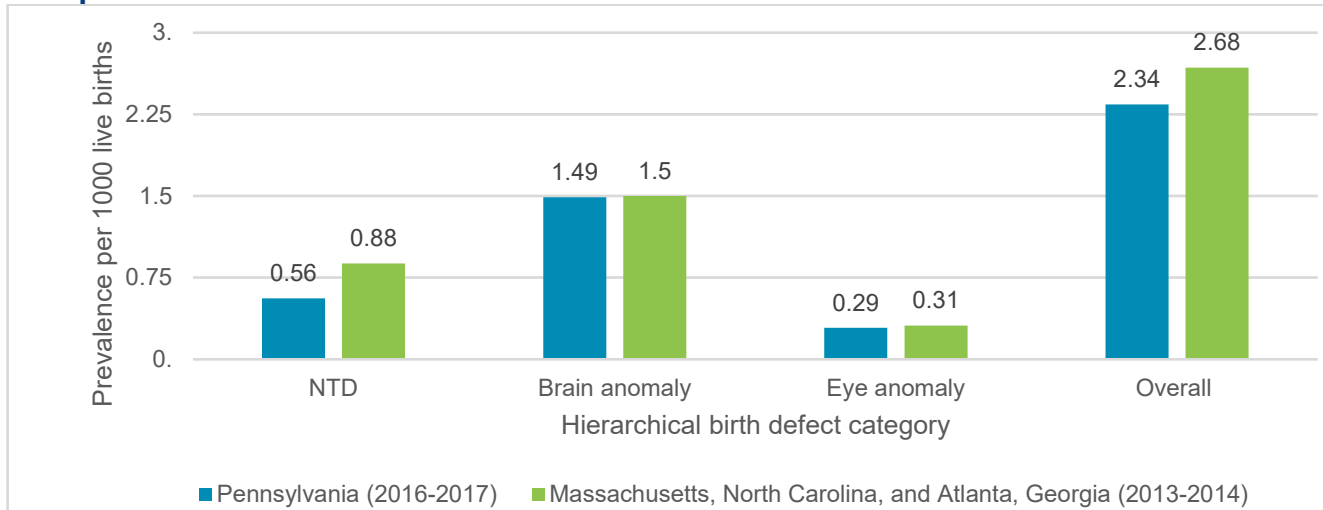
	NTDs and other early brain malformations		Brain abnormalities with or without microcephaly		Eye abnormalities		Total ZrBD cases		PA live births 2016-2017	
	N	%	N	%	N	%	N	%	N	%
Total	128	100	339	100	65	100	532	100	227 488	100
Pregnancy outcome										
Pregnancy loss	25	20	16	5	0	0	41	8	2023 ^a	0.9
Live birth	103	80	323	95	65	100	491	92	227 488	100
Gestational age at delivery										
<32 weeks	33	26	36	11	6	9	75	14	3425	2
32-36 weeks	31	24	78	23	3	5	112	21	17 384	8
37-41 weeks	64	50	223	66	55	86	342	65	204 918	90
41+ weeks	0	0	0	0	0	0	0	0	834	<1
Maternal age at delivery (years)										
<25	39	31	106	31	17	26	162	31	51 287	23
25-34	70	55	175	52	38	58	283	53	138 021	61
>34	18	14	58	17	10	15	86	16	38 138	17
Rates										
	Rate per 1000 NTD live birth cases		Rate per 1000 brain anomaly live birth cases		Rate per 1000 eye anomaly live birth cases		Rate per 1000 ZrBD live birth cases		Rate per 1000 live births^a	
Fetal death rate	242.7		49.5		0		83.5		8.9	

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017)

Statewide prevalence was obtained for each hierarchical birth defect category and compared to the 2017 MMWR report on ZrBDs in Table 6 below.

^a This value uses the “derived statewide” fetal death population: fetal deaths occurring to Pennsylvania residents in the state of Pennsylvania between 2016-2017, excluding Philadelphia residents.

Table 6 – Pennsylvania Prevalence of Birth Defects by Hierarchical Category in Comparison to National Data



SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017); Cragan et al., (2017)⁸

Infant deaths were determined from surveillance data and vital statistics data. Table 7 displays details. Of 491 live birth cases, there were 68 infant deaths (infant mortality rate=13.8%). Fifty-seven percent of deaths occurred in the neonatal period (less than 28 days of life) and 35% occurred during the postneonatal period (28 to 364 days of life). The age at death could not be determined for 7% of infants.

Each identified death was reviewed for consistency between data sources. Two infant deaths were identified by ZBDS only, 10 infant deaths were identified via VS records only, and 56 were identified via both.

Table 7 – Deaths among Infants with Zika-related Birth Defects, by Age at Death and Source of Data

	Identified by ZBDS only	Identified by VS only	Identified by ZBDS + VS	Total identified	Percent of total infant deaths (%)
Total live birth cases	491				
Neonatal death (< 28 days of life)		1	38	39	57%
Postneonatal death (28-364 days of life)	2	7	15	24	35%
Unknown age at death		2	3	5	7%
Total infant deaths	2	10	56	68	100%
				Percent	
Infant mortality rate (%)				13.8%	

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017)

Age at death was also obtained by hierarchical birth defect category. Infants with NTDs have the highest rate of infant deaths (38.2%), followed by infants with brain anomalies (11.8%) and lastly eye anomalies (1.5%). Most infant deaths in infants with NTDs occurred during the neonatal period (93%). More than half of infant deaths in infants with brain anomalies occurred during the postneonatal period (58%). One death occurred in infants in the eye anomaly category during the neonatal period. Table 8 below shows details. It should be noted again that infants represented in the table may have had other birth defects or comorbidities contributing to death, such as other non-ZrBD brain anomalies or critical congenital heart defects. This table does not account for other non-ZrBD factors that may have contributed to the infant's death and only reflects the presence of a noted ZrBD at time of death.

Table 8 – Age at Death for Infants with Zika-related Birth Defects by Hierarchical Category

	NTD		Brain		Eye		Total
	N	%	N	%	N	%	N
Total VS-matched population	103	100	323	100	65	100	491
Total neonatal deaths (<28 days of life)	27	93	11	29	1	100	39
Postneonatal death (28-364 days of life)	1	3	23	60	0	0	24
Unknown age at death	1	3	4	11	0	0	5
Total deaths identified	29	100	38	100	1	100	68
Rate of infant deaths (%)	28.2		11.8		1.5		13.8

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019), Pennsylvania Department of Health, Vital Statistics (2016-2017)

Rates of infant deaths derived above were compared to Pennsylvania's Healthy People 2020 statewide values from 2013-2017. Table 9 displays results. The ZrBD infant mortality rates are reported per 1000 ZrBD cases. The statewide rate is reported per 1000 live births and represents all state births, including Philadelphia residents and out-of-state births to residents. Because age at death could not be determined for select infants in some categories (NTD, Brain, and Overall), these infants are not included in the neonatal or postneonatal rate categories but are included in the overall infant mortality rate. For this reason, the neonatal mortality rate and postneonatal mortality rates do not sum to the total infant mortality rate displayed for these categories.

Table 9 – Infant Mortality Rates by ZrBD Hierarchical Category in Comparison to Statewide

Category	Per 1000 ZrBD cases				Per 1000 live births
	NTD ^b	Brain ^b	Eye	Overall ^b	Statewide (2013-2017)
Neonate (<28 days of life)	262.1	34.1	15.4	79.4	4.4
Postneonatal (28-364 days of life)	9.7	71.2	0.0	48.9	1.8
Infant mortality rate	281.6	117.6	15.4	138.5	6.2

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017); Pennsylvania Department of Health, Division of Health Informatics (2019)

To obtain true prevalence of each birth defect category, case counts and prevalence were also obtained without using a mutually exclusive hierarchy, but by counting each occurrence of the birth defect category in an infant. Using this method, infant or fetal death cases may be represented more than once across the birth defect categories if, for example, they have both an NTD-categorized birth defect and an eye-categorized birth defect. Case counts and prevalence were determined at the county level using VS-matched live births and fetal deaths in the numerator and the derived resident live births as the denominator. Table 10 shows case counts and prevalence.

Total pregnancy outcomes with a ZrBD ranged from 0 to 87 per county. As expected, the county with the most births had the highest case count. Incidence rate of pregnancy outcomes with a ZrBD per 1000 live births ranged from 0 to 5.2. As described above, Philadelphia data is not included in this report.

Table 10 – County-level Zika-related Birth Defect Case Counts and Prevalence per 1000 Live Births by Birth Defect Category

County	Total Births	NTD ^c		Brain abnormality ^c		Eye abnormality ^c		Total ZrBD category occurrences ^c		Total birth outcomes with ZrBDs ^d	
		COUNT	Rate	COUNT	Rate	COUNT	Rate	COUNT	Rate	COUNT	Rate
Adams	1751	0	0.0	1	0.6	2	1.1	3	1.7	2	1.1
Allegheny	25 950	10	0.4	67	2.6	16	0.6	93	3.6	84	3.2
Armstrong	1344	0	0.0	1	0.7	0	0.0	1	0.7	1	0.7
Beaver	3212	2	0.6	4	1.2	2	0.6	8	2.5	8	2.5

^b This category includes infants with unknown age at death; therefore, the infant mortality rate is greater than the sum of neonatal and postneonatal mortality rates.

^c Counts and rates refer to each occurrence; category is not mutually exclusive, so infants may be represented in more than one category.

^d Mutually exclusive total; each infant is represented only once.

County	Total Births	NTD ^c		Brain abnormality ^c		Eye abnormality ^c		Total ZrBD category occurrences ^c		Total birth outcomes with ZrBDs ^d	
		COUNT	Rate	COUNT	Rate	COUNT	Rate	COUNT	Rate	COUNT	Rate
Bedford	906	0	0.0	2	2.2	0	0.0	2	2.2	2	2.2
Berks	9474	4	0.4	9	0.9	5	0.5	18	1.9	15	1.6
Blair	2473	1	0.4	5	2.0	1	0.4	7	2.8	5	2.0
Bradford	1179	0	0.0	1	0.8	0	0.0	1	0.8	1	0.8
Bucks	9915	7	0.7	10	1.0	4	0.4	21	2.1	18	1.8
Butler	3554	5	1.4	10	2.8	1	0.3	16	4.5	14	3.9
Cambria	2617	1	0.4	3	1.1	1	0.4	5	1.9	4	1.5
Cameron	83	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Carbon	1187	0	0.0	1	0.8	1	0.8	2	1.7	2	1.7
Centre	2361	0	0.0	3	1.3	0	0.0	3	1.3	3	1.3
Chester	10 148	0	0.0	5	0.5	2	0.2	7	0.7	7	0.7
Clarion	774	1	1.3	3	3.9	1	1.3	5	6.5	4	5.2
Clearfield	1502	0	0.0	4	2.7	2	1.3	6	4.0	5	3.3
Clinton	788	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Columbia	1103	1	0.9	3	2.7	0	0.0	4	3.6	3	2.7
Crawford	1844	0	0.0	3	1.6	1	0.5	4	2.2	4	2.2
Cumberland	5281	3	0.6	11	2.1	2	0.4	16	3.0	15	2.8
Dauphin	6833	5	0.7	18	2.6	4	0.6	27	4.0	25	3.7
Delaware	12 888	9	0.7	14	1.1	6	0.5	29	2.3	25	1.9
Elk	572	1	1.7	1	1.7	1	1.7	3	5.2	3	5.2
Erie	6030	1	0.2	13	2.2	5	0.8	19	3.2	17	2.8
Fayette	2354	2	0.8	3	1.3	3	1.3	8	3.4	6	2.5
Forest	46	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Franklin	3314	0	0.0	2	0.6	2	0.6	4	1.2	4	1.2
Fulton	238	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Greene	512	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Huntingdon	739	1	1.4	0	0.0	0	0.0	1	1.4	1	1.4

County	Total	NTD ^c		Brain abnormality ^c		Eye abnormality ^c		Total ZrBD category occurrences ^c		Total birth outcomes with ZrBDs ^d	
	Births	COUNT	Rate	COUNT	Rate	COUNT	Rate	COUNT	Rate	COUNT	Rate
Indiana	1628	1	0.6	0	0.0	2	1.2	3	1.8	3	1.8
Jefferson	930	1	1.1	4	4.3	1	1.1	6	6.5	4	4.3
Juniata	553	1	1.8	1	1.8	0	0.0	2	3.6	1	1.8
Lackawanna	4306	5	1.2	11	2.6	0	0.0	16	3.7	14	3.3
Lancaster	14 205	11	0.8	23	1.6	6	0.4	40	2.8	37	2.6
Lawrence	1702	1	0.6	2	1.2	2	1.2	5	2.9	3	1.8
Lebanon	3176	3	0.9	6	1.9	3	0.9	12	3.8	9	2.8
Lehigh	8484	2	0.2	13	1.5	6	0.7	21	2.5	19	2.2
Luzerne	6433	3	0.5	7	1.1	0	0.0	10	1.6	9	1.4
Lycoming	2390	1	0.4	3	1.3	3	1.3	7	2.9	6	2.5
McKean	602	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Mercer	2194	0	0.0	5	2.3	2	0.9	7	3.2	5	2.3
Mifflin	1146	2	1.7	1	0.9	0	0.0	3	2.6	3	2.6
Monroe	2852	7	2.5	10	3.5	1	0.4	18	6.3	11	3.9
Montgomery	17 272	7	0.4	17	1.0	4	0.2	28	1.6	25	1.4
Montour	436	1	2.3	1	2.3	0	0.0	2	4.6	2	4.6
Northampton	5482	5	0.9	10	1.8	3	0.5	18	3.3	16	2.9
Northumberland	1865	1	0.5	4	2.1	1	0.5	6	3.2	6	3.2
Perry	1038	0	0.0	2	1.9	1	1.0	3	2.9	2	1.9
Pike	568	1	1.8	2	3.5	0	0.0	3	5.3	2	3.5
Potter	263	0	0.0	1	3.8	0	0.0	1	3.8	1	3.8
Schuylkill	2672	2	0.7	2	0.7	1	0.4	5	1.9	4	1.5
Snyder	879	1	1.1	1	1.1	0	0.0	2	2.3	2	2.3
Somerset	1284	1	0.8	3	2.3	1	0.8	5	3.9	5	3.9
Sullivan	83	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Susquehanna	520	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

County	Total	NTD ^c		Brain abnormality ^c		Eye abnormality ^c		Total ZrBD category occurrences ^c		Total birth outcomes with ZrBDs ^d	
	Births	COUNT	Rate	COUNT	Rate	COUNT	Rate	COUNT	Rate	COUNT	Rate
Tioga	594	0	0.0	1	1.7	0	0.0	1	1.7	1	1.7
Union	835	0	0.0	1	1.2	0	0.0	1	1.2	1	1.2
Venango	1016	0	0.0	2	2.0	3	3.0	5	4.9	5	4.9
Warren	740	1	1.4	1	1.4	0	0.0	2	2.7	1	1.4
Washington	3916	2	0.5	9	2.3	4	1.0	15	3.8	13	3.3
Wayne	778	0	0.0	1	1.3	0	0.0	1	1.3	1	1.3
Westmoreland	5879	4	0.7	10	1.7	3	0.5	17	2.9	13	2.2
Wyoming	521	0	0.0	1	1.9	1	1.9	2	3.8	2	3.8
York	9273	10	1.1	16	1.7	4	0.4	30	3.2	28	3.0
Total	227 487	128	0.56	368	1.62	114	0.50	610	2.68	532	

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017)

PHC4^e Data Inpatient Hospitalization and Outpatient Data Linkage

Of 489 ZBDS cases submitted to PHC4, 477 were matched to outpatient records and 476 were matched to inpatient records.

Infant deaths identified via PHC4 data were reviewed against those identified via vital statistics records and ZBDS. PHC4 deaths were identified by a discharge code indicating the infant expired. Of 477 cases matched with PHC4 data, there were 57 infant deaths. Forty-four (77%) were identified via both PHC4 data and ZBDS, and 13 deaths (23%) were identified by ZBDS only. Table 11 displays details.

Using infants with inpatient records, Table 12 shows the total number of rehospitalizations for all infants and by the hierarchical birth defect classification. Rates of readmissions per infant

^e The Pennsylvania Health Care Cost Containment Council (PHC4) is an independent state agency responsible for addressing the problem of escalating health care costs, ensuring the quality of health care, and increasing access to health care for all citizens regardless of ability to pay. PHC4 has provided data to this entity in an effort to further PHC4's mission of educating the public and containing health care costs in Pennsylvania. PHC4, its agents, and staff, have made no representation, guarantee, or warranty, express or implied, that the data – financial, patient, payor, and physician specific information – provided to this entity, are error-free, or that the use of the data will avoid differences of opinion or interpretation. This analysis was not prepared by PHC4. This analysis was done by the Pennsylvania Department of Health. PHC4, its agents and staff, bear no responsibility or liability for the results of the analysis, which are solely the opinion of this entity.

range from 71.9% in eye anomalies to 104.3% in NTDs, indicating that there is more than one readmission per infant on average for infants with NTDs.

Table 11 – Infant Deaths Identified via ZBDS and PHC4 by Hierarchical Zika-related Birth Defect Category

	NTD	Brain	Eye	Total
Total matched population	94	318	64	477
Identified via PHC4 only	0	0	0	0
Identified via DOH only	4	9	0	13
Identified via PHC4 and DOH	17	26	1	44
Total deaths identified	21	35	1	57

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017); PHC4 (2019)

Table 12 – Total Number of Rehospitalizations by Hierarchical Zika-related Category

Birth defect category	Total cases	Number of rehospitalizations	Rate of rehospitalizations (%)
NTD	94	98	104.3
Brain	318	275	86.5
Eye	64	46	71.9
Total	476	419	88.0

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017); PHC4 (2019)

Charges for inpatient and outpatient visits were calculated over the first 28 days of life and over the first total year of life. There were 472 infants with charges reported within the first 28 days of life and 477 infants with charges reported within the first year of life. The average inpatient and outpatient charges per infant totaled over \$284 000 in the first 28 days of life and over \$382 000 in the first year of life. The sum of inpatient and outpatient charges across all ZrBD cases in the first year of life totaled \$182.4 million, with 74% of charges occurring within the first 28 days of life. Table 13 displays details of charges.

Table 13 – Total Inpatient and Outpatient Charges for ZrBD Cases

	Per patient charges				Total sum of charges (\$)
	Total number of infants	Average charges (\$)	Median charges (\$)	Average non-covered charges (\$)	
Neonate (birth-28 days)	472	284 362	88 252	4675	134 218 671
Birth to 1 year	477	382 343	119 781	5834	182 373 544
Percent of year 1 charges occurring in first 28 days of life					74%

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017); PHC4 (2019)

Using inpatient data, total hospital days for all ZrBD cases combined was 14 986 days. The average total length of stay was determined in two ways: total average length of stay per infant (31.3 days) and average length of stay per admission (16.7 days). Maximum length of stay per infant ranged from 203 days for infants in the eye anomaly category to 289 days in the brain anomaly category. The average charge for inpatient stays per infant totaled over \$284 000, with patients being charged an average of \$9153 per day for care. Tables 14 and 15 below display details by total ZrBD cases and by hierarchical birth defect category.

Table 14 – Total Length of Stay per Infant and per Admission by Hierarchical Zika-related Birth Defect Category

	Total	By Birth defect category		
		Brain	NTD	Eye
Total number of Infants	476	318	94	64
Total LOS (days)	14 986	10 795	2296	1630
Total number of admissions	899	585	189	110
Average total length of stay per infant (days)	31.5	33.9	24.4	25.5
Average length of stay per admission (days)	16.7	18.5	12.1	14.8
Max total length of stay	289	289	285	203

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017); PHC4 (2019)

Table 15 – Charges for Inpatient Stays by Hierarchical Zika-related Birth Defect Category, Neonate Period Versus First Year of Life

Birth defect category	Neonate (birth-28 days)				Birth to 1 year			
	N	Average charge per patient (\$)	Average charge per day (\$)	Total charge (\$)	N	Average charge per patient (\$)	Average charge per day (\$)	Total charge (\$)
Total infants	472	284 251	9153	134 166 267	476	376 681	9672	179 302 726
Brain	315	326 242	8908		318	415 725	9575	
NTD	93	254 512	12 693		94	321 836	13 082	
Eye	64	120 786	5646		64	263 273	5625	

SOURCE: Pennsylvania Department of Health, Bureau of Epidemiology (2019); Pennsylvania Department of Health, Vital Statistics (2016-2017); PHC4 (2019)

Data Limitations

The original case lists of potential ZRBD cases were obtained via passive surveillance with facilities performing a data pull for the relevant discharge codes. Therefore, the total collected cases were dependent upon infants being coded correctly within the facility and the health information management team performing the data pull accurately according to the DOH-provided request.

The original funding period for the Zika-related Birth Defects grant ended early (1 year versus the 5 expected years), which limited resources available to complete the data collection. For this reason, facility outreach had to be prioritized to those with the most live births or those with neonatal intensive care units (NICUs) that were more likely to care for infants with complicated medical conditions than those without NICUs. Line lists of potential cases were received from only 70 of 120 facilities. However, these 70 facilities accounted for approximately 88% of the 2016-2017 live births according to vital statistics data for the same period.

The 50 facilities not contacted were further characterized to understand the outstanding population. Of the 50 facilities not contacted for case lists: 10 facilities were later identified as transferring one or more cases to a contacted medical facility, so infants were identified via the transfer facility; 22 facilities had a combined total of only 44 live births for the 2-year period (2016-2017); 4 facilities closed their labor and delivery units in either 2016 or 2017; and 5 of the 50 facilities had a level II NICU. With the level of care required for infants with an NTD meeting case definition or brain anomaly and the low number of facilities not contacted that had NICUs, it's unlikely that a large portion of live birth cases were left unidentified due to limitations on contacting all facilities. However, the facilities not contacted may be more likely to affect fetal death case finding since facilities were targeted based on annual numbers live births and those with NICUs to care for medically complex infants.

Because the case criteria included infants born in 2016 or 2017 and up to 1 year of age, admission dates included the period through December 31, 2018. Due to limited resources, we were unable to recontact a portion of the facilities from which case lists were received prior to the end of 2018. If infants seen at these facilities were not identified as having a Zika-related birth defect until a later date, these infants may not be included in our surveillance data.

Surveillance data collection was supplemented with vital statistics data, and this assisted with identifying additional infants. However, because birth records and fetal death records do not include all Zika-related birth defects for reporting, vital statistics case finding was also limited. Birth records and fetal death records included only 2 of the relevant birth defects: spina bifida and anencephaly. Therefore, infants with other ZrBD brain anomalies or eye anomalies that were not identified via facility outreach would also not be identified via a birth or fetal death certificate search.

Much of the data used for analysis was based upon matching the ZBDS data to other medical or vital record data. Because infants occasionally have name changes after birth and they may visit multiple facilities, matching is dependent upon using remaining available data. In spite of these complications, there was a 100% success rate for matching ZBDS live birth cases to vital statistics birth records, and a 98% success rate matching ZBDS live birth cases to PHC4 admissions data. Only 2% of ZBDS live births were unable to be matched to the PHC4 data.

The dataset that was provided to the bureau by PHC4 after matching was a deidentified dataset. Although a unique DOH-provided identifier was used to link data back to the original ZBDS dataset, any PHC4-specific identifiers were removed, including date of admission, date of discharge, age at admission or discharge, etc., to provide a deidentified dataset. This complicated the effort to determine true rehospitalizations after discharge versus transfers, and multiple assumptions were made for the purpose of data analysis. If a patient had a primary diagnosis code relating to birth (prefix "Z38") during the sequentially first inpatient visit, the visit was considered a birth admission and not a readmission. If the infant had a discharge noted as a transfer to a different facility and the next sequential record reported the patient transferring from a facility, the visit was considered a transfer and not a readmission. If an inpatient admission sequentially followed an outpatient visit, the admission was considered a readmission. If a subsequent inpatient record showed admission from a facility and the prior record showed discharge to home, the subsequent visit was considered a readmission.

Zika-related birth defects comprise a very small subset of birth defects. Infants with other birth defects that do not include a Zika-related birth defect according to CDC criteria are not represented by this report. Because a birth defects surveillance system was not established in Pennsylvania prior to the period in which Zika became a national priority for tracking, it is not possible to compare pre-Zika numbers to evaluate whether an increase in ZrBDs was seen in the state at the height of Zika. Further, infants may have a single birth defect or may be affected by multiple complex birth defects. This report does not attempt to distinguish between facility charges, mortality rates, and other measures that arise directly from ZrBDs versus other coexisting birth defects or other comorbidities. Any severe comorbidities in ZrBD case may therefore elevate the overall apparent impact of ZrBDs. However, given the sample size and span of ZrBDs included, it can be assumed the parameters presented generally represent the population of infants diagnosed with these birth defects, so these numbers provide a useful

reference point. This report is therefore intended to provide a reasonable estimation and means for national or future state comparisons regarding infant and maternal characteristics for Zika-related birth defect cases.

Discussion

This report presents the 2-year findings from Pennsylvania's first ever birth defects surveillance system. During this period, a total of 477 infants with Zika-related birth defects had inpatient and outpatient charges totaling \$182.4 million in the first year of life, and they spent a combined 14 986 days in the hospital. Out of 491 total live birth ZrBD cases, there were 68 deaths occurring within the first year of life, giving a ZrBD infant mortality rate of 138.5 per 1000 live births. This is more than 20 times greater than the statewide infant mortality rate of 6.2 infant deaths per 1000 live births^f reported for 2018 (Pennsylvania Department of Health, 2018). Out of 541 total ZrBD cases, including live births and pregnancy losses, fetal or infant death occurred in 22% of cases.

Of all potential live birth cases reported based upon an ICD-10-CM discharge code or a vital statistics record, 43% were positive. This discrepancy between administrative codes and true cases highlights the importance of active surveillance in accurately estimating overall prevalence. Because Pennsylvania has never previously done active surveillance of birth defects for case confirmation, this is an important first step for the state. It's important to note that many discharge codes that were used to identify potential Zika-related birth defects cases are comprehensive codes that include multiple different types of anomalies. This is demonstrated in the codes list in Appendix A, which shows multiple codes applicable to a single category of birth defect and multiple types of birth defects associated with the same code. The relatively low percentage of true cases is due in large part to this complication in combination with infants that were coded for a birth defect of interest but failed to ultimately meet the ZrBD case definition.

Although only 4% of fetal deaths were later identified as cases, these represented approximately 10% of the total cases in the state. This information is useful in guiding a case ascertainment approach for any future birth defects surveillance programs in Pennsylvania. In comparison, a 2017 Morbidity and Mortality Report (MMWR) study using 2013-2014 pre-Zika data from 2 states and a major metropolitan area found a fetal death rate of 22% among the same birth defect categories.⁸ Pennsylvania's fetal death rate was low in comparison. A portion of this difference may be in part due to unrecognized fetal death cases occurring at facilities that were not contacted.

Of the 33 potential cases identified via VS records that were not identified via ZBDS, 23 were matches, making the positive predictive value (PPV) 70% for these cases. Of the 84 VS records that were also identified via ZBDS, 79 of these were true cases, giving a 94% PPV for those infants coded with a qualifying ICD-10-CM discharge code. The overall PPV for VS identified records, including matched and unmatched to ZBDS records, was 87% (102

^fRefers to all Pennsylvania resident births, including Philadelphia county.

confirmed cases of 117 records). In comparison, a 2011 study using 1995-2005 VS record data found a 96% overall PPV across 6 target birth defects. The 2011 study data differed slightly from Pennsylvania's ZrBD data because it assessed only birth defects that are identifiable at birth, and not all ZrBDs are readily identifiable at birth.

Vital statistics records would have missed 81% of total ZrBD cases in the state as a stand-alone process for case ascertainment. This number reflects the limitations of vital statistics records for identifying birth defects that fall outside of those collected in VS records. However, after record abstraction and case confirmation of records not found via ZBDS, VS records contributed approximately 4% to the total ZrBD cases identified in the state, making it a useful complement to a birth defects surveillance system.

Compared to statewide data, mothers of ZrBD cases were more often young and African American, and they more often smoked, had Medicaid as the primary payor, and had a BMI indicating obesity. These statistics align with other studies suggesting that smoking and obesity are associated with an increased risk for congenital anomalies,^{11,12} while low socioeconomic status is also associated with increased risk for select birth defects.¹³ Infant ZrBD cases were more often male, low birthweight, and premature. Both low birthweight and prematurity are associated with birth defects.¹⁴

Although prevalence of brain and eye abnormalities was similar to those identified in the 2017 MMWR study (1.50 and 0.31, respectively), the prevalence of NTDs in Pennsylvania was statistically significantly lower (MMWR=0.88, PA=0.56). The fetal death rates for all categories except eye anomalies (including NTD, brain, and total) are larger than the statewide average of 8.9 fetal deaths per 1000 live births, with the overall rate for ZrBD cases more than 9 times greater (83.5 per 1000 live births) and the NTD rate more than 27 times greater (242.7 per 1000 live births) than statewide. Similarly, the infant mortality rate for infant with ZrBDs is over 20 times greater in infants with ZrBDs than the statewide average (135.5 infant deaths per 1000 cases versus 6.2 infant deaths per 1000 live births, respectively), while the rate in infants with NTDs (281.6 infant deaths per 1000 ZrBD cases) is more than 45 times greater than statewide. The neonatal and postneonatal mortality rates among infants with NTDs and eye anomalies aligned with the statewide breakdown, with a higher percentage of infant deaths occurring in the neonatal period. However, deaths in infants with ZrBD brain anomalies occurred approximately twice as often in the postneonatal stage than during the neonatal period.

The highest case counts by county align with the most populous counties. Although incidence rates appear to vary, the case counts per county are low and these differences should not be considered significant.

There were 11 infant deaths identified via ZBDS that were not matched to PHC4 data (68 versus 57, respectively). All of these infants had deaths on their dates of birth, while most matched cases had dates of death at a later age.

Readmissions in the ZrBD case population are high with an overall rate of 88%. A 2015 study using 2008 insurance data of New York resident births found a 4.4% infant rehospitalization rate overall.¹⁵ ZrBD cases are more likely to have low birthweight, and the study indicates this can affect rehospitalization rates. However, the highest readmission rate found among the

lowest birthweight category was 24.54%,¹⁵ indicating that low birthweight was not the sole contributor for high rehospitalizations in the ZrBD cases. Many of the infants with ZrBDs were medically complex cases.

Data on inpatient and outpatient charges shows a large difference between average and median values, which often suggests outliers. However, multiple rounds of eliminating outliers produced new outliers in the remaining dataset. For this reason, no outliers were removed, and the dataset was accepted as a highly skewed dataset. Most charges are incurred during the neonatal period. Although infants with brain anomalies incurred the highest average inpatient charges per patient and average length of stay, infants with NTDs incurred the highest average charges per day. Outpatient charges did not contribute a large portion of total overall charges, indicating that most charges are incurred from hospital stays.

The CDC funding period for Zika-related birth defects was unexpectedly shortened for all states from 5 years to 1 year. The Department of Health successfully gained multiple approvals from CDC to extend the original funding for more than 2 years. This allowed the department to build a successful surveillance infrastructure and to complete data collection and analyses on the target infant population to the extent described in this report.

At the time of this report, funding has ended and the birth defects surveillance program is no longer operational. Although additional funding opportunities are periodically available, Zika is no longer considered an emerging threat, and ZrBDs therefore no longer fall under the legislative authority to collect data. Continued surveillance would require making birth defects reportable in Pennsylvania, and revised authority could potentially limit, revise, or expand the scope of surveillance to other critical congenital defects or anomalies of relevance to Pennsylvania.

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Appendix A

List of ICD-10-CM Codes and Descriptions Provided to Facilities for Zika-related Birth Defect Case Finding:

Birth Defect	ICD-10 Code
Microcephaly	Q02
Intracranial Calcifications	Q04.8, Q04.9
Cerebral / Cortical Atrophy	Included in Q04.3
Abnormal Cortical Gyral Patterns	Q04.3, Q04.6, Q04.8
Corpus Callosum Abnormalities	Q04.0
Cerebellar abnormalities	Included in Q04.3
Porencephaly	Q04.6
Hydranencephaly	Included in Q04.3
Ventriculomegaly/Hydrocephaly	Q03.0, Q03.1, Q03.8, Q03.9
Fetal Brain Disruption Sequence	Q02, Q04.8, Q04.9
Other Major Brain Abnormalities	Q04.0, Q04.3-Q04.9, Q07.00, Q07.02
Anencephaly/Acrania	Q00.0, Q00.1, Q00.2
Encephalocele	Q01.0-Q01.9
Spina Bifida without Anencephaly	Q00.0-Q00.2, Q05.0-Q05.9, Q07.01, Q07.03
Holoprosencephaly/Arhinencephaly	Q04.1, Q04.2
Microphthalmia/Anophthalmia	Q11.0, Q11.1, Q11.2
Coloboma	Q12.2, Q13.0, Q14.1-Q14.8
Congenital Cataract	Q12.0
Intraocular Calcification	Q13.81, Q13.89 Q13.9, Q14.1-Q14.9
Chorioretinal Atrophy, Scarring, Pigmentary Changes, Retinitis	Q14.1, Q14.2, Q14.3, Q14.8, Q14.9
Optic Nerve Atrophy, Pallor, other Optic Nerve Abnormalities	Q14.2, H47.03

Inpatient visits for pregnant woman with the following diagnoses:	
Maternal Condition	ICD-10 Code
Intrauterine death affecting management of mother	O36.4XX0-O36.4XX9
Zika virus disease	A92.5
Outcome of delivery, single stillborn	Z37.1
Outcome of delivery, twins one liveborn and one stillborn	Z37.3
Outcome of delivery, twins, both stillborn	Z37.4
Outcome of delivery, other multiple birth, some liveborn	Z37.60-Z37.69
Outcome of delivery, other multiple birth, all stillborn	Z37.7