Medicaid healthcare expenditures for infants with birth defects potentially related to Zika virus infection in North Carolina, 2011–2016

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Abstract

Background: In 2016, Zika virus (ZIKV) was recognized as a human teratogen. North Carolina (NC) had no local transmission of ZIKV but infants with relevant birth defects, including severe brain anomalies, microcephaly, and eye abnormalities, require specialized care and services, the costs of which have not yet been quantified. The objective of this study is to examine NC Medicaid healthcare expenditures for infants with defects potentially related to ZIKV compared to infants with no reported defects.

Methods: Data sources for this retrospective cohort study include NC birth certificates, Birth Defects Monitoring Program data, and Medicaid enrollment and paid claims files. Infants with relevant defects were identified and expenditure ratios were calculated to compare distributions of estimated expenditures during the first year of life for infants with relevant defects and infants with no reported defects.

Results: This analysis included 551 infants with relevant defects and 365,318 infants with no reported defects born 2011–2016. Mean total expenditure per infant with defects was $69,244 (median $30,544) for the first year. The ratio of these expenditures relative to infants with no reported defects was 14.5. Expenditures for infants with select brain anomalies were greater than those for infants with select eye abnormalities only.

Conclusions: Infants with defects potentially related to ZIKV had substantially higher Medicaid expenditures than infants with no reported defects. These results may be informative in the event of a future outbreak and are a resource for program planning related to care for infants in NC.

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Keywords

birth defects; expenditures; Medicaid; North Carolina; Zika virus

1 | INTRODUCTION

In 2016, Zika virus (ZIKV) was recognized as a human teratogen, with infection during pregnancy associated with severe brain anomalies (Rasmussen, Jamieson, Honein, & Peterson, 2016). Infants with these defects may require unique care and access to specialized services, the costs of which have not yet been quantified. Numerous studies have examined hospital expenditures associated with birth defects diagnosis codes (Arth et al., 2017; Basseri et al., 2011; Hook-Dufresne, Yu, Bandla, Imseis, & Moore-Olufemi, 2015; Hsu et al., 2021; Moffitt, Case, Farag, & Canfield, 2015; Russo & Elixhauser, 2007; Shewale et al., 2019; Simeone et al., 2015). One such study analyzed expenditures for patients coded for microcephaly to estimate hospitalization costs following a potential ZIKV outbreak (Shewale et al., 2019). Several studies have used birth defects surveillance data linked to hospital discharge data to calculate hospitalization-related expenditures for infants with selected confirmed birth defects (Peterson et al., 2013; Pinto et al., 2018; Razzaghi, Oster, & Reefhuis, 2015; Weiss et al., 2009). Other studies have examined healthcare expenditures associated with selected birth defects (most commonly orofacial clefts or spina bifida) using health insurance claims data for a single payer (Medicaid), health plan, or multiple private payers (Boulet, Grosse, Honein, & Correa-Villaseñor, 2009; Boulet, Grosse, Riehle-Colarusso, & Correa-Villaseñor, 2010; Cassell, Grosse, Thorpe, Howell, & Meyer, 2011; Cassell, Meyer, & Daniels, 2008; Grosse, Waitzman, Yang, Abe, & Barfield, 2017; Ireys, Anderson, Shaffer, & Neff, 1997; Neff, Sharp, Muldoon, Graham, & Myers, 2004; Ouyang, Grosse, Armour, & Waitzman, 2007). Studies of all types have demonstrated disproportionately greater expenditures for children with birth defects compared to unaffected children.

In North Carolina (NC), statewide surveillance efforts during the ZIKV outbreak in the Americas included rapid surveillance of all birth defects potentially related to ZIKV, regardless of ZIKV exposure. While NC had no localized cases, the availability of data from both rapid surveillance and prior routine surveillance of these defects facilitates the monitoring of potential ZIKV cases not detected by laboratory testing. These data also enable us to examine other health-related outcomes for infants with these conditions, such as service utilization and costs to the healthcare system.

This study examines Medicaid healthcare expenditures for infants with birth defects potentially related to ZIKV and for infants with no reported birth defects. This examination will inform our understanding of the population-level economic burden of this group of birth defects. Our primary objectives are to (a) determine the number of recognized birth defects potentially related to ZIKV among the NC infant Medicaid population, (b) identify demographic and clinical differences between infants with birth defects potentially related to ZIKV and infants with no reported birth defects, (c) compare the distributions of estimated expenditures during the first year of life for infants with birth defects potentially related to

ZIKV and for infants with no reported birth defects, and (d) compare estimated expenditures across birth defect categories.

2 | METHODS

Data sources for this retrospective cohort study include NC Birth Defects Monitoring Program (NCBDMP) registry data, NC Medicaid enrollment records and paid claims, and NC birth certificate records. The NC Composite Linked Birth File, maintained by the NC State Center for Health Statistics, consists of all NC-resident birth certificates linked to maternal and infant Medicaid paid claims and health department service data. For birth years 2011–2016, 56.6% of infants were matched to Medicaid records.

This analysis includes NC-resident infants who were continuously enrolled in Medicaid during their first year of life and were born in NC between January 1, 2011 and December 31, 2016 (Figure 1). These data were used because they were the most recent years of complete data available. Continuous enrollment was defined as being enrolled in Medicaid for at least 11 months (334 of 365 days) during infancy. Infants who died prior to their first birthday and infants who were not continuously enrolled in Medicaid were excluded to ensure that the sample included infants with a full year of data only.

Infants in the NCBDMP registry with at least one documented British Pediatric Association (BPA) code indicating a birth defect potentially related to ZIKV (microcephaly, other brain abnormalities, or eye abnormalities) were included. Eligible BPA codes were defined in accordance with updated guidance from the Centers for Disease Control and Prevention (CDC) as selected brain anomalies with or without microcephaly (<3rd percentile) and selected eye abnormalities (Olson et al., 2019) (Table 1). Infants with other birth defects not potentially related to ZIKV, such as neural tube defects, were excluded.

All diagnoses were documented in maternal and infant medical records (up to 1 year of age) made available to NCBDMP through the Program's routine surveillance. Trained NCBDMP field staff abstracted records and assigned BPA codes. For this analysis, diagnostic details for all microcephaly and hydrocephaly diagnoses were reviewed for case inclusion. Microcephaly cases were excluded if head circumference measurements at birth were missing or greater than the third percentile for the infan's gestational age and sex (based on INTERGROWTH-21st standards; Villar et al., 2014). Hydrocephaly cases noted as mild in the absence of other brain anomalies were excluded as well, consistent with the CDC's case definition for ZIKV-related birth defect surveillance.

Demographic and clinical characteristics were examined for infants in the Medicaid population with birth defects potentially related to ZIKV compared to infants with no reported birth defects. The following variables were obtained from the infant's birth certificate information: maternal age (<20 years, 20–29 years, 30–39 years, or 40 years), maternal education (<high school diploma, high school diploma or GED, or >high school diploma), maternal race/ethnicity (non-Hispanic white, non-Hispanic Black, Hispanic, or other), number of living children in addition to the index infant (0, 1, or 2), maternal marital status (married or not married), initiation of prenatal care in the first trimester

(yes, no, or no prenatal care), birthweight, gestational age, infant sex, hospital size (<500, 500–999, 1,000–1,999, or 2000 average births per year), and perinatal care region of residence, which represents regional referral networks of perinatal care across the state (western, southwestern, eastern, southeastern, northeastern, northwestern). Relationships between maternal, infant, and health system characteristics among cases and controls were assessed using a chi-square test. A *p*-value <.05 was considered statistically significant. For each of the chi-square statistical tests, infants with missing data were dropped. Infants included in the cost analysis had all diagnostic expenditure information available but may or may not have had complete data for all demographic variables.

The main outcomes of interest were overall Medicaid expenditures over the first 60 days of life and overall Medicaid expenditures over the first year of life (365 days). Overall expenditures are a composite measure including hospital (inpatient facility) claims, outpatient facility claims, professional/physician service claims (including both inpatient and outpatient), outpatient drug and pharmacy claims, management fee claims, and any other claims not included in these categories. We calculated mean and median expenditures along with standard deviations and interquartile ranges. Infants missing information on expenditures were excluded.

The Personal Health Care (overall) price index was used to adjust pooled Medicaid expenditures to 2016 prices (Agency for Healthcare Research and Quality [AHRQ], n.d.; Dunn et al., 2018). Inflation-adjusted total paid claims and categories of inpatient facility services (including inpatient pharmacy), outpatient facility services, professional/physician services, and outpatient drug/pharmacy paid claims over the first 60 and 365 days of life were examined.

Expenditure ratios were calculated to compare mean expenditures for infants with diagnosed birth defects potentially related to ZIKV with expenditures for infants who had no diagnosed birth defects, for the overall sample and stratified by gestational age (<37 and 37 weeks). These ratios were evaluated for statistical significance using the Wilcoxon-Mann–Whitney test. A *p*-value <.05 was considered statistically significant.

Mean and median expenditure and range in dollars by claim service category were also tabulated for infants with select brain anomalies with or without microcephaly and for infants with select eye abnormalities only.

This study was conducted as part of routine surveillance linkages undertaken through an interagency agreement between the NC Divisions of Public Health and Health Benefits, and determined to be non-research public health surveillance exempt from review by the North Carolina Division of Public Health Institutional Review Board.

3 | RESULTS

The analysis included 365,869 NC-resident infants who were born in-state from 2011 to 2016 and were continuously enrolled in Medicaid during their first year of life. Of these, 365,318 infants had no birth defect diagnoses and 551 infants had birth defects potentially

related to ZIKV. Demographic and clinical characteristics of these two groups of infants are displayed in Table 2.

Non-Hispanic white infants made up a greater proportion of infants with birth defects potentially related to ZIKV (51.5%) compared to infants with no reported birth defects (40.5%). Of all infants with birth defects potentially related to ZIKV, 5.6% were born to women with no prenatal care, in contrast to 2.2% of infants with no reported birth defects. Of the infants with birth defects potentially related to ZIKV, 32.7% had a gestational age of <37 weeks and 31.2% had a birthweight of less than 2,500 g. In contrast, 9.9% of infants with no reported birth defects were considered preterm and 9.3% had a low birthweight. While most infants in this analysis were born in the largest hospitals (hospitals with at least 2,000 births per year), a greater proportion of infants with birth defects potentially related to ZIKV were born at these hospitals (77.4%) compared to infants with no reported birth defects (52.7%).

Mean total expenditure per infant with birth defects potentially related to ZIKV was $34,836 for the first 60 days (median of $11,192) and $69,244 (median of $30,544) for the first year (Table 3). The ratio of mean expenditures during the first year relative to infants with no reported birth defects ($4,771) was 14.5. Mean inpatient facility claims per infant with birth defects potentially related to ZIKV was 14.2 times that of an infant with no reported birth defects during the first 60 days ($28,031 vs. $1,977), and 18.1 times that of an infant with no reported birth defects during the first year ($39,156 vs. $2,159). Inpatient facility fees, which do not include professional/physician fees for inpatient care, comprised about half of total annual expenditures for both groups. Across claim types, expenditure ratios at 60 days were similar to expenditure ratios in the first year except for drug/pharmacy, which had an expenditure ratio of 2.9 for the first 60 days and 22.4 for the first year.

Mean total expenditure per infant with birth defects potentially related to ZIKV and a gestational age of <37 weeks was $93,209 (median of $50,669) for the first year (Table 4a). The ratio of mean expenditures during the first year relative to preterm infants with no reported birth defects ($17,366) was 5.4. For infants with a gestational age of 37 weeks or more, the mean total expenditure per infant with birth defects potentially related to ZIKV was $57,749 (median of $21,016) for the first year (Table 4b). The ratio of mean expenditures during the first year relative to term infants with no reported birth defects ($3,384) was 17.1.

Mean expenditure per infant with select brain anomalies with or without microcephaly was greater across most expenditure categories than the mean expenditure per infant with select eye abnormalities only (Table 5). During the first year, mean total expenditure was $74,875 (median of $32,109) per infant with select brain anomalies with or without microcephaly and $46,412 (median of $16,375) per infant with eye abnormalities only. Mean inpatient facility expenditure per infant with select brain anomalies with or without microcephaly was more than twice that of mean inpatient expenditure per infant with select eye abnormalities only ($43,657 vs. $20,907).

4 | DISCUSSION

In this study, we found infants born in NC during 2011–2016 with birth defects potentially related to ZIKV had substantially higher Medicaid expenditures than infants with no reported birth defects. A total of 551 eligible infants with relevant birth defects were continuously enrolled in Medicaid during this study period. Total expenditures during the first year averaged $69,244 per infant, 14.5 times that of infants with no reported birth defects. Expenditure ratios ranged from 8.2 to 22.4 across claims categories, consistent with other studies comparing infants with birth defects to unaffected infants (Boulet et al., 2009; Boulet et al., 2010; Cassell et al., 2008; Cassell et al., 2011; Ouyang et al., 2007). Inpatient facility claims accounted for the majority of expenditures during infancy, followed by professional/ physician services; during infancy most physician claims were likely associated with inpatient services. Inpatient and physician claims together comprised 75% of expenditures during infancy for infants with birth defects potentially related to ZIKV and 78% for infants with no reported birth defects. Across most categories, expenditure ratios at 60 days were similar to expenditure ratios in the first year of life, except for drug/ pharmacy claims, which were much more likely to occur after the first 60 days. For infants with relevant birth defects and infants with no reported birth defects, most expenditures during the first 60 days (including the delivery hospitalization) were for inpatient facility claims.

Within this population of Medicaid-enrolled infants, there were some differences in sociodemographic and clinical characteristics between those with birth defects potentially related to ZIKV and those with no reported birth defects. Infants with birth defects potentially related to ZIKV were more likely to be born to women with greater than a high school education, no other living children, women with no prenatal care or initiation of care after the first trimester, and women of non-Hispanic white race/ethnicity. These infants were also more likely to be delivered in a larger hospital and were more than three times as likely to have been born at low birthweight or preterm. Infants with major birth defects such as microcephaly are more likely to be born preterm, with shorter gestation likely resulting from the occurrence of a fetal anomaly (Honein et al., 2009).

It is well known that expenditures are typically much higher for infants with low birthweight or short gestations (Grosse et al., 2017). In this analysis, we stratified by gestational age because higher expenditures associated with major birth defects may be mediated by shortened gestations and because gestational age may be an effect modifier of the association (Grosse et al., 2017). We found evidence of effect modification, with birth defects-related expenditure ratios attenuated among infants born preterm relative to infants born at term. Nonetheless, total expenditures were still over five times higher for infants with birth defects potentially related to ZIKV who were born preterm compared to infants born preterm with no reported birth defects. Among both infants with birth defects potentially related to ZIKV and infants with no reported birth defects, expenditures were higher for those born preterm.

The results stratified by categories of birth defects potentially related to ZIKV showed that infants with select brain anomalies with or without microcephaly had higher medical

expenditures during an infan's first year of life when compared to medical expenditures for infants with select eye abnormalities only. These findings suggest that infants with select brain anomalies with or without microcephaly require more inpatient care or more complex medical procedures during their first year of life compared to infants with select eye abnormalities only. This may be because infants with brain anomalies are likely to have other comorbidities, such as seizures and difficulty swallowing, that require imaging or other tests as well as medical therapies, while infants with eye abnormalities only are managed more conservatively during the first year of life.

The study was restricted to infants enrolled in Medicaid and included live births with documented diagnoses available to NCBDMP, and NC Medicaid claims data obtained for billing purposes only. The use of Medicaid data limits the generalizability of these estimates as findings could be different for infants covered by other public insurance or private insurance. NC Medicaid expenditures may differ from other state Medicaid program expenditures due to variations in Medicaid reimbursement policies and rates. Cost categories included in this study differ slightly from those used in previous studies focused on Medicaid expenditures within NC (Cassell et al., 2008; Cassell et al., 2011), though other studies have examined similar categories of service (Neff et al., 2004). Additionally, microcephaly and hydrocephaly inclusion were reliant on physician diagnosis by age one; there is a possibility that additional infants with defects eligible for inclusion in this study were missed, although defects of this severity would likely be detected early. Infants who died prior to age one were also excluded, as full-year expenditures were the focus of this study. Studies of costs associated with other neonatal conditions have reported that first-year costs may be either higher or lower for decedents than for survivors, depending on the level of medical complexity. For example, Phibbs et al. (2019) reported that in California, average hospital costs during infancy were substantially higher for survivors than decedents for gestational ages under 30 weeks whereas costs were considerably lower for survivors at gestational ages greater than 32 weeks. Additional analyses could explore first-year costs for decedents excluded from this study.

This study had several strengths, including the use of a population-based cohort of Medicaid-enrolled infants linked to birth defects registry data from an active surveillance program. The demographic fields describing maternal characteristics in Table 2 are drawn from linked birth records, a high-quality data source. Additional record review of microcephaly and hydrocephaly cases was conducted to ensure included cases met CDC's definition of brain anomalies with or without microcephaly (<3rd percentile) and eye abnormalities which may be potentially related to ZIKV. Over half of all births in NC are financed by Medicaid and Medicaid costs accounted for approximately 30% of the state budget in 2019 (Kaiser Family Foundation, 2019; Kaiser Family Foundation, 2020). In addition to better understanding the ways that maternal and child health are related to state finances, studies utilizing Medicaid claims data provide insights into the health care utilization and expenditures for some of the most vulnerable Americans.

This study offers a unique insight into NC Medicaid expenditures for infants with the select brain anomalies with or without microcephaly and the select eye abnormalities included in this study. While NC did not experience any local transmission of ZIKV, this examination

broadly informs our understanding of the population-level economic burden of this group of birth defects which may be useful in the event of a future outbreak.

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DATA AVAILABILITY STATEMENT

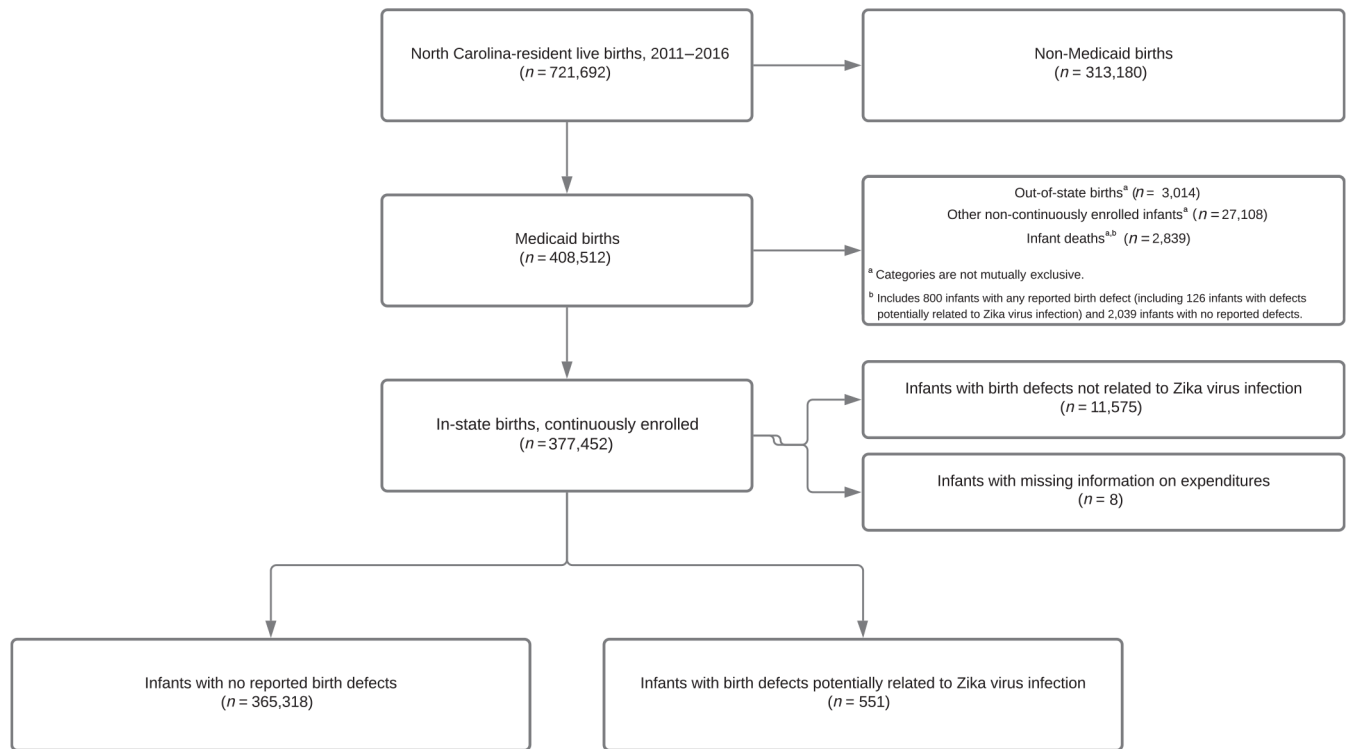The data that support the findings of this study are not publicly available due to privacy restrictions.

REFERENCES

Agency for Healthcare Research and Quality. (n.d.). Medical expenditure panel survey. Retrieved from https://www.meps.ahrq.gov/about_meps/Price_Index.shtml

Arth AC, Tinker SC, Simeone RM, Ailes EC, Cragan JD, & Grosse SD (2017). Inpatient hospitalization costs associated with birth defects among persons of all ages—United States, 2013. Morbidity and Mortality Weekly Report, 66(2), 41–46. 10.15585/mmwr.mm6602a1 [PubMed: 28103210]

Basseri B, Kianmahd BD, Roostaeian J, Kohan E, Wasson KL, Basseri RJ, & Bradley JP (2011). Current national incidence, trends, and health care resource utilization of cleft lip–cleft palate. Journal of the American Society of Plastic Surgeons, 127, 1255. 10.1097/PRS.0b013e3182043af6

Boulet SL, Grosse SD, Honein MA, & Correa-Villaseñor A (2009). Children with orofacial clefts: Health-care use and costs among a privately insured population. Public Health Reports, 124(3), 447–453. 10.1177/003335490912400315 [PubMed: 19445422]

Boulet SL, Grosse SD, Riehle-Colarusso T, & Correa-Villaseñor A (2010). Health care costs of congenital heart defects. In Wyszynski DF, Correa-Villaseñor A, & Graham TP (Eds.), Congenital heart defects: From origin to treatment (pp. 493–501). New York, NY: Oxford University Press, Inc.

Cassell CH, Grosse SD, Thorpe PG, Howell EE, & Meyer RE (2011). Health care expenditures among children with and those without spina bifida enrolled in Medicaid in North Carolina. Birth Defects Research. Part A, Clinical and Molecular Teratology, 91(12), 1019–1027. 10.1002/bdra.22864 [PubMed: 22021073]

Cassell CH, Meyer R, & Daniels J (2008). Health care expenditures among Medicaid enrolled children with and without orofacial clefts in North Carolina, 1995–2002. Birth Defects Research. Part A, Clinical and Molecular Teratology, 82(11), 785–794. 10.1002/bdra.20522 [PubMed: 18985685]

Dunn A, Grosse SD, & Zuvekas SH (2018). Adjusting health expenditures for inflation: A review of measures for health services research in the United States. Health Services Research, 53(1), 175–196. 10.1111/1475-6773.12612 [PubMed: 27873305]

Grosse SD, Waitzman NJ, Yang N, Abe K, & Barfield WD (2017). Employer-sponsored plan expenditures for infants born preterm. Pediatrics, 140(4), e20171078. 10.1542/peds.2017-1078 [PubMed: 28933347]

Honein MA, Kirby RS, Meyer RE, Xing J, Skerrette NI, Yuskiv N, … Network NBDP (2009). The association between major birth defects and preterm birth. Maternal and Child Health Journal, 13(2), 164–175. 10.1007/s10995-008-0348-y [PubMed: 18484173]

Hook-Dufresne DM, Yu X, Bandla V, Imseis E, & Moore-Olufemi SD (2015). The economic burden of gastroschisis: Costs of a birth defect. The Journal of Surgical Research, 195(1), 16–20. 10.1016/j.jss.2015.01.036 [PubMed: 25703160]

Hsu WH, Sommerhalter KM, McGarry CE, Farr SL, Downing KF, Lui GK, … Van Zutphen AR (2021). Inpatient admissions and costs for adolescents and young adults with congenital heart defects in New York, 2009–2013. Birth Defects Research, 113(2), 173–188. 10.1002/bdr2.1809 [PubMed: 32990389]

Ireys HT, Anderson GF, Shaffer TJ, & Neff JM (1997). Expenditures for care of children with chronic illnesses enrolled in the Washington State Medicaid program, fiscal year 1993. Pediatrics, 100(2 Pt 1), 197–204. 10.1542/peds.100.2.197 [PubMed: 9240799]

Kaiser Family Foundation. (2019). Medicaid expenditures as a percent of total state expenditures by fund. Retrieved from https://www.kff.org/medicaid/state-indicator/medicaid-expenditures-as-a-percent-of-total-state-expenditures-by-fund

Kaiser Family Foundation. (2020). Births financed by Medicaid. Retrieved from https://www.kff.org/medicaid/state-indicator/births-financed-by-medicaid

Moffitt KB, Case AP, Farag NH, & Canfield MA (2015). Hospitalization charges for children with birth defects in Texas, 2001 to 2010. Birth Defects Research. Part A, Clinical and Molecular Teratology, 106(3), 155–163. 10.1002/bdra.23470 [PubMed: 26690723]

Neff JM, Sharp VL, Muldoon J, Graham J, & Myers K (2004). Profile of medical charges for children by health status group and severity level in a Washington State Health Plan. Health Services Research, 39(1), 73–89. 10.1111/j.1475-6773.2004.00216.x [PubMed: 14965078]

Olson SM, Delaney A, Jones AM, Carr CP, Liberman RF, Forestieri NE, … Cragan JD (2019). Updated baseline prevalence of birth defects potentially related to Zika virus infection. Birth Defects Research, 111(13), 938–940. 10.1002/bdr2.1546 [PubMed: 31264801]

Ouyang L, Grosse SD, Armour BS, & Waitzman NJ (2007). Health care expenditures of children and adults with spina bifida in a privately insured U.S. population. Birth Defects Research. Part A, Clinical and Molecular Teratology, 79(7), 552–558. 10.1002/bdra.20360 [PubMed: 17335056]

Peterson C, Dawson A, Grosse SD, Riehle-Colarusso T, Olney RS, Tanner JP, … Cassell CH (2013). Hospitalizations, costs, and mortality among infants with critical congenital heart disease: How important is timely detection? Birth Defects Research Part A, Clinical and Molecular Teratology, 97(10), 664–672. 10.1002/bdra.23165 [PubMed: 24000201]

Phibbs CS, Schmitt SK, Cooper M, Gould JB, Lee HC, Profit J, & Lorch SA (2019). Birth Hospitalization Costs and Days of Care for Mothers and Neonates in California, 2009–2011. The Journal of Pediatrics, 204, 118–125.e14. 10.1016/j.jpeds.2018.08.041 [PubMed: 30297293]

Pinto NM, Waitzman N, Nelson R, Minich LL, Krikov S, & Botto LD (2018). Early childhood inpatient costs of critical congenital heart disease. The Journal of Pediatrics, 203, 371–379.e7. 10.1016/j.jpeds.2018.07.060 [PubMed: 30268400]

Rasmussen SA, Jamieson DJ, Honein MA, & Petersen LR (2016). Zika virus and birth defects—reviewing the evidence for causality. New England Journal of Medicine, 374(20), 1981–1987. 10.1056/NEJMsr1604338 [PubMed: 27074377]

Razzaghi H, Oster M, & Reefhuis J (2015). Long-term outcomes in children with congenital heart disease: National Health Interview Survey. The Journal of Pediatrics, 166(1), 119–124. 10.1016/j.jpeds.2014.09.006 [PubMed: 25304924]

Russo CA, & Elixhauser A (2007). Hospitalizations for birth defects, 2004: Statistical brief #24. In Healthcare cost and utilization project (HCUP) statistical briefs. Rockville (MD): Agency for Healthcare Research and Quality (US).

Shewale JB, Ganduglia Cazaban CM, Waller DK, Mitchell LE, Langlois PH, & Agopian AJ (2019). Microcephaly inpatient hospitalization and potential Zika outbreak in Texas: A cost and predicted economic burden analysis. Travel Medicine and Infectious Disease, 30, 67–72. 10.1016/j.tmaid.2019.01.001 [PubMed: 30639780]

Simeone RM, Oster ME, Hobbs CA, Robbins JM, Collins RT, & Honein MA (2015). Population-based study of hospital costs for hospitalizations of infants, children, and adults with a congenital heart defect, Arkansas 2006 to 2011. Birth Defects Research. Part A, Clinical and Molecular Teratology, 103(9), 814–820. 10.1002/bdra.23379 [PubMed: 26069215]

Villar J, Ismail LC, Victora CG, Ohuma EO, Bertino E, … Kennedy SH (2014). International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. The Lancet, 384(9946), 857–868. 10.1016/s0140-6736(14)60932-6

Weiss J, Kotelchuck M, Grosse SD, Manning SE, Anderka M, Wyszynski DF, … Higgins C (2009). Hospital use and associated costs of children aged zero-to-two years with craniofacial malformations in Massachusetts. Birth Defects Research. Part A, Clinical and Molecular Teratology, 85(11), 925–934. 10.1002/bdra.20635 [PubMed: 19830851]

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┌─────────────────────────────────┐          ┌─────────────────────────────────┐
│ North Carolina-resident live     │─────────▶│ Non-Medicaid births              │
│ births, 2011–2016                │          │ (n = 313,180)                    │
│ (n = 721,692)                    │          │                                  │
└─────────────────────────────────┘          └─────────────────────────────────┘
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Out-of-state births[a] (n = 3,014)
Other non-continuously enrolled infants[a] (n = 27,108)
Infant deaths[a,b] (n = 2,839)

[a] Categories are not mutually exclusive.

[b] Includes 800 infants with any reported birth defect (including 126 infants with defects potentially related to Zika virus infection) and 2,039 infants with no reported defects.

Medicaid births
(n = 408,512)

In-state births, continuously enrolled
(n = 377,452)

Infants with birth defects not related to Zika virus infection
(n = 11,575)

Infants with missing information on expenditures
(n = 8)

Infants with no reported birth defects
(n = 365,318)

Infants with birth defects potentially related to Zika virus infection
(n = 551)

FIGURE 1.

Flow diagram showing criteria used to identify infants for retrospective cohort study

TABLE 1

Grouping of birth defects potentially related to Zika virus infection and associated British Pediatric Association (BPA) codes

Birth defects	BPA codes[a]
Brain abnormalities or microcephaly	
Microcephaly[b]	742.100
Reduction defects of brain[c]	742.200–742.250, 742.280–742.290
Hydranencephaly[d]	742.300–742.387, 742.389–742.390
Other major brain abnormalities[e]	742.410–742.480, 742.486, 742.900
Eye abnormalities	
Microphthalmia/Anophthalmia	743.000–743.104
Congenital cataract	743.320–743.326, 743.340–743.344
Coloboma	743.430–743.434, 743.480–743.494
Retinal abnormalities	743.510–743.527, 743.529–743.594

[a]Possible/probable codes excluded.

[b]<3rd percentile for gestational age and sex at birth.

[c]Cerebral atrophy, corpus callosum abnormalities, hypothalamus abnormalities, cerebellar abnormalities, agyria and lissencephaly, microgyria/polymicrogyria, other reduction defects.

[d]Excludes isolated mild ventriculomegaly without other brain defects.

[e]Porencephaly and other specified anomalies of the brain.

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TABLE 2

Selected characteristics of infants with birth defects potentially related to Zika virus infection and infants with no reported birth defects during the first year of life in North Carolina, 2011–2016

Maternal characteristic	Infants with birth defects potentially related to Zika virus infection (*n* = 551)	Infants with no reported birth defects (*n* = 365,318)	*p*-value
Age			
<20 years	66 (12.0)	44,313 (12.1)	
20–29 years	326 (59.2)	225,702 (61.8)	
30–39 years	146 (26.5)	88,984 (24)	
40 years	13 (2.4)	6,310 (1.7)	
Education			.03 *
<High school diploma	140 (25.5)	100,584 (27.6)	
High school diploma or GED	158 (28.8)	117,308 (32.2)	
>High school diploma	251 (45.7)	146,622 (40.2)	
Race/ethnicity			<.001 *
White/non-Hispanic	284 (51.5)	148,058 (40.5)	
Black/non-Hispanic	165 (30.0)	121,050 (33.1)	
Hispanic	84 (15.3)	79,428 (21.7)	
Asian/PI/AIAN/other	18 (3.3)	16,782 (4.6)	
Number of other living children			.02 *
0	239 (43.4)	136,905 (37.5)	
1	146 (26.5)	107,513 (29.4)	
2	166 (30.1)	120,849 (33.1)	
Marital status			.06
Married	214 (38.9)	128,062 (35.1)	
Not married	336 (61.1)	237,102 (64.9)	
Initiation of prenatal care in the first trimester			<.001 *
Yes	282 (52.4)	221,404 (61.3)	
No	226 (42.0)	132,239 (36.6)	
No prenatal care	30 (5.6)	7,752 (2.2)	
Infant characteristic			

	Infants with birth defects potentially related to Zika virus infection (*n* = 551)	Infants with no reported birth defects (*n* = 365,318)	*p*-value
Birthweight/gestational age			<.001 [*]
<2,500 g, preterm (<37 weeks)	134 (24.3)	21,617 (5.9)	
<2,500 g, term (37 weeks)	38 (6.9)	12,439 (3.4)	
2,500 g, preterm (<37 weeks)	46 (8.4)	14,599 (4.0)	
2,500 g, term (37 weeks)	333 (60.4)	316,617 (86.7)	
Sex			.06
Female	294 (53.4)	180,344 (49.4)	
Male	257 (46.6)	184,973 (50.6)	
Healthcare system characteristic			
Hospital size			<.001 [*]
<500 births per year	25 (4.6)	42,004 (11.6)	
500–999 births per year	41 (7.5)	57,396 (15.8)	
1,000–1999 births per year	58 (10.6)	72,752 (20.0)	
2000 births per year	424 (77.4)	191,552 (52.7)	
Perinatal care region			<.002 [*]
Western	43 (7.8)	27,067 (7.4)	
Southwestern	71 (12.9)	71,126 (19.5)	
Eastern	79 (14.3)	54,405 (14.9)	
Southeastern	102 (18.5)	54,535 (14.9)	
Northeastern	119 (21.6)	69,036 (18.9)	
Northwestern	137 (24.9)	89,149 (24.4)	

[*]
p < 0.05 by chi-square test.

Table 3

Mean and median expenditure and range in 2016 dollars by claim service category for Medicaid-enrolled infants with birth defects potentially related to Zika virus infection and Medicaid-enrolled infants with no reported birth defects during the first year of life in North Carolina, 2011–2016

Claim service category	Infants with birth defects potentially related to Zika virus infection (n = 551)			Infants with no reported birth defects (n = 365,318)			
	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range	Mean expenditure ratio
<60 days							
Total paid	34,836 (81,129)	11,192 (33,462)	2–1,226,719	2,889 (9,401)	1,233 (690)	0–1,198,903	12.1 *
Inpatient facility	28,031 (75,773)	6,389 (26,266)	0–1,176,938	1,977 (8,236)	586 (308)	0–1,176,231	14.2 *
Outpatient facility	377 (989)	0 (319)	0–10,084	59 (225)	0 (19)	0–17,357	6.4 *
Professional/physician	5,765 (7,439)	2,477 (7,453)	0–49,763	682 (1,552)	410 (314)	0–36,900	8.5 *
Drug/pharmacy	38 (162)	0 (16)	0–2,113	13 (105)	0 (0)	0–32,321	2.9 *
<365 days							
Total paid	69,244 (134,362)	30,544 (64,056)	21–2,107,324	4,771 (13,809)	2,541 (2,044)	0–3,191,215	14.5 *
Inpatient facility	39,156 (106,890)	13,795 (32,172)	0–1,925,587	2,159 (10,193)	587 (338)	0–2,580,705	18.1 *
Outpatient facility	3,213 (4,018)	1,860 (3,806)	0–26,637	334 (807)	98 (360)	0–136,750	9.6 *
Professional/physician	12,932 (20,227)	6,774 (11,519)	0–188,971	1,576 (2,529)	1,204 (830)	0–167,985	8.2 *
Drug/pharmacy	5,164 (24,171)	254 (1,603)	0–294,689	231 (2,188)	47 (146)	0–544,974	22.4 *

*
$p < 0.05$ by chi-square test.

TABLE 4

Mean and median expenditure and range in 2016 dollars by claim service category for Medicaid-enrolled (a) preterm infants (<37 weeks) with birth defects potentially related to Zika virus infection and with no reported birth defects and (b) term infants (≥37 weeks) with birth defects potentially related to Zika virus infection and with no reported birth defects in North Carolina, 2011–2016

(a)

Claim service category	Preterm infants with birth defects potentially related to Zika virus infection (n = 180)			Preterm infants with no reported birth defects (n = 36,226)			
	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range	Mean expenditure ratio
<365 days							
Total paid	93,209 (113,458)	50,669 (78,095)	21–628,128	17,366 (33,406)	6,877 (13,439)	0–1,290,659	5.4 *
Inpatient facility	54,916 (80,716)	28,238 (40,951)	0–484,195	11,402 (24,947)	3,382 (9,871)	0–1,176,231	4.8 *
Outpatient facility	2,750 (3,463)	1,650 (3,480)	0–18,259	494 (1,067)	161 (509)	0–36,077	5.6 *
Professional/ physician	19,130 (23,047)	11,481 (21,219)	0–188,450	3,867 (6,801)	1,940 (2,679)	0–167,985	4.9 *
Drug/ pharmacy	6,311 (24,052)	648 (5,190)	0–265,077	803 (3,587)	63 (222)	0–328,699	7.9 *

(b)

Claim service category	Term infants with birth defects potentially related to Zika virus infection (n = 370)			Term infants with no reported birth defects (n = 328,835)			
	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range	Mean expenditure ratio
<365 days							
Total paid	57,749 (142,272)	21,016 (43,599)	84–2,107,324	3,384 (8,335)	2,433 (1,507)	0–3,191,215	17.1 *
Inpatient facility	31,579 (116,994)	7,232 (21,565)	0–1,925,587	1,141 (6,034)	580 (276)	0–2,580,705	27.7 *
Outpatient facility	3,444 (4,252)	2,072 (3,941)	0–26,637	316 (771)	92 (346)	0–136,750	10.9 *
Professional/ physician	9,947 (18,004)	5,058 (8,307)	0–188,971	1,324 (1,168)	1,172 (762)	0–104,180	7.5 *
Drug/pharmacy	4,620 (24,273)	181 (947)	0–294,689	168 (1,965)	46 (140)	0–544,974	27.5 *

*
$p < .05$ by Wilcoxon–Mann–Whitney test.

TABLE 5

Mean and median expenditure and range in 2016 dollars by claim service category for infants enrolled in Medicaid with either select brain anomalies with or without microcephaly or with select eye abnormalities only,[a] North Carolina, 2011–2016

Claim service category	Infants with select brain anomalies with or without microcephaly (n = 442)			Infants with select eye abnormalities only (n = 109)		
	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range
<365 days						
Total paid	74,875 (144,639)	32,109 (66,237)	177–2,107,324	46,412 (76,520)	16,375 (39,173)	21–412,923
Inpatient facility	43,657 (117,501)	15,533 (33,748)	0–1,925,587	20,907 (37,281)	4,131 (24,823)	0–195,193
Outpatient facility	3,184 (4,059)	1,788 (3,696)	0–26,637	3,327 (3,862)	2,187 (4,346)	0–17,385
Professional/physician	13,867 (21,717)	7,459 (11,965)	0–188,971	9,140 (11,817)	4,722 (9,402)	0–70,886
Drug/pharmacy	5,637 (26,379)	242 (1,610)	0–294,689	3,247 (11,362)	272 (1,090)	0–111,542

[a]Expenditures by mutually exclusive defect categories: (a) select brain anomalies (defined by CDC/BPA codes 742.200–742.250, 742.280–742.290, 742.300–742.387, 742.389–742.390, 742.410–742.480, 742.486, and 742.900) with or without microcephaly (defined by CDC/BPA code 742.100 with head circumference at delivery <3rd percentile for sex and gestational age), and (b) select eye abnormalities without mention of a brain abnormality (eye abnormalities defined by CDC/BPA codes 743.000–743.104, 743.320–743.326, 743.340–743.344, 743.430–743.434, 743.480–743.494, 743.510–743.527, and 743.529–743.594).