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TITLE: Congenital Infections as Contributors to the Onset of Diabetes in Children: A Longitudinal Study in the United States, 2001-2017

RUNNING HEAD: Congenital Infections and Diabetes

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## ABSTRACT

**Background:** Maternal infections during pregnancy, particularly with rubella virus, were reported to increase the risk of diabetes in children. Widespread vaccination has decreased the number of infants with congenital rubella syndrome in the United States, although it remains a problem in developing countries. Because vaccine hesitancy has recently increased, we investigated the association between congenital infections with subsequent diabetes risk in children in the United States.

**Methods:** Using data from a nationwide private health insurer for years 2001-2017, 1,475,587 infants were followed for an average of 3.9 years (maximum 16.5 years). Information was obtained regarding congenital infections (rubella, cytomegalovirus, other congenital infections) and perinatal infections, as well as for the development of diabetes mellitus and diabetic ketoacidosis.

**Results:** There were 781 infants with congenital infections and 73,974 with perinatal infections. Diabetes developed in 3,334 children. The odds of developing diabetes for infants with congenital rubella infection were 12 fold greater ( $P=0.013$ ) and, for infants with congenital cytomegalovirus infection, were 4 fold greater ( $P=0.011$ ) than infants without congenital or perinatal infection. Infants with other congenital infections had 3-fold greater odds of developing diabetes ( $P=0.044$ ). Results were similar for diabetes ketoacidosis. Infants with

other perinatal infections had 49% greater odds of developing diabetes during the follow-up period ( $P < 0.001$ ).

**Conclusion:** Congenital and other perinatal infections are associated with elevated risks of developing diabetes mellitus during childhood. Vaccination for rubella remains an important preventive action to reduce the incidence of diabetes in children.

## INTRODUCTION

Prior to widespread vaccination, maternal infections during pregnancy, particularly with rubella virus, were reported to increase the risk of diabetes in children.<sup>1</sup> Long-term observation of individuals with congenital rubella syndrome demonstrated that approximately 22% developed diabetes by 60 years of age.<sup>2</sup> In a cohort study of children from New York, 12.4% of the 242 children with congenital rubella syndrome developed diabetes by 17 years of age.<sup>3</sup> Given a background rate of approximately 22 incident cases of diabetes per 100,000 children/year in the United States,<sup>4</sup> one child would have been expected to develop type 1 diabetes by age 17 in the New York cohort, instead of the 30 cases that actually occurred.<sup>3</sup> The elevated rate of diabetes in children born with congenital rubella syndrome was often noted by physicians over the past half century.<sup>2</sup>

Congenital rubella infection remains an important public health issue in many countries and vaccination efforts to prevent rubella are ongoing.<sup>5</sup> Not all congenital infections, however, can be prevented through vaccination and, with increased world travel, exposures during pregnancy remain a concern.<sup>6</sup> Congenital cytomegalovirus infection, for example, occurs in both developed and developing countries and there is currently no vaccine, although vaccine development efforts are underway.<sup>7</sup> Because vaccine hesitancy has increased over the past 20 years in the United States – particularly for the measles, mumps, rubella (MMR) vaccine,<sup>8</sup> we investigated

associations between infection, both congenital and perinatal, with subsequent diabetes risk in a longitudinal study in the United States between 2001-2017.

## **METHODS**

Data were from a nationwide private health insurer in the United States (Clinformatics DataMart® Database, years 2001-2017). All infants with a minimum of 1 year of continuous insurance coverage were included, with the sole exclusion of infants with neonatal diabetes. Information was extracted regarding congenital rubella (ICD-9 771.0 or ICD-10 P35.0), congenital cytomegalovirus (ICD-9 771.1 or ICD-10 P35.1), other congenital infections (ICD-9 771.2 or ICD-10 P35.2, P37.0, P37.1, P37.3, P37.4, P37.8; listed as congenital herpes simplex, listeriosis, malaria, toxoplasmosis, or tuberculosis), and other perinatal infections (ICD-9 771.3 to ICD-9 771.8 or ICD-10 P35.2 to ICD-10 P35.9). Other perinatal infections were defined as acquired either *in utero*, during birth via the umbilicus, or during the first 28 days after birth. For purposes of this study and given the constraints of the ICD coding, we will refer to “other perinatal infections” as those infections acquired either *in utero*, during birth via the umbilicus, or during the first 28 days after birth – but excluding the congenital infections as categorized above (rubella, cytomegalovirus, herpes simplex, listeriosis, malaria, toxoplasmosis, tuberculosis). Because congenital rubella infection has been associated with both type 1 and type 2 diabetes,<sup>2,9</sup> diabetes was determined using ICD-9 codes 249.x or 250.x, or ICD-10 codes E08.x or E10.x or E11.x. Diabetic ketoacidosis was identified by ICD-9 codes 250.1x, 250.3x

and ICD-10 codes E10.1x, E11.1x, and E13.1x. In sensitivity analyses, the sample was restricted to type 1 diabetes, using only ICD-9 250.x1 or 250.x3, or ICD-10 E10.x. Logistic regression was performed to assess the association between congenital infections and diabetes, with Stata/MP 14.2 (College Station, TX). Two-sided *P*-values less than .05 were considered significant. This study was approved by the University of Michigan Institutional Review Board. Publicly available de-identified data were used and informed consent was not required.

## RESULTS

There were 1,475,587 infants who had insurance coverage for a minimum of 365 days (maximum 16.5 years). Infants were observed for a mean of 3.9 years (SD 2.9). Of the infants, 48.6% were girls and 51.4% were boys.

There were 781 infants (0.06%) who had congenital infections and 73,974 (5.01%) who had other perinatal infections. There were 38 infants with congenital rubella infection, 316 with congenital cytomegalovirus infection, and 427 infants with other congenital infections. During follow-up, diabetes occurred in 3334 children, 242 (0.33%) who had a perinatal infection and 7 (0.90%) with congenital infections (1 with rubella, 3 with cytomegalovirus, and 3 with other congenital infections), compared to 3085 (0.22%) without congenital/perinatal infection ( $P < 0.001$ ).

In a logit model, the odds of developing diabetes for infants with congenital rubella infection were 12 fold greater than those without (Table 1). Infants with congenital cytomegalovirus infection also had elevated odds of developing diabetes (Odds Ratio (OR)=4.34). Other congenital infections and other perinatal infections were also associated with diabetes mellitus (OR=3.21 and OR=1.50, respectively). The risk difference (attributable risk) for congenital rubella syndrome was 24 per 1000 births in this study. The median time from birth to diabetes diagnosis for infants with perinatal infections (congenital and other perinatal infections combined) was 1.6 years and for infants without was 3 years.

There was also an association between diabetic ketoacidosis in children and a prior history of congenital rubella infection (OR=12.41), congenital cytomegalovirus infection (OR=4.40), other congenital infections (OR=3.25), as well as other perinatal infections (OR=1.50).

Because rotavirus vaccination during infancy has been shown to lower rates of diabetes in childhood,<sup>10,11</sup> the results were adjusted for completion of the rotavirus vaccine series (Table 1). After adjustment, congenital infections and other perinatal infections remained significantly associated with the incidence of diabetes. Of note, of the 38 infants with congenital rubella syndrome, six completed the rotavirus vaccine series and none developed diabetes. In the 32



infants with congenital rubella syndrome who did not complete the rotavirus vaccine series, one developed diabetes. Of the 316 infants with congenital cytomegalovirus infection, 92 completed the rotavirus vaccine series (none developed diabetes) and 224 did not complete the rotavirus vaccine series (3 developed diabetes).

In sensitivity analysis, the OR for congenital rubella infection and type 1 diabetes was 23.53 (95% CI: 3.23, 171.62;  $P=0.002$ ). For congenital cytomegalovirus infection and type 1 diabetes, the OR was 8.35 (95% CI: 2.67, 26.04);  $P<0.001$ ). For other congenital infections, the OR was 2.04 (95% CI: 0.29, 14.55;  $P=0.475$ ). For other perinatal infections and type 1 diabetes, the OR was 1.39 (95% CI: 1.15, 1.68;  $P=0.001$ ).

The frequency of congenital and perinatal infections (combined) varied significantly ( $P<0.001$ ) across the country, from 7.0% in New York and Pennsylvania to 3.1% on the Pacific coast (Figure 1).

## **DISCUSSION**

Congenital infections increase the risk of diabetes in the offspring. Congenital rubella infection was rare but associated with risk, as was cytomegalovirus infection. Perinatal infections, in

general, were associated with diabetes and diabetic ketoacidosis in children in this study. Unfortunately, specific types of perinatal infections were only available for certain types of etiologic agents in this database. From previous research, various viruses have been implicated as triggers of islet autoimmunity and the onset of diabetes in children.<sup>12</sup> In a systematic review of maternal viral infections in pregnancy, a meta-analysis of five case-control studies indicated a two-fold increase in the risk of type 1 diabetes in the offspring when infected with enterovirus during pregnancy.<sup>13</sup> To our knowledge, our study is the first cohort study to report the association between congenital viral infections and type 1 diabetes in children. Our findings affirm the previous research regarding the association between congenital rubella infection and type 1 diabetes, but also suggest that congenital cytomegalovirus infection and other perinatal infections could also influence risk.

Because live attenuated vaccines are contraindicated for pregnant women, our findings emphasize the importance of completing the rubella vaccine series at age-appropriate times to reduce the likelihood of transmission from the general public to pregnant women. Moreover, our results indicate that, among children with congenital infections, completion of the rotavirus vaccine series may be a pragmatic option to lower their risk of developing type 1 diabetes.

Screening for gestational diabetes and screening for type 2 diabetes in adults is currently recommended, but there is insufficient evidence for childhood diabetes screening in high risk groups.<sup>14,15</sup> Our results suggest that screening in populations at high risk of diabetes, such as those with congenital rubella syndrome, should be evaluated. For children with a history of congenital infection, parental education regarding the symptoms of diabetic ketoacidosis is important. Diabetes ketoacidosis, common in children when first diagnosed, can be lethal and often results in hospitalization.<sup>16</sup>

In the United States, it is difficult to capture the total burden of congenital and perinatal infections because national surveillance is disease-specific, not all viral infections are under surveillance, and reporting criteria have changed over time. In our study, we found that perinatal infections (either *in utero*, during birth via the umbilicus, or during the first 28 days after birth) tended to occur more frequently in the eastern United States and ranged from 3.1 to 7.0% of live births. As more large national databases become available, it is possible that additional information will be reported.

In conclusion, congenital and other perinatal infections are associated with the onset of diabetes mellitus in children. For some infections such as rubella, vaccination is available and, therefore, the benefits of vaccination should be emphasized in the population as a whole. Recognition of

the early symptoms of type 1 diabetes is important for parents and guardians of children with a history of congenital infection.

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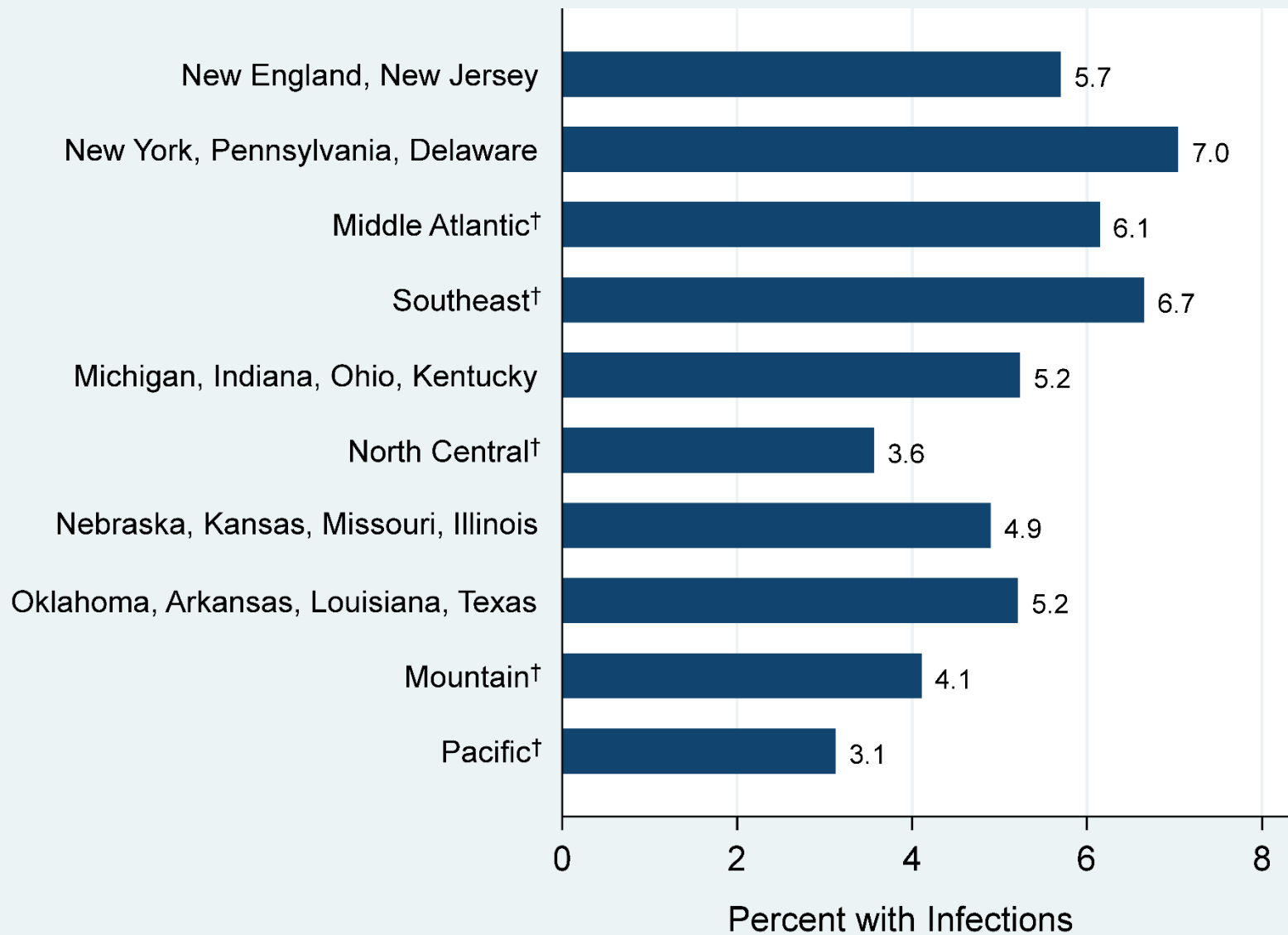
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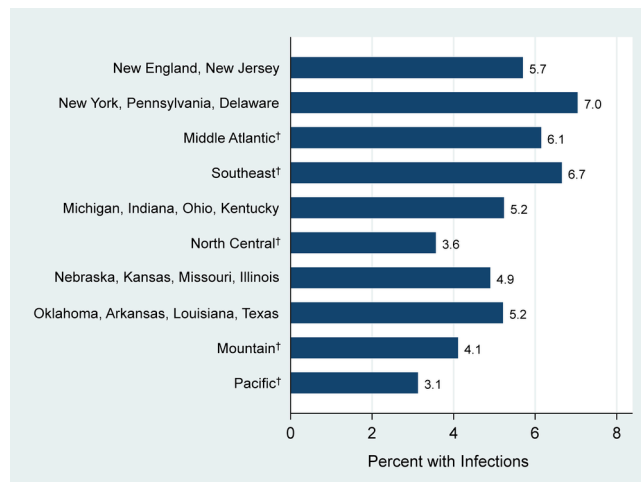
TABLE 1. Congenital and Perinatal Infections as Predictors of Diabetes Mellitus in Children, United States, 2001-2017

Category	Number	Unadjusted Odds Ratio	95% CI	P value	Adjusted Odds Ratio <sup>1</sup>	95% CI	P value
Predictors of Diabetes:							
Congenital rubella infection	38	12.25	1.68, 89.28	0.013	11.23	1.54, 81.92	0.017
Congenital cytomegalovirus infection	316	4.34	1.39, 13.55	0.011	4.23	1.36, 13.21	0.013
Other congenital infections	427	3.21	1.03, 9.98	0.044	3.33	1.07, 10.37	0.038
Other perinatal infections	73,974	1.49	1.30, 1.70	<0.001	1.47	1.28, 1.68	<0.001
No congenital or perinatal infections	1,400,832	1.00	Reference		1.00	Reference	
Predictors of Diabetic Ketoacidosis:							
Congenital rubella infection	38	12.41	1.70, 90.51	0.013	11.36	1.56, 82.89	0.017
Congenital cytomegalovirus infection	316	4.40	1.41, 13.73	0.011	4.29	1.38, 13.39	0.012
Other congenital infections	427	3.25	1.04, 10.12	0.042	3.38	1.08, 10.52	0.036
Other perinatal infections	73,974	1.50	1.32, 1.71	<0.001	1.48	1.29, 1.69	<0.001
No congenital or perinatal infections	1,400,832	1.00	Reference		1.00	Reference	

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1. Adjustment for completion of the rotavirus vaccine series during infancy.







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