Intrapartum Group B Streptococcal Prophylaxis and Childhood Allergic Disorders

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abstract

OBJECTIVES: To determine if maternal intrapartum group B *Streptococcus* (GBS) antibiotic prophylaxis is associated with increased risk of childhood asthma, eczema, food allergy, or allergic rhinitis.

METHODS: Retrospective cohort study of 14 046 children. GBS prophylaxis was defined as administration of intravenous penicillin, ampicillin, cefazolin, clindamycin, or vancomycin to the mother, ≥4 hours before delivery. Composite primary outcome was asthma, eczema, or food allergy diagnosis within 5 years of age, identified by diagnosis codes and appropriate medication prescription. Allergic rhinitis was defined by using diagnostic codes only and analyzed as a separate outcome. Analysis was a priori stratified by delivery mode and conducted by using Cox proportional hazards model adjusted for multiple confounders and covariates. Secondary analyses, restricted to children retained in cohort at 5 years' age, were conducted by using multivariate logistic regression.

RESULTS: GBS prophylaxis was not associated with increased incidence of composite outcome among infants delivered vaginally (hazard ratio: 1.13, 95% confidence interval [CI]: 0.95–1.33) or by cesarean delivery (hazard ratio: 1.08, 95% CI: 0.88–1.32). At 5 years of age, among 10 404 children retained in the study, GBS prophylaxis was not associated with the composite outcome in vaginal (odds ratio: 1.21, 95% CI: 0.96–1.52) or cesarean delivery (odds ratio: 1.17, 95% CI: 0.88–1.56) cohorts. Outcomes of asthma, eczema, food allergy, separately, and allergic rhinitis were also not associated with GBS prophylaxis.

CONCLUSIONS: Intrapartum GBS prophylaxis was not associated with subsequent diagnosis of asthma, eczema, food allergy, or allergic rhinitis in the first 5 years of age.

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WHAT'S KNOWN ON THIS SUBJECT: Early-life antibiotics have been associated with increased risk of allergic disorders in childhood. Maternal intrapartum antibiotic prophylaxis is one of the earliest antibiotic exposures for neonates, but its effect on childhood atopic diseases is unknown.

WHAT THIS STUDY ADDS: Maternal intrapartum antibiotic prophylaxis to prevent neonatal early-onset group B *Streptococcus* disease is not associated with increased diagnosis rates of asthma, eczema, food allergy, or allergic rhinitis within the first 5 years of age.

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The reduction of early-onset group B *Streptococcus* (GBS) disease in the United States is attributed to the use of universal GBS screening and administration of intrapartum antibiotic prophylaxis (IAP) to colonized women.[1] Despite this success, many high-income countries have not adopted this policy.[2] One concern that contributes to the lack of international consensus is the substantial antibiotic exposure, and potential consequent effects, to parturient women and their newborns.[3,4] With increasing understanding of the effect of early-life antibiotic therapy on the integrity of the microbiome and the microbiome's role in health outcomes, there is heightened concern about GBS IAP–induced microbiome alterations[5–7] and potential adverse health consequences for the infant.[3]

In the United States, with universal antenatal screening, ~30% of women are identified as colonized with GBS and ~20% are candidates for IAP.[1,4] GBS IAP is administered with the explicit goal of reducing maternal colonization with GBS and preventing mother to child transmission of this pathogen. However, GBS IAP is also associated with nonspecific changes to the neonatal microbiome lasting months beyond the neonatal period.[5–7] Mother to child microbiome transmission occurs as an expected part of delivery,[8] and thus, the interruption of this transmission at this critical developmental period may be hypothesized to change the immune priming associated with early microbial colonization.[9–11] The impact of GBS IAP may therefore be different from antibiotic exposure in mother during pregnancy, or to the infant later in childhood, because of the overlap in timing of GBS IAP administration and establishment of pioneer colonizers.

Allergic disease, defined as an exaggerated immune response to foreign antigens, has been a focus of study because of the link in multiple preclinical mechanistic studies between early-life antibiotic exposure and immune development.[9–13] Multiple epidemiological studies in human subjects have also reported an association of maternal antibiotics in pregnancy or pediatric antibiotics in early life with increased risk of childhood atopic diseases such as asthma, eczema, food allergy, and allergic rhinitis.[14–21] Few studies have explored the association of GBS IAP with the risk of childhood allergies.[22,23] Yet concern for such association with GBS IAP is apparent in information Web sites for pregnant women[24–26] and is clinically relevant for providers. To address the question, "Is GBS IAP, as recommended, increasing the prevalence of allergic diseases in the infant?," we used a large birth cohort of term infants without infection at birth to determine if GBS prophylaxis was associated with an increased incidence of childhood atopic diagnosis, specifically, asthma, eczema, food allergy, and allergic rhinitis during the first 5 years of age.

METHODS

Design

This is a retrospective cohort study.

Population

The study included mothers and their children with delivery between January 1, 2007, and December 31, 2012, at 2 perinatal centers in Philadelphia, who then established pediatric care within 30 days of birth at any 1 of the 33 Children's Hospital of Philadelphia (CHOP) primary care network sites located in Pennsylvania and New Jersey (Supplemental Fig 1). Medical records of infants from birth admission were linked with their pediatric care medical records to create a longitudinal database of 15 986 children from birth to 5 years of age (2012–2017), or until the child left the pediatric practice. Linking was achieved via deterministic matching by using names, date of birth, sex, address, and birth hospital. The study was approved by the Institutional Review Boards of University of Pennsylvania and CHOP with waiver of consent.

Infants born at gestational age ≥37 weeks and birth weight ≥2000 g were included in the study. Infants missing delivery room data, with culture-confirmed sepsis ≤72 hours after birth, and with major birth anomalies or congenital conditions (detected ≤6 months of age) that would result in chronic illness were excluded from the study (Supplemental Fig 1). We used the *International Classification of Diseases, Ninth Revision* (ICD-9) and *10th Revision* (ICD-10) codes based on previously validated criteria to identify infants with congenital conditions and manually verified the exclusion conditions for appropriateness.[27]

Exposure

Our primary exposure was maternal intrapartum GBS prophylaxis defined as intravenous penicillin, ampicillin, cefazolin, clindamycin, or vancomycin administered ≥4 hours before delivery during the hospital admission leading to birth. This definition was aligned with adequate GBS prophylaxis as recommended by national guidelines during the study period.[1,28] All other forms of maternal antibiotic therapy were classified as "other" antibiotic exposure, including antibiotics not considered GBS specific, GBS-specific antibiotics administered <4 hours before delivery, and surgical prophylaxis administered to women undergoing cesarean delivery. Exposure definition was the same for both delivery cohorts, but the reference group was "no intrapartum antibiotic" exposure among women who delivered vaginally and "other antibiotics" for the women delivering by cesarean delivery to accommodate surgical prophylaxis.

Outcomes

The primary outcome was a composite of any disorder (asthma, eczema, or food allergy) within the

TABLE 1 Characteristics of the Study Cohort

	Total (n = 14 046)	Vaginal Cohort (n = 9718)			Cesarean Cohort (n = 4328)	
		No IAP (n = 6989)	GBS IAP[a] (n = 1919)	Other Antibiotics (n = 810)	GBS IAP[a] (n = 573)	Other Antibiotics (n = 3755)
Maternal age,[b] y, median (IQR)	28 (23–33)	28 (23–33)	26 (21–31)	27 (22–31)	26 (21–31)	30 (25–35)
Maternal race and ethnicity, n (%)						
Black, non-Hispanic	8101 (57.7)	3987 (57.1)	1297 (67.6)	522 (64.4)	388 (67.7)	1907 (50.8)
White, non-Hispanic	3713 (26.4)	1807 (25.9)	403 (21.0)	159 (19.6)	111 (19.4)	1233 (32.8)
Asian	1007 (7.2)	575 (8.2)	88 (4.6)	65 (8.0)	30 (5.2)	249 (6.6)
Hispanic	474 (3.4)	238 (3.4)	49 (2.6)	27 (3.3)	9 (1.6)	151 (4.0)
Other or unknown	751 (5.4)	382 (5.5)	82 (4.3)	37 (4.6)	35 (6.1)	215 (5.7)
Maternal BMI,[b] n (%)						
<18.5	23 (0.2)	19 (0.3)	2 (0.1)	0	0	2 (0.1)
18.5 to <25.0	1868 (13.3)	1167 (16.7)	239 (12.5)	126 (15.6)	40 (7.0)	296 (7.9)
25.0 to <30.0	4978 (35.4)	2704 (38.8)	631 (32.9)	277 (34.3)	151 (26.4)	1215 (32.4)
≥30.0	7148 (50.9)	3081 (44.2)	1045 (54.5)	405 (50.1)	381 (66.6)	2236 (59.6)
Parity,[b] n (%)						
1	6377 (45.4)	2995 (42.8)	1060 (55.2)	325 (40.1)	444 (77.5)	1553 (41.4)
2 or more	7537 (53.7)	3916 (56.0)	852 (44.4)	476 (58.8)	126 (22.0)	2167 (57.7)
GBS status, n (%)						
Negative	9325 (66.4)	6119 (87.6)	62 (3.2)	258 (31.9)	31 (5.4)	2855 (76.0)
Positive	3927 (28.0)	432 (6.2)	1810 (94.3)	528 (65.2)	530 (92.5)	627 (16.7)
Unknown	794 (5.7)	438 (6.3)	47 (2.5)	24 (3.0)	12 (2.1)	273 (7.3)
Chorioamnionitis, n (%)	781 (5.6)	83 (1.2)	113 (5.9)	215 (26.5)	100 (17.5)	270 (7.2)
Maternal asthma, n (%)	1909 (13.6)	901 (12.9)	297 (15.5)	99 (12.2)	105 (18.3)	507 (13.5)
Maternal allergy, n (%)	923 (6.6)	427 (6.1)	127 (6.6)	55 (6.8)	43 (7.5)	271 (7.2)
Proportion of residents with less than high school education,[b,c] median (IQR)	0.17 (0.08–0.27)	0.17 (0.08–0.28)	0.18 (0.09–0.28)	0.18 (0.09–0.28)	0.19 (0.09–0.29)	0.15 (0.06–0.26)
Median HHI quartiles,[b,c] $, n (%)						
≤27 800	3490 (24.9)	1736 (24.8)	563 (29.3)	235 (29.0)	162 (28.3)	794 (21.2)
27 801 to ≤39 610	3489 (24.8)	1794 (25.7)	490 (25.5)	210 (25.9)	150 (26.2)	845 (22.5)
39 611 to ≤62 315	3489 (24.8)	1742 (24.9)	457 (23.8)	202 (24.9)	142 (24.8)	946 (25.2)
≥62 316	3487 (24.8)	1671 (23.9)	395 (20.6)	156 (19.3)	117 (20.4)	1148 (30.6)
Infant's sex (male), n (%)	7136 (50.8)	3446 (49.3)	998 (52.0)	415 (51.2)	260 (45.4)	1791 (47.7)
Birth weight, g, median (IQR)	3310 (3013–3613)	3290 (3000–3575)	3304 (3025–3600)	3290 (3013–3580)	3425 (3100–3745)	3340 (3020–3680)
Birth weight for GA z score,[d] mean (SD)	−0.17 (0.86)	−0.22 (0.82)	−0.22 (0.81)	−0.23 (0.79)	−0.13 (0.92)	−0.05 (0.94)
Neonatal antibiotics,[e] n (%)	1134 (8.1)	315 (4.5)	165 (8.6)	185 (22.8)	97 (16.9)	372 (9.9)
Breastfeeding at 3 mo,[b] n (%)	6077 (43.3)	3141 (44.9)	774 (40.3)	328 (40.5)	206 (36.0)	1628 (43.3)
Cohort retained at >4 completed years of age,[f] n (%)	10 404 (74.1)	5133 (73.4)	1425 (74.3)	604 (74.6)	414 (72.3)	2828 (75.3)
Asthma[g]	2208 (21.2)	1039 (20.2)	343 (24.1)	127 (21.0)	118 (28.5)	581 (20.5)
Eczema[g]	1331 (12.8)	629 (12.3)	216 (15.2)	71 (12.0)	74 (17.9)	341 (12.1)
Food allergy[g]	716 (6.9)	326 (6.4)	104 (7.3)	49 (8.1)	32 (7.7)	205 (7.3)
Allergic rhinitis[g]	1414 (13.6)	657 (12.8)	195 (13.7)	80 (13.3)	69 (16.7)	413 (14.6)

GA, gestational age; HHI, household income; IQR, interquartile range.

[a] GBS IAP is defined as the intrapartum administration of penicillin, ampicillin, cefazolin, clindamycin, or vancomycin 4 or more hours before delivery; antibiotics not meeting the definition of GBS IAP are categorized as other antibiotics.

[b] Missing values for each characteristic were <1% of the total cohort and, thus, are not displayed in the tables. Information is missing for the following numbers of study subjects: maternal age, 4; maternal BMI, 29; parity, 132; proportion of residents with less than high school education, 64; median household income, 91; breastfeeding at 3 mo, 10. The percent missing value is included in the denominator for total proportions; missing values are excluded in proportion for the columns stratified by delivery mode unless ≥1%.

[c] Proportion of residents with less than high school education and median household income are derived from American Community Survey 2009 to 2012 data including American Community Survey tract-level data (detailed definition in Supplemental Table 6).

[d] Sex-specific Birth weight for GA z scores were derived from Fenton growth charts.[38]

[e] Neonatal antibiotics are defined as any intravenous or intramuscular antibiotic administered to an infant within 72 h after birth.

[f] Includes all infants who had at least 1 pediatric visit after 4 completed years of age.

[g] Percent displayed are percentage of cohort retained for >4 completed years of age.

first 5 years of age. Asthma was defined as prespecified ICD-9 and ICD-10 diagnosis codes,[29] documented at least twice after 1 year of age and ≥6 months apart, combined with a prescription for asthma-related medication such as an inhaled β-agonist. Eczema was defined as prespecified diagnosis codes,[29] used at least twice and ≥6 months apart, combined with a prescription for topical steroids. Food allergy was defined as a prescription for epinephrine autoinjector (eg, EpiPen), with either

TABLE 2 Unadjusted HRs for the Composite Primary Outcome

	Vaginal Cohort (n = 9718)		Cesarean Cohort (n = 4328)	
	HR	95% CI	HR	95% CI
Exposure				
No GBS IAP	Reference	Reference	N/A	N/A
GBS IAP[a]	1.19	1.09–1.31	1.39	1.20–1.62
Other antibiotics	0.99	0.86–1.14	Reference	Reference
Maternal age	0.97	0.96–0.98	0.97	0.97–0.98
Maternal race and ethnicity				
White, non-Hispanic	Reference	Reference	Reference	Reference
Black, non-Hispanic	1.95	1.75–2.16	2.06	1.79–2.37
Asian	1.36	1.13–1.64	1.35	1.02–1.80
Hispanic	1.32	1.03–1.69	1.20	0.84–1.72
Other or unknown	1.23	0.98–1.53	1.19	0.88–1.62
Maternal BMI	1.02	1.01–1.03	1.02	1.01–1.03
Parity				
1	Reference	Reference	Reference	Reference
2 or more	0.88	0.82–0.95	0.91	0.81–1.02
GBS status				
Negative	Reference	Reference	Reference	Reference
Positive	1.11	1.02–1.20	1.27	1.12–1.43
Unknown	0.81	0.68–0.98	0.72	0.55–0.94
Chorioamnionitis	1.11	0.92–1.33	1.16	0.96–1.41
Maternal asthma	1.50	1.36–1.65	1.69	1.47–1.95
Maternal allergy	1.24	1.08–1.44	1.19	0.98–1.46
Proportion of residents with less than high school education[b]	1.92	1.48–2.49	3.20	2.17–4.71
Median HHI quartiles,[b] $				
≤27 800	1.17	1.05–1.29	1.40	1.20–1.64
27 801 to ≤39 610	1.04	0.94–1.16	1.18	1.00–1.39
39 611 to ≤62 315	Reference	Reference	Reference	Reference
≥62 316	0.74	0.66–0.84	0.79	0.67–0.94
Infant's sex (male)	1.33	1.23–1.44	1.58	1.40–1.77
Birth weight for GA z score	0.94	0.90–0.98	0.95	0.89–1.00
Neonatal antibiotics[c]	1.14	0.98–1.31	1.23	1.03–1.46
Breastfeeding at 3 mo[d]	0.78	0.72–0.84	0.76	0.68–0.86

GA, gestational age; HHI, household income; N/A, not applicable.

[a] GBS IAP is defined as the intrapartum administration of penicillin, ampicillin, cefazolin, clindamycin, or vancomycin 4 or more hours before delivery; antibiotics not meeting the definition of GBS IAP are categorized as other antibiotics.

[b] Proportion of residents with less than high school education and median household income are derived from the American Community Survey 2009 to 2012 data including American Community Survey tract-level data (detailed definition in Supplemental Table 6).

[c] Neonatal antibiotics defined as any intravenous or intramuscular antibiotic administered to an infant within 72 h after birth.

[d] Breastfeeding at 3 mo of age compared with not breastfeeding at 3 mo of age.

a specific food allergy entry in the electronic health record's module for capturing allergy information (Epic Systems, Verona, WI) or a prespecified diagnosis code for food allergy.[22,29,30] For entries in the allergy module, we manually verified text descriptions to adjudicate inclusion. Allergic rhinitis was not included in the primary composite outcome because of the nonavailability of consistent diagnosis-specific prescribed medications. It was defined as prespecified diagnosis codes,[29] documented at least twice ≥6 months apart. Secondary outcomes included asthma, eczema, food allergy, and allergic rhinitis in the first 5 years of age analyzed as separate outcomes. In Supplemental Table 5, we list diagnosis codes and medications used to define these outcomes.

Covariates

A priori covariates were chosen for potential association with exposure and/or outcome.[22,23,30–37] Maternal factors included maternal age, race and ethnicity, BMI, parity (postdelivery), history of asthma or allergy, GBS colonization, and diagnosis of intraamniotic infection. Infant covariates included sex and birth weight-for-gestation z scores.[38] To obtain markers of socioeconomic status, we linked the tract generated from the first residential address of the child with the American Community Survey Block Group data (2009–2012). We used these tract-level data to generate aggregate geographic surrogates of individual social markers, specifically, proportion of residents with less than high school education, and distribution of median household income.[39] Postexposure variables included neonatal antibiotics (intravenous antibiotics administered ≤72 hours after birth), and any breastfeeding at age 3 months. Covariate definitions are shown in Supplemental Table 6.

Analysis

The analysis was stratified by delivery mode. We chose stratification a priori to avoid confounding, because delivery mode affects perinatal antibiotic decisions and is associated with atopic outcomes.[1,8,34] Furthermore, perinatal antibiotics are administered in all cesarean deliveries for surgical skin prophylaxis, preventing any true "no antibiotic exposure" comparison among these dyads. Bivariate associations were measured by using χ^2 test, Student's t test, analysis of variance, and Kruskal–Wallis test, as appropriate. Our primary approach was to compare time to initial diagnosis of an atopic disorder in the first 5 years for infants with and without GBS IAP exposure. We used a Cox proportional hazards model to allow for censoring. We categorized GBS IAP by duration (4–<24 hours, ≥24 hours) and analyzed results in a separate model to detect impact of prolonged exposure. Secondary

TABLE 3 Adjusted HRs for Childhood Atopic Disorders

	Vaginal Cohort (n = 9718)		Cesarean Cohort (n = 4328)	
	HR	95% CI	HR	95% CI
Composite outcome[a]				
No GBS IAP	Reference	Reference	N/A	N/A
GBS IAP	1.12	0.95–1.32	1.07	0.88–1.31
Other antibiotics	0.96	0.80–1.16	Reference	Reference
Composite outcome without post exposure covariates[a,b]				
No GBS IAP	Reference	Reference	N/A	N/A
GBS IAP	1.12	0.95–1.32	1.07	0.88–1.31
Other antibiotics	0.97	0.80–1.16	Reference	Reference
Asthma[c]				
No GBS IAP	Reference	Reference	N/A	N/A
GBS IAP	1.10	0.89–1.35	1.02	0.80–1.31
Other antibiotics	0.96	0.77–1.21	Reference	Reference
Eczema[d]				
No GBS IAP	Reference	Reference	N/A	N/A
GBS IAP	1.30	0.99–1.69	1.29	0.94–1.77
Other antibiotics	1.05	0.78–1.41	Reference	Reference
Food allergy[d]				
No GBS IAP	Reference	Reference	N/A	N/A
GBS IAP	1.21	0.84–1.74	1.11	0.71–1.72
Other antibiotics	1.18	0.81,1.72	Reference	Reference
Allergic rhinitis[d]				
No GBS IAP	Reference	Reference	N/A	N/A
GBS IAP	0.87	0.67–1.14	1.05	0.76–1.45
Other antibiotics	0.94	0.71–1.25	Reference	Reference

Adjusted for maternal age, maternal race and ethnicity, maternal BMI, parity, GBS colonization status, chorioamnionitis, maternal asthma, maternal allergy, proportion of residents with less than high school education, median household income quartile, infant's sex, birth wt-for-gestation z score, neonatal antibiotics, and breastfeeding at 3 mo. N/A, not applicable.

[a] Includes asthma, eczema, and food allergy.

[b] Excludes covariates neonatal antibiotics and breastfeeding at 3 mo.

[c] Includes all covariates from primary model except maternal allergy.

[d] Includes all covariates from primary model except maternal asthma.

analyses were done restricting the cohort to infants who attended at least 1 primary care visit >4 years of age. In this cohort, we used a logistic regression model to investigate the association of GBS IAP with the composite and individual outcomes at any time in the first 5 years of age. Power calculation is described in Supplemental Information. Missing values occurred for <1% of the cohort and were incorporated as a separate category for categorical variables.

We conducted 5 additional analyses to assess possible gaps in the data. The first was effect of GBS IAP antibiotic spectrum; we recategorized GBS IAP exposure in a sensitivity analysis to only include penicillin and ampicillin and repeated the primary analysis to assess for changes in results. The second was effect of health care received outside of CHOP network; care received outside the CHOP network would not be captured in our data. Previous work has identified neighborhoods where >70% pediatric families preferentially choose CHOP for health care.[40] We performed a subgroup analysis among children receiving health care from 1 of the 4 CHOP-affiliated practices serving that region to detect differences from the main analysis. The third was effect of GBS colonization; to assess effect of IAP versus GBS colonization, we conducted a sensitivity analysis restricting the cohort to women with known GBS colonization. The fourth was effect of chorioamnionitis; among premature infants, chorioamnionitis has been associated with asthma diagnosis in childhood.[41] To assess effect of chorioamnionitis we ran a model after removing women with a diagnosis of chorioamnionitis. The fifth was effect of stratification; we analyzed the full cohort without stratification including delivery mode as a covariate to visualize changes on the main estimate. For this model, we coded the antibiotics potentially used as skin prophylaxis in cesarean deliveries as "no antibiotic exposure." Statistical significance was set at $P < .05$. Estimates from analytic models were considered significant when 95% confidence interval (CI) did not cross 1. Analyses were conducted by using Stata 14 (StataCorp, College Station, TX), SAS 9.4 (SAS Institute, Inc, Cary, NC), and R statistical packages version 3.5.1 (R Foundation, Vienna, Austria).

RESULTS

Of 15 986 children in the linked cohort, 14 046 met eligibility criteria (Supplemental Fig 1). Of these, 9718 (69%) were delivered vaginally and 4328 (31%) by cesarean delivery. Overall, 2492 (18%) mothers were exposed to GBS IAP: 1919 (20%) in the vaginal group and 573 (13%) in the cesarean delivery group.

Women and children in the GBS IAP group differed from the reference groups in multiple characteristics (Table 1). In both delivery groups, mothers exposed to GBS IAP were younger, primiparous, and Black and non-Hispanic, with history of asthma or allergy, delivery BMI ≥30, and residence in areas where a higher proportion of residents had less than high school education, and the lowest quartile of median household income. Infants in the reference groups of both delivery groups had greater frequency of breastfeeding at 3 months of age compared with infants exposed to GBS IAP. More than 90% of women who received GBS IAP were GBS positive. More women with chorioamnionitis received "other antibiotics" in the vaginal cohort and GBS IAP in the cesarean delivery cohort.

TABLE 4 Adjusted Odds for Childhood Atopic Disease in the Cohort Retained Beyond 4 Years

	Vaginal Cohort[a] (n = 7162)		Cesarean Cohort[a] (n = 3242)	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Composite outcome[b]				
No GBS IAP	Reference	Reference	N/A	N/A
GBS IAP	1.21	0.96–1.52	1.17	0.88–1.56
Other antibiotics	1.00	0.78–1.28	Reference	Reference
Asthma[c]				
No GBS IAP	Reference	Reference	N/A	N/A
GBS IAP	1.15	0.88–1.50	1.23	0.89–1.71
Other antibiotics	0.98	0.73–1.31	Reference	Reference
Eczema[d]				
No GBS IAP	Reference	Reference	N/A	N/A
GBS IAP	1.37	0.99–1.88	1.39	0.95–2.04
Other antibiotics	1.04	0.73–1.47	Reference	Reference
Food allergy[d]				
No GBS IAP	Reference	Reference	N/A	N/A
GBS IAP	1.37	0.87–2.15	1.02	0.61–1.73
Other antibiotics	1.46	0.93–2.29	Reference	Reference
Allergic rhinitis[d]				
No GBS IAP	Reference	Reference	N/A	N/A
GBS IAP	0.85	0.62–1.18	0.99	0.66–1.48
Other antibiotics	0.91	0.64–1.29	Reference	Reference

Adjusted for maternal age, maternal race and ethnicity, maternal BMI, parity, GBS colonization status, chorioamnionitis, maternal asthma, maternal allergy, proportion of residents with less than high school education, median household income quartile, infant's sex, birth wt-for-gestation z score, neonatal antibiotics, and breastfeeding at 3 mo. N/A, not applicable.

[a] Cohorts include all infants who had at least 1 pediatric visit after 4 completed years of age.

[b] Includes asthma, eczema, and food allergy.

[c] Includes all covariates from primary model except maternal allergy.

[d] Includes all covariates from primary model except maternal asthma.

Among women categorized as GBS IAP exposed, antibiotic type and duration differed by delivery mode (Supplemental Table 7). More women with cesarean delivery who received GBS IAP received ampicillin (23% vs 18%, P .005) and additional other antibiotics (15% vs. 6%, $P < .001$), and less received penicillin (69% vs. 76%, P .001), compared with women with vaginal delivery. They also received GBS-specific antibiotics for longer duration (median 13 vs 9 hours, $P < .001$).

A total of 3887 (28%) children had one of the composite outcomes of asthma, eczema, or food allergy by age 5 years. Separately, asthma was most frequent (18%), followed by eczema (11%), allergic rhinitis (11%) and food allergy (6%) (Supplemental Table 8).

In unadjusted analysis, GBS IAP was associated with the composite primary outcome in both vaginal (hazard ratio [HR]: 1.19, 95% CI: 1.09–1.31) and cesarean delivery (HR: 1.39, 95% CI: 1.20–1.62) cohorts (Table 2). Multiple other maternal and infant factors, in both cohorts, were associated with the composite outcome, including Black or Asian maternal race, high maternal BMI, maternal history of asthma or allergy, residence in areas of low education and income quartile, and male infant sex.

After adjusting for the prespecified covariates, the HR for asthma, eczema, or food allergy, in both vaginal (HR: 1.12, 95% CI: 0.95–1.32) and cesarean delivery (HR: 1.07, 95% CI: 0.88–1.31) cohorts, was not significantly different for children exposed to GBS IAP compared with children without such exposure (Table 3). Findings were similar after excluding postexposure variables (neonatal antibiotics and breastfeeding) and for models that analyzed asthma, eczema, food allergy, and allergic rhinitis separately (Table 3). Few women received GBS IAP for ≥24 hours: 82 women in the vaginal cohort and 99 in the cesarean delivery cohort. A numerically higher hazard for the primary composite outcome was noted with GBS IAP administered for ≥24 hours in both vaginal (HR: 1.23, 95% CI: 0.82–1.85) and cesarean delivery (HR: 1.22, 95% CI: 0.86–1.74) cohorts, but the results were not statistically significant.

A total of 10 404 (74%) children were retained at >4 years of age. In the adjusted analysis restricted to these infants, we found no significant difference in the odds of developing asthma, eczema, or food allergy as a composite outcome or individually, or of being diagnosed with allergic rhinitis, between GBS IAP–exposed and unexposed groups in either delivery cohorts (Table 4).

Analyses conducted to account for the effect of type of GBS IAP, health care outside the CHOP network, GBS colonization, and chorioamnionitis did not change the direction nor the significance of the main estimate for either cohort (Supplemental Table 9). Modeling the cohort without stratification did not show a significant association with either cesarean delivery compared with vaginal delivery (HR: 1.03, 95% CI: 0.96–1.10) or with GBS IAP (HR: 1.08, 95% CI: 0.96–1.23).

DISCUSSION

In a retrospective longitudinal birth cohort of >14 000 mothers and their children, we investigated the effect of GBS IAP on childhood asthma, eczema, and food allergy in the first 5 years of age. We did not find an association for any of the diagnoses when adjusting for potential confounders.

In contrast to our findings, multiple observational studies have reported an association of early-life antibiotics with atopic disease outcomes. Authors of a meta-analysis of 22 studies on risk of childhood asthma found a significantly increased pooled

adjusted odds of asthma among children with antibiotic exposure in infancy, which was attenuated but not eliminated when restricting to studies that adjusted for respiratory illness or later asthma diagnosis.[19] Odds of childhood asthma were also increased with antibiotic exposure in pregnancy. Similar increases in risk for food allergy,[18,30,37,42,43] allergic rhinitis,[44] and eczema[21,31,43,45] have been reported, although some studies have also reported a lack of association.[15,17,32,46,47] None of these studies explicitly include or focus on GBS IAP.

GBS IAP is different from outpatient prescribed antibiotics in timing, route, antibiotic type, and, perhaps most importantly, intention. Most outpatient antibiotics are prescribed for a change in clinical status, whereas GBS IAP is administered electively in asymptomatic women targeting colonizing microorganisms. Separating the effect of "changed clinical status" from the antibiotics can be challenging. GBS colonization, the main indication for GBS IAP, can be accounted for more robustly.[48] We adjusted for GBS colonization in the primary analysis to account for antenatal colonization and conducted a sensitivity analysis restricted to women who were colonized (Supplemental Table 9). Additionally, every dose of GBS IAP administered is scanned into the database, minimizing recall and information bias that may be present with prescription data or patient recall. These differences in exposure may account for our results compared with other epidemiological studies that report a higher risk of atopic outcomes among infants exposed to antenatal or childhood antibiotics.

Studies that are focused specifically on the effects of intrapartum antibiotics on atopic outcomes are limited and have not reported a significant relationship. Wohl et al[23] studied the effect of intrapartum antibiotics on atopic dermatitis diagnosed by 2 years of age in 492 mother-infant dyads and did not find an association. In a secondary analysis, they found a significant association with intrapartum antibiotic exposure for ≥24 hours, but this exposure occurred in only 11 women.[23] We did not find an association between GBS IAP for ≥24 hours and eczema. Researchers in a second case-control study of 99 infants with food allergy and 119 controls found no association of perinatal antibiotics with food allergy.[22] Finally, risk of drug allergy was investigated in a birth cohort of 804 infants, and no association was found with intrapartum exposure to penicillin, amoxicillin, or ampicillin.[49]

Our study has strengths and limitations. We used ICD-9 and ICD-10 diagnosis codes, prescriptions, and information from the electronic health record allergy module to identify outcomes and applied multiple criteria to reduce misclassification. For asthma and eczema, we required presence of a prespecified diagnosis code at 2 separate visits 6 months apart. We excluded asthma diagnosis in the first year after birth to minimize inclusion of early wheezing due to viral infections. All except 12 children with asthma diagnosis continued to have the diagnosis at >24 months age. The allergy module in electronic medical record often captures food allergy not documented elsewhere.[29] The descriptive text in the allergy module was manually reviewed by authors (S.M. and validated by J.M.S.), and only verified allergies were included to improve case identification. We additionally required all diagnoses comprising the composite outcome to be associated with a medication prescription specific to the diagnosis. Although this approach reduces capture of equivocal diagnoses and has been used in previous studies,[23,29,47] mild variants that did not trigger medication prescription would not be captured. Allergic rhinitis could not be included in the composite outcome because of this prespecification. Although electronic medical record data may not provide the same level of certainty as prospective diagnostic testing, the information is a robust reflection of burden of disease and is unlikely to miss severe cases, especially among the cohort retained for the full study period. We analyzed the data separately among the cohort retained after 4 years of age to account for selective loss of subjects and found similar results. We conducted multiple sensitivity analyses to mitigate gaps in the available data: none of the analyses altered the interpretation of the results. Finally, we accounted for multiple confounders in early life but were limited by a lack of detailed family history of atopic diseases, cigarette smoke exposure, exposure to pets, and day care history.

CONCLUSIONS

Longitudinal studies in which researchers investigate the effect of IAP on childhood health outcomes beyond the immediate neonatal period are needed for accurate risk/benefit assessment of GBS prevention strategies. We performed such a study in a large retrospective cohort of infants followed from birth to 5 completed years of age. We did not find an association between GBS IAP and increased risk for childhood asthma, eczema, food allergy, or allergic rhinitis.

ABBREVIATIONS

CHOP: Children's Hospital of Philadelphia
CI: confidence interval
GBS: group B *Streptococcus*
HR: hazard ratio
IAP: intrapartum antibiotic prophylaxis
ICD-9: *International Classification of Diseases, Ninth Revision*
ICD-10: *International Classification of Diseases, 10th Revision*

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