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Health effects in vaccinated versus unvaccinated children, with covariates for breastfeeding status and type of birth

Brian S. Hooker[1]* and Neil Z. Miller[2]

[1]Department of Sciences and Mathematics, Simpson University, Redding, California 96003 USA

[2]Institute of Medical and Scientific Inquiry, Santa Fe, New Mexico 87506 USA

Abstract

Using survey data from respondents associated with three medical practices in the US, vaccinated children were compared to unvaccinated children for the incidence of severe allergies, autism, gastrointestinal disorders, asthma, ADHD, and chronic ear infections. All diagnoses were based on parental reporting with chart review for confirmation of diagnoses. Cases were stratified with non-cases based on year of birth and sex, and compared using a logistic regression model which also accounted for breastfeeding status and type of birth (vaginal versus cesarean section). Vaccinated children were significantly more likely than unvaccinated children to be diagnosed with severe allergies (OR = 4.31, 95% CI 1.67 - 11.1), autism (OR = 5.03, 95% CI 1.64 - 15.5), gastrointestinal disorders (OR = 13.8, 95% CI 5.85 - 32.5), asthma (OR = 17.6, 95% CI 6.94 - 44.4), ADHD (OR = 20.8, 95% CI 4.74 - 91.2), and chronic ear infections (OR = 27.8, 95% CI 9.56 - 80.8). Vaccinated children were less likely to be diagnosed with chickenpox (OR = 0.10, 95% CI 0.029 - 0.36). Children who were "vaccinated and not breastfed" or "vaccinated and delivered via cesarean section" had the highest rates of adverse health outcomes. In this study, higher ORs were observed within the vaccinated versus unvaccinated groups for several adverse health conditions. Further research is essential to understand the full scope of health effects associated with childhood vaccination.

Introduction

Vaccination is the predominant public health practice utilized by nations to prevent the spread of communicable illnesses. In the United States, fully vaccinated children receive 26 vaccine doses by 15 months of age to protect against 14 different infections [1]. By 18 years of age, the Centers for Disease Control and Prevention (CDC) recommends 54 inoculations against 16 diseases: hepatitis A and B, *Haemophilus influenzae* type B (Hib), diphtheria, tetanus, pertussis, polio, rotavirus, influenza, pneumococcus, meningococcus, measles, mumps, rubella, varicella, and human papillomavirus [1].

In 2011, the National Academy of Medicine (NAM), formerly called the Institute of Medicine (IOM), published the report, *Adverse Effects of Vaccines: Evidence and Causality,* where the relationships between specific vaccines and different adverse health effects were considered [2]. Based on the scientific literature at the time, the IOM committee found inadequate evidence to accept or reject a causal association between 135 of 158 relationships between vaccines and adverse events. Among the remaining 23 adverse events, 18 were found to be associated with vaccination and five were not. That same year, the U.S. Department of Health and Human Services funded a health survey that estimated 54% of U.S. children have at least 1 of 22 chronic health conditions [3], up from 12.8% in 1994 [4]. Although the causes of these persistent health ailments are undoubtedly multifaceted, some studies have found significant relationships between vaccines and many of these conditions, including allergies [5,6], asthma [6,7], attention deficit disorder (ADD/ADHD) [5,8-10], autism [5,11-13], ear infections [5,14,15], seizures [16-18], developmental delay [5,9,19], diabetes [20-22], and more.

Several factors could contribute to whether a child will have a vaccine-associated adverse event, including a genetic predisposition, illness (which might be a contraindication to vaccine administration), quality of vaccines (which can vary by manufacturing methods), and sensitivity to one or more vaccine components. Some infants might be more susceptible to an adverse reaction due to biochemical or synergistic toxicity associated with concurrent administration of multiple vaccines. For instance, Goldman and Miller [23] found linear relationships between the number of vaccine doses administered at one time and rates of hospitalization and mortality; additionally, the younger the infant at the time of vaccination, the higher the risk of serious deleterious events.

In 2013, NAM acknowledged that studies are needed to compare health outcomes between fully vaccinated, partially vaccinated, and completely unvaccinated children [24]. Such research should investigate potential short- and long-term health effects associated with modified vaccine schedules, as occurs when children receive fewer vaccines per well-child visit than recommended or when vaccines are received later than recommended. Very few studies exist where health outcomes associated with the pediatric vaccination schedule have been assessed. This is partly due to ethical concerns of withholding vaccines from an unvaccinated control group within such a study [24]. Indeed, this precludes the use of double-blinded studies on vaccine health effects, and even in clinical trials an earlier version of the same vaccine is often used as the placebo control for the newly tested vaccine.

One study, by Mawson et al. [5], compared entirely unvaccinated children to partially vaccinated and fully vaccinated children. The

Correspondence to: Brian S. Hooker, Department of Sciences and Mathematics, Simpson University, Redding, California 96003 USA, E-mail: drbrianhooker@gmail.com

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vaccinated children showed higher odds of being diagnosed with pneumonia, ear infections, allergies and neurodevelopmental disorders. In another more recent study by Hooker and Miller [25], vaccinated children were compared to unvaccinated children during the first year of life for later incidence of health consequences. Vaccination before 1 year of age was associated with increased odds of being diagnosed with developmental delays, asthma, and ear infections. In secondary analyses, higher odds ratios (ORs) were also detected for gastrointestinal disorders. Lyons-Weiler and Thomas [26] found higher rates of office visits and diagnoses of common chronic ailments in the most vaccinated children as compared to children who were completely unvaccinated.

In the study presented here, children from three pediatric medical practices in the United States were used as a convenience sample to compare health outcomes in fully vaccinated, partially vaccinated, and completely unvaccinated populations. Vaccination records and diagnoses were based on a parental survey, though in a separate analysis diagnoses of children were confirmed with chart review from the participating pediatricians' electronic medical records. The evaluated health outcomes include severe allergies, autism, gastrointestinal disorders, asthma, attention deficit disorders (ADD/ADHD), and chronic ear infections. A control diagnosis of chickenpox was also evaluated. Breastfeeding status and type of birth—vaginal delivery versus a cesarean section—were considered.

Methods

Source of data: Patient data were obtained from a voluntary survey instrument (see Supplemental Appendix) given online primarily to participants in three pediatric practices in the United States. All questionnaire data including patient identification were kept on a separate, secure drive and all data files were de-identified, such that specific patient identification could not be made, prior to statistical analysis, in accordance with IRB guidelines. The Institutional Review Board at Simpson University for research with human subjects reviewed and authorized this analysis independent of the researchers.

A total of 1929 surveys were completed for the analysis. This was limited to children born between January 1, 1998 and December 31, 2016. In addition, children with congenital conditions leading to diagnoses (based on limited chart review) were omitted from the study. This left 1565 children in the cohort (Figure 1).

Parents who completed the survey rated their children's vaccination status as "no vaccines," "partially vaccinated" or "vaccines up-to-date." Parents then selected from the following health conditions/disorders that their child either had or had not been diagnosed with: severe allergy (requiring prescription epi-pen), autism, chronic gastrointestinal issues (recurrent or chronic constipation or diarrhea), asthma (moderate to severe), ADD/ADHD (requiring medication), and chronic ear infections (3 or more per 12 months). Seizures (requiring medication) and type

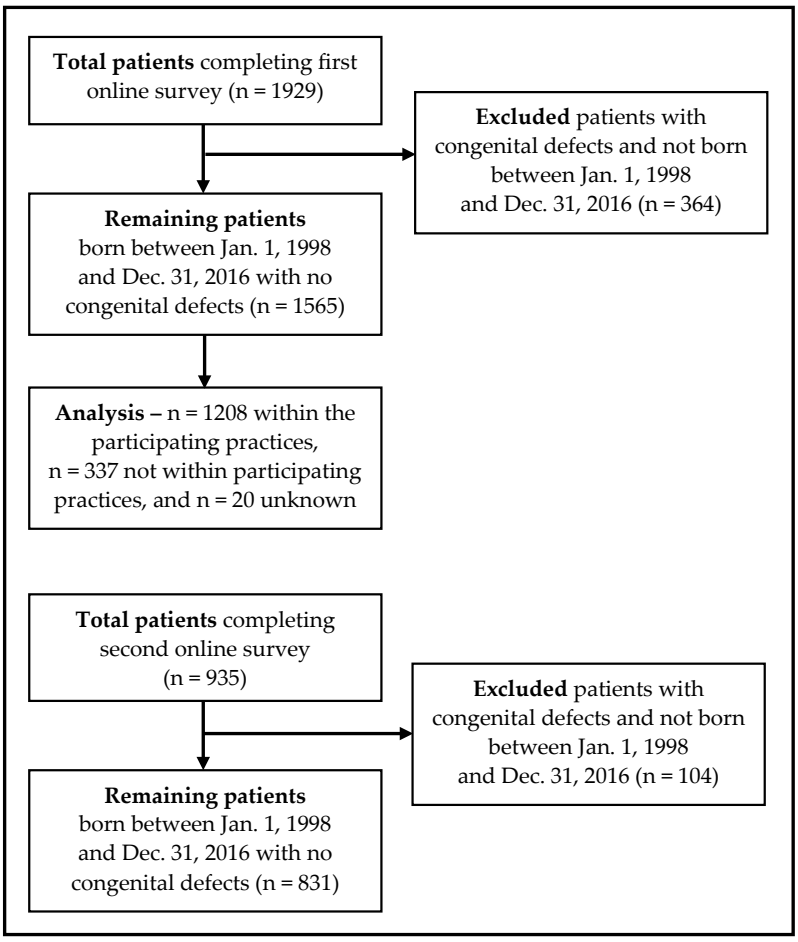

Figure 1. Creation of study cohorts for each analysis

1 diabetes were considered for assessment, but there were insufficient numbers of cases to complete a statistical analysis. Additionally, parents were asked about the type of birth (vaginal or cesarean), if the child was exclusively breastfed for a 6 month duration or longer, and current education status of the child (public/private school or home educated).

In a second, follow-up survey, parents were asked if their children ever had chickenpox (as a positive control diagnosis). There were 935 responses to the second survey (among those who also completed the first survey) and of those, 831 were carried forward to the main analysis, based on previously discussed exclusion criteria (Figure 1). Parents who completed the initial survey also indicated whether their children were patients in one of the three pediatric practices participating in the study. Of the 1565 children in the cohort, 77.2% were in a participating medical practice, 21.5% were not (typically, they were friends or relatives of families who were associated with one of the participating medical practices), and 1.3% did not respond to the question. Parents of children who were patients in the participating medical practices self-identified, which enabled diagnoses of children to be confirmed with chart review from the participating pediatricians' electronic medical records.

Analysis method: Data were analyzed for relationships between vaccination status and the different conditions considered using a cohort design in a logistic regression model. SAS® University Edition was used for statistical analyses with relationships deemed significant at $p < 0.05$ without correction for the number of statistical tests performed. For fully vaccinated versus unvaccinated, the study was designed to have a power of 80% to detect an odds ratio of 2.4 with a 95% probability and 90% to detect an odds ratio of 2.7. For partially vaccinated versus unvaccinated, the study was designed to have a power of 80% to detect an odds ratio of 1.8 with a 95% probability and 90% to detect an odds ratio of 1.96. Given that different diagnoses may be more or less likely depending on the age of patient and sex, cases and non-cases were stratified based on year of birth and sex. Each condition was evaluated with and without covariates, which included breastfeeding status and type of birth. In the first analysis, outcomes for children with "vaccines up-to-date" were compared directly to those for "unvaccinated" children. This analysis was completed with and without covariates. In the second analysis, outcomes for "partially vaccinated children" were compared directly to those for "unvaccinated children" which was also completed with and without covariates. In analyses based on children from participating medical practices only, and chart review to confirm diagnoses, unvaccinated children were compared to children who received any vaccine (where "partially vaccinated children" and children with "vaccines up-to-date" were combined into one cohort). In further analyses, odds ratios were assessed for separate categories of patients based on vaccination and breastfeeding status as well as vaccination and birth delivery status. Odds ratios and p-values were calculated using a simple 2x2 design with Fisher's exact test.

Results

Demographic data: Demographic data for the study sample are shown in table 1. After removing responses for children not within the specified age range, the cohort size was 1565, of which, 945 (60.4%) were completely unvaccinated, 484 (30.9%) were partially vaccinated and 136 (8.7%) had vaccines up-to-date. Within the cohort, 81.7% of the children were delivered vaginally and 18.3% were delivered via cesarean section. Also, 80.9% were breastfed for at least 6 months and 19.1% were not. In addition, 54.5% of the children were currently enrolled in a public or private school, 34.9% were home educated, and 10.6% were either too young or too old for school. The evaluated health conditions include allergies (4.3%), autism (2.9%), gastrointestinal disorders (6.2%), asthma (3.7%), ADD/ADHD (2.0%), and chronic ear infections (4.0%). Demographic data for the second survey are listed in table 2 which included 831 children among the first survey respondents. The proportions within this cohort were generally consistent with the first group listed in table 1. Chickenpox was reported in 15.6% of the children. Age data for the cohorts are listed in tables 3 and 4, where the mean age of the children is generally between 9 and 11 years and relatively consistent among the different subgroups.

Fully vaccinated versus unvaccinated children, with covariates: Results from the logistic regression analysis of fully vaccinated children ("vaccines up-to-date") versus unvaccinated children are shown in table 5. This model included covariates for breastfeeding status and type of delivery as well as strata for year of birth and sex. A consistent association was seen for all health conditions studied. Children up-to-date with their vaccines were significantly more likely than unvaccinated children to be diagnosed with severe allergies (OR = 4.31, 95% CI 1.67 - 11.1), autism (OR = 5.03, 95% CI 1.64 - 15.5), gastrointestinal disorders (OR = 13.8, 95% CI 5.85 - 32.5), asthma (OR = 17.6, 95% CI 6.94 -

Table 1. Demographic Data (First Questionnaire)

Category	Male	Female	Total
Total Sample	808	757	1565
Unvaccinated	482	463	945 (60.4%)
Partially Vaccinated	255	229	484 (30.9%)
Vaccines up-to-date	71	65	136 (8.7%)
Vaginal Delivery	643	636	1279 (81.7%)
Cesarean Section	172	114	286 (18.3%)
Breastfed	642	624	1266 (80.9%)
Not Breastfed	166	133	299 (19.1%)
Public/Private School	439	414	853 (54.5%)
Home Educated	288	258	546 (34.9%)
Not in School	81	85	166 (10.6%)
Allergies (severe)	43	25	68 (4.3%)
Autism	38	12	50 (3.2%)
Gastrointestinal Disorders	51	46	97 (6.2%)
Asthma	41	17	58 (3.7%)
ADD/ADHD	18	14	32 (2.0%)
Ear Infections (chronic)	40	23	63 (4.0%)

Table 2. Demographic Data (Second Questionnaire/Control Diagnosis)

Category	Male	Female	Total
Total Sample	444	387	831
Unvaccinated	253	213	466 (56.1%)
Partially Vaccinated	150	140	290 (34.9%)
Vaccines up-to-date	41	34	75 (9.0%)
Vaginal Delivery	339	325	664 (79.9%)
Cesarean Section	105	62	167 (20.1%)
Breastfed	349	317	666 (80.1%)
Not Breastfed	95	70	165 (19.9%)
Public/Private School	259	217	476 (57.3%)
Home Educated	143	121	264 (31.8%)
Not in School	42	49	91 (10.9%)
Chickenpox	70	60	130 (15.6%)

Table 3. Additional Demographic Data (First Questionnaire)

Age in Years	Mean	Standard Deviation	Minimum	Maximum
Total cohort	9.79	5.13	2.5	21.47
Unvaccinated	9.05	4.95	2.5	21.47
Partially vaccinated	10.89	5.15	2.52	21.33
Vaccines up-to-date	11.03	5.36	2.79	21.14
Vaginal Delivery	10.00	5.25	2.5	21.47
Cesarean Section	8.85	4.46	2.55	21.22
Breastfed	9.62	5.15	2.5	21.47
Not Breastfed	10.50	4.98	2.52	21.34

Table 4. Additional Demographic Data (Second Questionnaire)

Age in Years	Mean	Standard Deviation	Minimum	Maximum
Total cohort	9.99	5.17	2.5	21.34
Unvaccinated	8.88	4.93	2.5	21.34
Partially vaccinated	11.38	5.13	2.56	21.34
Vaccines up-to-date	11.56	5.19	3.26	20.75
Vaginal Delivery	10.32	5.30	2.5	21.34
Cesarean Section	8.69	4.40	2.56	21.23
Breastfed	9.81	5.24	2.5	21.34
Not Breastfed	10.73	4.84	2.56	21.34

Table 5. Fully vaccinated children ("vaccines up-to-date") versus unvaccinated children. Logistic regression model, stratified based on year of birth and sex, with covariates for breastfeeding status and type of birth.

Diagnosis	Vaccinated Cases/Non-cases	Unvaccinated Cases/Non-cases	Odds Ratio (95% CI)	p-value
Allergies (severe)	8/128	15/930	4.31 (1.67 – 11.1)	0.0025
Autism	7/129	9/936	5.03 (1.64 – 15.5)	0.0048
Gastrointestinal Disorders	22/114	12/933	13.8 (5.85 – 32.5)	<0.0001
Asthma	23/113	8/937	17.6 (6.94 – 44.4)	<0.0001
ADD/ADHD	10/126	3/942	20.8 (4.74 – 91.2)	<0.0001
Ear Infections (chronic)	23/113	5/940	27.8 (9.56 – 80.8)	<0.0001
Chickenpox	4/71	90/376	0.10 (0.029 – 0.36)	0.0004

44.4), ADD/ADHD (OR = 20.8, 95% CI 4.74 - 91.2), and chronic ear infections (OR = 27.8, 95% CI 9.56 - 80.8). The OR for chickenpox, our positive control, reflected the protective effect of vaccination with a significant relationship (OR = 0.10, 95% CI 0.029 - 0.36).

Partially vaccinated versus unvaccinated children, with covariates: Results from the logistic regression analysis of partially vaccinated children versus unvaccinated children are shown in table 6. This model also included covariates for breastfeeding status and type of delivery as well as strata for year of birth and sex. Again, a consistent association was seen for all conditions studied with ORs ranging from 4.45 (95% CI 2.36 - 8.38) for allergies to 13.1 (95% CI 4.89 - 34.8) for ear infections. All associations were statistically significant, and again vaccination was protective against chickenpox (OR = 0.31, 95% CI 0.085 - 0.53).

Vaccinated versus unvaccinated children, no covariates: Results from the logistic regression analysis with no covariates (but with strata for year of birth and sex) are shown in Supplemental tables S1 and S2 for fully vaccinated versus unvaccinated and partially vaccinated versus unvaccinated, respectively. These results are consistent with those obtained with covariates where all relationships are statistically significant and vaccination is protective against chickenpox.

Any vaccine versus unvaccinated children, participating medical practices only: In table 7, only children from participating medical practices (79.5% of the total cohort) were included in a logistic regression analysis of children who received "any vaccine" (fully and partially vaccinated children are counted together) versus unvaccinated children. This model included covariates for breastfeeding status and type of delivery as well as strata for year of birth and sex. Results were consistent with the main analyses (Tables 5 and 6). Vaccinated children were significantly more likely than unvaccinated children to be diagnosed with all health conditions under consideration, and vaccination was protective against chickenpox.

Any vaccine versus unvaccinated children, confirmed diagnoses only: In table 8, only children with diagnoses confirmed from electronic medical records (80.8% of the cohort of children who were patients in one of the three participating medical practices) were included in a logistic regression analysis of children who received "any vaccine" (fully and partially vaccinated children are counted together) versus unvaccinated children. This model included covariates for breastfeeding status and type of delivery as well as strata for year of birth and sex. Again, results were consistent with the main analyses. Vaccinated children were significantly more likely than unvaccinated children to be diagnosed with all health conditions under consideration.

Relationships between vaccination and breastfeeding status: Relationships between vaccination and breastfeeding status, and vaccination and birth delivery status, are shown in tables 9 and 10, respectively. In these tables, fully and partially vaccinated children are counted together. In table 9, children were placed into four groups: 1) unvaccinated and breastfed, 2) unvaccinated and not breastfed, 3) vaccinated and breastfed, 4) vaccinated and not breastfed. The proportion of children affected by each adverse health condition increases nearly consistently from one category to the next, with the lowest percentages observed mainly among the "unvaccinated and breastfed" children while the highest are observed among the "vaccinated and non-breastfed" children. A consistent increase was observed for allergies (1.5%, 2.1%, 6.0%, 13.9%), autism (0.8%, 2.1%, 5.3%, 9.4%), asthma (0.6%, 3.1%, 6.0%, 12.4%), and chronic ear infections (0.5%, 1.0%, 7.4%, 13.4%). Additionally, odds ratios (and p-values) were calculated utilizing "unvaccinated and breastfed" as the

Table 6. Partially vaccinated children versus unvaccinated children. Logistic regression model, stratified based on year of birth and sex, with covariates for breastfeeding status and type of birth

Diagnosis	Vaccinated Cases/ Non-cases	Unvaccinated Cases/ Non-cases	Odds Ratio (95% CI)	p-value
Allergies (severe)	45/439	15/930	4.45 (2.36 – 8.38)	<0.0001
Autism	34/450	9/936	5.13 (2.32 – 11.3)	<0.0001
Gastrointestinal Disorders	63/421	12/933	10.4 (5.39 – 20.0)	<0.0001
Asthma	27/457	8/937	5.30 (2.29 – 12.3)	0.0001
ADD/ADHD	19/465	3/942	8.25 (2.31 – 29.5)	0.0012
Ear Infections (chronic)	35/449	5/940	13.1 (4.89 – 34.8)	<0.0001
Chickenpox	36/254	90/376	0.31 (0.085 – 0.53)	<0.0001

Table 7. Children from participating medical practices only. Logistic regression model, "any vaccine received"* versus unvaccinated, stratified based on year of birth and sex, with covariates for breastfeeding status and type of birth.

Diagnosis	Vaccinated Cases/ Non-cases	Unvaccinated Cases/ Non-cases	Odds Ratio (95% CI)	p-value
Allergies (severe)	38/415	8/747	6.04 (2.67 – 13.7)	<0.0001
Autism	29/424	7/748	5.29 (2.17 – 12.9)	0.0003
Gastrointestinal Disorders	41/412	8/747	8.43 (3.76 – 18.9)	<0.0001
Asthma	22/431	5/750	5.95 (2.14 – 16.5)	0.0006
ADD/ADHD	17/436	3/752	5.97 (1.60 – 22.3)	0.0079
Ear Infections (chronic)	38/415	3/752	19.7 (5.83 – 66.2)	<0.0001
Chickenpox	33/239	70/340	0.32 (0.18 – 0.57)	<0.0001

*The vaccinated cohort includes children who received any vaccine (fully and partially vaccinated children are counted together).

Table 8. Children with diagnoses confirmed from electronic medical records.† Logistic regression model, "any vaccine received"* versus unvaccinated, stratified based on year of birth and sex, with covariates for breastfeeding status and type of birth.

Diagnosis	Vaccinated Cases/ Non-cases	Unvaccinated Cases/ Non-cases	Odds Ratio (95% CI)	p-value
Allergies (severe)	36/394	6/734	7.75 (3.11 – 19.3)	<0.0001
Autism	27/403	3/737	13.0 (3.73 – 45.0)	0.0001
Gastrointestinal Disorders	36/394	4/736	14.4 (4.94 – 41.7)	<0.0001
Asthma	18/412	4/736	6.06 (1.96 – 18.8)	0.0018
ADD/ADHD	12/418	1/739	12.7 (1.50 – 107)	0.020
Ear Infections (chronic)	28/402	2/738	22.6 (5.18 – 99.1)	<0.0001

* The vaccinated cohort includes children who received any vaccine (fully and partially vaccinated children are counted together). † Chickenpox diagnoses could not be confirmed via chart review because many families did not visit the physician for such a diagnosis.

Table 9. Relationships between vaccination* and breastfeeding status,† with odds ratios (and p-values) based on "unvaccinated and breastfed" as the reference group.

	Unvaccinated + Breastfed Reference diagnoses/total	Unvaccinated + Not Breastfed OR (p-value) diagnoses/total	Vaccinated + Breastfed OR (p-value) diagnoses/total	Vaccinated + Not Breastfed OR (p-value) diagnoses/total
Allergies (severe)	Ref. 13/848 (1.5%)	1.35 (0.66) 2/97 (2.1%)	**4.09 (<0.0001)** 25/418 (6.0%)	**10.3 (<0.0001)** 28/202 (13.9%)
Autism	Ref. 7/848 (0.8%)	2.53 (0.23) 2/97 (2.1%)	**6.67 (<0.0001)** 22/418 (5.3%)	**12.5 (<0.0001)** 19/202 (9.4%)
Gastrointestinal Disorders	Ref. 11/848 (1.3%)	0.79 (1.0) 1/97 (1.0%)	**9.87 (<0.0001)** 48/418 (11.5%)	**17.1 (<0.0001)** 37/202 (18.3%)
Asthma	Ref. 5/848 (0.6%)	**5.38 (0.040)** 3/97 (3.1%)	**10.7 (<0.0001)** 25/418 (6.0%)	**23.8 (<0.0001)** 25/202 (12.4%)
ADD/ADHD	Ref. 3/848 (0.4%)	- 0/97 (0%)	**9.04 (<0.0001)** 13/418 (3.1%)	**24.2 (<0.0001)** 16/202 (7.9%)
Ear Infections (chronic)	Ref. 4/848 (0.5%)	2.20 (0.42) 1/97 (1.0%)	**16.9 (<0.0001)** 31/418 (7.4%)	**32.6 (<0.0001)** 27/202 (13.4%)

*The vaccinated cohort includes children who received any vaccine (fully and partially vaccinated children are counted together). † Exclusively breastfed for ≥ 6 months versus not exclusively breastfed for ≥ 6 months.

Table 10. Relationships between vaccination* and birth delivery status, with odds ratios (and p-values) based on "unvaccinated and vaginal delivery" as the reference group.

	Unvaccinated + Vaginal Delivery Reference diagnoses/total	Unvaccinated + C-section OR (p-value) diagnoses/total	Vaccinated + Vaginal Delivery OR (p-value) diagnoses/total	Vaccinated + C-section OR (p-value) diagnoses/total
Allergies (severe)	Ref. 9/802 (1.1%)	**3.86 (0.017)** 6/143 (4.2%)	**7.41 (<0.0001)** 37/477 (7.8%)	**11.1 (<0.0001)** 16/143 (11.2%)
Autism	Ref. 5/802 (0.6%)	**4.59 (0.034)** 4/143 (2.8%)	**9.19 (<0.0001)** 26/477 (5.5%)	**18.7 (<0.0001)** 15/143 (10.5%)
Gastrointestinal Disorders	Ref. 8/802 (1.0%)	2.86 (0.093) 4/143 (2.8%)	**13.7 (<0.0001)** 58/477 (12.2%)	**23.1 (<0.0001)** 27/143 (18.9%)
Asthma	Ref. 3/802 (0.4%)	**9.65 (0.0028)** 5/143 (3.5%)	**25.0 (<0.0001)** 41/477 (8.6%)	**17.9 (<0.0001)** 9/143 (6.3%)
ADD/ADHD	Ref. 3/802 (0.4%)	- 0/143 (0%)	**11.7 (<0.0001)** 20/477 (4.2%)	**17.9 (<0.0001)** 9/143 (6.3%)
Ear Infections (chronic)	Ref. 4/802 (0.5%)	1.40 (0.56) 1/143 (0.7%)	**22.3 (<0.0001)** 48/477 (10.1%)	**15.0 (<0.0001)** 10/143 (7.0%)

* The vaccinated cohort includes children who received any vaccine (fully and partially vaccinated children are counted together).

reference group. Children who were "vaccinated and not breastfed" were significantly more likely than children who were "unvaccinated and breastfed" to be diagnosed with all health conditions studied.

Relationships between vaccination and birth delivery status: In table 10, children were also placed into four groups: 1) unvaccinated and vaginal delivery, 2) unvaccinated and C-section, 3) vaccinated and vaginal delivery, 4) vaccinated and C-section. Again, the proportion of children affected by each adverse health condition increases nearly consistently from one category to the next, with the lowest percentages observed mainly among the unvaccinated children delivered vaginally while the highest are observed mainly among the vaccinated children delivered via C-section. A consistent increase was observed for allergies (1.1%, 4.2%, 7.8%, 11.2%), autism (0.6%, 2.8%, 5.5%, 10.5%), and gastrointestinal disorders (1.0%, 2.8%, 12.2%, 18.9%). Additionally, odds ratios (and p-values) were calculated utilizing "unvaccinated and vaginal delivery" as the reference group. Children who were vaccinated and delivered via C-section were significantly more likely than children who were unvaccinated and delivered vaginally to be diagnosed with all health conditions studied.

Relationships between covariates and all health conditions under consideration: Relationships between covariates and all health conditions under consideration were analyzed as well (shown in Supplemental tables S3 and S4). Results were significant for breastfeeding in cases of allergies (p=0.0076), asthma (p=0.0016), ear infections (p=0.017) and chickenpox (p=0.0098). Breastfed children were less likely to be diagnosed with allergies, asthma and ear infections, but more likely to have had chickenpox. A significant relationship was seen between delivery status in the case of gastrointestinal disorders (p=0.011); this diagnosis was more common in children delivered via C-section.

Discussion

The National Academy of Medicine recently acknowledged that studies are needed to compare health outcomes between fully vaccinated, partially vaccinated, and completely unvaccinated children [26]. Thus far, this has not been undertaken by the institutions most capable of conducting such studies (e.g., the CDC and World Health Organization). Instead, more vigorous strategies are being employed to achieve the highest possible vaccine coverage rates, resulting in the loss of unvaccinated populations which are vital as control groups to scientifically monitor true rates of adverse events associated with vaccination.

In the study presented here, several acute and chronic adverse health outcomes were found to be more likely in fully and partially vaccinated children as compared to an unvaccinated child population. Within the logistic regression models that included covariates for breastfeeding status and type of delivery as well as strata for year of birth and sex (Tables 5 and 6), all health conditions under consideration showed highly significant relationships, with ORs ranging from 4.31 (95% CI 1.67 - 11.1) for allergies to 27.8 (95% CI 9.56 - 80.8) for chronic ear infections in fully vaccinated children. Although partially and fully vaccinated children were significantly more likely than unvaccinated children to have adverse health diagnoses, ORs were considerable more elevated in the fully vaccinated cohort, suggestive of a dose-response

relationship or synergisitic toxicity. In partially vaccinated versus fully vaccinated children, ORs increased from 10.4 to 13.8 for gastrointestinal disorders, 5.30 to 17.6 for asthma, 8.25 to 20.8 for attention deficit disorder, and 13.1 to 27.8 for chronic ear infections. For allergies and autism, the ORs declined slightly but remained highly significant. For chickenpox, the OR decreased from 0.31 to 0.10, confirming a protective benefit of vaccination. According to the CDC, two doses of the varicella vaccine are more than 90% effective at preventing this disease [27].

Data were available regarding each child's current education status (public/private school versus home educated). However, some of the children were not school-aged which decreased the cohort size and reduced statistical power, so covariates in this paper reflect breastfeeding status and birth type only. Also, it was not possible to distinguish between children who went to a public versus private school. Still, for comparative purposes Tables 5 and 6 were recalculated (in unpublished analyses) with current education status included as a covariant. Type of education correlated with vaccination status indicating that children in public/private schools were more likely than home educated children to be vaccinated. In addition, all ORs were within the 95% confidence interval of previous runs without the education variable, that is, they were consistent with findings in the main analyses. Vaccinated children were significantly more likely than unvaccinated children to be diagnosed with all health conditions under consideration, and vaccination was protective against chickenpox.

Within the logistic regression model that only considered children from participating medical practices (Table 7), all health conditions under consideration showed highly significant relationships, with ORs ranging from 5.29 (95% CI 2.17 - 12.9) for autism to 19.7 (95% CI 5.83 - 66.2) for chronic ear infections. Within the logistic regression model that only considered children with diagnoses confirmed from electronic medical records (Table 8), again, all health conditions under consideration showed highly significant relationships, with ORs ranging from 6.06 (95% CI 1.96 - 18.8) for asthma to 22.6 (95% CI 5.18 - 99.1) for chronic ear infections. (Chickenpox diagnoses could not be confirmed via chart review because many families did not visit the physician for such a diagnosis.)

Although some studies were unable to find correlations between vaccines and asthma [28,29], a relationship between vaccination and allergies, including asthma, has been reported. Hooker and Miller [25] found that vaccination before 1 year of age was associated with increased odds of asthma (OR = 4.49, 95% CI 2.04 - 9.88). McDonald et al. [7] analyzed the health records of 11,531 Canadian children and found that delayed administration of the first dose of a diphtheria, tetanus and pertussis vaccine was associated with a 50% reduced risk of childhood asthma. Hurwitz and Morgenstern [30] reported an association between DTP and tetanus toxoid vaccination and allergy symptoms and could not rule out a relationship with asthma. Klugman et al. [31] found that children who received a pneumococcal vaccine were nearly twice as likely as non-vaccine recipients to be diagnosed with hyperactive-airway disease and asthma treated with bronchodilator agents (relative risk = 1.91, CI 1.1 - 3.4). The authors suggest that an increase in asthma following vaccination may be expected, due to the hygiene hypothesis of decreased childhood infections. In a study of Korean children vaccinated against hepatitis B [32], a significantly higher asthma incidence was seen among children who had seroconverted to produce anti-hepatitis B ($p = 0.009$). In China, mice vaccinated according to the Chinese infant vaccine schedule showed airway hyper-responsiveness at a significantly higher rate than unvaccinated mice ($p < 0.01$) [33].

Mawson *et al.* [5] found a relationship between vaccination status and neurodevelopmental disorders, including autism (OR = 3.7, 95% CI 1.7 - 7.9). Delong [34] also reported a significant relationship to neurodevelopmental disorders—autism and speech and language delay—when looking at proportions of vaccine uptake in U.S. children. In a recent study by Eidi *et al.* [35], some neurobehavioral abnormalities, such as decreased sociability, increased anxiety-like behaviors, and alteration of visual-spatial learning and memory, were observed in baby mice treated with childhood vaccines. Geier *et al.* [12] found that children diagnosed with atypical autism—pervasive developmental disorder or Asperger syndrome—were more likely than controls to have received greater mercury exposure during infancy from thimerosal-containing hepatitis B vaccines (OR = 4.87, 95% CI 3.57 - 6.66). Although thimerosal has been phased out of most vaccines administered in the United States, it still remains in multi-dose vials of the influenza vaccine given to pregnant women and infants. The IOM Immunization Safety Review Committee [36] conducted an evaluation regarding thimerosal-containing vaccines and concluded that "the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopment disorders" was biologically plausible.

Hooker and Miller [25] reported an association between receipt of vaccines before 1 year of age and gastrointestinal disorders, most notably when time permitted for a diagnosis was extended from ≥ 3 years of age to ≥ 5 years of age (OR = 2.48, 95% CI 1.02 - 6.02). Although Wilson *et al.* [37] found an association between 12-month vaccinations and emergency room visits for non-infective gastroenteritis, there is a dearth of research elsewhere regarding gastroenteritis following vaccination, with the majority focused on intussusception following the rotavirus vaccine [38-41]. Other reports have attributed gastrointestinal disorders as adverse events following the oral polio vaccine [42] and the human papillomavirus vaccine [43].

The CDC's Vaccine Safety Datalink (VSD) database was recently evaluated to identify children with and without an attention deficit hyperactivity disorder (ADHD) diagnosis [9]. Children diagnosed with ADHD were significantly more likely than controls to have received greater mercury exposure from thimerosal-containing vaccines within the first 15 months of life (OR = 2.5, 95% CI 2.27 - 2.75). In a study of children 6-15 years of age [8], subjects diagnosed with ADHD were more likely than controls to have received any vaccination within the previous 6- and 12-month periods ($p = 0.05$). Mawson *et al.* [5] found a highly significant relationship between vaccines and ADHD as well.

Hooker and Miller [25] found that vaccination before 6, 12, 18, and 24 months of life was associated with increased odds of ear infections ($p < 0.05$). Mawson *et al.* [5] reported a significant relationship between vaccination status and ear infections. Wilson *et al.* [14] found that for both males and females, top reasons for emergency room visits and/or hospital admissions after their 12-month vaccinations included ear infections and non-infective gastroenteritis or colitis. Prior to the RotaTeq rotavirus vaccine achieving FDA approval, 71,725 infants were evaluated in three placebo-controlled clinical trials. Otitis media (middle ear infection) occurred at a statistically higher incidence ($p < 0.05$) within six weeks of any dose among recipients of RotaTeq as compared with recipients of placebo [15].

Within the logistic regression models that excluded covariates for breastfeeding status and type of delivery (*Tables S1 and S2*), all health conditions under consideration showed elevated ORs consistent with those obtained with covariates, and vaccination remained protective

against chickenpox. In a separate analysis (unpublished) we found a strong inverse relationship between breastfeeding status and vaccination status ($p < 0.0001$) as well as a direct relationship between type of birth and vaccination status ($p = 0.0037$). Given these relationships, it is not surprising that results with these covariates reinforce those obtained when considering vaccination status alone.

Vaccination and breastfeeding status: Results from the analysis of relationships when considering vaccination and breastfeeding status (Table 9) show that the lowest percentages of adverse diagnoses occurred in the two unvaccinated cohorts, most notably within the "unvaccinated and breastfed" group of children; the highest percentages of adverse diagnoses were observed for "vaccinated and not breastfed" children. A consistent linear increase was observed for allergies (1.5%, 2.1%, 6.0%, 13.9%), autism (0.8%, 2.1%, 5.3%, 9.4%), asthma (0.6%, 3.1%, 6.0%, 12.4%), and chronic ear infections (0.5%, 1.0%, 7.4%, 13.4%). Additionally, ORs in the two vaccinated cohorts, as compared to the "unvaccinated and breastfed" reference group, were significant for all health conditions under consideration. These findings suggest that breastfeeding has a protective effect against deleterious health outcomes associated with vaccination. Furthermore, vaccination appears to decrease the beneficial effects of breastfeeding, as indicated by the higher proportions of diagnoses in the "vaccinated and breastfed" group of children as compared to the "unvaccinated and breastfed" group. Breastfeeding benefits a baby's immune system and has been found to be protective against gastrointestinal issues (vomiting and diarrhea), allergies and ear infections [44]. Klopp et al. [45] reported that infants who were exclusively breastfed at 3 months of age were significantly protected against developing asthma by 3 years of age.

Vaccination and birth delivery status: Results from the analysis of relationships when considering vaccination and birth delivery status (Table 10) show that the lowest percentages of adverse diagnoses occurred in the two unvaccinated cohorts, most notably within the group of children who were unvaccinated and born vaginally; the highest percentages of adverse diagnoses occurred most notably in the children who were vaccinated and delivered via C-section. A consistent increase was observed for allergies (1.1%, 4.2%, 7.8%, 11.2%), autism (0.6%, 2.8%, 5.5%, 10.5%), and gastrointestinal disorders (1.0%, 2.8%, 12.2%, 18.9%). Additionally, ORs in the two vaccinated cohorts, as compared to the "unvaccinated and vaginal delivery" reference group, were significant for all health conditions under consideration. Cesarean births have been associated with a significantly increased rate of allergies [46], asthma [47], and hospitalizations for gastroenteritis [48], possibly linked to suboptimal intestinal flora from loss of contact with the mother's immune-stimulating vaginal and intestinal bacteria [49]. Cesarean births have also been linked to breastfeeding complications, including delayed onset of lactation [49]. Thus, many babies lack early immune support of breast milk, which has been shown to have a protective effect against several adverse health conditions.

Extended breastfeeding: Within the logistic regression model that compared infants who were breastfed for at least 6 months versus not (Table S3), breastfed children were 52%, 61%, and 49% less likely to have been diagnosed with allergies (OR = 0.48, 95% CI 0.28 - 0.82), asthma (OR = 0.39, 95% CI 0.22 - 0.70), or ear infections (OR = 0.51, 95% CI 0.29 - 0.88), respectively. They were more than twice as likely as non-breastfed children to have contracted chickenpox (OR = 2.66, 95% CI 1.27 - 5.60). Since some of the infants stratified as "not breastfed" actually did breastfeed for less than 6 months, this could be a factor as to why significance was not achieved for autism, gastrointestinal disorders and chronic ear infections. The mothers who breastfed their babies for at least 6 months might have also been less likely than non-breastfeeding mothers to vaccinate their children, which could explain why chickenpox was more common in this group, or perhaps there is an interactive effect between breastfeeding and chickenpox vaccine immune responses, as one study found with the rotavirus vaccine [50].

Vaginal birth versus cesarean: Within the logistic regression model that compared infants who were delivered via C-section versus a vaginal delivery (Table S4), cesarean babies were twice as likely to have been diagnosed with gastrointestinal disorders (OR = 1.92, 95% CI 1.16 - 3.18). Vaginally delivered babies receive most of their gut bacteria from their mother, while cesarean babies acquire much of their gut composition in the hospital [51]. Transmission of maternal gastrointestinal bacteria to the newborn is disrupted through delivery by cesarean section, predisposing newborns to opportunistic pathogens [51]. Healthy gut microbiota promotes development and maturation of the immune system [52] while an aberrant gut microbiome can increase the risk of disease [53], and has been linked to allergies [51,54], asthma [51,54], and severe gastrointestinal infections [52].

Study strengths: One of the main strengths of this study is the ability to complete chart review from the participating pediatricians' electronic medical records to confirm diagnoses indicated from parental surveys. This was possible because respondents voluntarily included contact information and a substantial majority of patients (79.5%) were from one of the participating medical practices. Diagnoses confirmed from electronic medical records are more reliable than survey responses, and findings associated with such analyses are more credible. In table 8, only children with diagnoses confirmed from electronic medical records were included in the analysis. This mitigated recall bias associated with studies that are based solely on parental surveys.

The survey included questions regarding breastfeeding status and type of birth, which allowed these covariates to be accounted for within all of the analyses except for supplementary tables S1 and S2 (where they were excluded for comparative purposes). The inclusion of these covariates within this study revealed several important relationships between vaccination status, breastfeeding status, type of birth, and health outcomes.

Some of the children were just 2.5 years of age when the survey was taken, limiting the time for additional diagnoses, especially those made later in development including autism and ADD/ADHD. Thus, the calculated ORs could be conservative estimates of the true relationship between vaccines and adverse health consequences as younger children would bias the results toward the null hypothesis. Hooker and Miller [25] found that when the time permitted for a diagnosis was extended from children ≥ 3 years of age to children ≥ 5 years of age, slightly higher ORs were detected for all four of the adverse health conditions under consideration. This is discussed further in Geier *et al.* [55] as length of follow-up period (i.e., patient age) allows additional opportunities to affirm diagnoses.

Some of the infants evaluated as "not breastfed" did actually breastfeed for less than 6 months. If the infants listed as "not breastfed" had truly *never* been breastfed, the findings in table 9 indicating that breastfeeding provides a protective benefit against adverse health consequences would likely show even stronger effect estimates. Additionally, in tables 7 thru 10, fully and partially vaccinated children are counted together. This was necessary to attain sufficient cohort size to complete the analyses. If all of the children in the analyses were fully vaccinated, rather than a mix of fully and partially vaccinated, the findings in these tables would likely be even more pronounced.

The addition of chickenpox as a positive control diagnosis also lends credibility to the study as a higher incidence of chickenpox would be expected—and was found—in the unvaccinated group. This is similar to the results of Mawson *et al.* [5] where unvaccinated children showed higher incidence of "vaccine-preventable" diseases including chickenpox and whooping cough.

Finally, effect estimates in this paper were above 4.0. Thus, for some confounder to explain this association it would need to be four times as frequent in vaccinated children [56].

Potential limitations: The main weakness of this study is the use of a convenience sample of three different pediatric practices. Also, this study was based on responses from parental surveys which can introduce both recall bias and selection bias. Recall bias was mitigated by providing survey questions that were closed-ended with yes/no and multiple choice options, and by requiring that each health condition affirmed by the parent had been diagnosed by a medical professional. Additionally, the electronic medical records of children in the three participating medical practices were reviewed for confirmation of diagnoses. Although the findings in this paper were based on a convenience sample and survey, a recent study [25] utilizing data taken directly from patient chart records and diagnosis codes reported results similar to those found in this paper, including increased rates of gastrointestinal disorders, asthma and ear infections in vaccinated children as compared to unvaccinated children.

Regarding selection bias, adults who took the survey may have been more likely than adults in the general population to have had a child who, after receiving vaccines, was diagnosed with one or more of the adverse health conditions investigated in this paper. It's also possible that parents of unvaccinated children without adverse health conditions were more motivated than other parents to participate and be represented in the survey. Either of these possibilities could have influenced the study results. Another consideration is that the proportions of unvaccinated and home educated children in the sample population, 60.4% and 34.9% respectively, are greater than proportions found in the general population. Also, mothers who breastfed for a minimum duration of 6 months could have been more "vaccine hesitant" than those who did not. And 21.5% of children included in the main analyses were not patients in one of the three participating medical practices. However, to overcome the effect of combining distinct populations, Table 7 included children from participating medical practices only. Results were consistent with the main analyses, lending credibility to the overall findings.

Differences in healthcare-seeking behavior among non-vaccinating, partially-vaccinating and fully-vaccinating families could also introduce selection bias. Glanz *et al.* [57] reported that undervaccinated children showed lower rates of outpatient medical provider visits (incidence risk ratio = 0.89, 95% CI 0.89-0.90) within a large retrospectively matched cohort study involving the CDC's Vaccine Safety Datalink. However, this difference would be insufficient to fully account for effect estimates observed in this paper that were greater than 4.0.

Ascertainment of vaccination status was limited to three broad categories that do not reflect the different numbers, types and timing of the various vaccinations received. Partially vaccinated children received at least one vaccine but less than the recommended quantity which represents a highly variable range. Also, younger children in the study who were up to date on their vaccines received fewer vaccines than older children who were up to date, representing again a variable range. This precluded the specificity that would have provided more options for analyses.

Several studies have shown that some vaccines have non-specific effects that either increase or decrease susceptibility to infectious diseases not targeted by the vaccine. The most recent vaccine administered exerts the greatest effect. Live vaccines such as measles, MMR and BCG tend to lower risk (providing a beneficial influence) while non-live vaccines such as hepatitis B [58], DTP (diphtheria-tetanus-pertussis) and IPV (inactivated polio) tend to increase risk. For example, Bardenheier *et al.* [59] found a lower risk of non-targeted infectious disease hospitalizations among children whose last vaccine received was live compared with inactivated vaccine (hazard ratio = 0.50, 95% CI 0.43 – 0.57). In a recent meta-analysis conducted by Aaby *et al.* [60], girls who received an inactivated vaccine *after* receiving a measles vaccine were significantly more likely to die from other causes compared with girls who received an inactivated vaccine *before* receiving a measles vaccine (mortality rate ratio = 1.89, 95% CI 1.27 – 2.80). Although this current study did not consider non-specific effects (due to the lack of specific vaccine data) it is possible that the most recent vaccine administered could have influenced the results.

The only demographic data available were breastfeeding status, type of birth (vaginal versus cesarean), and current education status. Other factors that may influence health outcomes, such as vaccinations during pregnancy and gestational age at birth, were not included on the questionnaire. There are undoubtedly demographic differences within the two groups studied (vaccinated versus unvaccinated), especially regarding socioeconomic status and maternal education. According to Smith *et al.* [61] mothers in families where vaccines were delayed and declined tended to have higher levels of college education and families were more affluent. Although there are no direct studies on gestational age at birth in vaccinating versus non-vaccinating families, Zerbo *et al.* [62] indicated that children born to women receiving the influenza vaccine during pregnancy had significantly higher gestational age. Dueker *et al.* [63] showed that each week of gestational age beyond 35 weeks through 41 weeks significantly decreased developmental delays in infants. Also, children born prematurely (34 to 37 weeks) showed a higher rate of hospitalizations for asthma [64].

Conclusion

In the study presented here, children from three pediatric medical practices in the United States were used as a convenience sample to compare health outcomes in fully vaccinated, partially vaccinated, and completely unvaccinated populations. Within the logistic regression models, higher ORs were observed within the fully and partially vaccinated groups versus the unvaccinated group for severe allergies, autism, gastrointestinal disorders, asthma, attention deficit disorder (ADD/ADHD), and chronic ear infections. The OR for chickenpox, our positive control, was significantly low, affirming the protective effect of vaccination. Similar results have been observed in earlier studies. Results from the analysis of relationships between vaccination and breastfeeding status showed that the lowest percentages of adverse diagnoses were observed for "unvaccinated and breastfed" children; the highest were observed for "vaccinated and not breastfed" children. Results from the analysis of relationships between vaccination and birth delivery status showed that the lowest percentages of adverse diagnoses were observed for unvaccinated children delivered vaginally and the highest were observed for vaccinated children delivered via cesarean section. These particular analyses, and results, appear to be unique in the medical literature.

The findings in this study must be weighed against the strengths and limitations of the available data and study design. Additional research utilizing a larger sample from diverse medical practices will yield greater certainty in results, essential to understanding the full scope of health effects associated with childhood vaccination.

Author contributions

BSH incepted the study design and analyzed the data. BSH also helped draft the manuscript and interpret the data. NZM contributed to the drafting of the manuscript, design of the study, analysis and interpretation of the data, and critical revisions of the work. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

Dr. Hooker is a paid scientific advisor and serves on the advisory board for Focus for Health (formerly Focus Autism). He also serves on the Board of Trustees for Children's Health Defense (formerly World Mercury Project) and is a paid independent contractor of Children's Health Defense as well. Dr. Hooker is the father of a 23 year old male who has been diagnosed with autism and developmental delays. Mr. Miller has written and lectured on vaccine safety and was a paid consultant to Physicians for Informed Consent.

References

1. CDC (2020) Recommended child and adolescent immunization schedule for ages 18 years or younger, United States, 2020. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html (accessed on 16 February 2021).

2. Institute of Medicine. *Adverse Effects of Vaccines: Evidence and Causality*. Washington, DC: National Academies Press, 2011.

3. Bethell CD, Kogan MD, Strickland BB, Schor EL, Robertson J, et al. (2011) A national and state profile of leading health problems and health care quality for US children: key insurance disparities and across-state variations. *Acad Pediatr* 11: S22-S33. [Crossref]

4. Van Cleave J, Gortmaker SL, Perrin JM (2010) Dynamics of obesity and chronic health conditions among children and youth. *JAMA* 303: 623-630. [Crossref]

5. Mawson AR, Ray BD, Bhuiyan AR, Jacob B (2017) Pilot comparative study on the health of vaccinated and unvaccinated 6- to 12-year-old U.S. children. *J Transl Sci* 3: 1-12.

6. Bernsen RMD, Nagelkerke NJD, Thijs C, van der Wouden JC (2008) Reported pertussis infection and risk of atopy in 8- to 12-yr-old vaccinated and non-vaccinated children. *Pediatr Allergy Immunol* 19: 46-52. [Crossref]

7. McDonald KL, Huq SI, Lix LM, Becker AB, Kozyrskyj AL, et al. (2008) Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma. *J Allergy Clin Immunol* 121: 626-631. [Crossref]

8. Leslie DL, Kobre RA, Richmand BJ, Guloksuz SA, Leckman JF, et al. (2017) Temporal association of certain neuropsychiatric disorders following vaccination of children and adolescents: a pilot case-control study. *Front Psychiatry* 8: 3. [Crossref]

9. Geier DA, Kern JK, Homme KG, Geier MR (2017) Abnormal brain connectivity spectrum disorders following Thimerosal administration: a prospective longitudinal case-control assessment of medical records in the Vaccine Safety Datalink. *Dose-Response* 15: 1-12. [Crossref]

10. Geier DA, Kern JK, Hooker BS, Sykes LK, Geier MR,et al. (2016) Thimerosal-preserved hepatitis B vaccine and hyperkinetic syndrome of childhood. *Brain Sci* 6: 9. [Crossref]

11. Hooker BS (2018) Reanalysis of CDC data on autism incidence and time of first MMR vaccination. *Journal of American Physicians and Surgeons* 23: 105-109.

12. Geier DA, Kern JK, Geier MR (2017) Increased risk for an atypical autism diagnosis following Thimerosal-containing vaccine exposure in the United States: a prospective longitudinal case-control study in the Vaccine Safety Datalink. *J Trace Elem Med Biol* 42: 18-24. [Crossref]

13. Morris G, Puri BK, Frye RE (2017) The putative role of environmental aluminum in the development of chronic neuropathology in adults and children. How strong is the evidence and what could be the mechanisms involved? *Metab Brain Dis* 32: 1335-1355. [Crossref]

14. Wilson K, Ducharme R, Ward B, Hawken S (2014) Increased emergency room visits or hospital admissions in females after 12-month MMR vaccination, but no difference after vaccinations given at a younger age. *Vaccine* 32: 1153-1159. [Crossref]

15. Merck & Co., Inc. RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent). *Product insert* 2017, Table 5, 6.

16. MacDonald SE, Dover DC, Simmonds KA, Svenson LW (2014) Exploring the risk factors for vaccine-associated and non-vaccine associated febrile seizures in a large pediatric cohort. *Vaccine* 32: 2574-2581. [Crossref]

17. MacDonald SE, Dover DC, Simmonds KA, Svenson LW (2014) Risk of febrile seizures after first dose of measles-mumps-rubella-varicella vaccine: a population-based cohort study. *CMAJ* 186: 824-829. [Crossref]

18. Sun Y, Christensen J, Hviid A, Li J, Vedsted P, et al. (2012) Risk of febrile seizures and epilepsy after vaccination with diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and *Haemophilus influenzae* type B. *JAMA* 307: 823-831. [Crossref]

19. Geier DA, Kern JK, Hooker BS, King PG, Sykes LK, et al. (2016) A longitudinal cohort study of the relationship between Thimerosal-containing hepatitis B vaccination and specific delays in development in the US: assessment of attributable risk and lifetime care costs. *J Epidemiol Glob Health* 6: 105-118. [Crossref]

20. Classen JB (2014) Review of vaccine-induced immune overload and the resulting epidemics of type 1 diabetes and metabolic syndrome, emphasis on explaining the recent accelerations in the risk of prediabetes and other immune-mediated diseases. *J Mol Genet Med* S1: 025.

21. Classen JB (2008) Clustering of cases of IDDM 2 to 4 years after hepatitis B immunization is consistent with clustering after infections and progression to IDDM in autoantibody positive individuals. *Open Pediatr Med J* 2: 1-6.

22. Classen JB and Classen DC (2002) Clustering of cases of insulin dependent diabetes (IDDM) occurring three years after *Hemophilus influenza* B (HiB) immunization support causal relationship between immunization and IDDM. *Autoimmunity* 35: 247-253. [Crossref]

23. Goldman GS and Miller NZ (2012) Relative trends in hospitalizations and mortality among infants by the number of vaccine doses and age, based on the Vaccine Adverse Event Reporting System (VAERS), 1990-2010. *Hum Exp Toxicol* 31: 1012-1021. [Crossref]

24. Institute of Medicine. *The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies.* Washington, DC: National Academies Press, 2013.

25. Hooker BS and Miller NZ (2020) Analysis of health outcomes in vaccinated and unvaccinated children: developmental delays, asthma, ear infections and gastrointestinal disorders. *SAGE Open Medicine* 8: 1-11. [Crossref]

26. Lyons-Weiler J and Thomas P (2020) Relative incidence of office visits and cumulative rates of billed diagnoses along the axis of vaccination. *Int. J. Environ. Res. Public Health* 17: 8674. [Crossref]

27. CDC. Chickenpox (varicella) vaccination. https://www.cdc.gov/chickenpox/vaccination.html (accessed on 16 February 2021).

28. Nilsson L, Kjellman NI, Björkstén BA (1998) Randomized controlled trial of the effect of pertussis vaccines on atopic disease. *Arch Pediatr Adolesc Med* 152: 734-738. [Crossref]

29. Anderson HR, Poloniecki JD, Strachan DP, Beasley R, Björkstén B, et al. (2001) Immunization and symptoms of atopic disease in children: results from the International Study of Asthma and Allergies in Childhood. *Am J Public Health* 91: 1126-1129. [Crossref]

30. Hurwitz EL and Morgenstern H (2000) The effect of diphtheria-tetanus-pertussis (DTP) or tetanus vaccination on allergies and allergy-related respiratory symptoms among children and adolescents in the United States. *J Manipulative Physiol Therapy* 23: 81-90.

31. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, et al. (2003) A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* 349: 1341-1348. [Crossref]

32. Yon DK, Ha EK, Lee S, Kim WK, Park YM, et al. (2018) Hepatitis B immunogenicity after a primary vaccination course associated with childhood asthma, allergic rhinitis and allergen sensitization. *Pediatr Allergy Immunol* 29: 221-224. [Crossref]

33. Zhang J, Ma Z, Sun W, Cao J, Wang Z, et al. (2016) Programmed vaccination may increase the prevalence of asthma and allergic diseases. *Am J Rhinol Allergy* 30: 113-117. [Crossref]

34. Delong GA (2011) Positive association found between autism prevalence and childhood vaccine uptake across the U.S. Population. *J Toxicol Environ Health A* 74: 903-916. [Crossref]

35. Eidi H, Yoo J, Bairwa SC, Kuo M, Sayre EC, et al. (2020) Early postnatal injections of whole vaccines compared to placebo controls: differential behavioral outcomes in mice. *Journal of Inorganic Biochemistry* 212: 111200.

36. Institute of Medicine, *Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders.* Washington, DC: National Academies Press, 2001.

37. Wilson K, Ducharme R, Ward B, Hawken S (2014) Increased emergency room visits or hospital admissions in females after 12-month MMR vaccination, but no difference after vaccinations given at a younger age. *Vaccine* 32: 1153-1159. [Crossref]

38. Haber P, Parashar UD, Haber M, DeStefano F (2015) Intussusception after monovalent rotavirus vaccine — United States, Vaccine Adverse Event Reporting System (VAERS), 2008-2014. *Vaccine* 33: 4873-4877. [Crossref]

39. Yih WK, Lieu TA, Kulldorff M, Martin D, McMahill-Walraven CN (2014) Intussusception risk after rotavirus vaccination in U.S. infants. *N Engl J Med* 370: 503-512. [Crossref]

40. Carlin JB, Macartney KK, Lee KJ, Quinn EH, Buttery J, et al. (2013) Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's National Immunization Program. *Clin Infect Dis* 57: 1427-1434. [Crossref]

41. Weintraub ES, Baggs J, Duffy J, Vellozzi C, Belongia EA, et al. (2014) Risk of intussusception after monovalent rotavirus vaccination. *N Engl J Med* 370: 513-519. [Crossref]

42. Nzolo D, Ntetani Aloni M, Ngamasta T, Luemba BM, Marfeza SB, et al. (2013) Adverse events following immunization with oral poliovirus in Kinshasa, Democratic Republic of Congo: preliminary results. *Pathog Glob Health* 107: 381-384. [Crossref]

43. Geier DA and Geier MR (2017) Quadrivalent human papillomavirus vaccine and autoimmune adverse events: a case-control assessment of the vaccine adverse event reporting system (VAERS) database. *Immunol Res* 65: 46-54. [Crossref]

44. American Academy of Pediatrics. Breastfeeding benefits your baby's immune system. https://www.healthychildren.org/English/ages-stages/baby/breastfeeding/Pages/Breastfeeding-Benefits-Your-Babys-Immune-System.aspx (accessed on 16 February 2021).

45. Klopp A, Vehling L, Becker AB, Subbarao P, Mandhane JP, et al. (2017) Modes of infant feeding and the risk of childhood asthma: a prospective birth cohort study. *J Pediatr* 190: 192-199.e2. [Crossref]

46. Bager P, Wohlfahrt J, Westergaard T (2008) Caesarean delivery and risk of atopy and allergic diseases: meta-analyses. *Clin Exp Allergy* 38: 634-642. [Crossref]

47. Thavagnanam S, Fleming J, Bromley A, Cardwell CR (2008) A meta-analysis of the association between Caesarean section and childhood asthma. *Clin Exp Allergy* 38: 629-633. [Crossref]

48. Håkansson S and Källén K (2003) Caesarean section increases the risk of hospital care in childhood for asthma and gastroenteritis. *Clin Exp Allergy* 33: 757-764. [Crossref]

49. Neu J and Rushing J (2011) Cesarean versus vaginal delivery: long-term infant outcomes and the hygiene hypothesis. *Clin Perinatol* 38: 321-331. [Crossref]

50. Moon S, Wang Y, Shane AL, Nguyen T, Ray P, et al. (2010) Inhibitory effect of breast milk on infectivity of live oral rotavirus vaccines. *Pediatr Infect Dis J* 29: 919-923. [Crossref]

51. Shao Y, Forster SC, Tsaliki E, Vervier K, Strang A, et al. (2019) Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth. *Nature* 574: 117-121. [Crossref]

52. Rutayisire E, Huang K, Liu Y, Tao F (2016) The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review. *BMC Gastroenterol* 16: 86. [Crossref]

53. Tamburini S, Shen N, Wu HC, Clemente JC, et al. (2016) The microbiome in early life: implications for health outcomes. *Nat Med* 22: 713-722. [Crossref]

54. Johnson CC and Ownby DR (2017) The infant gut bacterial microbiota and risk of pediatric asthma and allergic diseases. *Transl Res* 179: 60-70. [Crossref]

55. Geier DA, Hooker BS, Kern JK, King PG, Sykes LK, et al. (2013) A two-phased study evaluating the relationship between thimerosal-containing vaccine administration and the risk for an autism spectrum disorder diagnosis in the United States. *Transl Neurodegeneration* 2: 25-36. [Crossref]

56. Cornfield J, Haenszel W, Hammond EC, Shimkin MB, Wynder EL (1959) Smoking and lung cancer: recent evidence and a discussion of some questions. *J Natl Cancer Inst* 22: 173-203. [Crossref]

57. Glanz JM, Newcomer SR, Narwaney KJ, Hambidge SJ, Daley MF, et al. (2013) A population based cohort study of undervaccination in 8 managed care organizations across the United States. *JAMA Pediatr* 167: 274-281. [Crossref]

58. Garly ML, Jensen H, Martins CL, Balé C, Baldé MA, et al. (2004) Hepatitis B vaccination associated with higher female than male mortality in Guinea-Bissau: an observational study. *Pediatr Infect Dis J* 23: 1086-1092. [Crossref]

59. Bardenheier BH, McNeil MM, Wodi AP, McNichol JM, DeStefano F, et al. (2017) Risk of nontargeted infectious disease hospitalizations among US children following inactivated and live vaccines, 2005-2014. *Clin Infect Dis* 65: 729-737. [Crossref]

60. Aaby P, Ravn H, Benn CS, Rodrigues A, Samb B, et al. (2016) Randomized trials comparing inactivated vaccine after medium- or high-titer measles vaccine with standard-titer measles vaccine after inactivated vaccine: a meta-analysis. *Pediatr Infect Dis J* 35: 1232-1241. [Crossref]

61. Smith PJ, Humiston SG, Marcuse EK, Zhao Z, Dorell CG, et al. (2011) Parental delay or refusal of vaccine doses, childhood vaccination coverage at 24 months of age, and the health belief model. *Public Health Rep* 126: 135-146. [Crossref]

62. Zerbo O, Qian Y, Yoshisa C, Fireman BH, Klein NP, et al. (2017) Association between influenza infection and vaccination during pregnancy and risk of autism spectrum disorder. *JAMA Pediatr* 171: e163609. [Crossref]

63. Dueker G, Chen J, Cowling C, Haskin B (2016) Early development outcomes predicted by gestational age from 35 to 41 weeks. *Early Hum Dev* 103: 85-90. [Crossref]

64. Leung JY, Lam HS, Leung GM, Schooling CM (2016) Gestational age, birthweight for gestational age, and childhood hospitalisations for asthma and other wheezing disorders. *Paediatr Perinat Epidemiol* 30: 149-159. [Crossref]

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