

Pilot comparative study on the health of vaccinated and unvaccinated ...

Abstract

Vaccinations have prevented millions of infectious illnesses, hospitalizations and deaths among U.S. children, yet the long-term health outcomes of the vaccination schedule remain uncertain. Studies have been recommended by the U.S. Institute of Medicine to address this question. This study aimed 1) to compare vaccinated and unvaccinated children on a broad range of health outcomes, and 2) to determine whether an association found between vaccination and neurodevelopmental disorders (NDD), if any, remained significant after adjustment for other measured factors. A cross-sectional study of mothers of children educated at home was carried out in collaboration with homeschool organizations in four U.S. states: Florida, Louisiana, Mississippi and Oregon. Mothers were asked to complete an anonymous online questionnaire on their 6- to 12-year-old biological children with respect to pregnancy-related factors, birth history, vaccinations, physician-diagnosed illnesses, medications used, and health services. NDD, a derived diagnostic measure, was defined as having one or more of the following three closely-related diagnoses: a

learning disability, Attention Deficient Hyperactivity Disorder, and Autism Spectrum Disorder. A convenience sample of 666 children was obtained, of which 261 (39%) were unvaccinated. The vaccinated were less likely than the unvaccinated to have been diagnosed with chickenpox and pertussis, but more likely to have been diagnosed with pneumonia, otitis media, allergies and NDD. After adjustment, vaccination, male gender, and preterm birth remained significantly associated with NDD. However, in a final adjusted model with interaction, vaccination but not preterm birth remained associated with NDD, while the interaction of preterm birth and vaccination was associated with a 6.6-fold increased odds of NDD (95% CI: 2.8, 15.5). In conclusion, vaccinated homeschool children were found to have a higher rate of allergies and NDD than unvaccinated homeschool children. While vaccination remained significantly associated with NDD after controlling for other factors, preterm birth coupled with vaccination was associated with an apparent synergistic increase in the odds of NDD. Further research involving larger, independent samples and stronger research designs is needed to verify and understand these unexpected findings in order to optimize the impact of vaccines on children's health.

Key words

acute diseases, chronic diseases, epidemiology, evaluation, health policy, immunization,

neurodevelopmental disorders, vaccination

Abbreviations:

ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; AOM: Acute Otitis Media; CDC: Centers for Disease Control and Prevention; CI: Confidence Interval; NDD: Neurodevelopmental Disorders; NHERI: National Home Education Research Institute; OR: Odds Ratio; PCV-7: Pneumococcal Conjugate Vaccine-7; VAERS: Vaccine Adverse Events Reporting System.

Introduction

Vaccines are among the greatest achievements of biomedical science and one of the most effective public health interventions of the 20th century [1]. Among U.S. children born between 1995 and 2013, vaccination is estimated to have prevented 322 million illnesses, 21 million hospitalizations and 732,000 premature deaths, with overall cost savings of \$1.38 trillion [2]. About 95% of U.S. children of kindergarten age receive all of the recommended vaccines as a requirement for school and daycare attendance [3,4], aimed at preventing the occurrence and spread of targeted infectious diseases [5]. Advances in biotechnology are contributing to the development of new vaccines for widespread use [6].

Under the currently recommended pediatric vaccination schedule [7], U.S. children receive up to 48 doses of

vaccines for 14 diseases from birth to age six years, a figure that has steadily increased since the 1950s, most notably since the Vaccines for Children program was created in 1994. The Vaccines for Children program began with vaccines targeting nine diseases: diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b disease, hepatitis B, measles, mumps, and rubella. Between 1995 and 2013, new vaccines against five other diseases were added for children age 6 and under: varicella, hepatitis A, pneumococcal disease, influenza, and rotavirus vaccine.

Although short-term immunologic and safety testing is performed on vaccines prior to their approval by the U.S. Food and Drug Administration, the long-term effects of individual vaccines and of the vaccination program itself remain unknown [8]. Vaccines are acknowledged to carry risks of severe acute and chronic adverse effects, such as neurological complications and even death [9], but such risks are considered so rare that the vaccination program is believed to be safe and effective for virtually all children [10].

There are very few randomized trials on any existing vaccine recommended for children in terms of morbidity and mortality, in part because of ethical concerns involving withholding vaccines from children assigned to a control group. One exception, the high-titer measles vaccine, was withdrawn after several randomized trials in west Africa showed that it interacted with the diphtheria-

tetanus-pertussis vaccine, resulting in a significant 33% increase in child mortality [11]. Evidence of safety from observational studies includes a limited number of vaccines, e.g., the measles, mumps and rubella vaccine, and hepatitis B vaccine, but none on the childhood vaccination program itself. Knowledge is limited even for vaccines with a long record of safety and protection against contagious diseases [12]. The safe levels and long-term effects of vaccine ingredients such as adjuvants and preservatives are also unknown [13]. Other concerns include the safety and cost-effectiveness of newer vaccines against diseases that are potentially lethal for individuals but have a lesser impact on population health, such as the group B meningococcus vaccine [14].

Knowledge of adverse events following vaccinations is largely based on voluntary reports to the Vaccine Adverse Events Reporting System (VAERS) by physicians and parents. However, the rate of reporting of serious vaccine injuries is estimated to be <1% [15]. These considerations led the former Institute of Medicine (now the National Academy of Medicine) in 2005 to recommend the development of a five-year plan for vaccine safety research by the Centers for Disease Control and Prevention (CDC) [16,17]. In its 2011 and 2013 reviews of the adverse effects of vaccines, the Institute of Medicine concluded that few health problems are caused by or associated with vaccines, and found no evidence that the vaccination schedule was unsafe [18,19]. Another

systematic review, commissioned by the US Agency for Healthcare Research and Quality to identify gaps in evidence on the safety of the childhood vaccination program, concluded that severe adverse events following vaccinations are extremely rare [20]. The Institute of Medicine, however, noted that studies were needed: to compare the health outcomes of vaccinated and unvaccinated children; to examine the long-term cumulative effects of vaccines; the timing of vaccination in relation to the age and condition of the child; the total load or number of vaccines given at one time; the effect of other vaccine ingredients in relation to health outcomes; and the mechanisms of vaccine-associated injury [19].

A complicating factor in evaluating the vaccination program is that vaccines against infectious diseases have complex nonspecific effects on morbidity and mortality that extend beyond prevention of the targeted disease. The existence of such effects poses a challenge to the assumption that individual vaccines affect the immune system independently of each other and have no physiological effect other than protection against the targeted pathogen [21]. The nonspecific effects of some vaccines appear to be beneficial, while in others they appear to increase morbidity and mortality [22,23]. For instance, both the measles and Bacillus Calmette–Guérin vaccine reportedly reduce overall morbidity and mortality [24], whereas the diphtheria-tetanus-pertussis [25] and hepatitis B vaccines [26] have the opposite effect. The

mechanisms responsible for these nonspecific effects are unknown but may involve *inter alia*: interactions between vaccines and their ingredients, e.g., whether the vaccines are live or inactivated; the most recently administered vaccine; micronutrient supplements such as vitamin A; the sequence in which vaccines are given; and their possible combined and cumulative effects [21].

A major current controversy is the question of whether vaccination plays a role in neurodevelopmental disorders (NDDs), which broadly include learning disabilities, Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD). The controversy has been fueled by the fact that the U.S. is experiencing what has been described as a “silent pandemic” of mostly subclinical developmental neurotoxicity, in which about 15% of children suffer from a learning disability, sensory deficits, and developmental delays [27,28]. In 1996 the estimated prevalence of ASD was 0.42%. By 2010 it had risen to 1.47% (1 in 68), with 1 in 42 boys and 1 in 189 girls affected [29]. More recently, based on a CDC survey of parents in 2011–2014, 2.24% of children (1 in 45) were estimated to have ASD. Rates of other developmental disabilities, however, such as intellectual disability, cerebral palsy, hearing loss, and vision impairments, have declined or remained unchanged [30]. Prevalence rates of Attention Deficit Hyperactivity Disorder (ADHD) have also risen markedly in recent decades [31]. Earlier increases in the prevalence of learning disability have been followed by

declining rates in most states, possibly due to changes in diagnostic criteria [32].

It is believed that much of the increase in NDD diagnoses in recent decades has been due to growing awareness of autism and more sensitive screening tools, and hence to greater numbers of children with milder symptoms of autism. But these factors do not account for all of the increase [33]. The geographically widespread increase in ASD and ADHD suggests a role for an environmental factor to which virtually all children are exposed.

Agricultural chemicals are a current focus of research [34-37].

A possible contributory role for vaccines in the rise in NDD diagnoses remains unknown because data on the health outcomes of vaccinated and unvaccinated children are lacking. The need for such studies is suggested by the fact that the Vaccine Injury Compensation Program has paid \$3.2 billion in compensation for vaccine injury since its creation in 1986 [38]. A study of claims compensated by the Vaccine Injury Compensation Program for vaccine-induced encephalopathy and seizure disorder found 83 claims that were acknowledged as being due to brain damage. In all cases it was noted by the Court of Federal Claims, or indicated in settlement agreements, that the children had autism or ASD [39]. On the other hand, numerous epidemiological studies have found no association between receipt of selected vaccines (in particular the combined measles, mumps, and rubella

vaccine) and autism [10,40-45], and there is no accepted mechanism by which vaccines could induce autism [46].

A major challenge in comparing vaccinated and unvaccinated children has been to identify an accessible pool of unvaccinated children, since the vast majority of children in the U.S. are vaccinated. Children educated at home ("homeschool children") are suitable for such studies as a higher proportion are unvaccinated compared to public school children [47]. Homeschool families have an approximately equal median income to that of married-couple families nationwide, somewhat more years of formal education, and a higher average family size (just over three children) compared to the national average of just over two children [48-50]. Homeschooling families are slightly overrepresented in the south, about 23% are nonwhite, and the age distribution of homeschool children in grades K-12 is similar to that of children nationwide [51]. About 3% of the school-age population was homeschooled in the 2011-2012 school year [52].

The aims of this study were 1) to compare vaccinated and unvaccinated children on a broad range of health outcomes, including acute and chronic conditions, medication and health service utilization, and 2) to determine whether an association found between vaccination and NDDs, if any, remained significant after adjustment for other measured factors.

Methods

Study planning

To implement the study, a partnership was formed with the National Home Education Research Institute (NHERI), an organization that has been involved in educational research on homeschooling for many years and has strong and extensive contacts with the homeschool community throughout the country (www.nheri.org). The study protocol was approved by the Institutional Review Board of Jackson State University.

Study design

The study was designed as a cross-sectional survey of homeschooling mothers on their vaccinated and unvaccinated biological children ages 6 to 12. As contact information on homeschool families was unavailable, there was no defined population or sampling frame from which a randomized study could be carried out, and from which response rates could be determined. However, the object of our pilot study was not to obtain a representative sample of homeschool children but a convenience sample of unvaccinated children of sufficient size to test for significant differences in outcomes between the groups.

We proceeded by selecting 4 states (Florida, Louisiana, Mississippi, and Oregon) for the survey (Stage 1). NHERI compiled a list of statewide and local homeschool organizations, totaling 84 in Florida, 18 in Louisiana, 12 in Mississippi and 17 in Oregon. Initial contacts were made in

June 2012. NHERI contacted the leaders of each statewide organization by email to request their support. A second email was then sent, explaining the study purpose and background, which the leaders were asked to forward to their members (Stage 2). A link was provided to an online questionnaire in which no personally identifying information was requested. With funding limited to 12 months, we sought to obtain as many responses as possible, contacting families only indirectly through homeschool organizations. Biological mothers of children ages 6-12 years were asked to serve as respondents in order to standardize data collection and to include data on pregnancy-related factors and birth history that might relate to the children's current health. The age-range of 6 to 12 years was selected because most recommended vaccinations would have been received by then.

Recruitment and informed consent

Homeschool leaders were asked to sign Memoranda of Agreement on behalf of their organizations and to provide the number of member families. Non-responders were sent a second notice but few provided the requested information. However, follow-up calls to the leaders suggested that all had contacted their members about the study. Both the letter to families and the survey questions were stated in a neutral way with respect to vaccines. Our letter to parents began:

“Dear Parent, This study concerns a major current health question: namely, whether vaccination is linked in any way to childrens long-term health. Vaccination is one of the greatest discoveries in medicine, yet little is known about its long-term impact. The objective of this study is to evaluate the effects of vaccination by comparing vaccinated and unvaccinated children in terms of a number of major health outcomes ...”

Respondents were asked to indicate their consent to participate, to provide their home state and zip code of residence, and to confirm that they had biological children 6 to 12 years of age. The communications company Qualtrics (<http://qualtrics.com>) hosted the survey website. The questionnaire included only closed-ended questions requiring yes or no responses, with the aim of improving both response and completion rates.

A number of homeschool mothers volunteered to assist NHERI promote the study to their wide circles of homeschool contacts. A number of nationwide organizations also agreed to promote the study in the designated states. The online survey remained open for three months in the summer of 2012. Financial incentives to complete the survey were neither available nor offered.

Definitions and measures

Vaccination status was classified as unvaccinated (i.e., no previous vaccinations), partially vaccinated (received

some but not all recommended vaccinations) and fully vaccinated (received all recommended age-appropriate vaccines), as reported by mothers. These categories were developed on the premise that any long-term effects of vaccines would be more evident in fully-vaccinated than in partially-vaccinated children, and rare or absent in the unvaccinated. Mothers were asked to use their child's vaccination records to indicate the recommended vaccines and doses their child had received. Dates of vaccinations were not requested in order not to overburden respondents and to reduce the likelihood of inaccurate reporting; nor was information requested on adverse events related to vaccines, as this was not our purpose. We also did not ask about dates of diagnoses because chronic illnesses are often gradual in onset and made long after the appearance of symptoms. Since most vaccinations are given before age 6, vaccination would be expected to precede the recognition and diagnosis of most chronic conditions.

Mothers were asked to indicate on a list of more than 40 acute and chronic illnesses all those for which her child or children had received a diagnosis by a physician. Other questions included the use of health services and procedures, dental check-ups, "sick visits" to physicians, medications used, insertion of ventilation ear tubes, number of days in the hospital, the extent of physical activity (number of hours the child engaged in "vigorous" activities on a typical weekday), number of siblings, family

structure (mother and father living in the home, divorced or separated), family income and/or highest level of education of mother or father, and social interaction with children outside the home (i.e., amount of time spent in play or other contact with children outside the household). Questions specifically for the mother included pregnancy-related conditions and birth history, use of medications during pregnancy, and exposure to an adverse environment (defined as living within 1-2 miles of a furniture manufacturing factory, hazardous waste site, or lumber processing factory). NDD, a derived diagnostic category, was defined as having one or more of the following three closely related and overlapping diagnoses: a learning disability, Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) [53].

Statistical methods

Unadjusted bivariate analyses using chi-square tests were performed initially to test the null hypothesis of no association between vaccination status and health outcomes, i.e., physician-diagnosed acute and chronic illnesses, medications, and the use of health services. In most analyses, partially and fully vaccinated children were grouped together as the "vaccinated" group, with unvaccinated children as the control group. The second aim of the study was to determine whether any association found between vaccination and neurodevelopmental disorders remained significant after

controlling for other measured factors. Descriptive statistics on all variables were computed to determine frequencies and percentages for categorical variables and means (\pm SD) for continuous variables. The strength of associations between vaccination status and health outcomes were tested using odds ratios (OR) and 95% Confidence Intervals (CI). Odds ratios describe the strength of the association between two categorical variables measured simultaneously and are appropriate measures of that relationship in a cross-sectional study [54]. Unadjusted and adjusted logistic regression analyses were carried out using SAS (Version 9.3) to determine the factors associated with NDDs.

Results

Socio-Demographic characteristics of respondents

The information contained in 415 questionnaires provided data on 666 homeschool children. Table 1 shows the characteristics of the survey respondents. Mothers averaged about 40 years of age, were typically white, college graduates, with household incomes between \$50,000 to \$100,000, Christian, and married. The reasons for homeschooling for the majority of respondents (80-86%) were for a moral environment, better family relationships, or for more contact with their child or children.

Table 1. Characteristics of the respondents^a

	Mean (SD) ^a
Age (n=407)	40.59 (6.7)
	Number (%)^a
Race	
White	382 (92.5%)
Non-White	21 (7.6%)
Total	413
Education	
High School Graduate or Less	35 (8.5%)
Some College	114 (27.5%)
College Graduate	187 (45.2%)
Post-Graduates	78 (18.5%)
Total	414
Total Gross Household Income	
< \$49,999	123 (30.8%)
\$50,000-100,000	182 (45.5%)
> \$100,000	95 (23.8%)
Total	400
Religious Affiliation	
Christianity	375 (91.2%)
Non-Christianity	36 (8.8%)
Total	411
Marital Status	
Married	386 (93.7%)
Not Married	26 (6.3%)
Total	412

^a Missing observations are excluded.

The children as a group were similarly mostly white (88%), with a slight preponderance of females (52%), and averaged 9 years of age. With regard to vaccination status, 261 (39%) were unvaccinated, 208 (31%) were partially vaccinated, and 197 (30%) had received all of the recommended vaccinations. All statistical analyses are based on these numbers.

Acute illness

Vaccinated children (N=405), combining the partially and fully vaccinated, were significantly less likely than the unvaccinated to have had chickenpox (7.9% vs. 25.3%, $p < 0.001$; Odds Ratio = 0.26, 95% Confidence Interval: 0.2, 0.4) and whooping cough (pertussis) (2.5% vs. 8.4%, $p < 0.001$; OR 0.3, 95% CI: 0.1, 0.6), and less likely, but not significantly so, to have had rubella (0.3% vs. 1.9%, $p = 0.04$; OR 0.1, 95% CI: 0.01, 1.1). However, the vaccinated were significantly more likely than the unvaccinated to have been diagnosed with otitis media (19.8% vs. 5.8%, $p < 0.001$; OR 3.8, 95% CI: 2.1, 6.6) and pneumonia (6.4% vs. 1.2%, $p = 0.001$; OR 5.9, 95% CI: 1.8, 19.7). No significant differences were seen with regard to hepatitis A or B, high fever in the past 6 months, measles, mumps, meningitis (viral or bacterial), influenza, or rotavirus (Table 2).

Table 2. Vaccination status and health outcomes – Acute

Conditions

	Vaccinated (n=405)	Unvaccinated (n=261)	Total (n=666)	Chi- squa
Chickenpox				
Yes	32 (7.9%)	66 (25.3%)	98 (14.7%)	38.22
No	373 (92.1%)	195 (74.7%)	568 (85.3%)	
Otitis media				
Yes	80 (19.8%)	16(5.8%)	96 (14.4%)	26.64
No	325 (80.2%)	245 (94.2%)	507 (85.6%)	
Pneumonia				
Yes	26 (6.4%)	3 (1.2%)	29 (4.4%)	10.58
No	379 (93.6%)	258 (98.8%)	637 (95.6%)	
Whooping cough				
Yes	10 (2.5%)	22 (8.4%)	32 (4.8%)	12.32
No	395 (97.5%)	239 (91.6%)	634 (95.2%)	
Rubella				
Yes	1 (0.3%)	5 (1.9%)	6 (0.9%)	4.95
	404		660	

No	(99.6%)	256 (98.1%)	(99.1%)
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Chronic illness

Vaccinated children were significantly more likely than the unvaccinated to have been diagnosed with the following: allergic rhinitis (10.4% vs. 0.4%, $p < 0.001$; OR 30.1, 95% CI: 4.1, 219.3), other allergies (22.2% vs. 6.9%, $p < 0.001$; OR 3.9, 95% CI: 2.3, 6.6), eczema/atopic dermatitis (9.5% vs. 3.6%, $p = 0.035$; OR 2.9, 95% CI: 1.4, 6.1), a learning disability (5.7% vs. 1.2%, $p = 0.003$; OR 5.2, 95% CI: 1.6, 17.4), ADHD (4.7% vs. 1.0%, $p = 0.013$; OR 4.2, 95% CI: 1.2, 14.5), ASD (4.7% vs. 1.0%, $p = 0.013$; OR 4.2, 95% CI: 1.2, 14.5), any neurodevelopmental disorder (i.e., learning disability, ADHD or ASD) (10.5% vs. 3.1%, $p < 0.001$; OR 3.7, 95% CI: 1.7, 7.9) and any chronic illness (44.0% vs. 25.0%, $p < 0.001$; OR 2.4, 95% CI: 1.7, 3.3). No significant differences were observed with regard to cancer, chronic fatigue, conduct disorder, Crohn's disease, depression, Types 1 or 2 diabetes, encephalopathy, epilepsy, hearing loss, high blood pressure, inflammatory bowel disease, juvenile rheumatoid arthritis, obesity, seizures, Tourette's syndrome, or services received under the Individuals with Disabilities Education Act (Table 3).

Table 3. Vaccination status and health outcomes – Chronic Conditions

	Vaccinated	Unvaccinated	Chi-
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Chronic Disease	(n=405)	(n=261)	square
Allergic rhinitis			
Yes	42 (10.4%)	1 (0.4%)	26.21
No	363 (89.6%)	260 (99.6%)	
Allergies			
Yes	90 (22.2%)	18 (6.9%)	29.44
No	315 (77.9%)	243 (93.1%)	
ADHD			
Yes	19 (4.7%)	3 (1.0%)	6.23
No	386 (95.3%)	258 (99.0%)	
ASD			
Yes	19 (4.7%)	3 (1.0%)	6.23
No	386 (95.3%)	258 (99.0%)	
Eczema (atopic dermatitis)			
Yes	38 (9.5%)	9 (3.6%)	8.522
No	367 (90.5%)	252 (96.4%)	
Learning Disability			
Yes	23 (5.7%)	3 (1.2%)	8.6803
No	382 (94.3%)	258 (98.9%)	
Neurodevelopment Disorder			

Yes	42 (10.5%)	8 (3.1%)	12.198
No	313 (89.5%)	253 (96.9%)	
Any Chronic Condition			
Yes	178 (44.0%)	65 (24.9%)	24.8456
No	227 (56.0%)	196 (75.1%)	

Partial versus full vaccination

Partially vaccinated children had an intermediate position between the fully vaccinated and unvaccinated in regard to several but not all health outcomes. For instance, as shown in Table 4, the partially vaccinated had an intermediate (apparently detrimental) position in terms of allergic rhinitis, ADHD, eczema, and learning disability.

Table 4. Partial versus full vaccination and chronic health conditions

	Unvaccinated (n=261)	Partially Vaccinated (n=208)	Fully Vaccinated (n=197)	Total (n=)
Chronic Conditions				
Allergic rhinitis				
Yes	1 (0.4%)	17 (8.2%)	25 (12.7%)	43 (6.5)
No	260 (99.6%)	191 (91.8%)	172 (87.3%)	623 (93)

Allergies				
Yes	18 (6.9%)	47 (22.6%)	43 (21.8%)	108 (16.3%)
No	243 (93.1%)	161 (77.4%)	154 (78.2%)	558 (83.7%)
ADHD				
Yes	3 (1.2%)	8 (3.9%)	11 (5.6%)	22 (3.3%)
No	258 (98.8%)	200 (96.1%)	186 (94.4%)	644 (96.7%)
ASD				
Yes	3 (1.2%)	11 (5.3%)	8 (4.6%)	22 (3.3%)
No	258 (98.8%)	197 (94.7%)	189 (95.4%)	644 (96.7%)
Eczema (atopic dermatitis)				
Yes	9 (3.5%)	18 (8.7%)	20 (10.2%)	47 (7.1%)
No	252 (96.5%)	190 (91.3%)	177 (89.8%)	619 (92.9%)
Learning Disability				
Yes	3 (1.2%)	11 (5.3%)	12 (6.1%)	26 (3.9%)
No	258 (98.8%)	197 (94.7%)	185 (93.9%)	644 (96.1%)
NDD				
Yes	8 (3.1%)	21 (10.1%)	21 (10.7%)	50 (7.5%)

No	253 (96.9%)	187 (89.9%)	176 (89.3%)	616 (92)
Any Chronic Condition				
Yes	65 (24.9%)	94 (45.2%)	84 (42.6%)	243 (36)
No	196 (75.1%)	114 (54.8%)	113 (57.4%)	423 (63)

Gender differences in chronic illness

Among the vaccinated (combining partially and fully vaccinated children), boys were more likely than girls to be diagnosed with a chronic condition – significantly so in the case of allergic rhinitis (13.9% vs. 7.2%, $p = 0.03$; OR 2.1, 95% CI: 1.1, 4.1), ASD (7.7% vs. 1.9%, $p = 0.006$; OR 4.3, 95% CI: 1.4, 13.2), and any neurodevelopmental disorder (14.4% vs. 6.7%, $p = 0.01$; OR 2.3, 95% CI: 1.2, 4.6) (Table 5).

Table 5. Chronic conditions and gender among vaccinated children

	Male (n=194)	Female (n=209)	Total (n=403)	Chi- square	P- value
Allergic rhinitis					
	27	15	42		

Yes	(13.9%)	(7.2%)	(10.4%)	4.8964	0.0269
No	167 (86.1%)	194 (92.8%)	361 (90.0%)		
Allergies					
Yes	50 (25.8%)	40 (19.1%)	90 (22.3%)	2.5531	0.1101
No	144 (74.2%)	168 (80.9%)	313 (77.7%)		
ADHD					
Yes	13 (6.7%)	6 (2.9%)	19 (4.7%)	3.2856	0.0699
No	181 (93.3%)	203 (97.1%)	384 (95.3%)		
ASD					
Yes	15 (7.7%)	4 (1.9%)	19 (4.7%)	7.5810	0.0059
No	178 (92.3%)	205 (98.1%)	384 (95.3%)		
Eczema					
Yes	19 (9.89%)	19 (9.1%)	38 (9.4%)	0.0582	0.8094
No	175 (90.2%)	190 (90.9%)	365 (90.6%)		
Learning Disability					
Yes	14 (7.2%)	9 (4.3%)	23 (5.7%)	1.5835	0.2083
No	180 (92.8%)	200 (95.7%)	380 (94.3%)		
NDD					

Yes	28 (14.4%)	14 (6.7%)	42 (10.4%)	6.4469	0.0111
No	166 (85.6%)	195 (93.3%)	361 (89.6%)		
Any Chronic Condition					
Yes	94 (48.5%)	83 (39.7%)	177 (43.9%)	3.1208	0.0773
No	100 (51.5%)	126 (60.3%)	226 (56.1%)		

Use of medications and health services

The vaccinated (combining the partially and fully vaccinated) were significantly more likely than the unvaccinated to use medication for allergies (20.0% vs. 1.2%, $p < 0.001$; OR 21.5, 95% CI: 6.7, 68.9), to have used antibiotics in the past 12 months (30.8% vs. 15.4%, $p < 0.001$; OR 2.4, 95% CI: 1.6, 3.6), and to have used fever medications at least once (90.7% vs. 67.8%, $p < 0.001$; OR 4.6, 95% CI: 3.0, 7.1). The vaccinated were also more likely to have seen a doctor for a routine checkup in the past 12 months (57.6% vs. 37.2%, $p < 0.001$; OR 2.3, 95% CI: 1.7, 3.2), visited a dentist during the past year (89.4% vs. 80.5%, $p < 0.001$; OR 2.0, 95% CI: 1.3, 3.2), visited a doctor or clinic due to illness in the past year (36.0% vs. 16.0%, $p < 0.001$; OR 3.0, 95% CI: 2.0, 4.4), been fitted with ventilation ear tubes (3.0% vs. 0.4%, $p = 0.018$; OR 8.0, 95% CI: 1.0, 66.1), and spent one or more nights in a

hospital (19.8% vs. 12.3%, $p = 0.012$; OR 1.8, 95% CI: 1.1, 2.7) (Table 6).

Table 6. Vaccination status, medication use and health services utilization

	Vaccinated (n=405)	Unvaccinated (n=261)	Total (n=666)
Medication Use			
Medication for Allergy			
Yes	81 (20.0%)	3 (1.2%)	84 (12.6%)
No	324 (80.0%)	258 (98.8%)	582 (87.4%)
Used antibiotics in the past 12 months			
Yes	124 (30.8%)	40 (15.4%)	164 (24.7%)
No	279 (69.2%)	220 (84.6%)	499 (75.3%)
Used fever medication 1+ times			
Yes	350 (90.7%)	173 (67.8%)	523 (81.6%)
No	36 (9.3%)	82 (32.2%)	118 (18.4%)

Using fitted ear drainage tubes			
Yes	12 (3.0%)	1 (0.4%)	13 (2.0%)
No	389 (97.0%)	260 (99.6%)	649 (98.0%)
Used medication for ADHD			
Yes	7 (1.7%)	3 (1.2%)	10 (1.5%)
No	398 (98.3%)	256 (98.8%)	654 (98.5%)
Used medication for Seizures			
Yes	4 (1.0%)	1 (0.4%)	5 (0.8%)
No	400 (99.0%)	258 (99.6%)	658 (99.2)
Health Services Utilization			
Emergency Department visit in the past 12 months			
Yes	38 (9.5%)	23 (9.0%)	61 (9.3%)
No	364 (90.5%)	234 (91.0%)	598 (90.7%)
Sick visit to			

doctor in the past year			
Yes	145 (36.0%)	41 (16.0%)	186 (28.2%)
No	258 (64.0%)	216 (84.0%)	474 (71.8%)
Ever spent one or more nights in the hospital			
Yes	80 (19.8%)	32 (12.3%)	112 (16.8%)
No	325 (80.2%)	228 (87.7%)	553 (83.2%)
Seen doctor for checkup in past 12 months			
Yes	233 (57.6%)	97 (37.2%)	330 (49.6%)
No	172 (42.4%)	164 (62.8%)	336 (50.4%)
Seen dentist in the past 12 months			
Yes	362 (89.4%)	210 (80.5%)	572 (85.9%)
No	43 (10.6%)	51 (19.5%)	94 (14.1%)

Factors associated with neurodevelopmental

disorders

The second aim of the study focused on a specific health outcome and was designed to determine whether vaccination was associated with neurodevelopmental disorders (NDD) and, if so, whether the association remained significant after adjustment for other measured factors. As noted, because of the relatively small numbers of children with specific diagnoses, NDD was a derived variable combining children with a diagnosis of one or more of ASD, ADHD and a learning disability. The close association and overlap of these diagnoses in the study is shown in the figure above (Figure 1). The figure shows that the single largest group of diagnoses was learning disability (n=15) followed by ASD (n=9), and ADHD (n=9), with smaller numbers comprising combinations of the three diagnoses.

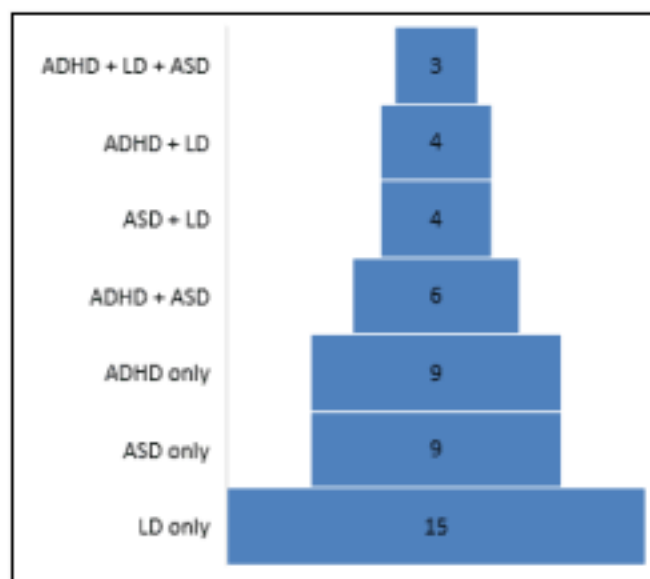
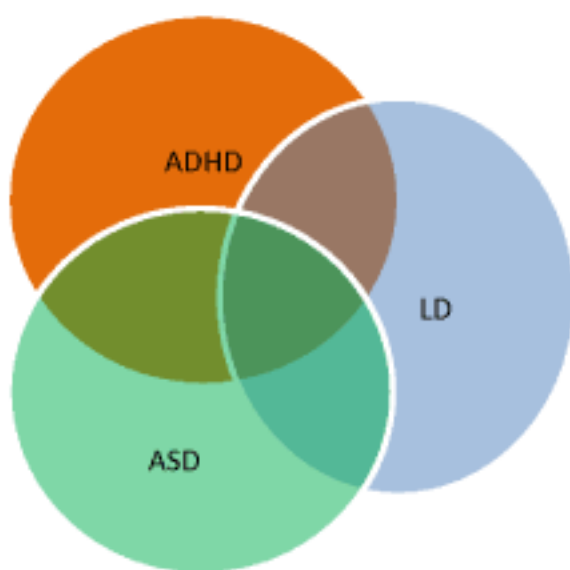


Figure 1. The overlap and distribution of physician-diagnosed neurodevelopmental disorders, based on

mothers' reports.

Unadjusted analysis

Table 7 shows that the factors associated with NDD in unadjusted logistic regression analyses were: vaccination (OR 3.7, 95% CI: 1.7, 7.9); male gender (OR 2.1, 95% CI: 1.1, 3.8); adverse environment, defined as living within 1-2 miles of a furniture manufacturing factory, hazardous waste site, or lumber processing factory (OR 2.9, 95% CI: 1.1, 7.4); maternal use of antibiotics during pregnancy (OR 2.3, 95% CI: 1.1, 4.8); and preterm birth (OR 4.9, 95% CI: 2.4, 10.3). Two factors that almost reached statistical significance were vaccination during pregnancy (OR 2.5, 95% CI: 1.0, 6.3) and three or more fetal ultrasounds (OR 3.2, 95% CI: 0.92, 11.5). Factors that were not associated with NDD in this study included mother's education, household income, and religious affiliation; use of acetaminophen, alcohol, and antacids during pregnancy; gestational diabetes; preeclampsia; Rhogham shot during pregnancy; and breastfeeding (data not shown).

Table 7. Unadjusted analysis of potential risk factors for neurodevelopmental disorders

	NDD				
Vaccination Status	Yes (N=50)	No (N=616)	Total* (N=666)	Chi-Square	P-value
Vaccinated	42	363	405		

Not Vaccinated	8	253	261	12.198	<0.0
Race					
Non-White	9	71	80	1.8208	0.17
White	41	544	585		
Childs Gender					
Male	32	283	315	5.9471	0.01
Female	18	331	349		
Adverse Environment					
Yes	6	27	33	5.8706	0.05
No	40	523	563		
Do not know	4	66	70		
Medication during Pregnancy -					
Antibiotics					
Yes	10	61	71	4.950	0.02
No	40	555	595		
Medication during Pregnancy –					

Vaccinated					
Yes	6	32	38	3.965	0.05
No	44	583	627		
Preterm birth					
Yes	12	37	49	22.910	< 0.001
No	38	578	616		
Ultrasound					
None	3	71	74	5.898	0.05
1-3 times	30	419	449		
> 3 times	17	124	141		

*Numbers may not add to column totals due to missing or incomplete data.

**Note that Odds Ratios are the cross-product ratios of the entries in the 2-by-2 tables, and are an estimate of the relative incidence (or risk) of the outcome associated with the exposure factor.

Adjusted analysis

After adjustment for all other significant factors, those that remained significantly associated with NDD were:

vaccination (OR 3.1, 95% CI: 1.4, 6.8); male gender (OR 2.3, 95% CI: 1.2, 4.3); and preterm birth (OR 5.0, 95% CI: 2.3, 11.1). The apparently strong association between both vaccination and preterm birth and NDD suggested the possibility of an interaction between these factors.

In a final adjusted model designed to test for this possibility, controlling for the interaction of preterm birth and vaccination, the following factors remained significantly associated with NDD: vaccination (OR 2.5, 95% CI: 1.1, 5.6), nonwhite race (OR 2.4, 95% CI: 1.1, 5.4), and male gender (OR 2.3, 95% CI: 1.2, 4.4). Preterm birth itself, however, was not significantly associated with NDD, whereas the combination (interaction) of preterm birth and vaccination was associated with 6.6-fold increased odds of NDD (95% CI: 2.8, 15.5) (Table 8).

Table 8. Adjusted logistic regression analyses of risk factors and NDD*

	Adjusted Model (Model 1)	Adjusted Model with Interaction (Model 2)
Vaccination Status		
Vaccinated	3.1 (1.4 - 6.8)	2.5 (1.1 - 5.6)
Not Vaccinated	Ref	Ref
Race		
Non-White	2.3 (1.0 - 5.2)	2.4 (1.1 - 5.4)

White	Ref	Ref
Childs Gender		
Male	2.3 (1.2 - 4.3)	2.3 (1.2 - 4.4)
Female	Ref	Ref
Preterm birth		NS
Yes	5.0 (2.3 - 11.1)	
No	Ref	
Preterm birth and Vaccination interaction		
No interaction	Not in the model	Ref
Preterm and Vaccinated		6.6 (2.8 - 15.5)

*Number of observation read 666, number of observations used 629. NDD=47, Not NDD = 582

Discussion

Following a recommendation of the Institute of Medicine [19] for studies comparing the health outcomes of vaccinated and unvaccinated children, this study focused on homeschool children ages 6 to 12 years based on mothers' anonymous reports of pregnancy-related conditions, birth histories, physician-diagnosed illnesses, medications and healthcare use. Respondents were mostly white, married, and college-educated, upper income women who had been contacted and invited to

participate in the study by the leaders of their homeschool organizations. Data from the survey were also used to determine whether vaccination was associated specifically with NDDs, a derived diagnostic category combining children with the diagnoses of learning disability, ASD and/or ADHD.

With regard to acute and chronic conditions, vaccinated children were significantly less likely than the unvaccinated to have had chickenpox and pertussis but, contrary to expectation, were significantly more likely to have been diagnosed with otitis media, pneumonia, allergic rhinitis, eczema, and NDD. The vaccinated were also more likely to have used antibiotics, allergy and fever medications; to have been fitted with ventilation ear tubes; visited a doctor for a health issue in the previous year, and been hospitalized. The reason for hospitalization and the age of the child at the time were not determined, but the latter finding appears consistent with a study of 38,801 reports to the VAERS of infants who were hospitalized or had died after receiving vaccinations. The study reported a linear relationship between the number of vaccine doses administered at one time and the rate of hospitalization and death; moreover, the younger the infant at the time of vaccination, the higher was the rate of hospitalization and death [55]. The hospitalization rate increased from 11% for 2 vaccine doses to 23.5% for 8 doses ($r^2 = 0.91$), while the case fatality rate increased significantly from 3.6% for those receiving from 1-4 doses

to 5.4 % for those receiving from 5-8 doses.

In support of the possibility that the number of vaccinations received could be implicated in risks of associated chronic illness, a comparison of unvaccinated, partially and fully vaccinated children in the present study showed that the partially vaccinated had increased but intermediate odds of chronic disease, between those of unvaccinated and fully vaccinated children, specifically for allergic rhinitis, ADHD, eczema, a learning disability, and NDD as a whole.

The national rates of ADHD and LD are comparable to those of the study. The U.S. rate of ADHD for ages 4-17 (twice the age range of children than the present study), is 11% [31]. The study rate of ADHD for ages 6 to 12 is 3.3%, and 4.7% when only vaccinated children are included. The national LD rate is 5% [32], and the study data show a rate of LD of 3.9% for all groups, and 5.6% when only vaccinated children are included. However, the ASD prevalence of 2.24% from a CDC parent survey is lower than the study rate of 3.3%. Vaccinated males were significantly more likely than vaccinated females to have been diagnosed with allergic rhinitis, and NDD. The percentage of vaccinated males with an NDD in this study (14.4%) is consistent with national findings based on parental responses to survey questions, indicating that 15% of U.S. children ages 3 to 17 years in the years 2006-2008 had an NDD [28]. Boys are also more likely than girls to be diagnosed with an NDD, and ASD in particular

[29].

Vaccination was strongly associated with both otitis media and pneumonia, which are among the most common complications of measles infection [56,57]. The odds of otitis media were almost four-fold higher among the vaccinated (OR 3.8, 95% CI: 2.1, 6.6) and the odds of myringotomy with tube placement were eight-fold higher than those of unvaccinated children (OR 8.0, 95% CI: 1.0, 66.1). Acute otitis media (AOM) is a very frequent childhood infection, accounting for up to 30 million physician visits each year in the U.S., and the most common reason for prescribing antibiotics for children [58,59]. The incidence of AOM peaks at ages 3 to 18 months and 80% of children have experienced at least one episode by 3 years of age. Rates of AOM have increased in recent decades [60]. Worldwide, the incidence of AOM is 10.9%, with 709 million cases each year, 51% occurring in children under 5 years of age [61]. Pediatric AOM is a significant concern in terms of healthcare utilization in the U.S., accounting for \$2.88 billion in annual health care costs [62].

Numerous reports of AOM have been filed with VAERS. A search of VAERS for "Cases where age is under 1 and onset interval is 0 or 1 or 2 or 3 or 4 or 5 or 6 or 7 days and Symptom is otitis media" [63] revealed that 438,573 cases were reported between 1990 and 2011, often with fever and other signs and symptoms of inflammation and central nervous system involvement. One study [64]

assessed the nasopharyngeal carriage of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* during AOM in fully immunized, partly immunized children with 0 or 1 dose of Pneumococcal Conjugate Vaccine-7 (PCV7), and “historical control” children from the pre-PCV-7 era, and found an increased frequency of *M. catarrhalis* colonization in the vaccinated group compared to the partly immunized and control groups (76% vs. 62% and 56%, respectively). A high rate of *Moraxella catarrhalis* colonization is associated with an increased risk of AOM [65].

Successful vaccination against pneumococcal infections can lead to replacement of the latter in the nasopharyngeal niche by nonvaccine pneumococcal serotypes and disease [66]. Vaccination with PCV-7 has a marked effect on the complete microbiota composition of the upper respiratory tract in children, going beyond shifts in the distribution of pneumococcal serotypes and known potential pathogens and resulting in increased anaerobes, gram-positive bacteria and gram-negative bacterial species. PCV-7 administration also correlates highly with the emergence and expansion of oropharyngeal types of species. These observations have suggested that eradication of vaccine serotype pneumococci can be followed by colonization of other bacterial species in the vacant nasopharyngeal niche, leading to disequilibria of bacterial composition (dysbiosis) and increased risks of otitis media. Long-term monitoring has been

recommended as essential for understanding the full implications of vaccination-induced changes in microbiota structure [67].

The second aim of the paper focused on a specific health outcome and sought to determine whether vaccination remained associated with neurodevelopmental disorders (NDD) after controlling for other measured factors. After adjustment, the factors that remained significantly associated with NDD were vaccination, nonwhite race, male gender, and preterm birth. The apparently strong association between both vaccination and preterm birth and NDD suggested the possibility of an interaction between these factors. This was shown in a final adjusted model with interaction (controlling for the interaction of preterm birth with vaccination). In this model, vaccination, nonwhite race and male gender remained associated with NDD, whereas preterm birth itself was no longer associated with NDD. However, preterm birth combined with vaccination was associated with a 6.6-fold increased odds of NDD.

In summary, vaccination, nonwhite race, and male gender were significantly associated with NDD after controlling for other factors. Preterm birth, although significantly associated with NDD in unadjusted and adjusted analyses, was no longer associated with NDD in the final model with interaction. However, preterm birth and vaccination combined was strongly associated with NDD in the final adjusted model with interaction, more than

doubling the odds of NDD compared to vaccination alone. Preterm birth has long been known as a major factor for NDD [68,69], but since preterm infants are routinely vaccinated, the separate effects of preterm birth and vaccination have not been examined. The present study suggests that vaccination could be a contributing factor in the pathogenesis of NDD but also that preterm birth by itself may have a lesser or much reduced role in NDD (defined here as ASD, ADHD and/or a learning disability) than currently believed. The findings also suggest that vaccination coupled with preterm birth could increase the odds of NDD beyond that of vaccination alone.

Potential limitations

We did not set out to test a specific hypothesis about the association between vaccination and health. The aim of the study was to determine whether the health outcomes of vaccinated children differed from those of unvaccinated homeschool children, given that vaccines have nonspecific effects on morbidity and mortality in addition to protecting against targeted pathogens [11]. Comparisons were based on mothers' reports of pregnancy-related factors, birth histories, vaccinations, physician-diagnosed illnesses, medications, and the use of health services. We tested the null hypothesis of no difference in outcomes using chi-square tests, and then used Odds Ratios and 96% Confidence Intervals to determine the strength and significance of the

association.

If the effects of vaccination on health were limited to protection against the targeted pathogens, as is assumed to be the case [21], no difference in outcomes would be expected between the vaccinated and unvaccinated groups except for reduced rates of the targeted infectious diseases. However, in this homogeneous sample of 666 children there were striking differences in diverse health outcomes between the groups. The vaccinated were less likely to have had chickenpox or whooping cough, as expected, but more likely to have been diagnosed with pneumonia and ear infections as well as allergies and NDDs.

What credence can be given to the findings? This study was not intended to be based on a representative sample of homeschool children but on a convenience sample of sufficient size to test for significant differences in outcomes. Homeschoolers were targeted for the study because their vaccination completion rates are lower than those of children in the general population. In this respect our pilot survey was successful, since data were available on 261 unvaccinated children.

To eliminate opportunities for subjectivity or opinion in the data, only factual information was requested and the questions involved memorable events such as physician-diagnosed diseases in a child. With regard to minimizing potential bias in the information provided by mothers, all

communications with the latter emphasized neutrality regarding vaccination and vaccine safety. To minimize recall bias, respondents were asked to use their child's vaccination records. To enhance reliability, closed-ended questions were used and each set of questions had to be completed before proceeding to the next. To enhance validity, parents were asked to report only physician-diagnosed illnesses.

Mothers' reports could not be validated by clinical records because the survey was designed to be anonymous. However, self-reports about significant events provide a valid proxy for official records when medical records and administrative data are unavailable [70]. Had mothers been asked to provide copies of their children's medical records it would no longer have been an anonymous study and would have resulted in few completed questionnaires. We were advised by homeschool leaders that recruitment efforts would have been unsuccessful had we insisted on obtaining the children's medical records as a requirement for participating in the study.

A further potential limitation is under-ascertainment of disease in unvaccinated children. Could the unvaccinated have artificially reduced rates of illness because they are seen less often by physicians and would therefore have been less likely to be diagnosed with a disease? The vaccinated were indeed more likely to have seen a doctor for a routine checkup in the past 12 months (57.5% vs. 37.1%, $p < 0.001$; OR 2.3, 95% CI: 1.7, 3.1). Such visits

usually involve vaccinations, which non-vaccinating families would be expected to refuse. However, fewer visits to physicians would not necessarily mean that unvaccinated children are less likely to be seen by a physician if their condition warranted it. In fact, since unvaccinated children were more likely to be diagnosed with chickenpox and whooping cough, which would have involved a visit to the pediatrician, differences in health outcomes are unlikely to be due to under-ascertainment.

Strengths of the study include the unique design of the study, involving homeschool mothers as respondents, and the relatively large sample of unvaccinated children, which made it possible to compare health outcomes across the spectrum of vaccination coverage. Recruitment of biological mothers as respondents also allowed us to test hypotheses about the role of pregnancy-related factors and birth history as well as vaccination in NDD and other specific conditions. In addition, this was a within-group study of a demographically homogeneous population of mainly white, higher-income and college-educated homeschooling families in which the children were all 6-12 years of age. Information was provided anonymously by biological mothers, obviously well-informed about their own children's vaccination status and health, which likely increased the validity of the reports.

Conclusions

Assessment of the long-term effects of the vaccination

schedule on morbidity and mortality has been limited [71]. In this pilot study of vaccinated and unvaccinated homeschool children, reduced odds of chickenpox and whooping cough were found among the vaccinated, as expected, but unexpectedly increased odds were found for many other physician-diagnosed conditions. Although the cross-sectional design of the study limits causal interpretation, the strength and consistency of the findings, the apparent "dose-response" relationship between vaccination status and several forms of chronic illness, and the significant association between vaccination and NDDs all support the possibility that some aspect of the current vaccination program could be contributing to risks of childhood morbidity. Vaccination also remained significantly associated with NDD after controlling for other factors, whereas preterm birth, long considered a major risk factor for NDD, was not associated with NDD after controlling for the interaction between preterm birth and vaccination. In addition, preterm birth coupled with vaccination was associated with an apparent synergistic increase in the odds of NDD above that of vaccination alone. Nevertheless, the study findings should be interpreted with caution. First, additional research is needed to replicate the findings in studies with larger samples and stronger research designs. Second, subject to replication, potentially detrimental factors associated with the vaccination schedule should be identified and addressed and underlying mechanisms better understood. Such studies

are essential in order to optimize the impact of vaccination of children's health.

Competing Interests

The authors declare that they have no financial interests that had any bearing on any aspect of the conduct or conclusions of the study and the submitted manuscript.

Author contributions

AM designed the study, contributed to data analysis and interpretation, and drafted the paper. BR designed the study, contributed to data collection, and edited the paper. AB contributed to data analyses and edited the paper. BJ contributed to data analyses and editing. All authors read and approved the final version of the paper.

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Disclaimer

This study was approved by the Institutional Review Board of Jackson State University and completed prior to Dr. Mawson's tenure-track appointment at Jackson State University.

References

1. »Centers for Disease Control and Prevention (CDC) (1999) Ten great public health achievements--United States, 1900-1999. *MMWR Morb Mortal Wkly Rep* 48: 241-243. [\[Crossref\]](#)
2. »Whitney CG, Zhou F, Singleton J, Schuchat A; Centers for Disease Control and Prevention (CDC) (2014) Benefits from immunization during the vaccines for children program era - United States, 1994-2013. *MMWR Morb Mortal Wkly Rep* 63: 352-355. [\[Crossref\]](#)
3. »Centers for Disease Control and Prevention (CDC) (2007) Vaccination coverage among children in kindergarten--United States, 2006-07 school year. *MMWR Morb Mortal Wkly Rep* 56: 819-821. [\[Crossref\]](#)
4. »Centers for Disease Control and Prevention (CDC) (2013) Vaccination coverage among children in

kindergarten - United States, 2012-13 school year. *MMWR Morb Mortal Wkly Rep* 62: 607-612.

[\[Crossref\]](#)

5. <http://www.cdc.gov/vaccines/vacgen/whatifstop.htm> (Accessed 19 June 2016)
6. http://www.hhs.gov/nvpo/vacc_plan/index.html (Accessed 19 June 2015).
7. <http://www.cdc.gov/vaccines/schedules/index.html> (Accessed 19 June 2016).
8. [Ward BJ \(2000\) Vaccine adverse events in the new millennium: is there reason for concern? *Bull World Health Organ* 78: 205-215. \[\\[Crossref\\]\]\(#\)](#)
9. [Sienkiewicz D, Kulak W, Okurowska-Zawada B, Paszko-Pateg G \(2012\) Neurologic adverse events following vaccination. *Prog Health Sci* 2: 129-141.](#)
10. [Pollard AJ \(2007\) Childhood immunisation: what is the future? *Arch Dis Child* 92: 426-433. \[\\[Crossref\\]\]\(#\)](#)
11. [\[Crossref\]](#) [Aaby P, Whittle H, Benn CS \(2012\) Vaccine programmes must consider their effect on general resistance. *BMJ* 344: e3769.](#)
12. [\[Crossref\]](#) [Cunningham AS \(2015\) Vaccine mandates in the US are doing more harm than good. *BMJ* 351: h4576.](#)
13. [Dórea JG. Exposure to mercury and aluminum in early life: developmental vulnerability as a modifying factor in neurologic and immunologic effects. *Int J Environ Res Public Health* \(2015\) 12\(2\):1295-313.](#)
14. [\[Crossref\]](#) [Crowcroft NS¹, Deeks SL², Upshur RE² \(2015\) Do we need a new approach to making](#)

vaccine recommendations? *BMJ* 350: h308.

15. [\[Crossref\]](#) Kessler DA1 (1993) Introducing MEDWatch. A new approach to reporting medication and device adverse effects and product problems. *JAMA* 269: 2765-2768.
16. http://www.nap.edu/catalog.php?record_id=11234 (Accessed 19 June 2016).
17. http://www.cdc.gov/vaccinesafety/pdf/iso-finalscientific_agenda-nov-10.pdf (Accessed 19 June 2016).
18. [Institute of Medicine \(2012\) Adverse Effects of Vaccines: Evidence and Causality. The National Academies Press, Washington, DC.](#)
19. [Institute of Medicine \(2013\) The childhood immunization schedule and safety: Stakeholder concerns, scientific evidence, and future studies. The National Academies Press, Washington, DC.](#)
20. [Maglione MA, Das L, Raaen L, Smith A, Chari R, et al. \(2014\) Safety of vaccines used for routine immunization of US children: a systematic review. *Pediatrics* 134: 325-337. \[\\[Crossref\\]\]\(#\)](#)
21. [Siegrist CA \(2008\) Vaccine Immunology. Vaccines. \(5th Edtn\). Saunders Elsevier.](#)
22. [Benn CS, Netea MG, Selin LK, Aaby P \(2013\) A small jab - a big effect: nonspecific immunomodulation by vaccines. *Trends Immunol* 34: 431-439. \[\\[Crossref\\]\]\(#\)](#)
23. [Jensen KJ, Benn CS, van Crevel R \(2016\) Unravelling the nature of non-specific effects of vaccines - A challenge for innate immunologists. *Semin Immunol*](#)

28: 377-383. [\[Crossref\]](#)

24. ▶Sørup S, Benn CS, Poulsen A, Krause TG, Aaby P, et al. (2014) Live vaccine against measles, mumps, and rubella and the risk of hospital admissions for nontargeted infections. *JAMA* 311: 826-835. [\[Crossref\]](#)
25. ▶Aaby P, Benn C, Nielsen J, Lisse IM, Rodrigues A, et al. (2012) Testing the hypothesis that diphtheria-tetanus-pertussis vaccine has negative non-specific and sex-differential effects on child survival in high-mortality countries. *BMJ Open* 2: e000707. [\[Crossref\]](#)
26. ▶Garly ML1, 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. [\[Crossref\]](#)
27. ▶Grandjean P, Landrigan PJ (2006) Developmental neurotoxicity of industrial chemicals. *Lancet* 368: 2167-2178. [\[Crossref\]](#)
28. ▶Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, , et al. (2011) Trends in the prevalence of developmental disabilities in US Children, 1997-2008. *Pediatrics* 127: 1034-1042. [\[Crossref\]](#)
29. ▶Baio J (2014) Prevalence of Autism Spectrum Disorder among children aged 8 years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010 Surveillance Summaries. *MMWR* 63: 1-21.
30. ▶Zablotsky B, Black LI, Maenner MJ, Schieve LA,

- Blumberg SJ (2015) Estimated prevalence of autism and other developmental disabilities following questionnaire changes in the 2014 National Health Interview Survey. *Natl Health Stat Report* 13: 1-20.
31. Visser SN, Danielson ML, Bitsko RH, Holbrook JR, Kogan MD, et al. (2014) Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011. *J Am Acad Child Adolesc Psychiatry* 53: 34-46.e2. [\[Crossref\]](#)
32. Cortiella C, Horowitz SH (2014) The State of Learning Disabilities: Facts, Trends and Emerging Issues. National Center for Learning Disabilities, New York:.
33. Cornwall W (2015) Autism rates are up, but is it really on the rise? *Science Magazine*.
34. Landrigan PJ (2010) What causes autism? Exploring the environmental contribution. *Curr Opin Pediatr* 22: 219-225. [\[Crossref\]](#)
35. Nevison CD (2014) A comparison of temporal trends in United States autism prevalence to trends in suspected environmental factors. *Environ Health* 13: 73. [\[Crossref\]](#)
36. Shaw CA, Seneff S, Kette SD, Tomljenovic L, Oller JW Jr, et al. (2014) Aluminum-induced entropy in biological systems: implications for neurological disease. *J Toxicol* 2014: 491316. [\[Crossref\]](#)
37. Sealey LA, Hughes BW, Sriskanda AN1, Guest JR1, Gibson AD1, et al. (2016) Environmental factors in the

development of autism spectrum disorders. *Environ Int* 88: 288-298. [[Crossref](#)]

38. ▶ <http://www.hrsa.gov/vaccinecompensation/data.html> (Accessed 20 June 2016).
39. ▶ Holland M, Conte L, Krakow R, Colin L (2011) Unanswered questions from the Vaccine Injury Compensation Program: A review of compensated cases of vaccine-induced brain injury. *Pace Envtl L Rev* 28: 480.
40. ▶ Doja A, Roberts W (2006) Immunizations and autism: a review of the literature. *Can J Neurol Sci* 33: 341-346. [[Crossref](#)]
41. ▶ Price CS, Thompson WW, Goodson B, Weintraub ES, Croen LA, et al. (2010) Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism. *Pediatrics* 126: 656-664. [[Crossref](#)]
42. ▶ DeStefano F, Price CS, Weintraub ES (2013) Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism. *J Pediatr* 163: 561-567. [[Crossref](#)]
43. ▶ McNeil MM, Gee J, Weintraub ES, Belongia EA, Lee GM, et al. (2014) The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. *Vaccine* 32: 5390-5398. [[Crossref](#)]
44. ▶ Taylor LE, Swerdfeger AL, Eslick GD (2014) Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. *Vaccine* 32: 3623-3629. [[Crossref](#)]

45. ›Jain A, Marshall J, Buikema A, Bancroft T, Kelly JP, et al. (2015) Autism occurrence by MMR vaccine status among US children with older siblings with and without autism. *JAMA* 313: 1534-1540. [[Crossref](#)]
46. ›Gerber JS, Offit PA (2009) Vaccines and autism: a tale of shifting hypotheses. *Clin Infect Dis* 48: 456-461. [[Crossref](#)]
47. ›Choi BK, Manning ML (2010) The immunization status of home-schooled children in America. *J Pediatr Health Care* 24: 42-47. [[Crossref](#)]
48. ›Ray BD (2010) Academic achievement and demographic traits of homeschool students: a nationwide study. *J Acad Leadership* 8: 1.
49. ›https://www.census.gov/library/publications/time-series/statistical_abstracts.html (Accessed 19 August 2016).
50. ›<http://files.eric.ed.gov/fulltext/ED505409.pdf> (Accessed 22 August 2016).
51. ›<http://nces.ed.gov/pubs2006/2006042.pdf> (Accessed 22 August 2016).
52. ›<http://eric.ed.gov/?id=ED544174> (Accessed 22 August 2016).
53. ›Surén P, Bakken IJ, Aase H, Chin R, Gunnes N, et al. (2012) Autism spectrum disorder, ADHD, epilepsy, and cerebral palsy in Norwegian children. *Pediatrics* 130: e152-158. [[Crossref](#)]
54. ›Zocchetti C, Consonni D, Bertazzi PA (1997) Relationship between prevalence rate ratios and odds ratios in cross-sectional studies. *Int J Epidemiol* 26:

220-223. [\[Crossref\]](#)

55. ▶ Goldman GS, 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. [\[Crossref\]](#)
56. ▶ Orenstein WA, Perry RT, Halsey NA (2004) The clinical significance of measles: a review. *J Infect Dis* 189: S4-S16. [\[Crossref\]](#)
57. ▶ CDC (2013) Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: Summary Recommendations of the Advisory Committee on Immunization Practices (ACIP). Recommendations and Reports. *MMWR* 62: 1-34.
58. ▶ Dhooge IJ (2003) Risk factors for the development of otitis media. *Curr Allergy Asthma Rep* 3: 321-325. [\[Crossref\]](#)
59. ▶ Siegel RM (2010) Acute otitis media guidelines, antibiotic use, and shared medical decision-making. *Pediatrics* 125: 384-386. [\[Crossref\]](#)
60. ▶ Casselbrant ML, Mandel EM (2003) Epidemiology. Evidence-based otitis media. BC Decker, Hamilton, ON, Canada. Pp. 147-162.
61. ▶ Monasta L1, Ronfani L, Marchetti F, Montico M, Vecchi Brumatti L, et al. (2012) Burden of disease caused by otitis media: systematic review and global estimates. *PLoS One* 7: e36226. [\[Crossref\]](#)
62. ▶ Ahmed S1, Shapiro NL, Bhattacharyya N (2014)

Incremental health care utilization and costs for acute otitis media in children. *Laryngoscope* 124: 301-305.

[\[Crossref\]](#)

63. [http://www.medalerts.org/vaersdb/findfield.php?TABLE=ON&GROUP1=AGE&EVENTS=ON&SYMPTOMS\[\]=Otitis+media+%2810033078%29&NUMDAYS\[\]=0&NUMDAYS\[\]=1&NUMDAYS\[\]=2&NUMDAYS\[\]=3&NUMDAYS\[\]=4&NUMDAYS\[\]=5&NUMDAYS\[\]=6&NUMDAYS\[\]=7&WhicAge=range&LOWAGE=0.0&HIGHAGE=1.0](http://www.medalerts.org/vaersdb/findfield.php?TABLE=ON&GROUP1=AGE&EVENTS=ON&SYMPTOMS[]=Otitis+media+%2810033078%29&NUMDAYS[]=0&NUMDAYS[]=1&NUMDAYS[]=2&NUMDAYS[]=3&NUMDAYS[]=4&NUMDAYS[]=5&NUMDAYS[]=6&NUMDAYS[]=7&WhicAge=range&LOWAGE=0.0&HIGHAGE=1.0) (Accessed 25 August, 2016).
64. [Revai K, McCormick DP, Patel J, Grady JJ, Saeed K, et al. \(2006\) Effect of pneumococcal conjugate vaccine on nasopharyngeal bacterial colonization during acute otitis media. *Pediatrics* 117: 1823–1829.](#) [\[Crossref\]](#)
65. [Faden H, Harabuchi Y, Hong JJ \(1994\) Epidemiology of Moraxella catarrhalis in children during the first 2 years of life: relationship to otitis media. *J Infect Dis* 169: 1312-1317.](#) [\[Crossref\]](#)
66. [Weinberger DM, Malley R, Lipsitch M \(2011\) Serotype replacement in disease after pneumococcal vaccination. *Lancet* 378: 1962-1973.](#) [\[Crossref\]](#)
67. [Biesbroek G, Wang X, Keijser BJ, Eijkemans RM, Trzcinski K, et al. \(2014\) Seven-valent pneumococcal conjugate vaccine and nasopharyngeal microbiota in healthy children. *Emerg Infect Dis* 20: 201-210.](#)
68. [Goldin RL, Matson JL \(2016\) Premature birth as a risk factor for autism spectrum disorder. *Dev Neurorehabil* 19: 203-206.](#) [\[Crossref\]](#)

69. »Padilla N, Eklöf E, Mårtensson GE, Bölte S, Lagercrantz H, et al. (2015) Poor brain growth in extremely preterm neonates long before the onset of autism spectrum disorder symptoms. *Cereb Cortex* 27: 1245-1252. [[Crossref](#)]
70. »Short ME, Goetzel RZ, Pei X, Tabrizi MJ, Ozminkowski RJ, et al. (2009) How accurate are self-reports? Analysis of self-reported health care utilization and absence when compared with administrative data. *J Occup Environ Med* 51: 786-796. [[Crossref](#)]
71. »Fisker AB, Hornshøj L, Rodrigues A, Balde I, Fernandes M, et al. (2014) Effects of the introduction of new vaccines in Guinea-Bissau on vaccine coverage, vaccine timeliness, and child survival: an observational study. *Lancet Glob Health* 2: e478-e487.