Impact of Childhood Vaccination on Short and Long-Term Chronic Health Outcomes in Children: A Birth Cohort Study

Lois Lamerato, PhD[1], Abigail Chatfield, MS[1], Amy Tang, PhD[1], Marcus Zervos, MD[2,3]

Henry Ford Health System, Detroit MI

Department of Public Health Sciences[1]

Division of Infectious Diseases[2]

Wayne State University School of Medicine, Detroit MI[3]

Running head: Association of childhood vaccination on chronic health in children

Word Count: 292 (Abstract), 4143 (Body)

Corresponding Author:

Lois Lamerato, PhD

Senior Scientist

Public Health Sciences

Henry Ford Health System

1 Ford Place – 5C

Detroit, MI 48202

Phone: 313-874-6367

llamera1@hfhs.org

Financial Disclosure: This study had no external funding.

Abstract

Objective: To compare the short and long-term health outcomes, within a captured payer environment, of children exposed to one or more vaccines to those unexposed.

Design: Birth cohort study

Setting: Integrated healthcare system in Michigan.

Participants: 18,468 children born between 2000 and 2016 enrolled in the health system insurance plan.

Main Outcome Measures: Development of a chronic health condition over time.

Results: A total of 18,468 consecutive subjects met eligibility criteria for the study, of which 1,957 had no exposure to vaccination and 16,511 had received at least one vaccine during their enrollment in the plan with various levels of exposure. After multivariate adjustment, Cox proportional hazards modeling demonstrated that exposure to vaccination was independently associated with an increased risk of developing a chronic health condition (HR 2.53, CI 2.16-2.96). Of the chronic health conditions, exposure to vaccination was independently associated with an increased risk of asthma (HR 4.25, CI 3.23-5.59), autoimmune disease (HR 4.79, CI 1.36-16.94), atopic disease (HR 3.03, CI 2.01-4.57), eczema (HR 1.31, CI 1.13-1.52), and neurodevelopmental disorder (HR 5.53, CI 2.91-10.51). There were no chronic health conditions associated with an increased risk in the unexposed group. The overall probability of being free of a chronic health condition at 10-years of follow up was 43% in the group exposed to vaccination and 83% in the unexposed group.

Conclusion: This study found that exposure to vaccination was independently associated with an overall 2.5-fold increase in the likelihood of developing a chronic health condition, when compared to children unexposed to vaccination. This association was primarily driven by asthma, atopic disease, eczema, autoimmune disease and neurodevelopmental disorders. This suggests that in certain children, exposure to vaccination may increase the likelihood of developing a chronic health condition, particularly for one of these conditions.

Introduction

Over the past 30 years, the prevalence of chronic health conditions in children has increased.[1] According to a 2011 study, approximately 43% of children in the United States (32 million) have at least 1 of the 20 chronic health conditions assessed in the study.[2] Despite this, there is a paucity of published data to determine contributing factors.

Vaccination has reduced the incidence of certain targeted childhood infections and their associated morbidity and mortality.[3] Nonetheless, vaccine hesitancy remains a significant barrier to maintaining and increasing vaccine uptake and the number of parents foregoing all vaccinations has been increasing.[4 5] Common parental concerns relate to the growth of the vaccine schedule, administering multiple vaccines contemporaneously, and the potential for long-term adverse health outcomes from vaccination.[6-9] Research addressing these vaccine safety concerns can assist clinicians in discussions with their patients and serve to reassure parents of the overall safety of vaccination.[10]

The safety review period in pre-licensure clinical trials is typically of insufficient duration ($\leq$30 days) to assess a vaccine's impact on long-term health outcomes.[11] However, a number of post-licensure observational studies have, with mixed results, examined whether certain vaccines are associated with developing certain health conditions.[12-16] An important limitation to these studies, as highlighted by the Institute of Medicine (IOM) report, The Childhood Immunization Schedule and Safety,[10] is that "most vaccine-related research focuses on the outcomes of single immunizations or combinations of vaccines administered at a single visit," instead of comparing completely unvaccinated populations with those receiving one or more vaccines. This led the IOM to recommend retrospective studies evaluating the health outcomes of vaccinated versus unvaccinated populations.

Hence, this study compared the short and long-term health outcomes, within a captured payer environment, of children unexposed to vaccines with those exposed to one or more vaccines. Addressing this significant data gap could allay parental concerns and bolster vaccine confidence.

Methods

Study Setting

Henry Ford Health System (HFHS) is a large, vertically integrated healthcare system, offering primary, pediatric, acute, and specialty services in Metropolitan Detroit, with 4.2 million ambulatory care visits annually. The Health Alliance Plan (HAP), a non-profit health maintenance organization (HMO) and subsidiary of HFHS, has approximately 570,000 enrolled members, approximately one-third of whom receive care within HFHS. HFHS's diverse patient population, clinical resources and information technology systems, make it uniquely suited for this study.

Study Design

This retrospective study evaluated health outcomes of a consecutive cohort of children born between 2000 and 2016 and enrolled in HAP. This cohort was identified using the HAP and HFHS administrative database. Subjects were observed from birth until the earlier of disenrollment in the plan or December 31, 2017. Data sources for this study included medical, clinical and payer records from HFHS and HAP, supplemented with data from the State of Michigan immunization registry. Data tables included encounters (outpatient and emergency), hospitalizations, diagnoses, procedures and billing data on all services. Vaccinations evaluated included all vaccines on the Centers for Disease Control & Prevention (CDC) Recommended Child and Adolescent Immunization Schedule (Vaccine Schedule). Death data was obtained from HFHS electronic medical records and the State of Michigan's Vital Records System and manual chart review was conducted to ascertain cause of death for subjects who died during plan enrollment. All HFHS patients receive a lifetime medical record number that links across data-tables.

The study was reviewed and approved by HFHS's Institutional Review Board and conducted in accordance with the International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices (https://www.pharmacoepi.org/resources/guidelines_08027.cfm).

Study Population

Inclusion criteria: born and enrolled in HAP for $\geq$ 60 days between January 1, 2000 and December 31, 2016 with HFHS designated as their primary care system.

Exclusion criteria: chromosomal abnormalities, cerebral palsy, cystic fibrosis, spina bifida, congenital heart disease, or brain, neurological, or other congenital conditions present or discovered after

birth. These exclusions correspond with the objective of evaluating long-term health outcomes in a generally healthy birth cohort.

Definitions and Outcomes Assessment

The primary outcome of this study was a chronic health composite outcome which included conditions identified by the Child and Adolescent Health Measurement Initiative,[2] and augmented with conditions considered to be of public concern or public health significance in the CDC's White Paper on Studying the Safety of the Childhood Immunization Schedule.[17] The composite includes: diabetes, asthma, food allergy, cancer, brain dysfunction, atopic and autoimmune disease, and neurological, neurodevelopmental, seizure and mental health disorder. A subject with one or more of these was classified as having a chronic health condition. Other health conditions evaluated, but not part of the composite, include asthma attack or bronchospasm, anaphylaxis, eczema (acute and chronic), ear infection (acute and chronic) and peanut allergy.

We identified the relevant International Classification of Diseases, Ninth and Tenth Revision (ICD-9-CM and ICD-10-CM) diagnoses from healthcare encounters during enrollment in the plan for the conditions of interest. Subjects were classified by exposure to immunizations prior to onset of each condition (exposed versus unexposed) and then compared based on exposure status.

Brain dysfunction was defined as encephalopathy or encephalitis. Neurodevelopmental disorders were defined as autism, tics, ADD/ADHD, developmental delay, speech disorder, and learning, motor, intellectual, behavioral, and other psychological disability. Mental health disorder was defined as anxiety, depression, bipolar, phobia, emotional disturbance, psychosis, somatoform, and eating, manic, mental, mood, obsessive compulsive, personality, and stress/adjustment disorder. Only children 2 years and older were evaluated for neurodevelopmental and mental health disorders. Chronic eczema was defined as at least 1 reoccurrence 60 days or more after first episode. Chronic ear infection was defined as at least 2 reoccurrences within a year after first episode.

Statistical Analysis

Descriptive characteristics are reported as percentages, mean values ± standard deviations, or

median values with interquartile ranges (IQRs). Chi-square tests were used to compare the difference in baseline characteristics differences between vaccinated and unvaccinated children at birth. The number of events for each outcome and incidence rate per 1,000,000 patient-years (pt-yrs) were calculated. Incidence-rate-ratios, calculated by Poisson regression models, are presented with their associated 95% confidence intervals. Univariate and multivariate Cox proportional-hazards models were used to evaluate the association between health outcomes and vaccination status. The Kaplan–Meier method was used to estimate the 10-year cumulative risk of developing a chronic health condition from birth to the first episode of the condition and classified by prior exposure to immunization (exposed versus unexposed). The groups were compared with the use of a log-rank test. A *P*-value <0.05 was considered statistically significant. Since enrollment time was shorter overall in the unexposed group, sensitivity analyses were conducted by repeating the above analyses for subjects enrolled for at least 1-year, 3-years and 5-years. Additionally, to overcome potential ascertainment bias in subjects with lower levels of health care utilization, we conducted a sensitivity analysis by repeating the above analyses in only those subjects with at least one encounter at HFHS during plan enrollment.

Results

Study Population

A total of 18,468 consecutive subjects met eligibility criteria, of which 1,957 were unexposed and 16,511 were exposed to at least one vaccine, see Table 1. In exposed subjects, the median number of vaccinations was 18 (IQR 2-28). Characteristics more common in the exposed group were female sex, African American race, low-birthweight, prematurity, respiratory distress and trauma at birth. The median follow-up time was 904 (IQR 392-1,954) days for all subjects, 970 (IQR 430-2,093) days for exposed subjects, and 461 (IQR 196-1,081) days for unexposed subjects (with enrollment up to 6,575 days in the exposed group and 6,386 days in the unexposed group).

Clinical Outcomes

Incidence rates and incidence rate ratios (IRR), based on exposure status prior to developing the condition, were calculated, see Table 2. Overall, the development of a chronic health condition occurred

more often in the group exposed versus unexposed to vaccination (277 vs. 112 per million pt-yrs, ($p<0.0001$) and was more common in those exposed to vaccination (IRR 2.48, CI 2.12-2.91).

A statistically significant association was found between vaccination and the incidence of asthma, atopic and autoimmune disease, and mental health and neurodevelopmental disorders including developmental delay and speech disorder. A statistically significant association was not found between vaccine exposure and the incidence of cancer, food allergy, autism, motor disability, or neurological or seizure disorder.

Other conditions occurring more frequently in exposed subjects included ear infection (IRR 6.63, CI 5.73-7.66), chronic ear infection (IRR 5.67, CI 4.37-7.37), anaphylaxis (IRR 8.88, CI 1.24-63.47), and asthma attack or bronchospasm (IRR 6.30, CI 3.85-10.31). Vaccine exposure was not associated with increased incidence of eczema (IRR 1.06, CI 0.91-1.23), chronic eczema (IRR 0.94, CI 0.74-1.20) or peanut allergy (IRR 6.80, CI 0.95-48.69).

After multivariate adjustment, Cox proportional hazards modeling demonstrated that exposure to vaccination was independently associated with an increased risk of developing a chronic health condition (HR 2.54, CI 2.16-2.97), see Table 3. Vaccine exposure was independently associated with an increased risk of asthma, eczema, atopic and autoimmune disease, and neurodevelopmental disorders including developmental delay and speech disorder. Other variables in the model independently associated with increased risk of developing a chronic health disorder were male gender (HR 1.33, CI 1.26-1.41), African-American race (HR 1.11, CI 1.04-1.18), low-birth-weight (HR 1.20, CI 1.01-1.42), very-low-birth-weight (HR 1.48, CI 1.14-1.91) and prematurity (HR 1.24, CI 1.09-1.41). Vaccine exposure was not significantly associated with higher risk for cancer, food allergy, autism, motor disability, or neurological, seizure or mental health disorder. Incident rate ratios and hazard ratios could not be calculated for brain dysfunction, diabetes, ADHD, tics, or behavioral, learning, intellectual, or other psychological disability since all cases occurred in the group exposed to vaccination and no cases occurred in the unexposed group.

Vaccine exposure was also independently associated with increased risk for developing other conditions, including ear infection (HR 7.00, CI 6.05-8.10), chronic ear infection (HR 7.89, CI 6.08-10.24), anaphylaxis (HR 5.64, CI 1.11-28.74), asthma attack or bronchospasm (HR 5.82, CI 3.58-9.47) and

eczema (HR 1.31, CI 1.13-1.52). Vaccine exposure was not associated with chronic eczema (HR 1.26, CI 0.98-1.60) or peanut allergy (HR 6.31, CI 0.88-45.37).

Time to event analysis demonstrated that the overall probability of being free of a chronic health condition at 10-years of follow up was 43% in the group exposed to vaccination and 83% in the unexposed group (log-rank test, $p<0.0001$), see Figure 1.

There were six deaths in the cohort during enrollment. After manual review of medical records, including death certificate where available, cause of death was determined to be due to a complicated clinical course from birth (2 exposed, 1 unexposed), brain injury (1 exposed), and unknown cause (2 exposed).

Sensitivity Analyses

Since median enrollment time was shorter in the unexposed group, a sensitivity analysis for developing a chronic health condition was conducted for subjects enrolled in the health plan for at least 1-year, 3-years and 5-years which demonstrated consistent results. Vaccine exposure was associated with higher incidence of a chronic health condition for subjects enrolled at least 1-year (IRR 2.75, CI 2.31-3.28), 3-years (IRR 3.38, CI 2.67-4.30), and 5-years (IRR 4.09, CI 2.84-5.90), as well as a higher risk for developing a chronic health condition for subjects enrolled at least 1-year (HR 2.84, CI 2.38-3.38), 3-years (HR 3.48, CI 2.74-4.42), and 5-years (HR 4.05, CI 2.82-5.83). To address the potential for ascertainment bias in subjects with lower levels of health care utilization, we conducted a sensitivity analysis by repeating the above analyses using only subjects with at least one encounter during enrollment. Vaccine exposure was associated with higher incidence of a chronic health condition for subjects with at least one healthcare encounter (IRR 1.83, CI 1.56-2.14) as well as a higher risk for developing a chronic health condition (HR 1.87, CI 1.60-2.19).

Discussion

Main Findings

This study is a comprehensive analysis to determine if exposure to vaccination is associated with the development of any long-term chronic health condition in children, or if outcomes are similar, or superior, to those unexposed. We did not find any statistical association between vaccine exposure and cancer, food allergy, autism, seizure disorder and certain other conditions. Statistical comparisons could not be conducted for certain conditions, such as diabetes and ADHD, because there were no cases in the unexposed group. Despite this and in contrast to our expectations, we found that exposure to vaccination was independently associated with an overall 2.5-fold increase in the likelihood of developing a chronic health condition, when compared to children unexposed to vaccination. This association was primarily driven by increased risk for asthma, atopy, eczema, autoimmune disease and neurodevelopmental disorders. Overall, our findings suggest that in certain children exposure to vaccination may increase the likelihood of developing a chronic health condition, particularly for one of these disorders.

Interpretation and comparison with previous studies

Vaccines have contributed to reducing many targeted infections and their related morbidity and mortality, and are regarded as an important public health achievement of the last century.[18] The CDC's Vaccine Schedule has evolved from five vaccines in 1994 to 15 in 2020. Despite these advancements, there is a paucity of data evaluating the impact of vaccination on long-term health outcomes, whether beneficial or detrimental, particularly for immune-related conditions.

Limited by ethical guidelines, pre-and-post-licensure clinical trials for vaccines rarely include a comparator arm unexposed to vaccination. These trials also generally have a shorter safety review period (<30 days) which limits their ability to assess long-term outcomes. Observational studies can address these data gaps but, to date, have produced conflicting results. Some studies have found an association between vaccination and an increased risk of asthma, atopy, eczema, autoimmune disease and neurodevelopmental disorders, as found in this study.[13 14 19-28] Other studies have found no association.[12 15 29-38] A common and important limitation in this body of work is that almost all studies lack a truly unexposed comparator group, such as the one in this study, and hence typically evaluate receiving

(vaccinated) versus not receiving one vaccine (unvaccinated) in a cohort that receives most other vaccinations (vaccinated).

For example, one study designed to evaluate the relationship between vaccination status (one or more versus none) and long-term health outcomes in children was a population-based parental survey conducted in Germany.[31] Although limited by selection bias and parental recall, it found no statistical association of vaccination with atopy, eczema, or asthma.[31] However, the measure of vaccination was limited to certain vaccines, and the very small unexposed group may have been exposed to other vaccinations such as varicella, rotavirus, pneumococcal, meningococcal, influenza and/or others. According to the IOM (2013), few studies have evaluated the Vaccine Schedule, or variations thereof, and its association with health outcomes and none have compared differences between entirely unvaccinated populations and those fully or partially vaccinated.[10] Our study, to our knowledge, is the first to compare multiple clinical outcomes over time between vaccinated (any vaccine) and completely unexposed children in a captured payer environment relying on diagnoses and vaccine status from medical records.

Biologic mechanisms elucidating how vaccine exposure in certain individuals might increase a health risk are unclear and beyond the scope of this study, but likely differ by condition, vaccine and recipient characteristics. A common theme in the literature is that vaccination may trigger a genetic and/or immunologic susceptibility.[39 40] Vaccines aim to stimulate an antigen-specific immune response, however there are significant gaps in understanding the complex immunological mechanisms involved, and concern has been raised about potential untoward or off-target immunological effects in susceptible recipients.[41 42] According to an IOM report, epidemiologic and mechanistic research suggest that most individuals who experience an adverse response to a vaccine have a preexisting susceptibility due to genetic variants (in human or microbiome DNA), environmental exposures, behaviors, intervening illness, developmental stage or others.[43] Viewed as an environmental exposure, in addition to antigens, vaccines also contain small amounts of preservatives, adjuvants, additives and residual substances from the manufacturing process.[44] While this study cannot delineate the impact of epigenetics or a particular vaccine component, the unexposed group was not exposed to vaccine components, and the exposed group to one or more.

Epigenetics is an emerging field of study which explores how the environment can influence how genes are expressed without involving alterations in the DNA gene sequence. Research has shown that epigenetics may play a role in the pathogenesis of many diseases, including asthma, atopy, eczema, autoimmune disease and neurodevelopmental disorders, though precise etiologies vary and remain largely unknown.[45-50] Genetically-mediated individual variations in the immunogenicity and reactivity of vaccines has been demonstrated.[51 52] The field of vaccine 'adversomics', though in its infancy, seeks to bring a precision medicine approach into vaccine practice by utilizing advanced genomic, epigenetic and biostatistical approaches to better identify individuals susceptible to an adverse vaccine outcome to prevent or minimize adverse consequences.[52 53] This is important because, as the CDC emphasizes, vaccines are generally given to healthy persons preventatively, and because of their widespread use, any safety issue, even if rare, can impact large numbers of people.[54] The results of this study, while preliminary, suggest that we currently underestimate the group susceptible to an adverse vaccine effect.

We found a 6-fold increased risk of autoimmune disease in the group exposed to vaccine(s). Certain vaccines, or adjuvants, have been implicated in autoimmune conditions such as thrombocytopenic purpura, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and Guillain-Barré syndrome.[10 23 24 55] The spectrum of autoimmunity encompasses around 80 disorders, most considered rare, but combined have an estimated population prevalence of 4.5% to 9.4%.[56 57] While pathogenic mechanisms of autoimmune disease are not well understood overall, and even less so with autoimmune sequelae following vaccination, contemporary thinking favors environmental factors triggering autoimmunity in genetically-susceptible individuals, involving epigenetic regulation.[45] Proposed mechanisms by which vaccines may contribute to autoimmune reactions are molecular mimicry (structural similarity between a vaccine component and self-antigen) and bystander activation (microbial agents activate pre-primed autoreactive immune cells).[40]

Some studies have found that vaccination and atopic disorders, such as asthma, eczema and other allergies, are associated, while others have not.[12 13 20 22 28] Childhood infections appear to provide significant protection from atopy and it has been suggested that vaccination can contribute to atopy by inducing an imbalance between the two classes of T helper cells (Th1 and Th2) in genetically-susceptible individuals.[58]

[59] We found an over 4-fold increased risk of asthma and over 6-fold risk of asthma attack in those exposed to vaccination. This finding is consistent with Odent et. al. which found receiving DTP vaccine, versus no receipt, was associated with increased risk of asthma (RR=5.43; CI=1.93-15.30).[20] In that study, over half of the group not receiving DTP were exposed to other vaccines and the group with the lowest prevalence of asthma were not exposed to any vaccine (10.7% for DTP group versus 1.1% in group receiving no vaccines), though the latter's small number limited statistical comparisons.

Most studies of vaccination and developmental outcomes evaluated MMR[35 36] or thimerosol[26 37 60] exposure and autism.[61] These studies typically found no association, which is consistent with the results of this study, though the number of autism cases in this study was small. The few studies that evaluate potential associations between vaccination and neurodevelopmental disorders beyond autism have typically used a small dataset of neuropsychiatric evaluations at 7-10 years from the 1990s in which all participants received all first-year vaccines.[38 62] Studies using this dataset have produced conflicting results.[38 62] A recent pilot study using claims data found a temporal relationship between vaccination and onset of certain neuropsychiatric disorders.[27]

While contributors to the rise of developmental disability in children from 9.5% in 2009 to 16.9%[63] has been grossly understudied, current thinking favors multiple contributors, including the immune system which is essential to normal brain development and is implicated in the pathogenesis of several neurodevelopmental disorders.[64-66] Epigenetic research is exploring the complex relationship between developmentally-regulated genetic expression and interplay of prenatal and childhood environmental risk factors and exposures,[47] in addition to factors such as socioeconomic status, preterm-birth, and birth-weight.[67] A study by Iqbal et al. did not find an association between the number of vaccine antigens and neuropsychological outcomes.[68] However, a recent study examined the feasibility of examining non-antigen vaccine ingredients and found that out of 34 ingredients, only aluminum exposure could be consistently quantified, but did not subsequently evaluate aluminum's impact on clinically meaningful outcomes.[69] We found a strong association between vaccine exposure (versus no exposure) and development of a neurodevelopmental disorder (HR 5.84, CI 3.02-11.27) even after controlling for gender, race, birth-weight prematurity, and other factors. This increased risk was primarily driven by speech

disorders, developmental delays, tics, ADHD, and behavioral and motor disabilities. The etiology of this association is unclear, but it suggests that vaccination may serve as an environmental influence in susceptible children.

Strengths of this Study

Major strengths of this study are that it evaluated a captured population, enrolled a consecutive birth cohort, evaluated subjects only while enrolled, only relied upon medical records to determine diagnoses, encounters and vaccines administered (unlike prior works which often relied upon parental recall and survey data), had a completely unexposed cohort, and utilized groupings of health conditions, which can reveal relationships that are not apparent when evaluating specific disorders individually (particularly if they are rare).

Though some results were unexpected, others are consistent with conclusions from prior systematic reviews, including by the IOM, such as the accepted causal relationship between vaccination and anaphylaxis, which we observed, or the rejection of a causal relationship between vaccination and cancer or MMR vaccine and autism.[43 70] This contributes to the internal validity of this study's findings.

This study also minimized the risk of misclassifying vaccine exposure. First, studies have shown good agreement between electronic vaccination and health records and both parental recall and manual medical record review, particularly for those unexposed to vaccines.[71 72] Second, each subject's EHR contained vaccine administration data from HFHS and the state immunization registry, ensuring full capture of vaccinations. In Michigan, all providers are required to report vaccinations to the state registry within 72 hours of administration. This study, to our knowledge, includes the largest cohort of children completely unexposed to vaccination with observation in some subjects up to 18 years.

Limitations of this Study

This study has limitations. As it is retrospective, we cannot exclude the possibility of unidentified confounders. However, this concern is tempered by the finding of significant associations between vaccination and particular outcomes, with some hazard ratios in the 2.5-6 times risk. We lacked information

on socioeconomic status, or potentially relevant post birth factors, such as diet or lifestyle, but did adjust for several important baseline confounders such as gender, ethnicity, gestational age and birthweight. To detect the potential for uncontrolled confounding, the literature suggests evaluating disorders with no expected causal association with vaccination, a control outcome, such as injuries or cancer.[17] Importantly in this regard we found no association between vaccine exposure and cancer. Additionally, we relied on diagnosis codes in administrative data, which is commonly used in epidemiologic research but has some inherent limitations.

Unvaccinated children have less healthcare utilization overall.[73] Well visits coincide with the vaccination schedule and provide more opportunities for assessment and diagnosis in those receiving vaccines, compared to unvaccinated children, which could introduce an ascertainment bias. In this study, exposed children had an average of 7 annual encounters, irrespective of having a chronic health condition. Unexposed children had an average of 2 annual encounters but an average of almost 5 annual encounters if diagnosed with a chronic health condition. This likely demonstrates that when a child had a medical condition, parents sought healthcare. In fact, many conditions evaluated in this study are serious and cannot be self-treated, such as asthma, diabetes, anaphylaxis or asthma attack, warranting urgent medical attention. We nonetheless conducted several sensitivity analyses to explore the influence of healthcare utilization in order to improve the internal validity of this study and minimize potential ascertainment bias. To ensure the unexposed group's shorter follow-up duration did not influence the results, we repeated the Cox proportional hazards analysis for the chronic health composite outcome for those in the plan for one, three and five years and for those who had at least one healthcare encounter, which demonstrated results consistent with the overall findings. The association between vaccination and developing a chronic health condition was independent of these factors. Therefore, our findings do not appear to be due to differential use of health resources.

Our study solely evaluated whether or not vaccination was associated with clinically relevant outcomes, conditions that currently contribute to the rising chronic health disease burden in children. We did not evaluate the influence of temporal relationships, individual vaccines, or the number of vaccines, which limits this investigation but also minimizes the potential for reverse causality.

Conclusion

In this study, we found vaccine exposure in children was associated with an increased risk of developing a chronic health disorder. This association was primarily driven by increased risk for asthma, atopy, eczema, autoimmune disease and neurodevelopmental disorders. This suggests that in certain susceptible children, exposure to vaccination may increase the likelihood of developing a chronic health condition, particularly for one of these conditions. Our preliminary findings cannot prove causality and warrant further investigation.

FIGURES AND TABLES

Table 1. Birth Characteristics and Demographics Stratified by Vaccine Exposure Status

Demographics	Study Population (n=18,468)	No Vaccine (n=1,957)	Any Vaccine (n=16,511)	*P*-value
Male	9,395 (51%)	1,077 (55%)	8,318 (50%)	<0.001
Race				<0.001
White	6,858 (37%)	900 (46%)	5,958 (36%)	
African American	6,625 (36%)	453 (23%)	6,172 (37%)	
Asian	1,131 (6%)	87 (4%)	1,044 (6%)	
Hispanic	503 (3%)	31 (2%)	472 (3%)	
Other	3,351 (18%)	486 (25%)	2,865 (17%)	
Birth weight				<0.001
Normal	17,701 (96%)	1,907 (97%)	15,794 (96%)	
Low	539 (3%)	21 (1%)	518 (3%)	
Very low	228 (1%)	29 (2%)	199 (1.2%)	
Prematurity	1,063 (6%)	34 (2%)	1,029 (6%)	<0.001
Respiratory Distress at Birth	685 (4%)	26 (1%)	659 (4%)	<0.001
Birth Trauma	200 (1%)	4 (0%)	196 (1%)	<0.001
Vaccine Injections				
0	1,958 (10.6%)			
1-10	3,330 (18.0%)			
11-20	7,476 (40.5%)			
21-30	4,981 (27.0%)			
>30	724 (3.9%)			

Definitions: Birth weight (Normal $\geq$ 2,500g; low birth weight = less than 2,500g; very low birth weight = less than 1,500g)
Vaccine exposure for the purpose of comparison of baseline characteristics was receipt of any vaccine during enrollment in the plan.

Table 2. Incidence of Chronic Health Conditions Stratified by Vaccine Exposure Status*

Outcome	Any Vaccine Exposure N (Incidence per 1,000,000 pt-yrs)	No Vaccine Exposure N (Incidence per 1,000,000 pt-yrs)	IRR (95% CI)	*P*
Chronic Health Condition	4,732 (277.3)	160 (111.7)	2.48 (2.12-2.91)	<0.0001
Asthma	2,867 (145.6)	52 (35.6)	4.09 (3.11-5.38)	<0.0001
Atopic Disease	946 (41.2)	23 (15.6)	2.64 (1.74-3.99)	<0.0001
Autoimmune Disease	201 (8.4)	2 (1.4)	6.16 (1.53-24.79)	0.01
Brain Dysfunction	8 (0.3)	0 (0.0)	∞	
Cancer	169 (7.0)	13 (8.8)	0.79 (0.45-1.39)	0.42
Diabetes	42 (1.7)	0 (0.0)	∞	
Food Allergy	577 (24.3)	30 (20.5)	1.19 (0.82-1.71)	0.36
Mental Health Disorder	341 (15.9)	5 (4.5)	3.50 (1.45-8.46)	<0.01
Neurodevelopmental Disorder	1,029 (50.2)	9 (8.2)	6.15 (3.19-11.86)	<0.0001
ADHD	262 (12.1)	0 (0.0)	∞	
Autism	23 (1.1)	1 (0.9)	1.16 (0.16-8.62)	0.88
Behavioral Disability	165 (7.6)	0 (0.0)	∞	
Developmental Delay	219 (10.1)	3 (2.7)	3.74 (1.20-11.68)	0.02
Learning Disability	65 (3.0)	0 (0.0)	∞	
Intellectual Disability	5 (0.2)	0 (0.0)	∞	
Speech Disorder	463 (21.8)	6 (5.4)	4.02 (1.80-9.00)	<0.001
Motor Disability	150 (6.9)	2 (1.8)	3.83 (0.95-15.47)	0.06
Tics	46 (2.1)	0 (0.0)	∞	
Other Psychological Disability	9 (0.4)	0 (0.0)	∞	
Neurological Disorder	127 (5.2)	12 (8.1)	0.64 (0.35-1.16)	0.14
Seizure Disorder	319 (13.3)	12 (8.2)	1.63 (0.92-2.91)	0.09

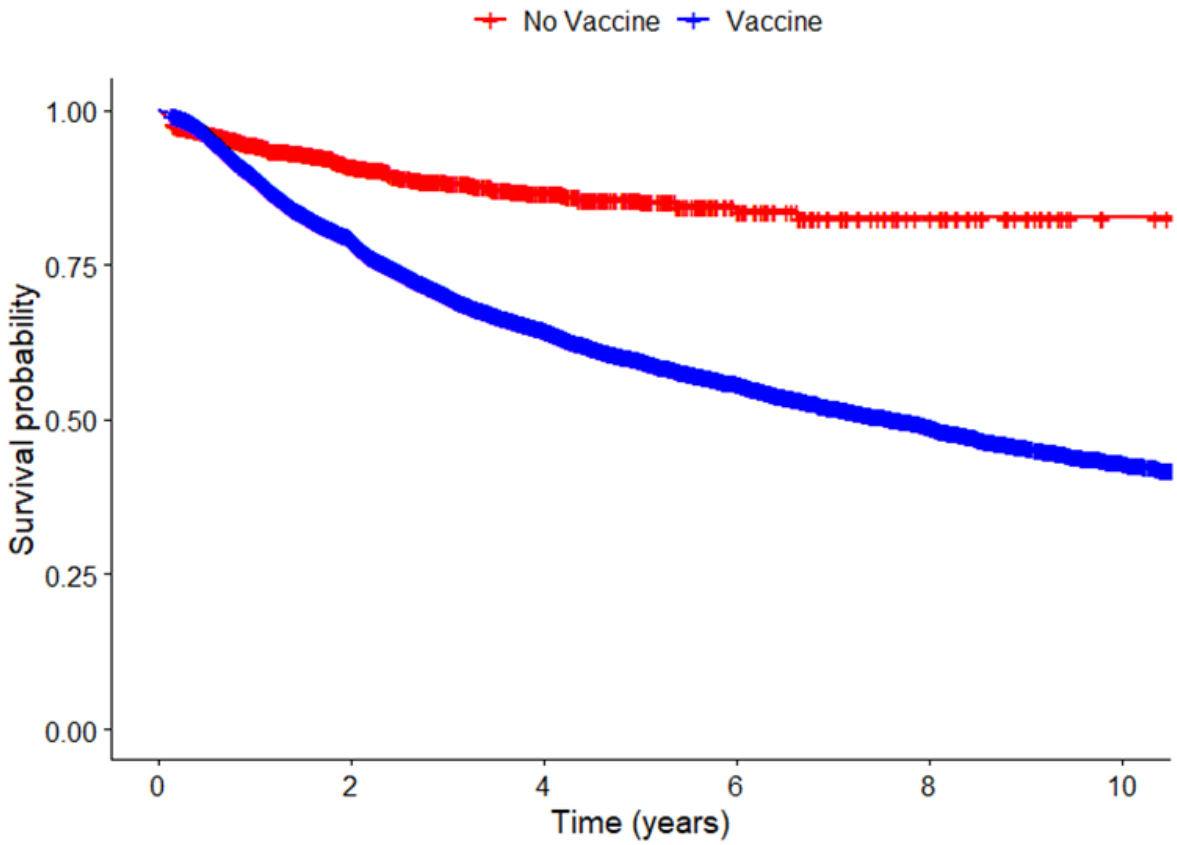
* Incident rate ratios could not be calculated for brain dysfunction, diabetes, ADHD, tics, or behavioral, learning, intellectual, or other psychological disability since all cases occurred in the group exposed to vaccination and no cases occurred in the unexposed group.

Table 3. Cox Proportional Hazards Regression Analysis for Vaccine Exposure and Development of a Chronic Health Condition*

Outcome	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Chronic Health Condition	2.59 (2.21-3.03)	<0.0001	2.54 (2.16-2.97)	<0.0001
Asthma	4.50 (3.42-5.93)	<0.0001	4.29 (3.26-5.65)	<0.0001
Atopic Disease	3.11 (2.06-4.71)	<0.0001	3.03 (2.01-4.57)	<0.0001
Autoimmune Disease	6.12 (1.52-24.67)	0.01	5.96 (1.48-24.11)	0.02
Brain Dysfunction	∞		∞	
Cancer	0.86 (0.49-1.52)	0.61	0.90 (0.51-1.59)	0.72
Diabetes	∞		∞	
Food Allergy	1.38 (0.96-2.00)	0.08	1.40 (0.97-2.02)	0.07
Mental Health Disorder	1.69 (0.70-4.09)	0.25	1.63 (0.69-3.82)	0.26
Neurodevelopmental Disorder	5.61 (2.91-10.82)	<0.0001	5.53 (2.91-10.51)	<0.0001
ADHD	∞		∞	
Autism	1.01 (0.13-7.55)	0.99	0.62 (0.10-3.69)	0.60
Behavioral Disability	∞		∞	
Developmental Delay	3.87 (1.24-12.10)	0.02	3.28 (1.13-9.55)	0.03
Intellectual Disability	∞		∞	
Learning Disability	∞		∞	
Motor Disability	3.33 (0.82-13.48)	0.09	2.92 (0.82-10.40)	0.10
Speech Disorder	4.84 (2.16-10.84)	0.0001	4.47 (2.05-9.74)	<0.001
Tics	∞		∞	
Other Psychological Disability	∞		∞	
Neurological Disorder	0.75 (0.41-1.36)	0.34	0.83 (0.46-1.51)	0.55
Seizure Disorder	2.01 (1.13-3.59)	0.02	1.66 (0.94-2.94)	0.08

HR adjusted for gender, race, birth weight, respiratory distress at birth, birth trauma and prematurity.
* Hazard ratios could not be calculated for brain dysfunction, diabetes, ADHD, tics, or behavioral, learning, intellectual, or other psychological disability since all cases occurred in the group exposed to vaccination and no cases occurred in the unexposed group.

Figure 1. Kaplan Meier Curve: 10-year Chronic Disease-Free Survival by Vaccine Exposure



Vaccine	1.00	0.79	0.65	0.56	0.49	0.43
No Vaccine	1.00	0.91	0.87	0.84	0.83	0.83

REFERENCES

1. Van Cleave J, Gortmaker SL, Perrin JM. Dynamics of obesity and chronic health conditions among children and youth. *JAMA* 2010;303(7):623-30. doi: 10.1001/jama.2010.104 [published Online First: 2010/02/18]
2. Bethell CD, Kogan MD, Strickland BB, et al. 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* 2011;11(3 Suppl):S22-33. doi: 10.1016/j.acap.2010.08.011 [published Online First: 2011/05/21]
3. Hinman AR, Orenstein WA, Schuchat A, et al. Vaccine-preventable diseases, immunizations, and MMWR--1961-2011. *MMWR Suppl* 2011;60(4):49-57. [published Online First: 2011/10/07]
4. Schuster M, Eskola J, Duclos P, et al. Review of vaccine hesitancy: Rationale, remit and methods. *Vaccine* 2015;33(34):4157-60. doi: 10.1016/j.vaccine.2015.04.035 [published Online First: 2015/04/22]
5. Hill HA, Elam-Evans LD, Yankey D, et al. Vaccination Coverage Among Children Aged 19-35 Months - United States, 2017. *MMWR Morb Mortal Wkly Rep* 2018;67(40):1123-28. doi: 10.15585/mmwr.mm6740a4 [published Online First: 2018/10/12]
6. Chen RT, DeStefano F, Pless R, et al. Challenges and controversies in immunization safety. *Infect Dis Clin North Am* 2001;15(1):21-39, viii. [published Online First: 2001/04/17]
7. Saada A, Lieu TA, Morain SR, et al. Parents' choices and rationales for alternative vaccination schedules: a qualitative study. *Clin Pediatr (Phila)* 2015;54(3):236-43. doi: 10.1177/0009922814548838 [published Online First: 2014/09/10]
8. Kennedy A, Basket M, Sheedy K. Vaccine attitudes, concerns, and information sources reported by parents of young children: results from the 2009 HealthStyles survey. *Pediatrics* 2011;127 Suppl 1:S92-9. doi: 10.1542/peds.2010-1722N [published Online First: 2011/04/20]
9. Gellin BG, Maibach EW, Marcuse EK. Do parents understand immunizations? A national telephone survey. *Pediatrics* 2000;106(5):1097-102. doi: 10.1542/peds.106.5.1097 [published Online First: 2000/11/04]
10. . The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies. Washington (DC)2013.
11. Chen R. Safety of Vaccines. Philadelphia: WB Saunders 1999:1144-1163.
12. DeStefano F, Gu D, Kramarz P, et al. Childhood vaccinations and risk of asthma. *Pediatr Infect Dis J* 2002;21(6):498-504. doi: 10.1097/00006454-200206000-00004 [published Online First: 2002/08/17]
13. McDonald KL, Huq SI, Lix LM, et al. Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma. *J Allergy Clin Immunol* 2008;121(3):626-31. doi: 10.1016/j.jaci.2007.11.034 [published Online First: 2008/01/22]
14. Hurwitz EL, Morgenstern H. Effects of diphtheria-tetanus-pertussis or tetanus vaccination on allergies and allergy-related respiratory symptoms among children and adolescents in the United States. *J Manipulative Physiol Ther* 2000;23(2):81-90. [published Online First: 2000/03/14]
15. Nilsson L, Kjellman NI, Bjorksten B. A randomized controlled trial of the effect of pertussis vaccines on atopic disease. *Arch Pediatr Adolesc Med* 1998;152(8):734-8. doi: 10.1001/archpedi.152.8.734 [published Online First: 1998/08/13]
16. DeStefano F, Price CS, Weintraub ES. Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism. *J Pediatr* 2013;163(2):561-7. doi: 10.1016/j.jpeds.2013.02.001 [published Online First: 2013/04/03]
17. Glanz JM, Newcomer SR, Jackson ML, et al. White Paper on studying the safety of the childhood immunization schedule in the Vaccine Safety Datalink. *Vaccine* 2016;34 Suppl 1:A1-A29. doi: 10.1016/j.vaccine.2015.10.082 [published Online First: 2016/02/03]
18. Centers for Disease C, Prevention. Ten great public health achievements--United States, 1900-1999. *MMWR Morb Mortal Wkly Rep* 1999;48(12):241-3. [published Online First: 1999/04/29]
19. Kemp T, Pearce N, Fitzharris P, et al. Is infant immunization a risk factor for childhood asthma or allergy? *Epidemiology* 1997;8(6):678-80. doi: 10.1097/00001648-199710000-00011 [published Online First: 1997/11/05]

20. Odent MR, Culpin EE, Kimmel T. Pertussis vaccination and asthma: is there a link? *JAMA* 1994;272(8):592-3. [published Online First: 1994/08/24]
21. Kiraly N, Koplin JJ, Crawford NW, et al. Timing of routine infant vaccinations and risk of food allergy and eczema at one year of age. *Allergy* 2016;71(4):541-9. doi: 10.1111/all.12830 [published Online First: 2015/12/29]
22. McKeever TM, Lewis SA, Smith C, et al. Vaccination and allergic disease: a birth cohort study. *Am J Public Health* 2004;94(6):985-9. doi: 10.2105/ajph.94.6.985 [published Online First: 2004/07/14]
23. Chen RT, Pless R, Destefano F. Epidemiology of autoimmune reactions induced by vaccination. *J Autoimmun* 2001;16(3):309-18. doi: 10.1006/jaut.2000.0491 [published Online First: 2001/05/04]
24. Karussis D, Petrou P. The spectrum of post-vaccination inflammatory CNS demyelinating syndromes. *Autoimmun Rev* 2014;13(3):215-24. doi: 10.1016/j.autrev.2013.10.003 [published Online First: 2014/02/12]
25. Miller E, Waight P, Farrington CP, et al. Idiopathic thrombocytopenic purpura and MMR vaccine. *Arch Dis Child* 2001;84(3):227-9. doi: 10.1136/adc.84.3.227 [published Online First: 2001/02/24]
26. Gallagher CM, Goodman MS. Hepatitis B vaccination of male neonates and autism diagnosis, NHIS 1997-2002. *J Toxicol Environ Health A* 2010;73(24):1665-77. doi: 10.1080/15287394.2010.519317 [published Online First: 2010/11/09]
27. Leslie DL, Kobre RA, Richmand BJ, et al. Temporal Association of Certain Neuropsychiatric Disorders Following Vaccination of Children and Adolescents: A Pilot Case-Control Study. *Front Psychiatry* 2017;8:3. doi: 10.3389/fpsyt.2017.00003 [published Online First: 2017/02/06]
28. Alm JS, Swartz J, Lilja G, et al. Atopy in children of families with an anthroposophic lifestyle. *Lancet* 1999;353(9163):1485-8. doi: 10.1016/S0140-6736(98)09344-1 [published Online First: 1999/05/08]
29. Mohrenschlager M, Haberl VM, Kramer U, et al. Early BCG and pertussis vaccination and atopic diseases in 5- to 7-year-old preschool children from Augsburg, Germany: results from the MIRIAM study. *Pediatr Allergy Immunol* 2007;18(1):5-9. doi: 10.1111/j.1399-3038.2006.00485.x [published Online First: 2007/02/14]
30. Matheson MC, Haydn Walters E, Burgess JA, et al. Childhood immunization and atopic disease into middle-age--a prospective cohort study. *Pediatr Allergy Immunol* 2010;21(2 Pt 1):301-6. doi: 10.1111/j.1399-3038.2009.00950.x [published Online First: 2009/12/17]
31. Schmitz R, Poethko-Muller C, Reiter S, et al. Vaccination status and health in children and adolescents: findings of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). *Dtsch Arztebl Int* 2011;108(7):99-104. doi: 10.3238/arztebl.2011.0099 [published Online First: 2011/03/18]
32. Grimaldi-Bensouda L, Le Guern V, Kone-Paut I, et al. The risk of systemic lupus erythematosus associated with vaccines: an international case-control study. *Arthritis Rheumatol* 2014;66(6):1559-67. doi: 10.1002/art.38429 [published Online First: 2014/03/05]
33. DeStefano F, Mullooly JP, Okoro CA, et al. Childhood vaccinations, vaccination timing, and risk of type 1 diabetes mellitus. *Pediatrics* 2001;108(6):E112. doi: 10.1542/peds.108.6.e112 [published Online First: 2001/12/04]
34. Baxter R, Bakshi N, Fireman B, et al. Lack of association of Guillain-Barre syndrome with vaccinations. *Clin Infect Dis* 2013;57(2):197-204. doi: 10.1093/cid/cit222 [published Online First: 2013/04/13]
35. Jain A, Marshall J, Buikema A, et al. Autism occurrence by MMR vaccine status among US children with older siblings with and without autism. *JAMA* 2015;313(15):1534-40. doi: 10.1001/jama.2015.3077 [published Online First: 2015/04/22]
36. DeStefano F, Bhasin TK, Thompson WW, et al. Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan atlanta. *Pediatrics* 2004;113(2):259-66. doi: 10.1542/peds.113.2.259 [published Online First: 2004/02/03]
37. Price CS, Thompson WW, Goodson B, et al. Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism. *Pediatrics* 2010;126(4):656-64. doi: 10.1542/peds.2010-0309 [published Online First: 2010/09/15]

38. Barile JP, Kuperminc GP, Weintraub ES, et al. Thimerosal exposure in early life and neuropsychological outcomes 7-10 years later. *J Pediatr Psychol* 2012;37(1):106-18. doi: 10.1093/jpepsy/jsr048 [published Online First: 2011/07/26]
39. Sibilia J, Maillefert JF. Vaccination and rheumatoid arthritis. *Ann Rheum Dis* 2002;61(7):575-6. doi: 10.1136/ard.61.7.575 [published Online First: 2002/06/25]
40. Vadala M, Poddighe D, Laurino C, et al. Vaccination and autoimmune diseases: is prevention of adverse health effects on the horizon? *EPMA J* 2017;8(3):295-311. doi: 10.1007/s13167-017-0101-y [published Online First: 2017/10/13]
41. Pulendran B, Ahmed R. Immunological mechanisms of vaccination. *Nat Immunol* 2011;12(6):509-17. [published Online First: 2011/07/09]
42. Kandasamy R, Voysey M, McQuaid F, et al. Non-specific immunological effects of selected routine childhood immunisations: systematic review. *BMJ* 2016;355:i5225. doi: 10.1136/bmj.i5225 [published Online First: 2016/10/16]
43. . In: Stratton K, Ford A, Rusch E, et al., eds. Adverse Effects of Vaccines: Evidence and Causality. Washington (DC)2011.
44. Offit PA, Jew RK. Addressing parents' concerns: do vaccines contain harmful preservatives, adjuvants, additives, or residuals? *Pediatrics* 2003;112(6 Pt 1):1394-7. doi: 10.1542/peds.112.6.1394 [published Online First: 2003/12/05]
45. Costenbader KH, Gay S, Alarcon-Riquelme ME, et al. Genes, epigenetic regulation and environmental factors: which is the most relevant in developing autoimmune diseases? *Autoimmun Rev* 2012;11(8):604-9. doi: 10.1016/j.autrev.2011.10.022 [published Online First: 2011/11/02]
46. Gomez JL. Epigenetics in Asthma. *Curr Allergy Asthma Rep* 2019;19(12):56. doi: 10.1007/s11882-019-0886-y [published Online First: 2019/11/30]
47. Millan MJ. An epigenetic framework for neurodevelopmental disorders: from pathogenesis to potential therapy. *Neuropharmacology* 2013;68:2-82. doi: 10.1016/j.neuropharm.2012.11.015 [published Online First: 2012/12/19]
48. Bollati V, Baccarelli A. Environmental epigenetics. *Heredity (Edinb)* 2010;105(1):105-12. doi: 10.1038/hdy.2010.2 [published Online First: 2010/02/25]
49. Kuriakose JS, Miller RL. Environmental epigenetics and allergic diseases: recent advances. *Clin Exp Allergy* 2010;40(11):1602-10. doi: 10.1111/j.1365-2222.2010.03599.x [published Online First: 2010/08/20]
50. Mervis JS, McGee JS. DNA methylation and inflammatory skin diseases. *Arch Dermatol Res* 2019 doi: 10.1007/s00403-019-02005-9 [published Online First: 2019/11/07]
51. Poland GA, Ovsyannikova IG, Jacobson RM. Vaccine immunogenetics: bedside to bench to population. *Vaccine* 2008;26(49):6183-8. doi: 10.1016/j.vaccine.2008.06.057 [published Online First: 2008/07/05]
52. Poland GA, Ovsyannikova IG, Jacobson RM. Adversomics: the emerging field of vaccine adverse event immunogenetics. *Pediatr Infect Dis J* 2009;28(5):431-2. doi: 10.1097/INF.0b013e3181a6a511 [published Online First: 2009/04/28]
53. Whitaker JA, Ovsyannikova IG, Poland GA. Adversomics: a new paradigm for vaccine safety and design. *Expert Rev Vaccines* 2015;14(7):935-47. doi: 10.1586/14760584.2015.1038249 [published Online First: 2015/05/06]
54. Centers for Disease C. Epidemiology and Prevention of Vaccine-Preventable Diseases [Available from: https://www.cdc.gov/vaccines/pubs/pinkbook/safety.html accessed 10/25/2019 2019.
55. Shoenfeld Y, Aron-Maor A. Vaccination and autoimmunity-'vaccinosis': a dangerous liaison? *J Autoimmun* 2000;14(1):1-10. doi: 10.1006/jaut.1999.0346 [published Online First: 2000/01/29]
56. Hayter SM, Cook MC. Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. *Autoimmun Rev* 2012;11(10):754-65. doi: 10.1016/j.autrev.2012.02.001 [published Online First: 2012/03/06]
57. Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. *J Autoimmun* 2009;33(3-4):197-207. doi: 10.1016/j.jaut.2009.09.008 [published Online First: 2009/10/13]

58. von Hertzen LC, Haahtela T. Could the risk of asthma and atopy be reduced by a vaccine that induces a strong T-helper type 1 response? *Am J Respir Cell Mol Biol* 2000;22(2):139-42. doi: 10.1165/ajrcmb.22.2.3753 [published Online First: 2000/02/05]
59. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299(6710):1259-60. doi: 10.1136/bmj.299.6710.1259 [published Online First: 1989/11/18]
60. Verstraeten T, Davis RL, DeStefano F, et al. Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases. *Pediatrics* 2003;112(5):1039-48. [published Online First: 2003/11/05]
61. Taylor LE, Swerdfeger AL, Eslick GD. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. *Vaccine* 2014;32(29):3623-9. doi: 10.1016/j.vaccine.2014.04.085 [published Online First: 2014/05/13]
62. Smith MJ, Woods CR. On-time vaccine receipt in the first year does not adversely affect neuropsychological outcomes. *Pediatrics* 2010;125(6):1134-41. doi: 10.1542/peds.2009-2489 [published Online First: 2010/05/26]
63. Zablotsky B, Black LI, Maenner MJ, et al. Prevalence and Trends of Developmental Disabilities among Children in the United States: 2009-2017. *Pediatrics* 2019 doi: 10.1542/peds.2019-0811 [published Online First: 2019/09/29]
64. Verlaet AA, Noriega DB, Hermans N, et al. Nutrition, immunological mechanisms and dietary immunomodulation in ADHD. *Eur Child Adolesc Psychiatry* 2014;23(7):519-29. doi: 10.1007/s00787-014-0522-2 [published Online First: 2014/02/05]
65. Martino D, Zis P, Buttiglione M. The role of immune mechanisms in Tourette syndrome. *Brain Res* 2015;1617:126-43. doi: 10.1016/j.brainres.2014.04.027 [published Online First: 2014/05/23]
66. Knuesel I, Chicha L, Britschgi M, et al. Maternal immune activation and abnormal brain development across CNS disorders. *Nat Rev Neurol* 2014;10(11):643-60. doi: 10.1038/nrneurol.2014.187 [published Online First: 2014/10/15]
67. United States. Environmental Protection Agency. America's children and the environment. Third edition. ed. Washington, D.C.: United States Environmental Protection Agency 2013.
68. Iqbal S, Barile JP, Thompson WW, et al. Number of antigens in early childhood vaccines and neuropsychological outcomes at age 7-10 years. *Pharmacoepidemiol Drug Saf* 2013;22(12):1263-70. doi: 10.1002/pds.3482 [published Online First: 2013/07/13]
69. Glanz JM, Newcomer SR, Daley MF, et al. Cumulative and episodic vaccine aluminum exposure in a population-based cohort of young children. *Vaccine* 2015;33(48):6736-44. doi: 10.1016/j.vaccine.2015.10.076 [published Online First: 2015/11/01]
70. Maglione MA, Das L, Raaen L, et al. Safety of vaccines used for routine immunization of U.S. children: a systematic review. *Pediatrics* 2014;134(2):325-37. doi: 10.1542/peds.2014-1079 [published Online First: 2014/08/03]
71. Mullooly J, Drew L, DeStefano F, et al. Quality of HMO vaccination databases used to monitor childhood vaccine safety. Vaccine Safety DataLink Team. *Am J Epidemiol* 1999;149(2):186-94. doi: 10.1093/oxfordjournals.aje.a009785 [published Online First: 1999/01/28]
72. Daley MF, Shoup JA, Newcomer SR, et al. Assessing Potential Confounding and Misclassification Bias When Studying the Safety of the Childhood Immunization Schedule. *Acad Pediatr* 2018;18(7):754-62. doi: 10.1016/j.acap.2018.03.007 [published Online First: 2018/04/01]
73. Wei F, Mullooly JP, Goodman M, et al. Identification and characteristics of vaccine refusers. *BMC Pediatr* 2009;9:18. doi: 10.1186/1471-2431-9-18 [published Online First: 2009/03/06]