HOW PREGNANT WOMEN IN THE UNITED STATES PERCEIVE VACCINES FOR THEMSELVES, THEIR CLOSE CONTACTS AND THEIR CHILDREN

by

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Abstract

Vaccine hesitancy has grown in recent decades [1-4], leading to the clustering of vaccine refusal and associated outbreaks of vaccine preventable diseases (VPDs) [5-11]. Vaccination rates of pregnant women in particular are suboptimal [12].

This dissertation contains three manuscripts discussing research performed as part of an NIH-funded large randomized controlled trial of a comprehensive prenatal intervention to increase uptake of maternal and infant vaccines (referred to as P3+) and its add-on study sponsored by Walgreen Co to increase knowledge and uptake of cocooning vaccines among close friends and family of participating P3+ pregnant women.

As part of the P3+ provider-level intervention package, we performed a systematic review to update and succinctly summarize the scientific evidence assessing possible causal associations of adverse events following immunization (AEFI), with refined causality conclusions intended for health care providers. Although for 12 of the 47 AEFI studied a causal relationship was established with at least one vaccine currently routinely recommended to the general population in the United States, most of these were rare or mild, and no causal relationship was established for the other 35 AEFI studied.

As part of the P3+ patient-level intervention package, we developed an application called MomsTalkShots for smartphones, tablets and computers that delivers patient-tailored education materials to pregnant women and collects survey data to monitor vaccine knowledge, attitudes and beliefs. As part of the add-on study, the MomsTalkShots app encouraged P3+ pregnant women to

refer their close friends and family to the app. Baseline survey data showed suboptimal maternal vaccine knowledge and intentions among P3+ pregnant women, especially among first-time pregnant women. In addition, pregnant women who valued vaccination and perceived their social network to value vaccination were more likely to refer their close friends and family to the app.

This research demonstrates the opportunity for individually-tailored vaccine education of pregnant women and their social networks to increase vaccine confidence and informed decision making at this stage of life.

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Preface

This dissertation is dedicated to my grandfather, Herman Stone, and his brother, Henry Stone. After escaping Nazi Germany for the U.S. as teenagers in 1939, Herman earned a PhD in Physical Organic Chemistry, and Henry a Master's of Science degree in Engineering and Physics, and both had long and successful careers in science and industry. Their achievements in science and their resolve to succeed in the face of adversity have been an inspiration to me in my own academic pursuits. Herman lives in Buffalo, NY with his wife Peggy and will receive a full copy of this dissertation upon finalization. Henry sadly passed away on December 1, 2018, shortly before this dissertation's completion, but will be remembered fondly by his many family and friends.

Thank you to the National Institutes of Health and Walgreen Co for their funding support. Thank you as well to everyone who contributed to or reviewed some or all of the content of our book discussed in manuscript 1, as well as everyone who contributed to survey design and/or participant recruitment in the studies providing data for manuscripts 2 and 3. A final and special thank you to my soon-to-be wife, Emily, for her unyielding support of my elongated student status, and to my parents for emphasizing and supporting education and learning from my earliest years of life.

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Abbreviations

95% CI	95% Confidence Interval
ADEM	Acute Disseminated Encephalomyelitis
aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
AEFI	Adverse events following immunization
ACIP	Advisory Committee on Immunization Practice
AHRQ	Agency for Healthcare Research and Quality
AAAAI	American Academy of Allergy, Asthma, and Immunology
AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
AASLD	American Association for the Study of Liver Diseases
ACNM	American College of Nurse-Midwives
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
AMA	American Medical Association
ASD	Autism spectrum disorder
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
CIN	Cervical intraepithelial neoplasia
CFS	Chronic fatigue syndrome
CISA	Clinical Immunization Safety Assessment network
CRPS	Complex regional pain syndrome
CRS	Congenital Rubella Syndrome
cGMP	Current Good Manufacturing Practice
DSMB	Data Safety Monitoring Board
DoD	Department of Defense
HHS	Department of Health and Human Services
VA	Department of Veterans Affairs
DTaP	Diphtheria, Tetanus and acellular Pertussis combination vaccine
DTP	Diphtheria, Tetanus and whole-cell Pertussis combination vaccine
EPA	Environmental Protection Agency
EN	Erythema nodosum
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
Hib	*Haemophilus influenzae* type b
HR	Hazard ratio
H, as in H1N1	Hemagglutinin
HAV	Hepatitis A Virus
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBIG	Hepatitis B immune globulin

HBV	Hepatitis B Virus
HSV	Herpes simplex virus
HPV	Human Papillomavirus
ITP	Immune thrombocytopenia purpura
IIV	Inactivated Influenza Vaccine
IPV	Inactivated Polio Vaccine
IRR	Incidence rate ratio
IHS	Indian Health Services
IOM	Institute of Medicine
IRB	Institutional Review Board
ID	Intradermal
IM	Intramuscular
IND	Investigational New Drug
IVS	Johns Hopkins Institute for Vaccine Safety
LAIV	Live Attenuated Influenza Vaccine
MCO	Managed care organizations
MIBE	Measles inclusion body encephalitis
MMR	Measles, Mumps and Rubella vaccine
MMRV	Measles, Mumps, Rubella and Varicella combination vaccine
MCV	Meningococcal conjugate vaccine
MPSV	Meningococcal polysaccharide vaccine
MS	Multiple sclerosis
MBP	Myelin basic protein
MI	Myocardial infarction
NAM	National Academy of Medicine
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NVAC	National Vaccine Advisory Committee
VICP	National Vaccine Injury Compensation Program
NVPO	National Vaccine Program Office
N, as in H1N1	Neuraminidase
NMO	Neuromyelitis optica
ORS	Oculorespiratory syndrome
OR	Odds ratio
OMS	Opsoclonus myoclonus syndrome
OPV	Oral poliovirus vaccine
pH1N1	Pandemic H1N1 influenza
PCV	Pneumococcal conjugate vaccine
PAN	Polyarteritis nodosa
PRISM	Post-Licensure Rapid Immunization Safety Monitoring Network
POI	Primary ovarian insufficiency
RIV	Recombinant influenza vaccine
RR	Relative risk/risk ratio
RV	Rotavirus vaccine
SCID	Severe combined immunodeficiency
SFN	Small fiber neuropathy

SGA	Small for gestational age
SAb	Spontaneous abortion
SSPE	Subacute sclerosing panencephalitis
SIDS	Sudden Infant Death Syndrome
SLE	Systemic lupus erythematosus
Th1	T helper type 1 cells
Tdap	Tetanus, Diphtheria and acellular Pertussis booster vaccine
TIV	Trivalent inactivated influenza vaccine
US	United States
VAERS	Vaccine Adverse Events Reporting System
VIP	Vaccine in Pregnancy Registry
VSD	Vaccine Safety Datalink
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System
VZV	Varicella zoster virus
WHO	World Health Organization

Introduction

Immunization is one of the most effective ways to prevent infectious diseases and their associated morbidity and mortality [13]. Vaccine coverage among children in the United States remains high [14]. However, vaccine hesitancy has emerged in recent decades as a threat to this high coverage [1-4], leading to the clustering of vaccine refusal and associated outbreaks of vaccine preventable diseases (VPDs) [5-11].

Most people in the U.S., including parents who are vaccine hesitant, rely on health care providers as their most frequently used and credible source for vaccine information [15-17]. To be confident in answering increasingly wide-ranging patient questions about vaccine safety, clinicians desire vaccine safety information which is evidence-based, objective, and provides clear guidance [18-23]. In particular, the first pregnancy is seen as a "teachable moment" – a key opportunity for clinicians to provide accurate information about both maternal and infant vaccinations to new parents – since one's vaccine attitudes and beliefs are often forming at this point as they are considering vaccines for themselves during pregnancy and considering vaccination of their child [24].

Both the Advisory Committee on Immunization Practices (ACIP) and the American College of Obstetricians and Gynecologists (ACOG) recommend that pregnant women are vaccinated against influenza and pertussis during pregnancy to best protect themselves and their infants [25-28]. Pregnant women are at increased risk of influenza morbidity and mortality [29-37]. Infants have the highest risk of complication, hospitalization and death from influenza and pertussis [38, 39], and are too young to complete the primary three dose series of pertussis vaccine or receive their

first influenza vaccine until six months of age [28, 40]. However, vaccination rates of pregnant women are suboptimal: 49% and 54% of pregnant women were vaccinated against influenza and pertussis during the 2017-18 season, respectively [12]. Additional strategies are needed to optimally protect infants against these diseases.

Most infants with pertussis were infected either by a parent or a relative in close contact with the infant [41-45]. The cocoon vaccination strategy entails vaccinating as many of the close contacts of the incoming newborn as possible, thereby lowering the risk of disease transmission and forming a protective "cocoon" around the infant. In tandem with maternal vaccination, cocooning is a method of further lowering the risk of potentially deadly pertussis and influenza infections in young infants [46-48].

Factors associated with higher rates of cocooning in the U.S. include high perceived benefits of vaccine, high perceived susceptibility to disease, and low perceived barriers to vaccination [49]. One potential intervention to influence perceived benefits of vaccine and susceptibility to disease is education. Another potential intervention that may be able to reduce perceived barriers to vaccination is the distribution of financial incentives.

As part of an NIH-funded large randomized controlled trial of a prenatal intervention to increase uptake of maternal and infant vaccines (referred to as P3+), we developed a patient-level application (called MomsTalkShots) for smartphones, tablets and computers that delivers patient-tailored education materials to pregnant women and collects patient-level survey data to monitor changes in their vaccine knowledge, attitudes and beliefs over time. As part of an add-on study sponsored by Walgreen Co., the MomsTalkShots app encouraged P3+ pregnant women to refer their close friends and family to the app so they could receive the patient-tailored education materials as well as a small financial incentive for receiving cocooning vaccinations at Walgreens.

This thesis includes three distinct manuscripts to be submitted for publication in scientific journals: a systematic review of vaccine safety; a thorough examination of the baseline vaccine intentions, knowledge, attitudes and beliefs of the pregnant women enrolled in P3+; and an analysis of the factors associated with these women referring their close friends and family to the MomsTalkShots app.

Research Questions and Hypotheses

The three distinct manuscripts included in this thesis are: a systematic review of a broad range of vaccine safety issues; a thorough examination of the baseline vaccine intentions, knowledge, attitudes and beliefs of the pregnant women enrolled in P3+; and an analysis of the factors associated with these women referring their close friends and family to the MomsTalkShots app. The primary and secondary research questions for each of these manuscripts is detailed below along with testable hypotheses and analysis plans when appropriate.

Manuscript 1: Systematic Literature Review of U.S. Vaccine Safety

Primary Research Question: Which adverse events following immunization (AEFI) have been shown to be caused by vaccines routinely administered to the general population in the United States based on the current evidence, and which have not?

Analysis Plan: systematic literature review.

Secondary Research Question: For those AEFI that are confirmed to be caused by vaccines, what is the risk attributable to vaccination?

Analysis Plan: systematic literature review.

Manuscript 2: Characterizing pregnant women's vaccine attitudes and beliefs

Primary Research Question: What are the baseline vaccine intentions, attitudes, beliefs, norms, and levels of trust among recently pregnant women in GA and CO?

Analysis Plan: univariate analysis.

Secondary Research Question 1: Do these intentions, attitudes, beliefs, norms, and levels of trust differ by state, ethnicity, education, and having prior children?

$H1_0$: Pregnant women's vaccine intentions, attitudes, beliefs, norms, and levels of trust do not differ by state, ethnicity, education, or having prior children.

$H1_A$: Pregnant women's vaccine intentions, attitudes, beliefs, norms, and levels of trust do differ by state, ethnicity, education, or having prior children.

Analysis Plan: stratified analysis using Pearson's chi-squared test for independence.

Secondary Research Question 2: Which attitudes, beliefs, norms, and levels of trust affect vaccine intentions?

$H1_0$: Pregnant women's vaccine attitudes, beliefs, norms, and levels of trust do not affect their vaccine intentions.

$H1_A$: Pregnant women's vaccine attitudes, beliefs, norms, and levels of trust do affect their vaccine intentions.

Analysis Plan: simple logistic regressions with dichotomous indicators for vaccine intentions as dependent variables and dichotomous or categorical indicators for attitudes, beliefs, norms, trust and number of specific vaccine safety concerns as independent variables.

Secondary Research Question 3: Which demographics, attitudes, beliefs, norms, and levels of trust are the best predictors of vaccine intentions?

$H1_0$: Pregnant women's demographics and vaccine attitudes, beliefs, norms, and levels of trust do not affect their vaccine intentions.

$H1_A$: Pregnant women's demographics and vaccine attitudes, beliefs, norms, and levels of trust do affect their vaccine intentions.

Analysis Plan: best-fit multiple logistic regression models created by backwards selection to include only those variables with statistical significance ($P<0.05$) in both the simple and multiple models. Dichotomous indicators for vaccine intentions used as dependent variables, and dichotomous or categorical indicators for demographics and vaccine attitudes, beliefs, norms, trust and number of specific vaccine safety concerns as independent variables.

Secondary Research Question 4: How many groups of pregnant women with distinct patterns of vaccine intentions, attitudes, beliefs, norms, and levels of trust can be identified, and how are they characterized?

$H1_0$: Pregnant women's vaccine intentions, attitudes, beliefs, norms, and levels of trust are best characterized by one homogenous group.

$H1_A$: Pregnant women's vaccine intentions, attitudes, beliefs, norms, and levels of trust are best characterized by multiple homogenous groups.

Analysis Plan: latent class analysis (using categorical indicators for vaccine intentions, attitudes, beliefs, norms, and trust) performed sequentially, increasing one group at a time, until the new model does not fit the data better than the last based on the Lo-Mendell-Rubin likelihood ratio test.

Manuscript 3: Factors associated with referring close contacts to an app with individually-tailored vaccine information

Primary Research Question: Which demographics and vaccine intentions, attitudes, beliefs, norms, and levels of trust are associated with higher likelihood of a pregnant woman referring friends and family to an educational app about vaccines?

$H1_0$: Pregnant women's demographics and vaccine attitudes, beliefs, norms, and levels of trust are not associated with likelihood of referring contacts to app.

$H1_A$: Pregnant women's demographics and vaccine attitudes, beliefs, norms, and levels of trust are associated with likelihood of referring contacts to app.

Analysis Plan: simple logistic regressions with a dichotomous indicator for referring contacts to app as the dependent variable and dichotomous or categorical indicators for demographics and vaccine intentions, attitudes, beliefs, norms, trust and number of specific vaccine safety concerns as independent variables.

Secondary Research Question 1: How many contacts were referred per pregnant woman, and of each type of relationship to the referring pregnant woman?

Analysis Plan: univariate analysis.

Secondary Research Question 2: Which types of contacts based on relationship to the referring pregnant woman are more likely to enroll in such an app upon invitation to do so?

$H1_0$: Contacts who enroll in app do not differ from contacts who do not enroll in app based on relationship to the referring pregnant woman.

$H1_A$: Contacts who enroll in app do differ from contacts who do not enroll in app based on relationship to the referring pregnant woman.

Analysis Plan: stratified analysis using Pearson's chi-squared test for independence.

Background and Significance

The Importance of Vaccines

Immunization is one of the most effective ways to prevent infectious diseases and their associated morbidity and mortality [13]. High vaccine coverage has succeeded in controlling or eliminating many vaccine-preventable diseases (VPDs) from the United States. The effectiveness of vaccinations is particularly evident when examining the morbidity and mortality from VPDs in the eras prior to vaccine introduction compared to the present day. The percent reduction in estimated annual average number of VPD cases comparing the pre-vaccine era to the 21st century has been calculated as 100% for diphtheria, 99.9% for measles, 95.9% for mumps, 92.2% for pertussis, 100% for poliomyelitis, 99.9% for rubella, 100% for smallpox, 92.9% for tetanus, 87% for hepatitis A, 80.1% for acute hepatitis B, ≥99.8% for Hib, 34.1% for invasive pneumococcal disease, and 85% for varicella. Similarly, the percent reduction in estimated annual average number of deaths from VPDs has been calculated as 100% for diphtheria, 100% for measles, 100% for mumps, 99.3% for pertussis, 100% for poliomyelitis, 100% for rubella, 100% for smallpox, 99.2% for tetanus, 86.9% for hepatitis A, 80.2% for acute hepatitis B, ≥99.5% for Hib, 25.4% for invasive pneumococcal disease, and 81.9% for varicella [50].

High vaccine coverage is crucial to preventing the spread of VPDs, especially as populations become denser and average frequency and distance of travel increase. This is because if enough people in a population are immune to an infectious disease, transmission of the disease is interrupted, and the disease can be eliminated from the population. This concept is commonly

known as “community protection”, “community immunity” or “herd immunity”. Each VPD has its own threshold for vaccine coverage required to interrupt transmission, depending primarily on the effectiveness of the vaccine and the contagiousness of the disease. For example, a highly contagious disease such as measles requires vaccine coverage of over 90% to have a chance at interruption of transmission, whereas less contagious diseases such as diphtheria and polio may only require 80-85% vaccine coverage [51, 52]. The safest way to ensure “community protection” from VPDs is to obtain the highest vaccine coverage possible. However, it is not enough to have high vaccine coverage on a national or state level; to be most effective, vaccine coverage also must be consistently high on a community level. Geographic clustering of unvaccinated and under-vaccinated persons interferes with interruption of disease transmission from otherwise high vaccine coverage [53-55], and has led to sustained outbreaks of VPDs such as pertussis and measles [56-59].

Vaccines have made an immense positive impact on the health of the world population and stand as one of the greatest achievements of biomedical science and public health to date [50]. Maintaining high coverage is essential to preventing VPDs [51, 52]. However, the importance of vaccination to individual and population health is not recognized by everyone, as evidenced by the phenomenon of vaccine hesitancy [1-4].

Vaccine Hesitancy

What is Vaccine Hesitancy?

Vaccine hesitancy has been defined in several ways. The Strategic Advisory Group of Experts (SAGE) on Immunization of the World Health Organization (WHO) defined vaccine hesitancy as a "delay in acceptance or refusal of vaccines despite availability of vaccinations services. Vaccine hesitancy is complex and context specific, varying across time, place, and vaccines. It is influenced by factors such as complacency, convenience, and confidence" [60]. Salmon et al. defined vaccine hesitancy as "concerns about the decision to vaccinate oneself or one's children" [24]. Larson et al. described the utility of the term "vaccine hesitancy" as "de-polarizing earlier attention to 'pro'- versus 'anti'-vaccination individuals and groups", and defined vaccine-hesitant individuals as "a heterogeneous group in the middle of a continuum ranging from total acceptors to complete refusers" [61]. Edwards et al. expanded upon this idea, stating: "vaccine-hesitant individuals may accept all vaccines but remain concerned about them, they may refuse or delay some vaccines but accept others, or they may refuse all vaccines" [62].

Measuring Vaccine Hesitancy and Refusal

Several tools to measure vaccine hesitancy have been developed and validated within the last decade, including most prominently the Vaccine Hesitancy Scale (VHS) created by SAGE [63-66] and the Parent Attitudes about Childhood Vaccines (PACV) scale developed by Opel et al. [67-71], among others [72-74]. However, these tools have so far only been used in isolated instances among non-representative study populations. To accurately assess changes in vaccine hesitancy in the U.S. over time, a nationally representative, serial cross-sectional survey using a validated measurement tool like those described above is needed [24].

Fluctuations in vaccine refusal in the U.S. over time is much easier to quantify than vaccine hesitancy due to the presence of mandatory vaccination requirements for school entry, as rates of exemptions from these requirements are recorded in each state.

From 1991 to 2004, the mean state-level rate of nonmedical exemptions in the U.S. increased from 0.98 to 1.48%. This was primarily due to an increase from 0.99 to 2.54% for states that allowed exemptions for philosophical or personal beliefs, as states that allowed only religious exemptions remained at approximately 1% during this period [6]. The rate of increase in nonmedical exemptions continued to increase between 2005 and 2013 before stabilizing in 2015-2016 [5, 7]. Exemptions for philosophical beliefs has risen since 2009 in 12 of the 18 states in which they are offered [75, 76]. A 2014 systematic review including 42 studies also concluded that exemption rates are rising, and that high rates of exemptions tend to occur in clusters [77]. Clustering of nonmedical vaccine exemptions has been shown to be associated with increased outbreaks of pertussis and measles [56-59].

Occasional changes in state laws can dramatically impact rates of nonmedical exemptions by making them easier or more difficult to obtain [78-81]. Easier exemption procedures have been shown to increase rates of exemptions, in turn increasing individual and community disease risk. Although most parents who obtained exemptions questioned the safety of vaccines, some did so simply out of convenience [77].

Nonmedical exemption rates capture the percentage of parents who refuse at least one vaccine required by state law for school entry; however, it does not distinguish between those who refuse one vaccine and those who refuse many vaccines. Only approximately 3% of U.S. parents refuse all vaccines, although this likely varies substantially geographically [62, 82, 83].

The Origins of Vaccine Hesitancy and Refusal

Vaccine hesitancy and refusal is as old as vaccines themselves. Perhaps even older; before the invention of vaccination, proponents of variolation (purposely infecting patients with smallpox material in such a way to cause a milder form of the disease than the dangerous natural infection typically did) faced resistance from critics who feared the benefits of the practice did not outweigh the harm it caused [84]. The first vaccine, which induced the even milder cowpox disease to its recipient in order to confer immunity against smallpox, became widespread in the United Kingdom in the early 1800s, was simultaneously met with great enthusiasm from some and great fear from others [85]. For example, Reverend Edmund Massey went as far as to call vaccines "diabolical operations" in his 1772 sermon entitled "The Dangerous and Sinful Practice of Inoculation", in which he also denounced vaccines as an attempt to bypass the punishments handed down by God for mankind's sins [86].

Despite early opposition, vaccination was such a revelation that the U.K. government enacted the Vaccination Act of 1840 to provide free vaccines to the poor and the Vaccination Act of 1853 to require vaccination for all infants within the first three months of life, holding parents liable to a fine or imprisonment if the law was disobeyed. The Vaccination Act of 1867 then extended the age range for required vaccination to 14 years and added further penalties for noncompliance [85, 87]. However, once vaccination was made compulsory by law, resistance grew even further, centered around the laws' infringements of personal freedom. Founding of the Anti-Vaccination League and the Anti-Compulsory Vaccination League occurred immediately after the 1853 and 1867 laws, respectively. Violent riots took place. Anti-vaccination messages grew, primarily in

the form of books and journals. As public pressure mounted, the English government finally passed a new Vaccination Act in 1898 to allow parents to obtain an exemption from penalties for non-compliance [85, 88-90].

As vaccination and mandatory vaccination laws spread to other countries in Europe and North America, so did the anti-vaccination movement [85, 91, 92]. The first U.S. state law mandating smallpox vaccination was passed in Massachusetts in 1809, and similar legislation soon spread to other states as well [93-95]. As more states passed and enforced mandatory vaccination laws, opposition rose and court battles over these laws became commonplace with some states even repealing their previously enacted laws [92, 93, 95]. The Anti-Vaccination Society of America was founded in 1879 [85, 92]. In 1905, the legality of mandatory vaccine laws was ruled upon in the U.S. Supreme Court in the case *Jacobson v. Massachusetts*, and the right of states to pass and enforce such laws was upheld [93].

The Modern Reemergence of the Anti-Vaccination Movement

Over a century after the beginnings of the anti-vaccination movement in the U.S., skepticism and fear of vaccines resurfaced dramatically in the public eye. In 1998, Andrew Wakefield, a gastroenterologist at the Royal Free Hospital in England, published a case series in the medical journal *The Lancet*. In this article he described 12 children with pervasive developmental disorder associated with gastrointestinal symptoms, 8 of whom had behavioral issues temporally associated with MMR vaccination via retrospective accounts by their parents or physicians [96]. Despite study authors acknowledging that this did not prove an association between the vaccine and autism,

the lead author went far beyond the paper's conclusions in a press release and ongoing interactions with the media [97, 98]. Public concern on the topic grew quickly. In 2010, Dr. Wakefield's license to practice medicine in the UK was revoked by the British General Medical Council and his study was retracted by *The Lancet* as evidence of serious professional misconduct mounted. Among other infractions, Wakefield was found to have ordered unnecessary invasive procedures on children without approval of the hospital ethics committee and received undeclared financial considerations from the Legal Aid Board, a group pursuing multiparty legal action for allegedly vaccine-damaged children [99-104]. In addition, he had applied for patents for vaccines to rival MMR vaccine. It was also revealed that, for most of the children in the original study, their symptoms either started well before or long after MMR vaccination. Despite the complete refutation of Wakefield's fraudulent findings by the scientific community, concern about autism and vaccines still exists among some parents; nationally representative data from 2010 indicate that about 30% of parents still have this concern [2].

As strong epidemiological evidence mounted that MMR vaccine was not associated with autism [105-118], some autism interest groups shifted their hypothesis from MMR vaccine to the belief that thimerosal, an ethylmercury-containing preservative that was present in some vaccines at the time, was causing autism in children. This theory was based upon observed similarities in some features of ASD and mercury poisoning [119]. As part of the Food and Drug Administration (FDA) Modernization Act of 1997, the FDA had conducted an analysis on exposure to mercury in children, leading them to examine the risk of thimerosal in vaccines. The FDA risk assessment determined that, when applying the methylmercury standard to ethylmercury (thimerosal), the vaccine thimerosal exposure was above EPA but not FDA or ATSDR guidelines [120]. Considerable uncertainty remained as the differences between ethyl and meth mercury were not

known and the guidelines were based on chronic rather than bolus exposure such as vaccines. Long term follow-up of children to evaluate the risk of mild neurologic effects from ethylmercury had not been conducted at that time. Because of the uncertainty in the risk assessment, as a precautionary measure thimerosal was removed as a preservative from most vaccines administered to children (small amounts of thimerosal are still present in multi-dose vials of influenza vaccine). The plausibility of this suspected association was later refuted by neurologists, and several large studies have documented that thimerosal was not associated with an increased risk of ASD [121].

Causes of Vaccine Hesitancy

A number of factors contribute to vaccine hesitancy. Vaccines are the victims of their own success; the more effective and widespread vaccines are, the less prominent VPDs are, and the less the general population is familiar with these VPDs. Most vaccines are given to healthy people to prevent disease instead of to sick people to treat disease like most medicine, thus the positive outcome of vaccinating (absence of disease) is less tangible than the reduction of existing symptoms from medication. Most healthy people (especially young children) get vaccinated at multiple timepoints throughout life, thus adverse health outcomes will coincidentally occur after vaccinations occasionally simply by chance. By human nature many people are susceptible to the logical fallacy “post hoc ergo propter hoc” (after this, therefore because of this), sometimes even if the scientific and medical community concludes otherwise [24]. Heuristics that impact risk perception, including a preference for errors of omission over errors of commission, lead some to miscalculate the risk of not vaccinating as less than vaccinating [122]. Trust is low in government agencies and the pharmaceutical industry, who mandate and manufacture vaccines, respectively

[16, 123, 124]. Other factors such as needle aversion and the rapid spread of misinformation via the internet may also contribute [10, 24]. To better understand how all these and other factors combine and interact to comprise vaccine hesitancy, data on vaccine intentions, attitudes and beliefs in a variety of populations has been collected and analyzed.

Surveys of Vaccine Intentions, Knowledge, Attitudes and Beliefs

Childhood and Adolescent Vaccines

There have been numerous individual surveys assessing attitudes and beliefs parents regarding childhood vaccines conducted since the turn of the century in the U.S. [2, 10, 15, 82, 125-138] and Canada [139-142] which show that although most parents believe vaccines to be important, safe and effective, concerns are very prevalent. A 1999 nationally representative telephone survey found that about 25% of parents of children under 6 years old believed their child's immune system could be weakened by too many vaccines and 23% believed that children get more immunizations than are good for them [125]. A 2009 nationally representative online survey found that 54% of parents were concerned about serious adverse effects of vaccines and 25% thought some vaccines cause autism in healthy children [133]. National data from the 2010 HealthStyles Panel found that 77% of parents reported having at least one concern about vaccines. Some of these reported concerns were relatively minor such as pain (38%) or fever (32%), but other concerns were much more serious, such as too many vaccines given at once (36%) or during the first two years of life (34%), autism (30%), unsafe ingredients (26%), and inadequate safety testing (17%) [2]. Nationally representative data on the prevalence of vaccine attitudes and beliefs are not available in the published literature since these 2010 HealthStyles data.

Many of the most recent surveys assessing vaccine attitudes and beliefs focus specifically on HPV vaccine, either from the viewpoint of parents [131, 143-161], young adults [162-171], or both [172]. These surveys illustrate the importance of a strong provider recommendation [143-145, 147,

151, 155, 159, 167] and parental vaccine knowledge/education [151, 152, 155] in increasing HPV vaccine uptake.

Numerous recent surveys have also demonstrated substantial differences in vaccine knowledge, attitudes and beliefs by gender, education, socioeconomic status, residence, ethnicity and race [133, 151, 159, 163, 166, 173-193]. For example, Hispanics and blacks are less likely to have heard of HPV and HPV vaccine than whites [163, 173]. Blacks are also less likely to vaccinate against HPV [177, 184, 187, 188] or to report trust in the flu vaccine [178, 192]. Although Hispanics are more likely to be concerned about series adverse effects of vaccines than whites, they are also more likely to follow their doctor's recommendation and vaccinate [133, 151, 185].

The vast majority of parents [16, 123, 129] cite health care providers as their most trusted source of vaccine information. In contrast, much lower levels of trust are reported in government and its associated agencies as well as in the pharmaceutical industry among those who express vaccine hesitancy compared to those who do not [16, 123, 124].

Maternal Vaccines

Recent surveys assessing attitudes and beliefs of pregnant women in the U.S. [49, 194-207] and Canada [22, 208-210] highlight the existing gaps in vaccine knowledge, attitudes, beliefs and intentions. Among 325 pregnant women in GA during the 2012-2013 season who had not yet received maternal vaccinations, most believed flu (75%) and whooping cough (81%) would be serious during pregnancy, and even more believed flu (87%) and whooping cough (92%) would be serious to their infants; however, less than half intended to receive maternal flu (34%) and Tdap

(44%) vaccines, perhaps partly due to low perceptions of safety of the vaccines during pregnancy (46%) [196].

Most parents primarily seek out vaccine information during and immediately after their first pregnancy [211-214]. In one study, about two-thirds of first-time pregnant women in their second trimester had not yet received information about childhood vaccines directly from their obstetrician/gynecologist (OB/GYN) or midwife, despite expressing interest in the topic [207]. This highlights the first pregnancy as a "teachable moment" – a key opportunity to provide accurate information about both maternal and childhood vaccinations – since one's vaccine attitudes and beliefs are being formed at this point as they are after making vaccine decisions for themselves and their infant [24]. The vast majority of pregnant women [22, 195, 198, 200, 202, 204, 208] also cite health care providers as their most trusted source of vaccine information, indicating that obstetricians and midwives are in a unique position to provide vaccine information to soon-to-be mothers and their partners who have not yet made firm vaccine decisions for themselves and their children.

Identifying Homogeneous Groups of Parents Based on Their Vaccine Intentions, Knowledge, Attitudes and Beliefs

Historically, vaccine attitudes were often looked at by researchers and medical professionals as dichotomous: either one was completely supportive of vaccines or one was "anti-vaccine" [215]. However, as more data on vaccine attitudes and beliefs was collected and examined, vaccine hesitancy began to be understood as a spectrum with more than just two contrasting viewpoints

[82, 134]. Gellin et al. analyzed data from a 1999 national telephone survey, of which three main (yet overlapping) subgroups of parents were identified: those who rated immunization as "extremely important" (87%), those who considered government or school requirements as the principal motivation for immunization (8%), and those who would choose to opt out of at least one immunization for their child (14%) [125]. Gust et al. performed a K-means clusters technique on data from 2002 HealthStyles and ConsumerStyles surveys and identified five homogeneous groups of parents: Immunization Advocates (33.0%), Go Along to Get Alongs (26.4%), Health Advocates (24.8%), Fencesitters (13.2%), and Worrieds (2.6%) [134]. Benin et al. used grounded theory to analyze qualitative data from open-ended interviews of 33 postpartum mothers in 2002-2003, and identified two main groups, each with two subgroups: Vaccinators (subgroups: accepters and vaccine-hesitant) and NonVaccinators (subgroups: late vaccinators and rejecters) [216]. Downs et al. used a mental models approach to analyze qualitative data from open-ended interviews of 30 parents recruited from three cities providing diversity in race, background, and vaccination attitudes, and identified two main vaccine decision making types: health oriented (trusting anecdotal information more than statistical) and risk oriented (trusting statistical information more than anecdotal). Smith et al. analyzed data of over 11,000 parents of young children from the 2009 National Immunization Survey (NIS) and categorized parents as neither delaying nor refusing vaccines (60%), only delaying one or more vaccines (26%), only refusing one or more vaccines (8%), and both delaying and refusing vaccines (6%) [217]. Leask et al. used a literature review to identify five distinct parental groups as part of a framework for health professionals: the "unquestioning acceptor" (30–40%), the "cautious acceptor" (25–35%), the "hesitant" (20–30%), the "late or selective vaccinator" (2–27%), and the "refuser" of all vaccines (<2%) [83]. Weiss et al. performed a latent class analysis (LCA) on 14 5-point Likert scale belief statements from 189

questionnaires completed by Swiss mothers living in the Aargau region and identified three latent classes: positive attitudes (58%), fearful/uncertain attitudes (28%), and critical attitudes (14%) [218].

Providers Need Better and More Accessible Vaccine Safety Information

Most patients and parents, including parents who are vaccine hesitant, rely on health care providers as their most frequently used and credible source for vaccine information [15-17]. Providers need information on a broad range of vaccine safety issues to be confident in answering patient questions about vaccine safety as those questions become more specific, complex and wide-ranging. Clinicians desire vaccine safety information which is evidence-based, objective, and provides clear guidance on whether or not vaccines cause specific adverse event following immunization (AEFI), and the risk for AEFI that caused by vaccines [18-23].

Websites that include reliable sources of vaccine safety information for providers include the Centers for Disease Control and Prevention (CDC) [219, 220], the American Academy of Pediatrics, the Food and Drug Administration, and the Immunization Action Coalition [221]. However, much of the information available is not based on systematic comprehensive reviews and lacks clear statements on causality. The most comprehensive source of vaccine safety information available to date is the independent 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), entitled *Adverse Effects of Vaccines: Evidence and Causality,* [222] which builds on previous vaccine safety reports from the IOM [113, 114, 223-225]. These extraordinarily comprehensive reviews were conducted at the request of the Department of Health and Human Services (HHS) and its agencies, for the primary purpose of updating the National Vaccine Injury Compensation Program [226]. Final products from these committees are books; they are neither succinct nor readily available to clinicians. In the 2012 report, the IOM concluded that the evidence is inadequate to accept or reject a causal relationship for 135 of 158 (85%) of vaccine-AEFI relationships studied. The 2014 report by the Agency for

Healthcare Research and Quality (AHRQ) entitled *Safety of Vaccines Used for Routine Immunization in the United States: Evidence Report/Technology Assessment No. 215* [117, 227], was intended to expand upon and update the 2012 IOM report and was commissioned by HHS for the purpose of developing a federal vaccine safety research agenda. While these reports are useful for policy makers and vaccine safety scientists, they were not designed specifically for use by clinicians, and their length, writing style, and framing of causality assessments do not translate well to the practicing clinician. In addition, the IOM and AHRQ reports do not cover all AEFIs of current interest and many assessments are now out of date due to evidence emerging since their publications. An updated and comprehensive systematic literature review of vaccine safety tailored for provider needs is presented in Manuscript 1.

Vaccines Recommended During Childhood

The Advisory Committee on Immunization Practices (ACIP), a committee of 15 experts which advises the Centers for Disease Control and Prevention (CDC) on vaccine practice, issues comprehensive statements on the recommended use of individual vaccines, including information on the burden of the disease the vaccine prevents, vaccine effectiveness, vaccine safety, indications, precautions, contraindications, and other critical information. Most relevant information is also provided in the CDC textbook entitled Epidemiology and Prevention of Vaccine-Preventable Diseases, also known as the "Pink Book" [40]. The CDC also reports vaccination coverage data via its VaxView websites. This information is summarized below for each vaccine recommended during childhood.

The ACIP individual vaccine recommendations can be accessed at the following website: http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. The CDC's Recommended Immunization Schedule for Children and Adolescents can be accessed at the following website: https://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html. The Pink Book can be accessed at the following website: http://www.cdc.gov/ vaccines/pubs/pinkbook/index.html. The CDC's VaxView websites can be accessed at the following link: https://www.cdc.gov/vaccines/vaxview/index.html.

Haemophilus influenzae type b (Hib)

Hib Disease

Haemophilus influenzae is an aerobic gram-negative coccobacillus bacterium with encapsulated typeable strains and unencapsulated nontypeable strains. There are six serotypes of encapsulated Hib, identified by their antigenically and biochemically distinct polysaccharide capsules. Serotype b (Hib) was responsible for 95% of *Haemophilus influenzae* disease prior to vaccine introduction. Hib generally enters the body via respiratory droplets through the nasopharynx but can cause conjunctivitis or cellulitis from entry via the skin. Bacteremia occurs when Hib organisms invade the bloodstream and cause infection elsewhere. The most common clinical feature of invasive Hib disease is meningitis, which can then lead to residual hearing impairment, neurologic sequelae, or even death. Fatality rates range from 3%-6% for Hib meningitis, even despite appropriate antimicrobial therapy. Invasive Hib disease accounted for 50-65% of cases of bacterial meningitis prior to introduction of Hib vaccine. Other clinical features of Hib disease include otitis media, epiglottitis, pneumonia, septic arthritis, cellulitis, osteomyelitis, and bacteremia. Hib disease is uncommon after 5 years of age, presumably due to acquisition of immunity either from asymptomatic Hib infection or from exposure to other organisms with antigenic structures resembling the capsule of Hib (i.e. cross protection). Incidence of Hib has decreased by over 99% since the introduction of Hib vaccines [40].

Hib Vaccine

There are two conjugate *Haemophilus influenzae* type b (Hib) vaccines used in the United States: PRP-OMP (trade name: PedvaxHIB®) and PRP-T (trade names: ActHIB®, Hiberix®; also included in the DTaP-Hib-IPV combination vaccine Pentacel®). Hib polysaccharide is chemically

bound to a non-Hib protein carrier, creating a more effective antigen and therefore stimulating a better immune response, particularly in infants, than with the plain polysaccharide. PRP-OMP uses meningococcal group B outer membrane protein, and PRP-T uses tetanus toxoid protein.

ACIP Recommendations

The ACIP recommends that all infants without contraindications should receive the conjugate Hib vaccine series; either as 3 doses of PRP-OMP, or as 4 doses of PRP-T. Doses of Hib vaccine should be given at least 4 weeks apart, with the first dose administered at a minimum of 6 weeks of age. Doses are generally recommended to be given at 2 and 4 months of age, and for the PRP-T vaccines, 6 months of age as well. A booster dose should then be given a minimum of 8 weeks after the previous dose, generally between 12-15 months of age [40, 228, 229]. Although Hib vaccine is generally not recommended for those over 59 months of age, there are exceptions for certain persons at increased risk; for example, previously unimmunized asplenic patients should receive one dose of Hib vaccine, and recipients of a hematopoietic cell transplant should be given the full three-dose series beginning 6-12 months after the transplant regardless of their vaccination history [229].

The Hib-MenCY-TT combination vaccine MenHibrix® was discontinued in the United States in 2016 [230]. The Hib-Hep B combination vaccine Comvax® was discontinued in the United States in 2014 [231].

Vaccine Coverage

Hib vaccine coverage in 2017 among children aged 19-35 months was estimated at 92.8% (95%CI: 91.9–93.6%) for the primary series and 80.7% (95%CI: 79.4–82.0%) for the full series. This is relatively consistent with the level of coverage seen over the past five years [14].

Contraindications and Precautions

Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component is a contraindication to further Hib vaccination. Current moderate to severe acute illness is a precaution to any vaccination [40].

Vaccine Effectiveness

Hib vaccines are very immunogenic in infants. Over 95% of primary series recipients develop immunity, and clinical efficacy has been estimated at 95-100% [40].

Vaccine Safety

Minor local reactions such as pain, redness or swelling occur in approximately 5-30% of Hib vaccine recipients and usually resolve within a day or two. Systemic reactions such as irritability and fever are infrequent, and serious adverse reactions are rare [40].

Hepatitis A

Hepatitis A Disease

Hepatitis A Virus (HAV) is a nonenveloped RNA picornavirus that enters the body through the mouth via the fecal-oral route of transmission and replicates in the liver. Infected persons excrete virus beginning 10-12 days after infection and continuing up to 3 weeks after appearance of symptoms. The incubation period of HAV ranges from 15 to 50 days. Common symptoms are generalizable to all acute viral hepatitis disease, such as fever, malaise, nausea, anorexia, jaundice and dark urine, and generally persist no more than 2 months, although relapses may occur. About 70% of infections in children under 6 years of age are asymptomatic. Rarely, infection results in fulminant hepatitis, a severe complication with mortality rates estimated to be up to 80% [40].

Hepatitis A Vaccine

Hepatitis A vaccines are aluminum hydroxide-adjuvanted formalin-inactivated whole virus vaccines. There are two hepatitis A vaccines used in the United States: Havrix®, which is prepared with the preservative 2-phenoxyethanol, and Vaqta®, which does not contain a preservative. These vaccines are available in pediatric and adult formulations. There is also a hepatitis A-hepatitis B combination vaccine (trade name: Twinrix®) that is approved for use in persons over 18 years of age with an indication for both hepatitis A and hepatitis B vaccine. This vaccine should be administered according to the recommended schedule for hepatitis B vaccine in this age group [40].

ACIP Recommendations

The ACIP recommends all infants without contraindications should receive two doses of hepatitis A vaccine between 12-23 months of age. Doses should be given at least 6 months apart. Infants

between 6-11 months of age traveling internationally to countries with high or intermediate endemicity should also receive hepatitis A vaccine. Such children should still receive hepatitis vaccine between 12-23 months of age as normally recommended. Older children and adults without contraindications who are at increased risk of hepatitis A infection (such as international travelers to countries with high or intermediate endemicity; men who have sex with men; illegal drug users; contacts of recent international adoptees from countries endemic with hepatitis A virus; persons working with hepatitis A-infected primates; and those with a clotting factor disorder) as well as persons at risk of severe complications from hepatitis A infection (such as those with chronic liver disease) should also be routinely vaccinated. Hepatitis A vaccine is also now recommended for post-exposure prophylaxis for all persons age one year and older [40, 232, 233].

Vaccine Coverage

Hepatitis A vaccine coverage in 2017 among children aged 19-35 months was estimated at 86.0% (95%CI: 84.8–87.1%) for at least one dose and 59.7% (95%CI: 58.2–61.3%) for at least two doses. Coverage appears to have increased slightly since 2013 (83.1% for at least one dose and 54.7% for at least two doses) [14].

Contraindications and Precautions

Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component is a contraindication to further vaccination with hepatitis A vaccine. Current moderate to severe acute illness is a precaution to any vaccination [40].

Vaccine Effectiveness

Hepatitis A vaccines are very immunogenic. Over 95% of adults and 97% of children and adolescents develop immunity within a month of the first dose of vaccine, and 96-100% of children

and adults develop immunity after the second dose. In clinical trials, vaccine efficacy of Havrix® was estimated to be 94% and Vaqta® estimated to be 100% [40].

Vaccine Safety

Self-limited, minor local reactions such as pain, redness or swelling are reported in approximately 20-50% of vaccine recipients. Mild systemic reactions such as fatigue, malaise and low-grade fever are reported in less than 10%. Besides very rare occurrences of anaphylaxis, no serious adverse events have been shown to be caused by to hepatitis A vaccination. Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component is a contraindication to further hepatitis A vaccination [40].

Hepatitis B

Hepatitis B Disease

Hepatitis B Virus (HBV) is a small, double-shelled DNA virus in the *Hepadnaviridae* family. HBV is transmitted via mucosal exposure to infected body fluids, often during birth, sexual contact, via blood or blood exposure, needlesticks, or injection drug use [40]. It is highly infectious to susceptible individuals exposed in these manners. Thirty percent of infected individuals in the US have no known exposures [234, 235]. The incubation period averages 120 days. Approximately 90% of infants and 50% of adult infections are asymptomatic, and when there are symptoms, they are indistinguishable from those of other types of acute viral hepatitis. Initial symptoms include malaise, anorexia, nausea, vomiting, fever, headache, myalgia, arthralgia, arthritis and dark urine. Further symptoms such as jaundice, light or gray stools, hepatic tenderness and hepatomegaly typically last 1-3 weeks, and begin 3-10 days after the onset of most initial symptoms (1-2 days following the onset of dark urine). Most acute HBV infections result in complete recovery; however, 1-2% of cases result in fulminant hepatitis, which has a case-fatality rate of 63-93% and causes roughly 200-300 deaths in the United States annually. Up to 90% of infants infected at birth by their mothers become chronically infected, and about 25% of those chronically infected will die from cirrhosis or liver cancer. This risk of chronic infection decreases with age, to about 5% of acute infections in adults become chronic. Chronic infection is often asymptomatic until complications develop [40].

Hepatitis B Vaccine

Hepatitis B vaccines are yeast-derived recombinant vaccines containing HBsAg protein. There are three hepatitis B vaccines used in the United States: Recombivax HB®, which is adjuvanted with

aluminum hydroxyphosphate sulfate; Engerix-B®, which is adjuvanted with aluminum hydroxide; and HEPLISAV-B™, which is adjuvanted with cytosine phosphoguanine (CpG) 1018. Engerix-B® and Recombivax HB® are approved for use in all ages. HEPLISAV-B™ is only approved for use in persons aged 18 years and older, administered as two doses (0.5 mL each) given one month apart [40, 236].

There are also several combination vaccines that include hepatitis B vaccine. Hep A-Hep B (Twinrix®) is approved for use in persons over 18 years of age, administered in a three-dose series at 0, 1 and 6 months. DTaP-Hep B-IPV (Pediarix®) is approved for use at 2, 4 and 6 months of age. Pediarix® cannot be used before 6 weeks of age, but can be substituted for doses 2 or 3 of hepatitis B vaccine. Infants may also receive a fourth dose of hepatitis B vaccine as part of a combination vaccine schedule [40].

The Hib-Hep B combination vaccine Comvax® was discontinued in the United States in 2014 [231].

ACIP Recommendations

The ACIP recommends that all medically stable infants weighing ≥2,000 grams without contraindications should receive the first dose of hepatitis B vaccine within 24 hours of birth. Certain infants at increased risk of acquisition of hepatitis B, such as infants born to hepatitis B-infected mothers or mothers with unknown status, should receive hepatitis B vaccine as soon as possible after birth along with a dose of hepatitis B immune globulin. The second dose should be administered a minimum of 4 weeks after the first dose and between 1-2 months of age. The third dose should be administered a minimum of 8 weeks after the second and 16 weeks after the first, between 6-18 months of age. All children not previously vaccinated should receive the age-appropriate dose of hepatitis b vaccine, preferably at 11 or 12 years but up to 18 years of age. The

usual schedule for adolescents is two doses separated by no less than 4 weeks, and a third dose at least 8 weeks from the second dose and 16 weeks from the first dose, and preferably 4 to 6 months after the second dose. An approved alternative schedule for adolescents 11 to 15 years of age is two 1.0-mL doses of the Recombivax HB® vaccine separated by 4 to 6 months [40, 236-239].

Vaccine Coverage

Hepatitis B vaccine coverage in 2017 among children aged 19-35 months was estimated at 91.4% (95%CI: 90.5–92.3%) for at least three doses and 73.6% (95%CI: 72.0–75.2%) for the birth dose. This is relatively consistent with the level of coverage seen over the past five years [14].

Contraindications and Precautions

Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component is a contraindication to further vaccination with hepatitis B vaccine. Current moderate to severe acute illness is a precaution to any vaccination [40].

Vaccine Effectiveness

Over 90% of adults and 95% of children develop protective antibody responses after three doses of Recombivax HB® or Engerix-B®. These vaccines are $\geq$ 95% effective at preventing clinical disease and the chronic carrier state after infection, and estimated to be 80-100% effective in preventing hepatitis B infections after completion of the series. Although antibody levels decline, immunologic memory induced from vaccination persists and serologic responders have been shown to be protective for at least 20 years. Follow-up studies of infants vaccinated at birth have revealed that many adolescents do not develop an anamnestic response (i.e. renewed rapid antibody production on a subsequent encounter with the same antigen) to a booster dose of vaccine, but there is no evidence of an increased rate of breakthrough disease and no routine booster dose has been recommended [40].

Studies of HEPLISAV-B™ have so far demonstrated high rates of seroprotection (90.0-100.0% of HEPLISAV-B™ recipients versus 70.5-90.2% of subjects in comparison group) [236].

Vaccine Safety

Anaphylaxis occurs approximately once per every 1.1 million doses of hepatitis B vaccine administered. Alopecia has been suggested to be rarely associated with hepatitis B vaccination. No causal association between any chronic illnesses and hepatitis B vaccine have been shown [40].

Post-licensure safety studies will be carried out by the manufacturer and CDC independently to monitor the safety of the new vaccine HEPLISAV-B™ [236].

Human Papillomavirus (HPV)

HPV Disease

HPV is a small DNA virus that is transmitted by direct contact with an infected person. Over 120 types of HPV have been identified, about 80 of which infect nonmucosal epithelium and 40 of which infect the mucosal and genital epithelium. Infection with one HPV type does not necessarily prevent later infection with another type.

Genital HPV infection is generally transmitted via direct sexual contact but can rarely be transmitted by nonsexual routes. Risk of transmission is reduced but not eliminated by using physical barriers such as condoms. HPV is the most common sexually transmitted infection in the U.S., with an estimated 79 million persons currently infected. 14 million new infections are estimated to occur each year, about half of which are in persons 15-24 years old. HPV infection often occurs very soon after onset of sexual activity, further illuminating the need for vaccination well prior to the onset of sexual activity. Infected mothers can transmit HPV to their infants during childbirth resulting in juvenile onset recurrent respiratory papillomatosis. Onset can occur at up to 18 years of age [240].

Although HPV infection is quite common, most infections are asymptomatic and resolve spontaneously. Possible clinical manifestations include anogenital warts, recurrent respiratory papillomatosis, cervical intraepithelial neoplasia (CIN), and cancer [40]. High-risk HPV types, including types 16, 18, 31, 45 and others, can cause high-grade cervical lesions and cancer, as well as vulvar, vaginal, penile, anal, and oropharyngeal cancers. HPV has been detected in 99% of cervical cancers (of which 70% are types 16 and 18), as well as 70% of vulvar and vaginal cancers (49-55% type 16), 91% of anal cancers (77% type 16), 72% of oropharyngeal cancer (61% type

16), and 40-50% of penile cancers [240]. Infection with several low-risk HPV types (such as types 6 and 11) can cause low-grade cervical cell abnormalities, anogenital warts, and laryngeal papillomas [40]. In the U.S. between 2006 and 2010, an average of 33,160 HPV-associated cancers were diagnosed annually, 62% were among females and 38% among males. Of these, cervical and oropharyngeal cancers were the most common, with an estimated 10,400 cervical cancers and 9,000 oropharyngeal cancers (80% of which were in men) diagnosed annually [240].

HPV Vaccine

HPV vaccines are subunit vaccines using a recombinant HPV L1 major capsid protein as the vaccine antigen. These L1 proteins self-assemble into virus-like particles (VLP), which are both noninfectious and nononcogenic [40]. HPV vaccines include bivalent (abbreviation: 2vHPV; trade name: Cervarix®), quadrivalent (4vHPV; Gardasil®), and 9-valent (9vHPV; Gardasil 9®) vaccines. However, as of 2018, only 9vHPV is being distributed in the U.S. 9vHPV includes HPV types 16, 18, 6, 11, 31, 33, 45, 52, and 58 [241].

ACIP Recommendations

The ACIP recommends that all males and females without contraindications ages 11-12 years should receive two doses of HPV vaccine administered 6-12 months apart. Vaccination can be started as young as 9 years of age. Those who start the series after the age of 15 should receive three doses of HPV vaccine, with the second and third doses administered 1-2 months and 6 months after the first dose, respectively. If not previously vaccinated, catch-up vaccination is recommended for all males through age 21 and females through age 26. Males ages 22-26 years may also be vaccinated. If doses are delayed there is no need to repeat doses since increasing the interval between doses is generally associated with enhanced immune responses [40, 241].

Vaccine Coverage

HPV vaccine coverage among adolescents in 2017 was estimated at 65.5% (95%CI: 64.3–66.7%) for at least one dose. Coverage was higher among females (68.6%) than males (62.6%) [242].

Contraindications and Precautions

Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component is a contraindication to further HPV vaccination. 2vHPV is contraindicated for persons with anaphylactic latex allergy. 4vHPV and 9vHPV are contraindicated for persons with a history of immediate hypersensitivity to yeast. HPV vaccination is not recommended during pregnancy. Current moderate to severe acute illness is a precaution to any vaccination [40, 241, 243].

Vaccine Effectiveness

HPV vaccines are very immunogenic, with at least 97.9% of vaccine recipients developing antibody responses to all the types included in their respective vaccines after completing the two-dose series. Estimates of efficacy against cervical intraepithelial neoplasia (CIN) after three doses have ranged from 93-97%, depending on the vaccine. 4vHPV efficacy against genital warts related to vaccine types after three doses was shown to be 99% in women and 88% in men. Studies comparing two doses to three doses and 9vHPV to 4vHPV have shown noninferior immunogenicity [40, 241, 243].

Vaccine Safety

Mild local reactions such as pain and swelling are the most common adverse reactions following HPV vaccination, reported in 20-90% of recipients [40]. Because syncope has been reported among adolescents receiving vaccinations, adolescent recipients should always receive the vaccine while sitting and not in view of others awaiting vaccination, and be observed for up to 15 minutes immediately after vaccination [244-247].

HPV vaccines are among the most rigorously studied vaccines for safety; except for very rare occurrences of anaphylaxis, no serious adverse events have been associated with HPV vaccination. Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component is a contraindication to further HPV vaccination [40].

Receiving HPV vaccine at the recommended ages does not increase likelihood of sexual activity [248], nor does it influence fertility [249].

Influenza

Influenza Disease

Influenza is caused by RNA viruses of three types. Type A influenza is the cause of most human illness and has many subtypes based on the variations in the surface antigens (i.e., hemagglutinin (H) and neuraminidase (N)), such as H1N1 or H3N2. Type B influenza also infects humans but generally causes milder illness. Type C only very rarely causes human disease [35, 40, 250].

The surface antigens on influenza viruses are always evolving, faster than most other viruses that cause human disease. This continuous stream of minor mutations is called antigenic drift and is what makes influenza so adept at evading immunity induced by prior infection or vaccination. In most years, at least some of the circulating influenza strains have drifted compared to prior years, thus even those who were infected or vaccinated in years prior may develop influenza disease again [35, 40, 250, 251].

Occasionally a major change in one or both surface antigens occurs, known as antigenic shift; the majority of the population is usually susceptible to the new virus. The new strains generated in this manner, such as the 2009 influenza A H1N1, have the potential to cause a worldwide pandemic [35, 40, 250, 251].

Influenza circulates throughout the United States seasonally every year, typically starting in late fall and remaining through spring [28, 30-32, 252-254]. The incubation period for influenza is generally 1-2 days [35, 40]. The major clinical symptoms typically last a median of 4 days without treatment and include sore throat, fever, headache, myalgia, and nonproductive cough [40, 255].

Pneumonia is the most common complication of influenza. Other complications include Reye syndrome and myocarditis [40, 255].

Most people infected with influenza recover without sequelae. However, influenza is capable of causing serious illness and death, especially in high risk groups such as older adults, young children, pregnant women, and people with certain medical conditions [28, 30-32, 35, 252-254]. The CDC estimated an average of 23,607 annual influenza-associated deaths in the United States between 1976 and 2007, although these estimates ranged widely from year to year [256]. Studies have also estimated an average of approximately 130,000 annual influenza-associated hospitalizations in the United States [257, 258]. There was an average of 113 annual pediatric deaths from influenza in the United States between 2010 and 2016, and about half of these were in children with no preexisting medical condition [259]. During the 2016-2017 U.S. influenza season, there were 18,256 laboratory-confirmed influenza-associated hospitalizations, which equates to a rate of 65.2 hospitalizations per 100,000 people (as of May 20, 2017). There were also 110 influenza-associated pediatric deaths [260].

Influenza Vaccine

Two types of vaccines are available to protect against influenza: inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV). LAIV (trade name: FluMist®) was not recommended for use during the 2016-2017 or 2017-2018 flu seasons due to problems with low effectiveness during the previous several seasons, but is again an option for the 2018-2019 season for non-pregnant persons 2-49 years of age for whom it is otherwise appropriate [261]. LAIV is administered intranasally using a single dose sprayer containing 0.2 mL, with about half (0.1 mL) sprayed in each nostril [40, 261, 262]. In the United States, quadrivalent IIV (IIV4) vaccines include Fluarix® Quadrivalent, FluLaval® Quadrivalent, and Fluzone® Quadrivalent; trivalent

IIV (IIV3) include Afluria®, Fluvirin®, and Fluzone®. There are two recombinant influenza vaccines, Flublok® (RIV3) and Flublok® Quadrivalent (RIV4). Trivalent vaccines contain one A/H3N2 strain, one A/H1N1 strain, and one B strain from one of the two B lineages (Yamagata and Victoria). The Quadrivalent vaccines contain a second B strain [40, 262]. The Food and Drug Administration (FDA) has recommended that the trivalent influenza vaccines used in the United States during the 2018-19 season contain an A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, and a B/Colorado/06/2017-like (B/Victoria lineage) virus; and that the quadrivalent vaccines also contain a B/Phuket/3073/2013-like (B/Yamagata lineage) virus [263].

ACIP Recommendations

The ACIP recommends all persons without contraindications who are 6 months of age and older receive annual vaccination with influenza vaccine. IIV is recommended for all age groups and during pregnancy [262]. LAIV is also an option for non-pregnant persons between 2 and 49 years of age [261]. Influenza vaccine should be given as soon as it becomes available (usually between August and October in the U.S.) in order to ensure the highest possible level of protection before rates of transmission increase. Peak transmission season is usually between December and March in the United States [40]. Children less than 9 years of age receiving IIV for the first time ever should receive two doses at least one month apart; otherwise, one dose per year is sufficient [262].

Vaccine Coverage

Seasonal influenza vaccine coverage in children between 6 months and 17 years old in the United States was reported at 57.9% for the 2017-2018 flu season. Coverage increased incrementally each year between the 2009-2010 (43.7%) and 2014-2015 (59.3%) seasons before plateauing in recent years. Seasonal influenza vaccine coverage in adults in the United States was reported at 37.1%

for the 2017-2018 flu season, the lowest mark of the last decade. Prior to this, adult coverage had remained between 38.8% and 43.6% since the 2009-2010 flu season [264].

Influenza vaccine has been shown to be capable of inducing community protection (herd immunity) [265-267], but higher coverage rates are needed to fully realize the benefits of such protection [268].

Contraindications and Precautions

An important contraindication is having had a severe allergic reaction (e.g. anaphylaxis) to a vaccine component or previous vaccination. However, this does not include egg allergies, even though most influenza vaccines are grown in embryonated chicken eggs (an exception being the egg-free recombinant influenza vaccine, Flublok®) [262]. This is because the vaccines marketed in the United States have been found to contain extremely small amounts or undetectable amounts of egg protein and recent studies have indicated that egg allergic patients can safely receive influenza vaccines [269, 270]. The ACIP recommends that persons with a severe egg allergy (who have had associated angioedema, respiratory distress, lightheadedness, or recurrent emesis, or who required epinephrine or another emergency medical intervention following egg ingestion) can receive these vaccines, but the vaccine should be administered in an inpatient or outpatient medical setting [262]. However, the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American Academy of Pediatrics (AAP) do not recommend any special precaution because there does not appear to be any increased risk of severe allergic reactions to these vaccines in persons with egg allergy [271, 272].

Precautions include moderate to severe acute illness with or without fever, as well as a diagnosis of Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of influenza vaccine [262].

Vaccine Effectiveness

The effectiveness of influenza vaccines varies each year in relation to the match between the vaccine strains and the circulating strain. Effectiveness can also vary by the age and health status of the vaccine recipient [40]. Effectiveness has been shown to decline significantly over the first six months post-vaccination, albeit at different rates depending on the vaccine [273-275]. However, even in years when the vaccine has a lower effectiveness relative to other years, receiving the vaccine still reduces risk of infection, severe illness, hospitalization, and death due to influenza. In addition, high vaccine coverage prevents disease transmission and helps to protect those most vulnerable to serious influenza illness [276].

Vaccine Safety

Common adverse reactions to IIV include local reactions such as soreness, erythema and induration at the injection site, which are reported at variable rates, but are usually mild and typically last no more than 2 days. Systemic symptoms such as sensation of fever, chills, malaise, and myalgia are also common. These symptoms typically begin within 6–12 hours of vaccination and usually last for only a few hours. Such symptoms are usually mild but have been reported in 4-<30% of children receiving IIV [277-283]. Myalgia within a week of vaccination has been reported among 14-16% of adults receiving unadjuvanted IIV and 31-39% of adults receiving adjuvanted IIV [284], with even higher rates among recipients of the 2009 pandemic H1N1 vaccine [285].

Rarely, allergic reactions such as hives, angioedema, allergic asthma, or systemic anaphylaxis occur after vaccination, probably due to hypersensitivity to a vaccine component.

Influenza vaccination in recent years has been associated with a very small increased risk of GBS in adults, leading to about 1-3 excess cases of GBS per million persons vaccinated. This is much

less than the estimated risk after wild-type influenza infection, providing further evidence that the benefits of influenza vaccination greatly outweigh the risks [286, 287].

IIV cannot cause influenza, as all viruses contained in the vaccine are inactivated and noninfectious [288]. LAIV also cannot cause influenza as it is made from weakened flu virus [289].

Measles, Mumps and Rubella

Measles, Mumps and Rubella Disease

Measles is a highly contagious acute disease caused by an RNA paramyxovirus, genus *Morbillivirus*, with one antigenic type. Measles is transmitted via the respiratory route and secondary attack rates in families among susceptible persons are often greater than 90%. Measles virus can survive up to 2 hours in air or on surfaces. The average incubation period of 10-12 days is followed by cough, runny nose, and stepwise increase in fever up to 103-105°F. A maculopapular rash begins on the face and head a few days after onset of respiratory symptoms and persists for 5-6 days. Common complications include diarrhea, otitis media, and pneumonia, and rare complications include encephalitis, seizures, and death. Measles illness during pregnancy increases the risk of premature labor, low-birthweight children, spontaneous abortion, as well as pneumonia and encephalitis [40].

Mumps is caused by an RNA paramyxovirus with one antigenic type and is acquired through respiratory transmission. The incubation period is 12-25 days. Symptoms are generally nonspecific at first, including myalgia, malaise, headache, and fever. Approximately one-third of mumps infections are asymptomatic; however, asymptomatic persons can transmit the virus. Possible complications of mumps infection include parotitis, orchitis, oophoritis, deafness, meningitis, encephalitis, and pancreatitis [40].

Rubella, also known as “German measles”, is caused by an RNA togavirus, genus *Rubivirus*, with one antigenic type. Rubella is acquired through respiratory transmission and the incubation period is about 14 days. Symptoms include mild fever and malaise; up to 50% of cases are subclinical. A maculopapular rash lasting about 3 days generally occurs 14 to 17 days after infection, beginning

on the face and spreading downwards. This rash is usually fainter than the measles rash, and does not coalesce. Arthralgia and arthritis are common after puberty, especially in females [40]. Among pregnant women who are infected with wild-type rubella virus, transplacental infection of the fetus can occur, causing congenital defects or stillbirth [40, 290].

Measles, Mumps and Rubella Vaccine

Measles, mumps and rubella vaccines are all live attenuated viral vaccines that are only available in combination as MMR (trade name: M-M-R II®) in the United States. The MMRV vaccine (trade name: ProQuad®) also includes varicella vaccine [40].

ACIP Recommendations

The ACIP recommends that all children without contraindications should receive two doses of measles-mumps-rubella combination vaccine after 1 year of age and at least 4 weeks apart. The first dose is usually administered at a minimum of 12 months of age, and is generally given between 12 and 15 months of age. The second dose is usually given between 4 and 6 years of age, prior to entering school, although it can be given anytime at least 4 weeks after the first dose for children at increased risk of exposure. The CDC recommends that MMR and varicella vaccine be administered separately for the first dose in order to reduce the small increased risk of febrile seizures in toddlers associated with the measles-mumps-rubella-varicella combination vaccine compared to the separate but simultaneous administration of MMR and varicella vaccines. MMRV is generally preferred for the second dose [40, 290].

Vaccine Coverage

MMR vaccine coverage in 2017 among children aged 19-35 months was estimated at 91.5% (95%CI: 90.6–92.3%) for at least one dose. This is relatively consistent with the level of coverage seen over the past five years [14].

Contraindications and Precautions

Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component such as neomycin is a contraindication to further vaccination with MMR. Other contraindications include pregnancy, immunosuppression, and family history of altered immunocompetence. Current moderate to severe acute illness is a precaution to any vaccination. Other precautions for MMR vaccination include recent receipt of antibody-containing blood products and personal or family history of seizures [40, 244].

Vaccine Effectiveness

One dose of MMR vaccine is estimated to be 93% effective in preventing measles and 97% effective in preventing rubella. A second dose has been shown to increase the effectiveness of measles vaccine to an estimated 97%, mainly by producing immunity in those who failed to respond to the initial dose [40, 290, 291]. Effectiveness of two doses of MMR vaccine against mumps is estimated to be between 66 and 95%, and vaccine-induced protection has been shown to wane over time [292].

Vaccine Safety

Mild illness in people receiving their first dose of MMR can occur due to replication of the attenuated measles vaccine virus. Between 5% and 15% develop a 1-2 day fever up to 103°F approximately 7 to 12 days after the first dose. A transient rash may also appear during this time frame, occurring in approximately 5% of those vaccinated [40].

Vaccines which may induce fever may also rarely induce febrile seizures. Febrile seizures are a common and typically benign childhood condition, occurring in 2-5% of children at some point during their first five years of life. Febrile seizures have an estimated background incidence of 240–480 per 100,000 person-years in children under five years, although this varies considerably

by age, genetics, co-morbidities and environmental risk factors. There are no long-term effects of simple febrile seizures, with the possible exception of an increased risk of recurrence [293-296]. [5-8]. The rate of febrile seizures in the 7-10 days after vaccination was approximately 2-3 times higher for children who received MMRV as compared to MMR and varicella vaccines administered separately on the same day, and 4 times higher as compared to MMR alone [297]. There is no increased risk of fever or febrile seizures in children receiving their second dose of measles-containing vaccine at 4 to 6 years of age, whether given MMR or MMRV [40, 220].

Mild, acute joint symptoms occur in approximately 25% of susceptible adult women after rubella vaccination, but are less common in men and rare in children. Rare adverse events from MMR vaccine include thrombocytopenia, parotitis, lymphadenopathy and encephalopathy. Very rare adverse events from MMR vaccine include measles inclusion body encephalitis (MIBE). Immune thrombocytopenia purpura (ITP) occurs after approximately 1 in 30,000 doses. Allergic reactions are also rare. There is convincing evidence that MMR does not cause autism [40].

Meningococcal

Meningococcal Disease

Neisseria meningitidis, or meningococcus, is an aerobic gram-negative diplococcus. Meningococci colonize the nasopharynx, and in less than 1% of colonized persons the organism invades the bloodstream. Most strains are not pathogenic; five serogroups cause almost all invasive disease (A, B, C, W, and Y). Serogroup prevalence depends heavily on geographic location as well as other factors including age. In the United States, groups B, C, and Y are primarily responsible for meningococcal disease. Rates of meningococcal disease in the US have been declining for the last few decades, so that in 2016, there were 375 reported cases in the entire US. *N. meningitides* can cause bacteremia, meningococcemia, meningitis, pneumonia, and/or septic arthritis. The average incubation period is 3-4 days for meningococcemia. Disease usually presents with an abrupt onset of fever, hypotension, and rash with or without meningeal symptoms. The most common presentation of invasive disease is meningitis, usually accompanied by fever, headache and stiff neck. Fatality rates range from 10%-15% (and up to 40% in meningococcemia) for meningococcal meningitis. Less common presentations include pneumonia (5-15%), arthritis (2%), otitis media (1%) and epiglottitis (<1%) [40].

Meningococcal Vaccine

There are several meningococcal conjugate vaccines (MCVs) licensed in the United States. The MCV4 vaccines MenACWY-D (Menactra®) and MenACWY-CRM (Menveo®) protect against serogroups A, C, W and Y [40], and the single-component vaccines MenB-FHbp (Trumenba®) and MenB-4C (Bexsero®) protect against serogroup B [298]. Both MenACWY-D and MenACWY-CRM are administered via intramuscular injection and contain no preservatives or

adjuvants. MenACWY-D is approved for use in persons 9 months through 55 years of age, and MenACWY-CRM is approved for use in persons 2-55 years of age [40]. MenB-FHbp and MenB-4C are approved for use in persons 10-25 years of age [298]. Hib-MenCY-TT is approved for use as a four-dose series at 2, 4, 6, and 12-18 months of age.

Quadrivalent meningococcal polysaccharide vaccine which was a plain polysaccharide vaccine not conjugated to protein, MPSV4 (Menomune®), is no longer recommended for routine use [40]. The Hib-MenCY-TT combination vaccine MenHibrix® was discontinued in the United States in 2016 [230].

ACIP Recommendations

The ACIP recommends that all adolescents 11-18 years of age without contraindications should receive two doses of meningococcal conjugate, routinely given at 11 or 12 years of age and a booster at 16 years of age. Adolescents who receive a first dose after their 16th birthday do not need a booster dose unless they become at increased risk for meningococcal disease. Vaccination to prevent meningococcal disease is also recommended for all persons starting at 9 months of age who are at increased risk for meningococcal disease (such as travelers to hyperendemic or epidemic countries; those with asplenia; or those with persistent complement component deficiency). Serogroup B meningococcal vaccine is recommended for all persons starting at 10 years of age who are at increased risk for serogroup B meningococcal disease (such as those with persistent complement component deficiencies; those with anatomic or functional asplenia; microbiologists routinely exposed to N. meningitides; and anyone identified to be at increased risk during an outbreak of serogroup B meningococcal disease). Adolescents and young adults aged 16–23 years may also receive this vaccine, even if they are not at increased risk [298, 299].

Vaccine Coverage

MenACWY coverage among adolescents in 2017 was estimated at 85.1% (95%CI: 84.2–86.1%) for at least one dose [242].

Contraindications and Precautions

Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component is a contraindication to further vaccination with meningococcal vaccines. Current moderate to severe acute illness is a precaution to any vaccination [40].

Vaccine Effectiveness

Meningococcal serogroups A and C polysaccharide vaccines have demonstrated estimated clinical efficacies of at least 85% among children and adults during outbreaks. Meningococcal conjugate vaccines were shown to achieve a seroresponse comparable to the MPSV4 and are able to elicit better immunologic memory [40].

Vaccine Safety

The most common adverse events reported for MenACWY-D are fever (17%), headache (16%), injection-site erythema (15%), dizziness (13.4%), and syncope (10%); the most common reported for MenACWY-CRM are injection site reactions (20%), injection site erythema (14%), and syncope (9%) [40]. Because syncope has been reported among adolescents receiving vaccinations, adolescent recipients should always receive the vaccine while sitting and not in view of others awaiting vaccination, and be observed for up to 15 minutes immediately after vaccination [244-247]. Serious adverse events are rare. Hib-MenCY-TT had rates of adverse events comparable to Hib-TT vaccine [40].

The most common adverse reactions reported for both MenB-FHbp and MenB-4C included pain at the injection site (≥83%), fatigue (≥35%), headache (≥33%), and myalgia (≥30%) [298].

Pneumococcal

Pneumococcal Disease

Streptococcus pneumoniae is a facultative anaerobic gram-positive bacterium. 92 serotypes of *S. pneumoniae* have been documented, classified by their antigenic polysaccharide capsules. Antibodies provide protection specific to serotype. Pneumococci are often asymptomatically carried in the respiratory tracts of healthy persons.

Pneumococcal infections can cause pneumonia, sepsis, meningitis, otitis media, bone and joint infections, sinusitis, orbital cellulitis and skin infections. Pneumonia occurs at all ages and is the most common cause of death from *Streptococcus pneumoniae*. The incubation period of pneumococcal pneumonia is 1-3 days and is associated with fever, rigors (in adults), pleuritic chest pain, productive cough, dyspnea, tachypnea, hypoxia, tachycardia, malaise and weakness. Pneumococcal pneumonia has a case-fatality rate of 5-7% (may be substantially higher among the elderly). Roughly 25-30% of adult patients with pneumococcal pneumonia also develop pneumococcal bacteremia, which has a case-fatality rate of about 20% (may be as high as 60% among the elderly). Pneumococcal meningitis has a case-fatality rate of about 8% among children and 22% among adults, with neurologic sequelae often persisting among survivors. Over half of all cases of bacterial meningitis in the United States are caused by pneumococci [40]. WHO estimates that over 1.6 million people, including 0.7-1 million children under 2 years of age, die every year from pneumococcal infections worldwide [300].

Pneumococcal Vaccine

The pneumococcal conjugate vaccine licensed for use in the United States is the aluminum phosphate-adjuvanted 13-valent PCV13 (trade name: Prevnar13®), which contains the purified

capsular polysaccharide from 13 serotypes of *S. pneumoniae* conjugated to a nontoxic diphtheria toxin known as CRM_{197}. The pneumococcal polysaccharide vaccine licensed for use in the United States is PPSV23, which contains the purified capsular polysaccharide antigen from 23 serotypes of *S. pneumoniae* [40].

ACIP Recommendations

The ACIP recommends that all infants without contraindications should receive four doses of pneumococcal conjugate vaccine, beginning no earlier than 6 weeks of age. The primary series of three doses is generally administered at 2, 4 and 6 months of age. A booster dose should be administered between 12-15 months of age. The minimum interval between doses is 4 weeks for infants under one year of age, and 8 weeks for infants over one year of age. Children 6-18 years of age who have not previously received PCV13 or who have specific risk factors (such as anatomic asplenia including sickle-cell disease; immunocompromising conditions including HIV infection; cochlear implant; or cerebrospinal fluid leak) should receive a dose of PCV13 [40, 301].

PPSV23 is also recommended for persons over 2 years of age with any of the following specific risk factors (anatomic or functional asplenia; cochlear implant; cerebrospinal fluid leak; immunocompromising conditions including HIV infection, disease, chemotherapy and steroids; chronic illness including heart, pulmonary and liver disease; alcoholism; or asthma or cigarette smoking in adults over 19 years of age), with a revaccination dose after 5 years, and a third dose after the 65^{th} birthday at least 5 years from the second dose. When both the conjugate and plain polysaccharide pneumococcal vaccines are recommended for a given individual, the conjugate vaccine should be given first. If the plain polysaccharide vaccine was given first, the conjugate vaccine should be administered one year after the polysaccharide vaccine [40, 301].

Vaccine Coverage

PCV coverage in 2017 among children aged 19-35 months was estimated at 91.9% (95%CI: 90.9–92.8%) for at least three doses and 82.4% (95%CI: 81.1–83.6%) for at least four doses. This is relatively consistent with the level of coverage seen over the past five years [14].

Contraindications and Precautions

Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component is a contraindication to further vaccination with pneumococcal vaccines. Current moderate to severe acute illness is a precaution to any vaccination [40].

Vaccine Effectiveness

PPSV23 is 60-70% effective against invasive pneumococcal disease caused by vaccine serotypes, although ineffective in children younger than 2 years of age. PCV13 is highly immunogenic and estimated to be over 90% effective in children against invasive pneumococcal disease caused by vaccine serotypes. In addition, PCV13 has been shown to reduce nasopharyngeal carriage of vaccine serotypes, which is important in reducing the disease burden by further limiting the spread of *S. pneumonia* from person to person [40].

Vaccine Safety

Local reactions such as pain, redness and swelling occur in 30-50% of PPSV23 recipients and 5-49% of PCV13 recipients. Moderate reactions such as fever and myalgia are uncommon (<1%) and severe adverse reactions are rare in PPSV23 recipients. However, about 8% of PCV13 local reactions are considered severe, for example causing tenderness that interferes with movement of the limb. Local reactions are typically more common after the fourth dose of PCV13 than after the first three. Fever over 100.4°F within 7 days after vaccination was reported in 24-35% of PCV13

recipients in clinical trials; high fever was reported in less than 1% [40]. Cellulitis-like reactions after Pneumovax 23® vaccination have also been reported in the literature [302, 303].

Vaccines which may induce fever may also rarely induce febrile seizures. Febrile seizures are a common and typically benign childhood condition, occurring in 2-5% of children at some point during their first five years of life. Febrile seizures have an estimated background incidence of 240–480 per 100,000 person-years in children under five years, although this varies considerably by age, genetics, co-morbidities and environmental risk factors. There are no long-term effects of simple febrile seizures, with the possible exception of an increased risk of recurrence [293-296]. Febrile seizures were estimated to occur at a rate of 5.3 per 100,000 doses in children aged 6-59 months receiving PCV13, and 17.5 per 100,000 doses after receiving PCV13 and concomitant trivalent inactivated influenza vaccine. These risk differences varied with age due to the age-dependent background rates of febrile seizures, with the highest estimates at 16 months and the lowest at 59 months [296].

Polio

Polio Disease

Poliovirus is an RNA enterovirus of the Picornaviridae family. Transmission is primarily through the fecal oral route, and the virus replicates in the pharynx, local lymphatics and gastrointestinal tract. Spread of the virus from blood to nerves to the central nervous system can cause destruction of motor neurons. The incubation period is 3-6 days for nonparalytic poliomyelitis and 7-21 days for onset of paralysis in paralytic poliomyelitis. Up to 72% of all infections in children are asymptomatic, but these persons can shed the virus in their stool and respiratory secretions and transmit the virus to others. Approximately 24% of infections in children result in minor, nonspecific illness without viral spread to the central nervous symptoms, followed by complete recovery within a week. 1-5% of infected children experience nonparalytic aseptic meningitis, lasting between 2-10 days. Paralysis occurs in less than 1% of infections in children. Paralytic symptoms typically progress for 2 to 3 days then plateau as the fever subsides. Many of those with paralytic poliomyelitis recover completely, and most recover some muscle function. However, any paralysis or weakness that persists after the first year is generally permanent. Paralysis predominantly affects the proximal muscles, especially of the legs in an asymmetric fashion. Between 2-5% of cases of paralytic polio in children and 15-30% in adults die from the disease, primarily because of paralysis of the muscles of respiration [40].

Polio Vaccine

Inactivated poliovirus vaccine (abbreviation: IPV; trade name: Ipol®) is formaldehyde-inactivated and contains all three serotypes of polio vaccine virus. Combination vaccines that contain IPV

include DTaP-IPV (trade names: Kinrix®, Quadracel®), DTaP-Hep B-IPV (Pediarix®) and DTaP-Hib-IPV (Pentacel®) [40].

Oral poliovirus vaccine (OPV) is a live-attenuated vaccine that is no longer used in the United States [40].

ACIP Recommendations

The ACIP recommends that all infants without contraindications should receive 3 doses of inactivated polio vaccine, given at least 4 weeks apart, with the first dose administered at a minimum of 6 weeks of age, routinely at 2, 4, and 6-18 months of age. A fourth dose is recommended at 4-6 years of age, though this dose is not needed if the third dose was received after 4 years of age and at least 6 months after the second dose [40, 304].

The following is a direct excerpt from the 2009 ACIP recommendations which clarifies the vaccination schedule to be used for specific combination vaccines: “When DTaP-IPV/Hib (Pentacel®) is used to provide 4 doses at ages 2, 4, 6, and 15--18 months, an additional booster dose of age-appropriate IPV-containing vaccine (IPV [Ipol®] or DTaP-IPV [Kinrix®]) should be administered at age 4--6 years. This will result in a 5-dose IPV vaccine series, which is considered acceptable by ACIP. DTaP-IPV/Hib is not indicated for the booster dose at age 4--6 years. ACIP recommends that the minimum interval from dose 4 to dose 5 should be at least 6 months to provide an optimum booster response” [304].

Vaccine Coverage

Polio vaccine coverage in 2017 among children aged 19-35 months was estimated at 92.7% (95%CI: 91.9–93.5%) for at least three doses. This is relatively consistent with the level of coverage seen over the past five years [14].

Contraindications and Precautions

Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component (such as streptomycin, polymyxin B, and neomycin) is a contraindication to further vaccination with IPV [40].

Vaccine Effectiveness

At least 90% of recipients of two doses of IPV develop immunity to all three poliovirus types, and at least 99% develop immunity after three doses. The exact duration of immunity is unknown but appears to be long term [40].

Vaccine Safety

Minor local reactions such as pain and redness occur occasionally occur after receiving IPV [40].

Rotavirus

Rotavirus Disease

Rotavirus is a very stable double-stranded RNA virus of the *Reoviridae* family. There are five predominant strains which historically have accounted for 90% of isolates in the United States, 75% of which being the G1 strain. Rotavirus is transmitted through the fecal-oral route and replicates in the epithelium of the small intestine. The incubation period is generally less than 48 hours, after which decreased intestinal absorption of sodium, glucose and water can result in isotonic diarrhea. Clinical manifestations of rotavirus infection are nonspecific and range from asymptomatic to severe with fever, vomiting and dehydrating diarrhea. Potential complications include dehydration, electrolyte imbalance, and metabolic acidosis. Symptoms usually fully resolve within 3-7 days. However, if rotavirus infection is not treated, it can be fatal. Multiple infections are sometimes necessary to confer permanent immunity, although subsequent infections are typically less severe than the first and may even be asymptomatic [40, 305].

Rotavirus Vaccine

Rotavirus vaccines (RV) are live attenuated oral vaccines containing no preservatives. There are two rotavirus vaccines currently licensed in the United States: RV5 (RotaTeq®), which contains five reassortant rotaviruses suspended in a buffer solution, and RV1 (Rotarix®), which contains one attenuated strain of human rotavirus and is reconstituted from lyophilized powder prior to administration [40]. Both vaccines provide protection against the majority, but not all strains of rotavirus circulating in the United States.

ACIP Recommendations

The ACIP recommends that all infants without contraindications should receive the rotavirus vaccine series; consisting of either two oral doses of RV1 or three oral doses of RV5 beginning at about 2 months of age (no earlier than 6 weeks of age). Each dose should be separated by at least 4 weeks, and given at the same time as other normal childhood vaccinations. Maximum age of the first dose of rotavirus vaccination is 14 weeks and 6 days, and maximum age for any dose is 8 months [40, 305].

Vaccine Coverage

Rotavirus vaccine coverage in 2017 among children aged 19-35 months was estimated at 73.2% (95%CI: 71.6–74.7%). This is relatively consistent with the level of coverage seen over the past five years [14].

Contraindications and Precautions

Severe allergic reaction (e.g. anaphylaxis) to a previous dose, vaccine component or component of the oral applicator is a contraindication to further vaccination with RV. The oral applicator for RV1 vaccine contains latex, but the applicator for RV5 does not. Other contraindications for RV include severe combined immunodeficiency (SCID) and a history of intussusception. Altered immunocompetence other than SCID is a precaution to RV. Current moderate to severe acute illness is a precaution to any vaccination [40].

Vaccine Effectiveness

In very large clinical trials, effectiveness against severe gastroenteritis was estimated to be 85-98% and effectiveness against any rotavirus gastroenteritis was estimated to be 74-87% after

completion of a full series of RV. RV also significantly reduced physician visits related to diarrhea and hospitalization related to rotavirus [40].

Vaccine Safety

In RV5 clinical trials, small but statistically significant increases were shown among vaccine versus placebo recipients in rates of diarrhea (18.1% vs 15.3%) and vomiting (11.6% vs 9.9%) within the first week after vaccination; slightly increased rates of diarrhea, vomiting, otitis media, nasopharyngitis and bronchospasm occurred within 42 days after vaccination. In RV1 clinical trials, small but statistically significant increases were shown among vaccine versus placebo recipients in Grade 3 cough (i.e. a cough that prevents normal everyday activities) or runny nose (3.6% vs 3.2%); increased rates of irritability and flatulence occurred within 31 days after vaccination [40]. Recent post-licensure studies in the United States have shown RV5 to be associated with approximately 1.1 excess cases of intussusception per 100,000 vaccine recipients in the 7 days after the first dose, and 1.5 excess cases per 100,000 recipients in the 21 days after the first dose. Data from some countries show an increased risk of intussusception with both RV5 and RV1 of one to six excess cases per 100,000 vaccinated infants [306, 307]. However, this small risk is outweighed greatly by the large health benefit of RV [40, 220, 308].

Children with SCID have developed persistent diarrhea caused by rotavirus vaccines that was cured only after the infants received bone marrow transplants to correct the immune deficiency [309, 310]. Rarely, RV5 has been shown to cause moderate to severe diarrhea associated with internal recombination of the vaccine strains [40].

Tetanus, Diphtheria and Pertussis

Tetanus, Diphtheria and Pertussis Disease

Diphtheria disease is mediated by the toxin of the aerobic gram-positive bacterium *Corynebacterium diphtheria*. The incubation period is generally 2-5 days. Diphtheria can infect almost any mucous membrane, but most commonly infects the pharynx and tonsils. Disease begins insidiously with mild symptoms such as malaise, sore throat, low-grade fever and anorexia. A membrane forms and expands within 2-3 days potentially causing respiratory obstruction, and sometimes results in coma and death within 6-10 days. Complications from diphtheria are mostly attributable to the toxin, and the most common complications other than respiratory obstruction are paralysis and myocarditis [40].

Tetanus is caused by an exotoxin of the anaerobic gram-positive spore-forming bacterium *Clostridium tetani*. The spores can survive for years in harsh conditions and are widely distributed in animal feces and soil. The organism generally enters the human body through a cut in the skin at which point the spores germinate and toxins spread through the circulatory and lymphatic systems, interfering with neurotransmitters and leading to muscle contractions and spasms. Incubation averages 8 days but ranges from 3-21 days. The most common type of disease is generalized tetanus, which typically begins with lockjaw and culminates in frequent spasms lasting up to a month. Tetanus is fatal in approximately 11% of cases even when intensive care is available; the disease is twice as likely to be fatal in persons who have never been vaccinated. Neonatal tetanus, although rare in the U.S., can occur when infants are born to mothers who lack tetanus immunity, usually via infection in an unhealed umbilical stump. Because it is an environmental pathogen, there is no community protection (also known as “herd immunity”) [40].

Pertussis, also known as whooping cough, is a highly communicable disease caused by the aerobic gram-negative rod bacterium *Bordetella pertussis*. The incubation period for pertussis most commonly is 7-10 days. The illness begins with runny nose, sneezing, low-grade fever and mild cough. This cough gradually becomes more severe, progressing into frequent bursts of numerous rapid coughs after 1-2 weeks. These coughing fits (paroxysms) result in the characteristic whooping sound during efforts to inspire. These coughing fits generally continue for 1-6 weeks but can persist up to 10 weeks. Infants are at the highest risk for complications associated with pertussis. The most common complication and cause of most deaths related to pertussis is pneumonia. Pertussis used to be a substantial cause of death in children in the U.S., but since introduction of the vaccine, incidence of pertussis has decreased by more than 80% [40]. However, incidence has risen steadily over the past ten years, and in 2012 the U.S. had its highest case number reported since 1955 at 48,277 [311], although this has decreased somewhat in recent years to 20,762 in 2015 and 15,737 in 2016 [312]. There has also been an increase in pertussis incidence in recent years among children worldwide [313]. Immunity from the acellular pertussis vaccine has been shown to wane over time, considered the main factor behind the recent pertussis resurgence [40]. In addition, acellular pertussis vaccine may not confer mucosal immunity and thus community protection (herd immunity) to the same degree as the previously used whole cell pertussis vaccines [314, 315]. Studies have suggested that clustering of unvaccinated individuals may be another factor behind recent U.S. pertussis outbreaks [57-59].

Tetanus, Diphtheria and Pertussis Vaccine

Acellular pertussis vaccines are inactivated, subunit vaccines, and are only available in combination with diphtheria and tetanus toxoids. DTaP vaccine (trade names: Daptacel®, Infanrix®) is approved for children between six weeks and 7 years of age. Tdap vaccine (trade

names: Boostrix®, Adacel®) contains reduced antigen amounts for diphtheria and pertussis, and is approved for persons either 10 through 64 years (Boostrix®) or 11 through 64 years (Adacel®) of age [40].

ACIP Recommendations

The ACIP recommends that all infants without contraindications receive three doses of the child formulation of DTaP, given at 2, 4, and 6 months of age. A fourth dose should be given 6 to 12 months after the third dose, preferably between 15 and 18 months of age. A fifth dose is recommended between 4 and 6 years of age. One dose of the Tdap should be given to all adolescents between the ages of 11 through 18 years.

Vaccine Coverage

DTaP coverage in 2017 among children aged 19-35 months was estimated at 94.0% (95%CI: 93.3–94.7%) for at least three doses and 83.2% (95%CI: 82.0–84.3%) for at least four doses. This is relatively consistent with the level of coverage seen over the past five years [14]. Tdap coverage among adolescents in 2017 was estimated at 88.7% (95%CI: 87.8–89.6%) for at least one dose [242].

Contraindications and Precautions

Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component is a contraindication to further vaccination with DTaP and Tdap. Another contraindication for both vaccines is encephalopathy within 7 days after previous vaccination without an identifiable alternative cause. Current moderate to severe acute illness is a precaution to any vaccination [40].

Precautions to DTaP include the following occurrences within 48 hours after previous vaccination: a hypotonic hyporesponsive episode, which is a sudden episode of unresponsiveness and limpness [316], a fever above 105°F, or persistent, inconsolable crying lasting over 3 hours. Other

precautions include convulsions within 3 days after previous vaccination or an unstable progressive neurologic disorder [40].

Precautions to Tdap include a history of Guillain-Barré syndrome within 6 weeks after previous vaccination containing tetanus toxoid, or a history of a severe local reaction immediately following previous vaccination containing either tetanus or diphtheria toxoid [40].

Vaccine Effectiveness

A complete primary three-dose series of diphtheria toxoid and tetanus toxoid results in estimated clinical efficacies of 95% and 100%, respectively. The efficacy of the acellular pertussis component of DTaP vaccines licensed in the U.S. has been estimated to be 84% in the short-term (i.e., within 3 years of series completion). The antibody response to one dose of Tdap in adults is similar to that in infants after three doses of DTaP [38, 40, 317]. Infants born to mothers immunized during pregnancy have between 50-100% of the pertussis antibody titers of their mothers at birth, although this passive immunity wanes rapidly [318].

Vaccine-induced active immunity also wanes over time. By ten years after vaccination, the tetanus antitoxin levels in some individuals decreases below the minimal protective level. Of particular concern is the more rapid waning immunity from the acellular pertussis vaccine, which has contributed to the resurgence of pertussis in the United States. The rapid waning of antibody is one of the main reasons for vaccinating with Tdap during every pregnancy [40].

Vaccine Safety

Local reactions including pain, redness and swelling occur in 20-40% of infants after the first three doses of DTaP. Self-limited fever of greater than 101°F occurs in 3-5% of DTaP recipients. Extensive swelling of the injection-site limb and increased local reactions and fever has been

reported after the fourth or fifth dose of DTaP. Moderate to severe systemic reactions such as fever above 105°F, febrile seizures, persistent crying lasting longer than 3 hours and hypotonic hyporesponsive episodes occur in less than 1 in 10,000 doses of DTaP [40].

Local reactions occur in 21-66% of adults after Tdap. Fever greater than 100.4°F occurs in 1.4% of Tdap recipients. Mild systemic reactions such as headache or drowsiness occasionally occur after vaccination. Besides very rare occurrences of anaphylaxis, no serious adverse events have been shown to be caused by Tdap vaccination. Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component is a contraindication to further Tdap vaccination [40].

Vaccines which may induce fever may also rarely induce febrile seizures. Febrile seizures are a common and typically benign childhood condition, occurring in 2-5% of children at some point during their first five years of life. Febrile seizures have an estimated background incidence of 240–480 per 100,000 person-years in children under five years, although this varies considerably by age, genetics, co-morbidities and environmental risk factors. There are no long-term effects of simple febrile seizures, with the possible exception of an increased risk of recurrence [293-296].

Because syncope has been reported among adolescents receiving vaccinations, adolescent recipients should always receive the vaccine while sitting and not in view of others awaiting vaccination, and be observed for up to 15 minutes immediately after vaccination [244-247].

Varicella

Varicella Disease

Varicella is a highly infectious acute disease caused by the DNA herpesvirus varicella zoster virus (VZV). VZV is transmitted via the respiratory route. The incubation period generally lasts about 15 days. Symptoms of primary infection with VZV, also known as chickenpox, include mild fever, malaise and a generalized vesicular rash.

Although varicella disease is usually mild, there are potentially serious complications including bacterial infection of skin lesions, pneumonia, Reye syndrome, cerebellar ataxia, aseptic meningitis or encephalitis. Infants under 1 year of age have an increased risk of complications.

Congenital varicella syndrome, resulting from maternal primary infection with varicella during the first 20 weeks of gestation, is associated with low birth weight, localized muscular atrophy, skin scarring and eye and neurologic abnormalities.

Herpes zoster, also known as shingles, occurs after reactivation of latent VZV and is associated with aging, immunosuppression, and other factors. Between 0.5 and 1 million episodes of herpes zoster occur in the United States every year, and half of all persons living until age 85 will develop zoster [40].

Varicella Vaccines

Varicella vaccine (trade name: Varivax®) is a live attenuated viral vaccine. MMRV (trade name: ProQuad®) is a combination vaccine that includes measles, mumps, rubella and varicella vaccines [40].

ACIP Recommendations

The ACIP recommends that all children without contraindications receive two doses of varicella vaccine after 1 year of age and at least 3 months apart. The first dose should be administered between 12 and 15 months of age and the second between 4 and 6 years of age, generally at the same time as measles-mumps-rubella combination vaccine (MMR). The CDC recommends that MMR and varicella vaccine be administered separately albeit simultaneously for the first dose in order to reduce the risk of infant fever and febrile seizures, but MMRV can be administered for the second dose. The ACIP also recommends all persons over 13 years of age without evidence of varicella immunity receive 2 doses of varicella vaccine separated by a minimum of 4 weeks. Immunity to varicella is especially important for health care personnel [40, 319].

Vaccine Coverage

Varicella vaccine coverage in 2017 among children aged 19-35 months was estimated at 91.0% (95%CI: 90.1–91.8%) for at least one dose. This is relatively consistent with the level of coverage seen over the past five years [14].

Contraindications and Precautions

Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component is a contraindication to further vaccination with any varicella-containing product. Other contraindications to vaccination with varicella-containing vaccines include pregnancy, altered immunity, and family history of altered immunocompetence [40, 244, 319]. The following is a direct excerpt from the 2007 ACIP recommendations regarding the contraindication of varicella vaccine in persons with altered immunity:

“Single-antigen varicella and combination MMRV vaccines are not licensed for use in persons who have any malignant condition, including blood dyscrasias, leukemia, lymphomas of any type,

or other malignant neoplasms affecting the bone marrow or lymphatic systems. Combination MMRV vaccine should not be administered to persons with primary or acquired immunodeficiency, including immunosuppression associated with AIDS or other clinical manifestations of HIV infections, cellular immunodeficiencies, hypogammaglobulinemia, and dysgammaglobulinemia. Combination MMRV vaccine should not be administered as a substitute for the component vaccines when vaccinating HIV-infected children.

"Varicella vaccines should not be administered to persons who have a family history of congenital or hereditary immunodeficiency in first-degree relatives (e.g., parents and siblings) unless the immune competence of the potential vaccine recipient has been clinically substantiated or verified by a laboratory.

"Varicella vaccines should not be administered to persons receiving high-dose systemic immunosuppressive therapy, including persons on oral steroids >2 mg/kg of body weight or a total of >20 mg/day of prednisone or equivalent for persons who weigh >10 kg, when administered for >2 weeks. Such persons are more susceptible to infections than healthy persons. Administration of varicella vaccines can result in a more extensive vaccine-associated rash or disseminated disease in persons receiving immunosuppressive doses of corticosteroids. This contraindication does not apply to persons who are receiving inhaled, nasal, or topical corticosteroids or low-dose corticosteroids as are used commonly for asthma prophylaxis or for corticosteroid-replacement therapy." [319]

Current moderate to severe acute illness is a precaution to any vaccination. Recent receipt of antibody-containing blood products is a precaution to both varicella and MMRV vaccination and may require waiting until the antibodies wane before administering the vaccine. Personal or family history of seizures is a precaution to MMRV vaccination [40, 319]. "Receipt of specific antiviral

drugs (acyclovir, famiciclovir, or valacyclovir) 24 hours before vaccination (avoid use of these antiviral drugs for 14 days after vaccination)" has also recently been added to the list of precautions in the CDC's *General Best Practice Guidelines for Immunization* report [244].

Vaccine Effectiveness

Varicella vaccine effectiveness after a single dose is estimated to be 76-94% in preventing clinically diagnosed or laboratory confirmed disease and 78-100% effective for prevention of severe cases of varicella in children [320-322]. Effectiveness decreases with time since vaccination [319]. Effectiveness after two doses is estimated to be 94% against any varicella and 98% against moderate or severe varicella [322].

Vaccine Safety

Mild injection site reactions such as pain and/or erythema are the most common adverse reactions following varicella vaccination, reported in roughly 21-25% of children within three days of vaccination. Rash is reported in 1-4% of children after varicella vaccination. Fever is reported in 4-7% of children between 7 and 21 days after vaccination [319].

Mild zoster illness resulting from a latent infection with varicella vaccine virus has been reported [323]. This has been very rarely associated with viral meningitis, although affected patients without immune deficiencies recover fully without any lasting effects. Varicella vaccine can also cause hepatitis if mistakenly administered to severely immune deficient individuals [40].

Vaccines which may induce fever may also rarely induce febrile seizures. Febrile seizures are a common and typically benign childhood condition, occurring in 2-5% of children at some point during their first five years of life. Febrile seizures have an estimated background incidence of 240–480 per 100,000 person-years in children under five years, although this varies considerably

by age, genetics, co-morbidities and environmental risk factors. There are no long-term effects of simple febrile seizures, with the possible exception of an increased risk of recurrence [293-296]. The rate of febrile seizures in the 7-10 days after vaccination was approximately 2-3 times higher for children who received MMRV as compared to MMR and varicella vaccines administered separately on the same day, and 4 times higher as compared to MMR alone [297]. There is no increased risk of fever or febrile seizures in children receiving their second dose of measles-containing vaccine at 4 to 6 years of age, whether given MMR or MMRV [40, 220].

Although transmission of varicella vaccine virus is rare, it may very occasionally occur if a recently vaccinated person develops a rash. To be safe, close contact with persons without varicella immunity at high risk of complications, especially those who are immunocompromised, should be avoided until such a rash has disappeared [40].

Vaccines Recommended During Pregnancy

ACIP Recommendations in Pregnancy

The Advisory Committee on Immunization Practices (ACIP) recommends that pregnant women receive two vaccines during pregnancy: tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap), and seasonal inactivated influenza vaccine (IIV) [27, 28].

The recommendations of the American College of Obstetricians and Gynecologists (ACOG) are consistent with ACIP. From their 2013 publication entitled *ACOG Committee Opinion No. 566: update on immunization and pregnancy: tetanus, diphtheria, and pertussis vaccination*: "Obstetric care providers should administer the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine to all pregnant patients during each pregnancy, as early in the 27–36-weeks-of-gestation window as possible. Pregnant women should be counseled that the administration of the Tdap vaccine during each pregnancy is safe and important to make sure that each newborn receives the highest possible protection against pertussis at birth. Obstetrician–gynecologists are encouraged to stock and administer the Tdap vaccine in their offices" [324]. From their 2014 publication entitled *ACOG Committee Opinion No. 608: influenza vaccination during pregnancy*: "It is particularly important that women who are or will be pregnant during influenza season receive an inactivated influenza vaccine as soon as it is available. It is critically important that all obstetrician–gynecologists and all providers of obstetric care advocate for influenza vaccination, provide the influenza vaccine to their pregnant patients, and receive the influenza vaccine themselves every season" [325].

This recommendation is meant to prevent pertussis and influenza disease in both the pregnant women themselves as well as in their infants [25-28]. Children too young to be vaccinated against pertussis are at high risk for contracting pertussis disease, and they also have the highest complication rates [27, 38, 324, 326]. Almost all pertussis deaths in the United States occur in children less than 6 months of age [27, 324]. For influenza, there is no licensed vaccine for infants less than 6 months of age, and this is the group at highest risk for influenza-associated hospitalization and death [39].

Vaccine Coverage in Pregnancy

Maternal vaccine coverage is much lower than childhood vaccine coverage, which is both understandable considering the relative ages of the recommendations and indicative of vast room for improvement. Influenza vaccine coverage among U.S. pregnant women has slowly risen over time before stagnating; coverage was 49% during the 2010-11 season, 53.6% during the 2016-17 season, and 49.1% during the 2017-18 season [12, 327-332]. Tdap vaccine coverage among pregnant women was measured at 54.4% in the 2017-18 season [12]. During the 2017-18 season, pregnant white women had roughly equivalent coverage of influenza (52.5%) and higher coverage of Tdap (59.3%) vaccines than pregnant Hispanic women (51.3% for flu, 48.8% for Tdap), and much higher coverage than pregnant black women (36.5% for flu, 42.9% for Tdap). Pregnant women with at least a college degree had higher rates of coverage for influenza (59.7%) and Tdap (59.0%) than women who did not attend college (41.8% for flu, 46.2% for Tdap). Women whose provider recommended and offered the vaccine had substantially higher rates of coverage for flu

(63.8%) and Tdap (73.5%) than those who received a recommendation with no offer (37.6% for flu, 38.3% for Tdap) or no recommendation (9.0% for flu, 1.6% for Tdap) [12].

Prospective cohort studies have found several attitudinal constructs associated with receiving maternal flu vaccination, including perceived susceptibility to influenza, perceived severity of influenza illness during pregnancy, perceived vaccine safety and effectiveness, perceived social norms, and self-efficacy [200, 203, 206].

The Centers for Disease Control and Prevention (CDC) has pertinent information on vaccinating during pregnancy available online at https://www.cdc.gov/vaccines/pregnancy/pregnant-women/index.html. ACOG also provides resources on vaccinating during pregnancy online at http://immunizationforwomen.org/patients/pregnancy/pregnancy.php.

Influenza in Pregnancy and Infancy

Influenza Disease in Pregnant Women and Young Infants

Pregnant women and young children are at increased risk of complications and hospitalizations from influenza [29-37]. Infection with influenza during pregnancy has been associated with an increased risk of adverse outcomes to the mother, including respiratory hospitalization, pneumonia, adult respiratory distress syndrome, overwhelming sepsis and death [29]. A recent CDC study estimated that 12% of all pregnancy-related deaths during the 2009-2010 pandemic season were attributed to confirmed or possible infection with pandemic influenza [333]. Some studies have suggested associations between infection with influenza during pregnancy and an increased risk of adverse outcomes to the unborn infant, including preterm birth, low birth weight,

and stillbirth; however, these studies are limited in number and quality, preventing firm conclusions from being drawn [334, 335]. The biological mechanism for such adverse outcomes in infants is unclear, as influenza virus is rarely transmitted across the placenta; more likely potential mechanisms include maternal fever, inflammation, and other immunological responses [335].

Maternal Influenza Vaccine

Two types of vaccines are available to protect against influenza: inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV). However, LAIV is contraindicated during pregnancy. Pregnant women may receive any licensed, recommended, age-appropriate influenza vaccine [28].

Vaccination during pregnancy is beneficial both for the mother and her unborn child, as women who receive influenza vaccine during pregnancy transfer vaccine-specific antibody to their infants [336-342]. A prospective, controlled, blinded, randomized trial of 340 mothers in Bangladesh observed between August 2004 and December 2005 found that maternal vaccination with IIV reduced about one third of non-specific febrile respiratory illness in both pregnant women and their infants, and reduced laboratory-confirmed influenza illness in infants under 6 months of age by 63% [343]. The effectiveness of maternal vaccination in preventing infant influenza was most pronounced between March and November 2005. A case-control study among 492 pregnant women in California and Oregon during the 2010-2011 and 2011-2012 influenza seasons found that maternal vaccination with the current season's influenza vaccine reduced the risk of laboratory-confirmed influenza-associated acute respiratory illness during that season by about half, and receipt of the prior season's vaccine had an effect similar to receipt of the current season's vaccine [344].

Not every study has found maternal influenza vaccination to be effective. In a cohort of almost 50,000 live births in northern California, no reduction in hospital admissions and physician visits was found for pregnant women who received maternal influenza vaccination or for their infants, although this may have been due to the unreliability of typical influenza surveillance measures in distinguishing influenza from other respiratory illness [336]. A 2014 review of efficacy and effectiveness of maternal influenza vaccination found its effectiveness in pregnant women reported from -15% to +70% [336, 343, 345-348], and its effectiveness in infants reported from +41 to +91% [31, 336, 341, 343, 348-350]; however, many of these studies had major limitations [351].

Maternal vaccination with IIV reduces the risk of low birthweight and premature birth [345, 352-354]. Some studies also found that pregnant women who received influenza vaccine had a lower likelihood of stillbirth than those who did not [355-357], although the evidence for this is inconsistent and has methodological limitations [357-359].

A large body of evidence demonstrates the safety of IIV for both pregnant women and their unborn children [348, 360-370]. Concomitant administration of Tdap and influenza vaccines during pregnancy is not associated with a higher risk of adverse outcomes compared to sequential vaccination [371].

Donahue et al. recently reported results from a case-control study examining the risk of spontaneous abortion (SAb) following receipt of inactivated influenza vaccines containing A/H1N1pdm2009 antigen in the 2010-11 and 2011-12 seasons [372]. The study found an association between influenza vaccine and SAb, particularly among women who had received pandemic H1N1 vaccine in the previous year as well [372]. The findings were most striking in the 2010-2011 season, and were far less pronounced in the 2011-2012 season. The Donahue et al. findings need to be interpreted in the context of other epidemiological data [373]. One recent

randomized trial recruiting women at 17-34 weeks gestation [374], thirteen other observational studies [375-387], two systematic reviews [364, 388], and one meta-analysis [355] have assessed a potential association between influenza vaccine and SAb or a related outcome, and none have found an association. However, none of these studies examined the effect of multiple dosing. Studies are in progress to assess whether this association is seen in subsequent influenza seasons.

Pertussis in Pregnancy and Infancy

Pertussis Disease in Pregnant Women and Young Infants

Almost all deaths from pertussis occur in the first few months of life. Infants under 3 months of age accounted for 83% of deaths from pertussis reported to the CDC between 2008 and 2011 [40]. Active immunization of infants against pertussis does not begin until 2 months of age, and the initial three-dose DTaP vaccine series is typically not completed until 6 months of age. Since several doses are needed to induce protection against pertussis in most infants, newborns and infants in the first few months of life are dependent on transplacentally acquired maternal pertussis antibodies and prevention of exposure from their mothers and other close contacts for protection against pertussis disease [27, 38, 324, 326].

Maternal Tdap Vaccine

One dose of Tdap is routinely recommended during each pregnancy, preferably between 27 and 36 weeks of gestation. If a mother is not vaccinated during pregnancy and has never received the Tdap vaccination, the vaccine should be administered to her immediately postpartum [27, 324, 389].

Vaccination during pregnancy is beneficial both for the mother and her unborn child, as women who receive Tdap vaccine during pregnancy transfer vaccine-specific antibody to their infants [318, 370, 390, 391]. Infants born to immunized mothers have between 50-100% of the pertussis antibody titers of their mothers [318]. Maternal Tdap vaccination was shown to be effective in preventing pertussis disease in infants when used as part of a large-scale vaccination effort in the United Kingdom [392].

A large body of evidence demonstrates the safety of the Tdap vaccine for both pregnant women and their unborn children [27, 324, 367, 370, 393, 394]. Receipt of Tdap during pregnancy is not associated with an increased risk of hypertensive disorders of pregnancy or preterm or small for gestational age (SGA) birth [395].

Waning immunity of acellular pertussis vaccine is one of the main rationales for vaccinating with Tdap during every pregnancy [40]. Having recently received a tetanus-containing vaccination does not increase the risk of adverse outcomes after Tdap vaccination in pregnancy [396]. Concomitant administration of Tdap and influenza vaccines during pregnancy is not associated with a higher risk of adverse outcomes compared to sequential vaccination [371].

Cocooning Vaccination Strategy

Infants have the highest risk of complication, hospitalization and death from influenza and pertussis [38, 39], and are too young to complete the primary three dose series of pertussis vaccine or receive their first influenza vaccine until six months of age [28, 40]. Both the Advisory Committee on Immunization Practices (ACIP) and the American College of Obstetricians and Gynecologists (ACOG) recommend that pregnant women are vaccinated against influenza and pertussis during pregnancy to best protect themselves and their infants [25-28]. However, vaccination rates of pregnant women for pertussis and influenza are suboptimal [370, 397-399]. Influenza and Tdap vaccine coverage among U.S. pregnant women was 49.1% and 54.4% during the 2017-18 season, respectively [12]. Additional strategies are needed to optimally protect infants against these diseases.

The majority of infants with pertussis (76-83%) were infected either by either a household contact or caregiver [41-45, 400-402]; and most commonly by either their mother (33%) or their father (16%) [401]. The cocoon vaccination strategy entails vaccinating as many of the close contacts of the incoming newborn as possible, thereby lowering the risk of disease transmission and forming a protective "cocoon" around the infant. In tandem with maternal vaccination, cocooning is a method of further lowering the risk of potentially deadly pertussis and influenza infections in young infants [46-48].

This strategy is endorsed by ACIP, who "concluded that cocooning likely provides indirect protection to infants and firmly supports vaccination with Tdap for unvaccinated persons who anticipate close contact with an infant" [26]. ACIP recommends that all "adolescents and adults (e.g., parents, siblings, grandparents, child-care providers, and health-care personnel) who have or

anticipate having close contact with an infant aged less than 12 months should receive a single dose of Tdap to protect against pertussis if they have not received Tdap previously" [26, 27]. ACIP also recommends routine annual influenza vaccination for all persons over 6 months of age who do not have contraindications, and that "continued emphasis should be placed on vaccination of persons who live with or care for persons at higher risk for influenza-related complication", such as "household contacts (including children) and caregivers of children aged ≤59 months (i.e., aged <5 years) and adults aged ≥50 years, particularly contacts of children aged <6 months" [28].

Again, the recommendations of ACOG are consistent with ACIP. From their 2013 publication entitled *ACOG Committee Opinion No. 566: update on immunization and pregnancy: tetanus, diphtheria, and pertussis vaccination*: "Partners, family members, and infant caregivers should be offered the Tdap vaccine if they have not previously been vaccinated. Ideally, all family members should be vaccinated at least 2 weeks before coming in contact with the newborn" [324]. The recommendations of the American Academy of Pediatrics (AAP) are also consistent with ACIP and ACOG: "Special effort should be made to vaccinate individuals in the following groups… All household contacts and out-of-home care providers of children with high-risk conditions or younger than 5 years, especially infants younger than 6 months… Pediatric offices may choose to serve as an alternate venue for providing influenza vaccination for parents and other care providers of children, if the practice is acceptable to both pediatricians and the adults who are to be vaccinated" [403]. The recommendations of the Global Pertussis Initiative (GPI) are consistent with the ACIP as well: "all individuals having close contact with infants <6 months old be immunized consistent with local health authority guidelines. A high priority should be given to achieving a complete cocoon, defined as full immunization of the family, since the robustness of protection against pertussis is a function of the number of infant contacts vaccinated. If a complete

cocoon is not possible, then the next priority is vaccination of both parents, followed by the mother only" [46].

The efficiency of the cocoon strategy has been widely debated [46]. Some have argued that it is difficult, inefficient and resource-intensive [404-406], or even outright ineffective [407-410], as it is nearly impossible to vaccinate every contact of every infant. An analysis by Lim et al. demonstrated that a cocooning strategy would not be efficient to implement in Ontario, Canada, as their vaccine coverage is relatively high and disease incidence low [404]. Skowronski et al. in Quebec and British Columbia, Canada, and Meregaglia et al. in Italy both came to a similar conclusion, also primarily due to low disease incidence [405]. Carcione et al. found no reduction in pertussis diagnoses in infants whose parents were both vaccinated against pertussis in the first four weeks after the infant was born during a 2011-2012 Australian pertussis epidemic [407]. Healy et al. did not find a reduction in pertussis illness in infants under 6 months of age during a cocooning program in Houston [408]. Maltezou et al. found that although maternal postpartum influenza vaccination reduced influenza-related morbidity in infants in Greece, the postpartum vaccination of other household contacts showed no impact [409]. Althouse et al. suggested that asymptomatic transmission may be the main reason for the recent resurgence of pertussis, and would also help explain the failure of postnatal cocooning programs [410].

Some studies suggest that the cocoon strategy is beneficial and ultimately cost-effective [411-414]. Van Rie et al. ran computer simulations to predict the impact of various vaccination strategies in the United States, and found that the cocoon strategy had a predominantly indirect effect on young infants, and had the lowest number needed to vaccinate to prevent a case of typical pertussis in young infants when compared to routine childhood, adolescent and adult vaccination [411]. Coudeville et al. performed two analyses on adult pertussis vaccination strategies in the United

States: a compartmental, age-structured mathematical model using recent U.S. pertussis epidemiology data [412]; and an economic evaluation including dynamic population effects that had been lacking from previous studies [413]. Both analyses concluded that the cocoon strategy in combination with by a single adult booster dose was the most cost-effective option for controlling pertussis nationwide, and that the impact of the cocoon strategy would be greatest among young children [412, 413]. Westra et al. analyzed various pertussis vaccination strategies in the Netherlands and found that both maternal immunization and cocooning were likely to be cost-effective. Although cocooning was the most expensive intervention to implement, it also resulted in the highest number of quality-adjusted life-years gained [414].

Some have argued that although the cocoon strategy is effective, it is a much less cost-effective option compared to maternal pertussis vaccination, and thus resources should primarily be focused on increasing maternal vaccination coverage [415, 416]. Finally, a 2014 systematic review concluded that the evidence is insufficient to determine whether cocooning is a cost-effective strategy or not due to a lack of evidence showing the efficacy of the strategy in preventing disease [417].

An Australian government-funded cocooning program starting in 2009 was shown to be effective, with a reduction in pertussis in infants under 4 months of age of 51% when both parents were immunized (up from 42% when just the mother was immunized) [418]. However, other cocooning programs have proven difficult to implement [46, 401, 419-427], despite the willingness of many close contacts of pregnant women and infants to be vaccinated [428, 429]. ACIP has stated: "Programmatic challenges make implementation of cocooning programs complex and also impede program expansion and sustainability" [26]. The GPI has outlined challenges to implementation such as cost, logistics, family acceptance, and local sociologic factors, and suggested that some of

these challenges can be overcome by providing education and making vaccines easily accessible to family members [46]. Healy et al. also provided insight into some of these challenges and how they could potentially be conquered: “Establishing a platform to vaccinate family and household contacts is particularly challenging. Ideally, this platform should deliver the service prior to the infant's birth, thus allowing time for protective immunity to develop before the infant's birth. In practice, this is unlikely to occur, given that preventative services often are not a priority for healthy adults… Ideally, the service should be delivered either before or as soon as possible after birth and not restricted to 8 am to 5 pm on Monday through Friday, but scheduled for the convenience of working contacts. A variety of vaccination providers should be used. It is only through the investment of time and finances and by using innovative models in a co-operative fashion that a successful infant cocoon program can be achieved.” [401]

Free provision of cocooning vaccines has been shown to increase coverage [402, 430]. The previously mentioned Australian government-funded cocooning program had excellent uptake of the vaccine among both mothers (80%) and fathers (70%) [430]. A California hospital-based vaccine clinic found that offering free Tdap vaccine to family members of newborns was effective in increasing coverage, with 76% of households during the intervention period reporting a complete cocoon compared to 29.3% of households during the control period [402]. However, free provision of vaccines is not always a viable option, highlighting the importance of identifying other successful strategies.

Although certain hospital-based cocooning programs have achieved some levels of success [402, 431-436], as well as certain pediatric office-based programs [420, 437], a pharmacy-based cocooning program has certain advantages that may allow it to be more effective than previously attempted programs [438]. Using a pharmacy-based cocooning program fits the directives from

Healy et al. to use innovative methods and a variety of vaccine providers to offer the vaccine in a convenient manner and on a flexible schedule not limited by the normal work week.

There is a precedent for a successful Walgreens pharmacy-led education-based cocooning program, although this particular Walgreens pharmacy was on-site in a women's hospital, which may have offered it convenience advantages to family visiting the mother and infant just after birth [436]. In a study by Buttenheim et al., the delivery of retail pharmacy vouchers during newborn visits (covering either the full amount or $5 off of the Tdap vaccine depending on study arm) was not shown to be an effective strategy for promoting vaccination of adult caregivers with Tdap (only 1 of 95 participants had confirmed voucher redemption, although vaccination itself was not confirmed) [439]. To avoid a similar fate, pharmacy-based cocooning programs should learn from the lessons of the Buttenheim study. Implementation issues reported in the article included delaying planned vaccination, perceived inconvenient pharmacy locations, and false beliefs about pertussis risk and severity. This study did not intervene until after the infant was born; the issue of delayed planned vaccination could potentially be mitigated by intervening earlier on in pregnancy. Vaccinating adult caregivers earlier also has the benefit of allowing enough time for the caregivers to benefit from the vaccine's full protection prior to the birth of the child; for example, maximum antibody titer generally takes up to 14 days to be reached after pertussis vaccine in women of childbearing age [401, 440]. The vouchers were only redeemable at four nearby branches of the chosen national retail pharmacy chain; making the vouchers redeemable at any location of a national retail pharmacy chain may reduce the barrier of perceived inconvenient pharmacy locations. The reported barrier regarding beliefs about pertussis risk and severity implies a need for education.

Factors associated with higher rates of cocooning in the U.S. include maternal vaccination, obstetrician recommendation, high perceived benefits of vaccine, high perceived susceptibility to disease, and low perceived barriers to vaccination [49]. Studies in Europe have also identified factors influencing intention to accept pertussis vaccine for cocooning, such as risk perception, outcome expectations, general vaccination beliefs, moral norms, opinion of others, perceived autonomy, anticipated regret, decisional uncertainty, and perceived organizational barriers [441, 442]. One potential intervention to influence perceived benefits of vaccine and susceptibility to disease is education. Another potential intervention that may be able to reduce perceived barriers to vaccination is the distribution of financial incentives.

Potential Interventions to Increase Vaccine Coverage

Education

In 2015, the Community Preventive Services Task Force (CPSTF), an independent, nonfederal, unpaid panel of public health and prevention experts appointed by the Director of the Centers for Disease Control and Prevention (CDC), performed systematic reviews of intervention approaches for increasing vaccination (see: https://www.thecommunityguide.org/content/task-force-findings-increasing-vaccination) and found insufficient evidence to determine if education was effective in increasing vaccination rates when implemented alone [443]. The majority of included studies of clinic-based education provided sufficient evidence of effectiveness but were limited to pneumococcal polysaccharide vaccine among older adults [444-448], and included studies of community-wide education showed inconsistent results in limited populations [449-455]. CPSTF did find strong evidence that education used in combination with other health care system-based or community-based interventions was effective in increasing vaccination rates.

There are few examples of stand-alone patient education programs that have had success in increasing vaccine uptake. Educational pamphlets given to pregnant women in the northeastern U.S. were associated with significant increases in perceptions of the safety and benefit of maternal influenza vaccine as well as overall uptake [456]. An 8-minute video focusing on parental accounts of their children contracting vaccine-preventable diseases, shown exclusively to vaccine-hesitant parents via a laptop in pediatric waiting rooms, was associated with a significant decrease in Parent Attitudes about Childhood Vaccines (PACV) survey score measured two months later, although no difference in timely receipt of vaccines was shown [457]. A 3-arm, randomized controlled trial

conducted in Colorado from 2013-2016 found that infants of pregnant women assigned to a website with vaccine information and interactive social media components were statistically significantly more likely to be up-to-date on recommended vaccines at 200 days of age than infants of pregnant women given usual care, whereas infants of pregnant women assigned to a website with vaccine information but without interactive social media components were non-statistically significantly more likely to be up-to-date on recommended vaccines at 200 days of age than infants of pregnant women given usual care [458]. Among 272 mothers with vaccine concerns from Tennessee and California, distribution of vaccine information pamphlets and Vaccine Information Statements (VIS) significantly improved vaccine attitudes, although vaccine uptake was not measured [211].

Other patient education programs have been unsuccessful in increasing vaccine uptake. Strategies based on correcting vaccine misinformation or exposure to fear appeals have shown mixed results [459-461]. Despite demonstrating some effectiveness in knowledge gain [462], correcting vaccine misinformation often leaves vaccine intentions unchanged, and has even been shown to further reducing the vaccine intentions of some sub groups [459-461]. This backfiring effect has been shown to be especially likely among those with high levels of preexisting vaccine hesitancy [460, 461].

Attitudes and beliefs about vaccines vary substantially among adults [134, 463]. These attitudes and beliefs influence the response to vaccine messages [460, 461]. This highlights the need for individual tailoring of vaccine messaging depending on these underlying attitudes and beliefs.

When given in combination with other effective interventions, and tailored to each individual's vaccine attitudes and beliefs, vaccine education could contribute to increasing adult vaccine coverage.

Educational Vaccine Apps

Several educational vaccine apps have been developed previously [464-467]. Dempsey et. al provided a tailored, interactive website to 42 parents in waiting rooms of primary care clinics and found a slight but non-statistically significant increase in mean adolescent vaccination intention, yet no increase in actual adolescent vaccination [464]. Atkinson et. al studied the effect of ImmunizeCA, a Pan-Canadian immunization app, in in a cohort of 50 childbearing women [465]. Although changes in vaccine attitudes occurred in both directions, about a third of these women perceived that the app increased their likelihood of vaccinating on time. Fadda et. al found that smartphone-based interventions using gamification features and videos in combination with text messages increased vaccine knowledge, intent, and decision confidence among parents of young children in Italy [466]. Bednarczyk et. al describe the global reach of their mobile smartphone app ReadyVax, which provides access to evidence-based vaccine information for both providers and patients, but does not test its effect on vaccine knowledge, attitudes or intention [467]. None of these apps have incorporated referral of friends and family.

Financial Incentives

Financial incentives have mostly been shown to be effective in encouraging relatively discrete, infrequent behaviors, particularly among low income groups [468, 469]. As most vaccinations are discrete, infrequent behaviors, financial incentives may be an effective method of promoting them [470].

In 2015, the Community Preventive Services Task Force (CPSTF) recommended "client or family incentive rewards, used alone or in combination with additional interventions, based on sufficient evidence of effectiveness in increasing vaccination rates in children and adults", as stated in their Task Force Finding and Rationale Statement available at https://www.thecommunityguide.org/findings/vaccination-programs-client-or-family-incentive-rewards [443].

In low- and middle-income countries, there is conflicting evidence for whether financial incentive programs increase vaccine coverage. A 2016 Cochrane Database Systematic Review found that monetary incentives in these countries may have little or no effect on childhood immunization coverage in unless combined with regular outreach [471]. Similarly, a 2013 systematic review and meta-analysis found that financial incentives have no effect on coverage of individual vaccines in such countries, although a small and nonsignificant increase in coverage of full, age-appropriate immunization was noted [472]. A 2015 systematic review and meta-analysis found that incentives led to a significantly higher receipt of childhood vaccines; however, this may be misleading as their analysis pooled both monetary and non-monetary incentives together [473]. A recent cluster randomized controlled trial in Kenya showed that text message reminders combined with mobile-money incentives successfully improved timely childhood immunization, even in a setting with high baseline vaccine coverage [474].

In high-income countries such as the United States, the evidence base for financial incentive programs increasing vaccine coverage is more promising. A 1999 review found several successful examples both financial and non-financial (such as lottery tickets or food vouchers) incentive programs for increasing immunization coverage in the U.S. and the U.K. [475]. A 2002 meta-analysis found that patient financial incentives increased coverage of influenza and pneumococcal

vaccines in adults, with an adjusted odds ratio of 3.42 (95% CI: 2.89–4.06) [476]. A 2014 systematic review of parental financial incentives for increasing preschool vaccination uptake found insufficient evidence to conclude whether such interventions were effective [477]. Monetary incentives were shown to be effective in increasing adherence to the multi-dose hepatitis B vaccine series among drug users [478-483], as well as increasing coverage of influenza vaccine in the workplace setting [484, 485] and increasing uptake of HPV vaccinations among adolescent girls [486, 487].

Study Context

A Comprehensive Pre-Natal Intervention to Increase Vaccine Coverage (P3+)

P3+ (full title: *A Comprehensive Pre-Natal Intervention to Increase Vaccine Coverage*) is sponsored by the National Institutes of Health (NIH) via an R01 grant (1R01AI11048201A) and is a collaboration between Emory University Rollins School of Public Health and School of Medicine, Johns Hopkins Bloomberg School of Public Health (JHSPH), and University of Colorado Anschutz Medical Campus. The mPrincipal Investigators are Saad B. Omer, MBBS MPH PhD (Emory) and Daniel Salmon, PhD MPH (JHSPH).

P3+ is one of the first large randomized controlled trials of a prenatal intervention package to increase uptake of maternal and infant vaccines. The intervention package was developed to meet the diverse and complex information needs of mothers in a novel, innovative, evidence based and comprehensive manner, and intervenes at the Practice, Provider, and Patient (P3) levels. Practice-level interventions include: establishment of immunization champions; introduction of standing orders; addition of immunization information to the practice website; and provision of immunization rate feedback via the AFIX program (Assessment, Feedback, Incentives, and eXchange). Provider-level interventions include: a provider training module eligible for continuing education credits on how to talk to patients about vaccines; Maintenance of Certification (MOC) Part 4 credit for completion of the training modules and attendance at AFIX meetings; and a comprehensive written resource on vaccines, vaccine recommendations, vaccine-preventable diseases, and systematic reviews of a large number of vaccine safety concerns, with

standardized talking points on each topic for use during discussions with patients. Some of the content from this written resource (systematic reviews of safety concerns) is a portion of this dissertation and the entire resource is being published by Springer in October 2018. The patient-level intervention includes: a text message reminder program for upcoming vaccinations due; and an individually-tailored educational application for smartphones, tablets and computers. This app, called MomsTalkShots, collects patient-level survey data to monitor changes in vaccine knowledge, attitudes and beliefs over time, and delivers a selection of educational videos about vaccines specific to each individual's responses to these survey questions.

The JHSPH study team members that overlap both the P3+ and Walgreens Cocooning studies were primarily responsible for the development of the P3+ patient-level app (and the surveys and educational videos that comprise it). This app is the one piece of the P3+ intervention package that is also used in the Cocooning study. The app has been updated to fit the Cocooning study, and the surveys and videos edited to reflect the change in target population (from pregnant women to their close contacts).

Final analysis will primarily focus on vaccine uptake both for pregnant women and for their children, through 20 months of age, to test the hypothesis that increasing acceptability of vaccines during pregnancy will lead to positive changes in acceptance of vaccines for children.

Theoretical Framework

Development of the P3+ intervention package was guided by the Systems Model of Clinical Preventive Care, as it encouraged the development of a comprehensive intervention acting at

multiple levels (e.g., practice, provider, and patient) [488]. Development of the P3+ patient-level educational app was guided by the Elaboration Likelihood Model (ELM), a behavior change model that encourages concurrent use of peripheral and central route processing [489].

Recruitment

The intervention is currently taking place in a geographically and socio-demographically diverse set of obstetrician-gynecologist offices in Georgia and Colorado. Recruitment goals of enrolling 1100 patients per state have been reached.

Randomization

The study uses a two-by-two factorial design, randomizing at both the practice and the patient level (Figure 1). Obstetric and midwife practices in both Georgia and Colorado have been randomized to be either an intervention practice or a control practice, and each patient that is enrolled into the study at any of these practices is randomized to be either an intervention patient or a control patient. Intervention patients receive the patient-level intervention regardless of whether they are enrolled at an intervention or control practice; both intervention and control patients enrolled at an intervention practice benefit from the practice- and provider-level interventions. This will allow for independent assessment of the practice- and provider-level interventions versus the patient-level interventions.

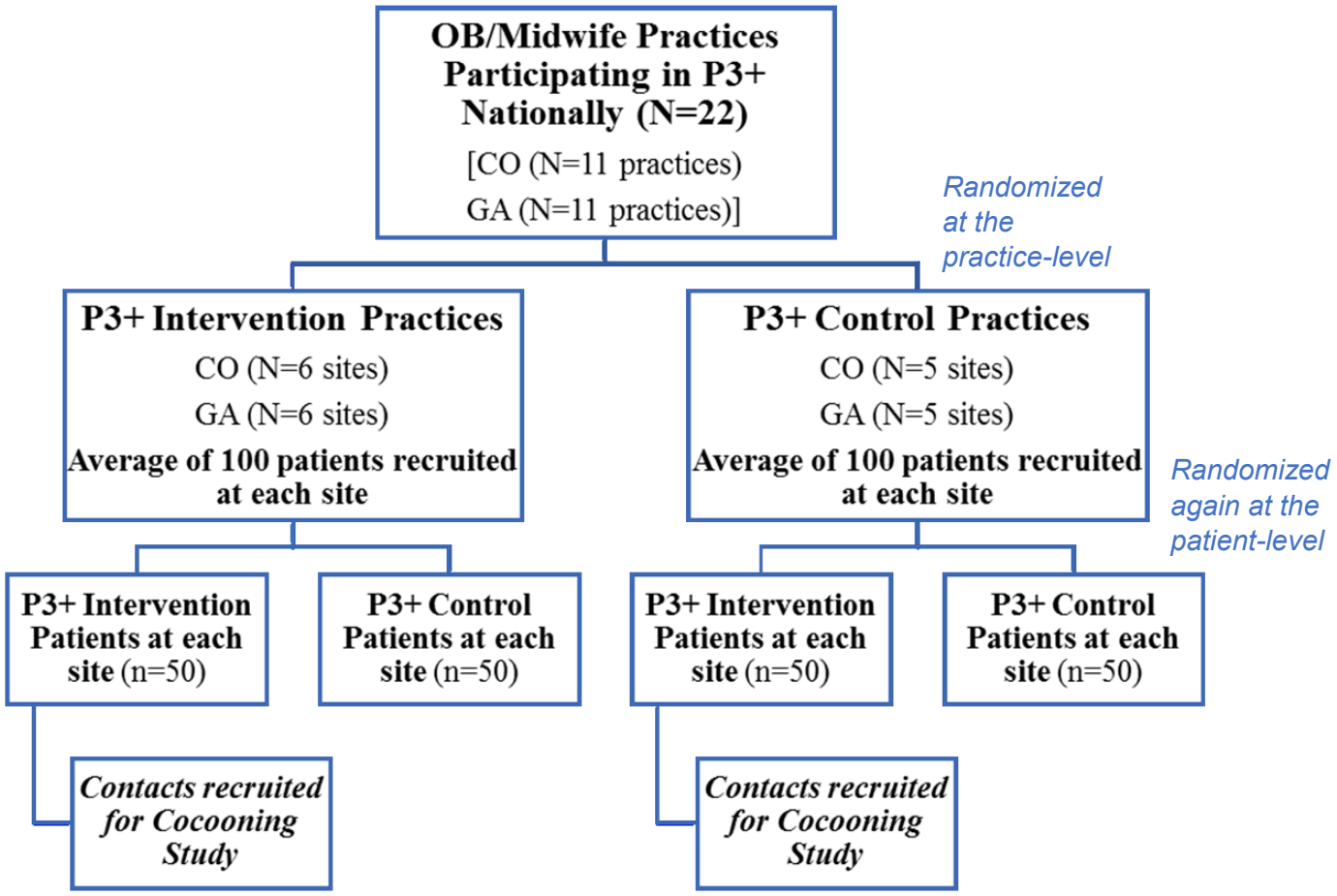

Figure 1. Randomization for P3+ Study (factorial design randomized at *both* the practice- and patient-levels)

Surveys

All P3+ participants receive three surveys: one at baseline, one at approximately 30 days post-birth of infant, and a final follow-up survey at approximately 18 months post-birth of infant. Survey reminders are being sent by email and text. All surveys are administered through the MomsTalkShots app and collect data on vaccine intentions, knowledge, attitudes, beliefs, norms

and levels of trust (see *Appendix 1: Baseline Survey for Pregnant Women in P3+*). Upon completion of each survey, participants receive a $20 gift card.

Walgreens Cocooning Study

As part of an add-on study sponsored by Walgreens, the MomsTalkShots app from P3+ encouraged its users to refer their close friends and family to the app as well. The app then administered surveys and provided individually-tailored educational videos to these referred contacts, as well as linking them to a Walgreens Balance Rewards points incentive redeemable for use in any Walgreens store immediately after vaccination at a Walgreens pharmacy. This study will evaluate these interventions in improving cocooning among the infants' family and friends.

Pharmacies such as Walgreens are numerous and widespread throughout the United States. As of August 2016, there were 8,175 total Walgreens drugstores in the U.S., located across all 50 states, the District of Columbia, Puerto Rico and U.S. Virgin Islands [490]. Walgreens purchased an additional 1,932 Rite Aid stores in 2017 [491]. There is a Walgreens store within 5 miles of each P3+ practice; most are within 1 mile.

Many Walgreens pharmacies are located in areas that are otherwise medically underserved. These pharmacies provide convenient locations for obtaining certain vaccinations, most notably seasonal influenza vaccine. For example, over 43% of the United States population resides in medically underserved areas (MUAs), and almost half of this population is served by Walgreens pharmacies. During the 2009-2010 influenza season, over one third of influenza immunizations were administered by pharmacies located in MUAs [492]. Pharmacies such as Walgreens also provide convenient hours, as working-age adults in particular generally prefer to receive vaccines during non-working hours, when traditional vaccine providers are often unavailable [438]. Finally,

receiving a vaccine at a pharmacy does not require the additional time and costs inherent in scheduling an appointment with a primary care provider [493].

Pharmacies providing vaccinations greatly improves vaccine accessibility, which is especially important for adult vaccinations for which coverage is typically low [438]. Although regulatory barriers and logistic challenges must be accounted for during program implementation [494], including pharmacies in influenza and pertussis vaccination efforts has been shown to be successful in increasing vaccine coverage [495, 496], and patients consistently report satisfaction with pharmacist-led vaccinations [493, 496].

The Walgreens Balance Rewards program is free to join and allows its members to accrue points for each purchase that can be used towards future Walgreens purchases. Prospective members must be at least 13 years of age to enroll. Further information is available at https://www.walgreens.com/topic/balancerewards/balance-program-details.jsp [497]. Walgreens currently has about 100 million Balance Rewards Members, or a third of the US population.

Theoretical Framework

Development of the Cocooning study intervention package was guided by the Health Belief Model (HBM), as it tries to identify beliefs that influence behavior change, such as perceived susceptibility and severity of a negative health outcome, and perceived benefits of and barriers to adapting a preventive health behavior [498]. Perceived benefits and barriers have consistently been shown to be the strongest predictors included in HBM [499]. HBM has been studied in the context of childhood vaccines, and parents who delay or refuse vaccines are more likely to have safety

concerns and perceive fewer benefits associated with vaccines than parents who vaccinate on time [217]. By offering a financial incentive, we hope to increase the perceived benefits of cocooning vaccinations, and by offering these vaccines at Walgreens pharmacies, we hope to reduce the barriers to receiving these vaccines, especially for working adults who do not regularly see a doctor. Perceived susceptibility and severity of pertussis and influenza disease are also addressed in the educational videos offered in the patient-level app.

Development of the Cocooning study intervention package was also guided by Social Cognitive Theory (SCT), which examines the influence of one's social environment on health behavior at the interpersonal level [500]. This intervention package adheres to SCT's concept of reciprocal determinism by concurrently affecting both environmental and personal factors; it alters the environment surrounding cocooning vaccination via financial incentives and more convenient pharmacy access, and influences personal attitudes via the educational videos in the app. These videos will also ideally empower pregnant women to talk to their close contacts about vaccination by providing them confidence through increased knowledge; this will then hopefully increase the self-efficacy of these women in regards to discussing this topic with their friends and family, as well as encourage the interpersonal influence on behavior potentially imparted by these discussions.

Recruitment

The Cocooning study targets close contacts of pregnant women to accomplish cocooning. The Cocooning study makes use of the study population of P3+ to recruit its own study participants,

by having the app encourage all P3+ intervention patients (maximum n=1100) to refer friends and family members to the app if they so choose upon finishing one of their first two surveys. P3+ intervention patients are then asked to identify the first name of and relationship to up to six contacts (as well as the contact's email address and/or phone number) with whom they speak most about vaccine-related issues and will likely come into regular contact with the infant (maximum n=6600). These contacts can be friends, relatives, significant others, etc. This recruitment process is included in the P3+ protocol and has been approved by the Emory IRB. For referring friends and family, P3+ intervention patients receive a $10 gift card. The contacts identified during this process are then recruited to enroll in the Cocooning study by email (see *Appendix 2: Email to Invite Close Contacts to Join the Cocooning Study*).

Randomization

The Cocooning study has three study arms: Education and Financial Intervention, Financial Intervention Only, and Control. Roughly one third of participants in the Cocooning study are enrolled into each study arm (depending on how many contacts are successfully recruited for each pregnant woman, as all contacts of a particular pregnant woman are enrolled into the same arm). The randomization of contacts into these three study arms takes place at the level of the P3+ intervention patient before they are asked to join the study; that is, all contacts of a particular P3+ intervention patient are in the same study arm (Figure 2). Randomization is stratified by P3+ study clinic to ensure a geographic spread in each arm and reduce the chance of residual confounding by differences among clinic location or practices and procedures.

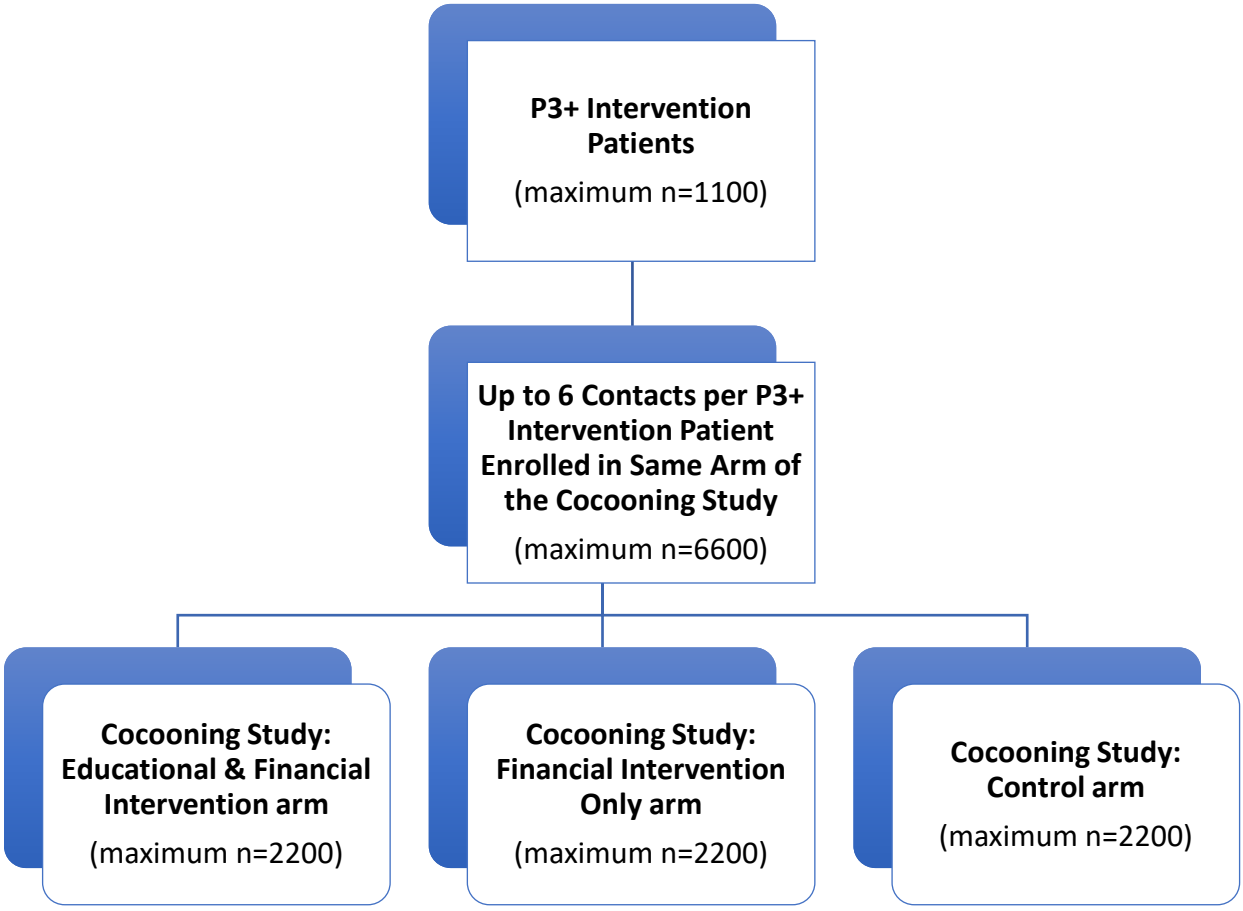

Figure 2. Randomization for Cocooning Study

Contacts randomized to either the Education and Financial Intervention or the Financial Intervention Only arm (to be referred to as intervention contacts) are eligible to receive a financial incentive for vaccination at Walgreens, and are enrolled in the app developed for P3+ and given the baseline survey there. Contacts randomized to the Education and Financial Intervention arm receive the educational intervention immediately after completing the baseline survey. The educational intervention consists of educational videos originally developed for P3+. Contacts randomized to the control arm do not enroll in the MomsTalkShots app and thus receive no

educational intervention, eligibility for financial incentive for vaccination, or baseline survey (Figure 3).

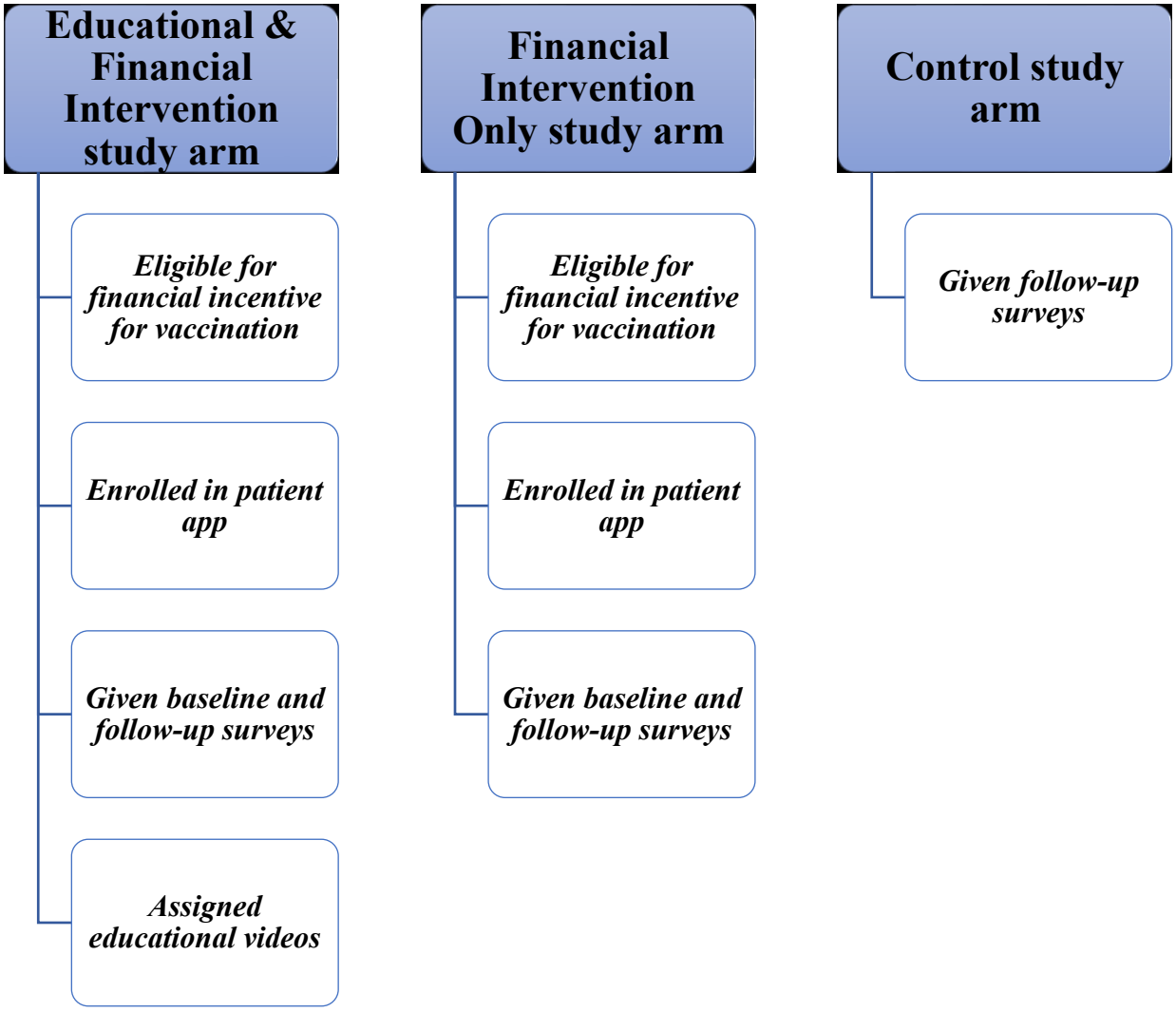

Figure 3. Interventions by Study Arm in Cocooning Study

Financial Incentive

The financial incentive for vaccination is the receipt of Walgreens Balance Rewards points in exchange for purchasing one or both of the vaccines of interest (i.e., influenza and Tdap) at a Walgreens. This incentive is only made available to those who vaccinate at a Walgreens as confirmed through Walgreens' internal system upon vaccination. Intervention contacts who receive the influenza and/or the Tdap vaccine at Walgreens would benefit from $10 worth of Walgreens Balance Rewards points for each vaccine (those who receive both vaccines would benefit from a total of $20 worth of Walgreens Balance Rewards points). To receive these incentives, participants must be enrolled in the Walgreens Balance Rewards program; therefore immediately after the baseline survey the app redirects intervention contacts to the Walgreens Balance Rewards program website, where they are encouraged to either login to an existing account or sign up for a new account. Immediately upon receiving vaccinations, participants' accounts would be credited with the balance rewards points, which participants could then use for front-of-store purchases on the same visit. Walgreens then tracks this purchase data, as well as other pertinent sales data such as the number of new pharmacy patients and new Balance Rewards members, and provide it to our JHSPH study team securely via Box, so that we are able to use this data to determine the financial viability of this incentive program from Walgreens perspective. Participant consent includes that Walgreens may track purchase data via the balance rewards program for analysis purposes. If the data shows the incentive program to be financially viable, this would make a convincing case for this program to be rolled out on a larger scale.

Surveys

All intervention contacts are assigned both baseline and follow-up surveys, with survey reminders sent by email and text. The baseline survey was administered through the MomsTalkShots app and collected data on baseline vaccine intentions, knowledge, attitudes and beliefs, as well as any changes to vaccine intentions after notification of eligibility for the financial incentive (see *Appendix 3: Intervention Contact Registration Survey*). Contacts randomized to the Education and Financial Intervention arm also received a short survey immediately after watching their assigned educational videos to assess the usability of the app and identify any subsequent changes in vaccine intentions, knowledge, attitudes and beliefs (see *Appendix 4: Intervention Contact Post-Video Survey*).

The follow-up survey is administered to both intervention and control contacts approximately 60 days after the P3+ intervention patient who referred them gives birth (see *Appendix 5: Intervention Contact 60 Day Post-Birth Survey* and *Appendix 6: Control Contact 60 Day Post-Birth Survey*). The primary objective of the follow-up survey is to assess whether the vaccines of interest were received by the contact during the pregnancy of the P3+ intervention patient, and if so, when and where. However, for the intervention contacts, the follow-up survey also collects data on changes to vaccine knowledge, attitudes and beliefs, the feasibility of the Walgreens Balance Rewards system, contacts' experience receiving the vaccine at Walgreens, and facilitators and barriers to the receipt of these vaccines at Walgreens and redeeming the Balance Rewards incentives as implemented in this study (if applicable).

For enrolling and completing the baseline survey, intervention contacts received a $20 gift card. For completing the follow-up survey, intervention and control contacts receive a $10 gift card.

These gift cards are not the same as the financial incentive for vaccination; they are simply an incentive to get study participants to enroll and complete the surveys (Figure 4).

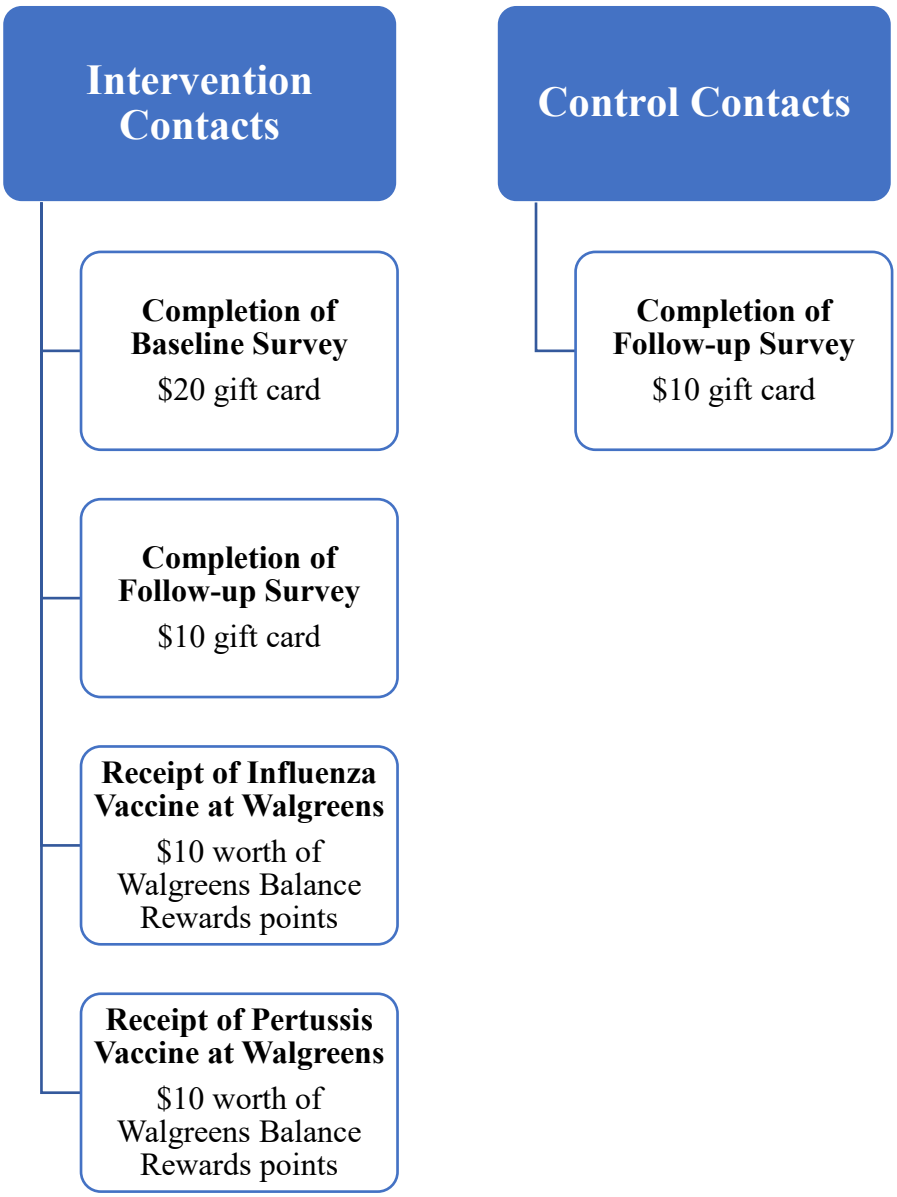

Figure 4. All Incentives Potentially Received by Participants in Cocooning Study

Manuscript 1: The State of Vaccine Safety Science: Systematic Reviews of the Evidence

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Key Points

Question

Which adverse events following immunization (AEFI) have been shown to be caused by vaccines, and which have not?

Findings

For 12 of the 47 AEFI studied, a causal relationship has been established. For the other 35, there are no studies of quality that show an association with routine immunization in the United States.

Meaning

Although vaccines currently recommended for the general population in the U.S. do cause some adverse reactions, vaccines have an excellent safety profile overall and provide protection against infectious diseases to individuals and the general population.

Abstract

Importance

Vaccine safety concerns contribute to gaps in immunization coverage and disease outbreaks. Health care providers desire objective and clear information on a broad range of vaccine safety issues to assist them in answering patient questions. There have been no recent comprehensive reviews on adverse events following immunization (AEFI), and previous reviews were not written for providers.

Objective

This systematic review provides an update to the scientific evidence assessing possible causal associations of AEFI compiled in the 2012 report from the Institute of Medicine (IOM) and the 2014 report from the Agency for Healthcare Research and Quality (AHRQ), along with refined causality conclusions intended for health care providers.

Evidence Review

We updated the evidence base for 44 AEFI studied in the 2012 IOM and 2014 AHRQ reports using systematic English-language PubMed literature reviews. We also reviewed 3 other AEFI and 2 special topics which have been raised as concerns among the media. We provide causality conclusions for each of these AEFIs, and the attributable risk (when possible) for AEFIs caused by vaccines.

Findings

For 12 of the 47 AEFI studied, a causal relationship has been established with at least one vaccine currently routinely recommended to the general population in the United States. These 12 confirmed adverse reactions are: anaphylaxis, arthralgia/arthritis (mild, acute and transient, not chronic), deltoid bursitis (when vaccine is administered improperly), disseminated varicella infection (in immune deficient individuals for whom the varicella vaccine is contraindicated), encephalitis, febrile seizures, Guillain-Barré Syndrome, hepatitis (in immune deficient individuals for whom the varicella vaccine is contraindicated), herpes zoster, immune thrombocytopenic purpura, meningitis, and syncope. Most of these adverse reactions are rare. For the other 35 AEFIs, the evidence does not support a causal relationship with vaccines recommended for routine use in the U.S. In-depth evidence bases for each AEFI are available in the *Full Vaccine Safety Review* section at the end of this thesis document; examples of which for three of the most common vaccine safety concerns expressed by parents (autism, vaccine ingredients, and simultaneous vaccination) are presented in this manuscript.

Conclusions and Relevance

Although vaccines currently recommended for the general population in the U.S. do cause some adverse reactions, vaccines have an excellent safety profile overall and provide protection against infectious diseases to individuals and the general population.

Full Text

Introduction

Immunization is one of the most effective ways to prevent morbidity and mortality from infectious diseases [13]. Vaccine coverage among children in the United States remains high [14]. However, vaccine hesitancy (concerns about the decision to vaccinate oneself or one's children) has risen in recent decades [1-4], and clustering of vaccine refusal has contributed to outbreaks of vaccine preventable diseases [5-11].

Most patients and parents, including parents who are vaccine hesitant, rely on health care providers as their most frequently used and credible source for vaccine information [15-17]. Providers need information on a broad range of vaccine safety issues to be confident in answering patient questions about vaccine safety as those questions become more specific, complex and wide-ranging. Clinicians desire vaccine safety information which is evidence-based, objective, and provides clear guidance on whether or not vaccines cause specific adverse event following immunization (AEFI), and the risk for AEFI that caused by vaccines [18-23].

Websites that include reliable sources of vaccine safety information for providers include the Centers for Disease Control and Prevention (CDC) [219, 220], the American Academy of Pediatrics, the Food and Drug Administration, and the Immunization Action Coalition [221]. However, much of the information available is not based on systematic comprehensive reviews and lacks clear statements on causality. The most comprehensive source of vaccine safety information available to date is the independent 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), entitled *Adverse Effects of Vaccines: Evidence and Causality,* [222] which builds on previous vaccine safety reports from the IOM [113, 114, 223-225]. These extraordinarily comprehensive reviews were conducted at the request of the Department of Health and Human Services (HHS) and its agencies, for the primary purpose of updating the National Vaccine Injury Compensation Program [226]. Final products from these

committees are books; they are neither succinct nor readily available to clinicians. In the 2012 report, the IOM concluded that the evidence is inadequate to accept or reject a causal relationship for 135 of 158 (85%) of vaccine-AEFI relationships studied. The 2014 report by the Agency for Healthcare Research and Quality (AHRQ) entitled *Safety of Vaccines Used for Routine Immunization in the United States: Evidence Report/Technology Assessment No. 215* [117, 227], was intended to expand upon and update the 2012 IOM report and was commissioned by HHS for the purpose of developing a federal vaccine safety research agenda. While these reports are useful for policy makers and vaccine safety scientists, they were not designed specifically for use by clinicians, and their length, writing style, and framing of causality assessments do not translate well to the practicing clinician. In addition, the IOM and AHRQ reports do not cover all AEFIs of current interest and many assessments are now out of date due to evidence emerging since their publications.

This systematic review presents providers with accurate, succinct and useful causality conclusions for a comprehensive list of AEFIs based on an objective and thorough systematic examination of the current scientific evidence.

Methods

We systematically reviewed the current scientific evidence to determine if a causal relationship could be established for 47 AEFIs of interest to the public and clinicians. This list of AEFIs was determined by reviewing prior IOM reports [113, 114, 222-225], the AHRQ report [117, 227], and

surveys of the public and clinicians that identified AEFIs of concern [23, 82, 131-133, 136, 137, 501-505].

Our search strategy expanded upon that of the IOM and AHRQ reports. Searches were performed in PubMed and combined Medical Subject Headings (MeSH) indexing terms for vaccines and vaccination with terms specific to each AEFI on our list. MeSH and free text terms for each AEFI and their relevant synonyms (listed as Entry Terms on the MeSH page) were included. Searches for AEFI included in the above reports were restricted to articles published since the end of the searches performed in those reports. Searches for topics not included in the above reports were not restricted by date of publication. Articles were excluded from consideration for epidemiological evidence if they: did not have human data; did not have appropriate controls; only included passive surveillance data (such as from the Vaccine Adverse Event Reporting System); had insufficient sample size to study the AEFI; reported on vaccines not currently routinely recommended for the general U.S. population; reported no primary data; were simulations, cross-sectional studies, or ecological studies; were letters, editorials, commentaries, or news articles; or were not in English. Case reports and uncontrolled cases series were only considered for inclusion for review of the *proposed biological mechanism* section, not the *epidemiologic evidence* section. Search results were exported to EndNote (Clarivate Analytics) and upon review relevant articles were added to the evidence base for each topic. Searches were initially performed in 2015 and updated in July 2018. General search terms used are listed in Appendix 1, and terms for each AEFI are in Appendix 2.

For each AEFI, the authors reviewed the epidemiological evidence and proposed biological mechanisms and drew conclusions using standardized categories of causality conclusions that were devised to be both scientifically accurate and useful to health care providers (Table 1). To be

considered a confirmed causal association, the evidence had to show a clear association between the event and at least one vaccine routinely recommended in the U.S. The frequency of confirmed vaccine adverse reactions was expressed using the World Health Organization definitions (Table 2).

Results

Our combined searches identified 25,103 unique articles (Figure 1). Excluded were: articles published prior to the IOM and AHRQ reports (20,690), non-contributing article types (394), non-human studies (849), and non-English articles (253). Articles indexed as case reports (203) were not considered as epidemiologic evidence. After review of the remaining 2,714 articles, 155 unique articles were added to the existing epidemiologic evidence base from the IOM and AHRQ reports (Appendix 3), cited a total of 198 times due to overlap among multiple AEFIs (Tables 3 and 4).

A causal relationship has been established for 12 of the 47 AEFI reviewed (Table 3). These 12 confirmed adverse reactions are: anaphylaxis, arthralgia/arthritis (mild, acute and transient, not chronic), deltoid bursitis (when vaccine is administered improperly), disseminated varicella infection (in immune deficient individuals for whom the varicella vaccine is contraindicated), encephalitis, febrile seizures, Guillain-Barré Syndrome, hepatitis (in immune deficient individuals for whom the varicella vaccine is contraindicated), herpes zoster, immune thrombocytopenic purpura, meningitis, and syncope. Most of these adverse reactions are rare. For 35 AEFI, there are no studies of quality that establish a causal association with routine vaccines used in the United States (Table 4). In particular, the evidence shows a clear lack of association between certain

vaccines and AEFIs: influenza vaccines do not cause asthma, childhood vaccines do not cause autism, vaccines do not cause diabetes, vaccines given to immunocompetent persons do not cause hepatitis, influenza vaccines do not cause Multiple Sclerosis (MS) in adults, and DTP and hepatitis B vaccines do not cause Sudden Infant Death Syndrome (SIDS).

Below we present the full evidence supporting conclusions for autism, vaccine ingredients, and simultaneous vaccination as these topics are frequently raised by parents [501, 502]. The evidence supporting all other conclusions is available in the *Full Vaccine Safety Review* section at the end of this thesis document, as well as on the website for the Johns Hopkins Institute for Vaccine Safety (IVS), http://www.vaccinesafety.edu/, and in the book entitled *The Clinician's Vaccine Safety Resource Guide: Optimizing Prevention of Vaccine-Preventable Diseases Across the Lifespan*, written by the authors of this manuscript and published by Springer Publishing Company [506, 507].

Autism

Epidemiological evidence: There have been 15 methodologically sound, controlled epidemiological studies exploring an association between ASD and receipt of MMR vaccine [105-112], thimerosal in vaccines [112, 508-512], and simultaneous vaccination with multiple vaccines [513, 514], in addition to the relevant systematic reviews [113-117] and one meta-analysis [118]. Together, these studies included more than 1.8 million children. Notwithstanding 11 studies from a pair of authors [515-525], all of which had substantial methodological flaws [114-116, 526], the epidemiological evidence consistently shows no association between MMR vaccine, thimerosal in

vaccines, or simultaneous vaccination and ASD. One recent study suggested a possible increased risk of ASD among children whose mothers received an influenza vaccination during their first trimester of pregnancy, although this association was not statistically significant after a post hoc analysis adjusting for multiple comparisons, and there was no association between ASD and influenza vaccination received during any trimester [527]. Another recent study showed that receiving Tdap vaccine during pregnancy is not associated with increased risk of ASD in the child [528].

Proposed biological mechanism: The overlapping times of childhood vaccine administration and usual onset of ASD symptoms have led to speculations about a possible causal pathway; however, the proposed links have been unsubstantiated [529]. Several different theories were proposed to attribute the cause of ASD to vaccines. In his since retracted 1998 study, Wakefield suggested that a dysregulated immune response to measles antigen in the MMR vaccine led to persistent intestinal infection, allowing "toxins" to enter the blood stream and enter the central nervous system leading to developmental regression in children [96]. He claimed support for this because of his alleged detection of measles virus RNA in bowel specimens of several children with ASD. However, his referenced study was found to be fraudulent, and no evidence of persistent infection has been shown in studies that used appropriate methods [530-532]. Another proposed trigger for ASD was thimerosal, an ethylmercury-containing preservative that used to be present in some vaccines, although not in the MMR vaccine. This theory was based on observed similarities in some features of ASD and mercury poisoning [119]; however, the degree of these similarities and the plausibility of this suspected association was refuted by neurologists [121]. The IOM found no valid mechanistic evidence connecting MMR or thimerosal-containing vaccines and ASD [114, 222].

Conclusion: Childhood vaccines **do not cause** autism. Maternal vaccines **have not been shown to cause** autism. The IOM concluded in 2004 that the body of evidence favors rejection of a causal relationship between autism and MMR vaccine and thimerosal-containing vaccines [114, 222]. No evidence has become available since the IOM report that changes this conclusion. MMR vaccine prevents rubella disease and congenital rubella syndrome, a cause of autism.

Vaccine Ingredients

Epidemiological evidence: A few studies have reported an association between vaccines containing aluminum adjuvants and persistent nodules at the injection site, at an estimated rate of 0.03-0.83% [533-536]. Two studies examining infant exposure to aluminum from both diet and vaccines concluded that aluminum adjuvants at the levels of in vaccines are well below the calculated safe body burden [537, 538]. A 2017 review found that current data do not support a causal relationship between aluminum containing vaccines and a variety of autoimmune disorders [539]. A meta-analysis of clinical trials of 25,056 children under 10 years of age who received vaccines with newer adjuvants AS01, AS02, AS03 or MF59 found no safety concerns [540].

Allergic reactions to vaccines (including immediate hypersensitivity reactions) have been estimated to occur approximately once per 50,000-1,000,000 doses. Anaphylaxis, the most concerning type of such reactions, has been estimated to occur approximately once per 100,000-1,000,000 doses for most commonly administered vaccines [272]. Rates of anaphylaxis can differ depending on the vaccine, age of the recipient, and gender; for example, adult females are at a

relatively higher risk of hypersensitivity reactions, including anaphylaxis, than males [541]. Hives occurs more commonly, but no precise rate is available.

A review of data on substances sometimes found in certain vaccines in very small quantities, such as aluminum, gelatin, human serum albumin, formaldehyde, antibiotics, egg proteins, and yeast proteins, found no evidence of harm other than rare instances of hypersensitivity reactions such as anaphylaxis in those with severe allergies to either gelatin or egg proteins [542].

Conclusion: Certain ingredients that are present in some vaccines (other than disease-specific antigens), such as gelatin or neomycin, **can very rarely cause** severe hypersensitivity reactions (e.g. anaphylaxis) in vaccines with those specific allergies. Allergic reactions occur approximately once every 50,000-1,000,000 doses and anaphylaxis occurs approximately once every 100,000-1,000,000 doses for most commonly administered vaccines.

Some adjuvants **can cause** increased rates of local reactions, and alum containing adjuvants **can cause** nodules at the injection site (at an estimated rate of 0.03-0.83%).

Ingredients in vaccines currently routinely recommended to the general population in the U.S.* **have not been shown to cause** any other adverse reactions.

Simultaneous Vaccination

Epidemiological evidence: Vaccines which may induce fever may also rarely induce febrile seizures. Febrile seizures are a common and typically benign childhood condition, occurring in 2-

* These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

5% of children at some point during their first five years of life. Febrile seizures have an estimated background incidence of 240–480 per 100,000 person-years in children under five years, although this varies by age, genetics, co-morbidities and environmental risk factors. Although potentially frightening to witness, there are no long-term effects of simple febrile seizures [293-296].

Febrile seizures occurred at a rate of 26.4 per 1000 person-years after MMR and 84.6 per 1,000 person-years after MMRV (ProQuad®) in the 7-10 days after vaccination [297]. Several studies have confirmed that MMRV combination vaccine has a higher risk of febrile convulsions than simultaneous yet separate administration of the first dose of MMR and varicella vaccine (Varivax®), resulting in 1 additional febrile seizure for every approximately 2300-4587 MMRV doses administered [297, 543-547]. There is no increased risk of fever or febrile seizures in children receiving their second dose of measles-containing vaccine at 4 to 6 years of age, whether given MMR or MMRV [40, 220]. Delaying MMR or MMRV vaccines past 15 months of age results in a higher risk of seizures than vaccinating according to the recommended schedule [548, 549].

Febrile seizures were estimated to occur at a rate of 17.5 per 100,000 doses in children aged 6-59 months after receiving concomitant trivalent inactivated influenza vaccine (abbreviation: TIV) and 13-valent pneumococcal conjugate vaccine (abbreviation: PCV13; trade name: Prevnar13®); lower rates of 4.9 per 100,000 doses and 5.3 per 100,000 doses were estimated in children who received TIV without concomitant PCV13 and in children who received PCV13 without concomitant TIV, respectively, resulting in an additional 7.3 febrile seizures per 100,000 doses of concomitant TIV and PCV13 versus separate day administration. However, these risk differences varied substantially with age due to the age-dependent background rates of febrile seizures, with

the highest estimates at 16 months (45 per 100,000 doses of concomitant vaccination) and the lowest at 59 months (4 per 100,000 doses of concomitant vaccination) [296].

A large cohort study found a small increased risk of febrile seizures after the first two doses of the DTaP-IPV-Hib combination vaccine in Denmark, with an absolute risk of less than 4 per 100,000 vaccinations [550]. A large Vaccine Safety Datalink (VSD) study found no association between seizures and the DTaP-IPV combination vaccine (Kinrix®) among children 4 to 6 years of age [551].

The 2012 IOM report found that the evidence favors rejection of a causal relationship between multiple immunizations and increased risk for infections and for type I diabetes [224].

A 2013 IOM report uncovered no evidence of major safety concerns associated with adherence to the childhood immunization schedule [552].

A randomized trial in France and Belgium during the 2014–2015 influenza season found no difference in rates of symptoms among older adults comparing co-administration of quadrivalent inactivated influenza vaccine and 23-valent pneumococcal polysaccharide vaccine (abbreviation: PPSV23; trade name: Pneumovax 23®) with separate administration, with the exception of injection site pain which occurred more frequently in the co-administration group [553]. A 2016 report summarizing ten phase 3 and 4 studies found no impact on vaccine reactogenicity or safety when co-administering routine vaccines with meningococcal conjugate vaccine (abbreviation: MenACWY-CRM; trade name: Menveo®) [554]. A phase II randomized study found that co-administration of bivalent meningococcal B vaccine and DTaP/IPV was safe and well tolerated [555].

Retrospective cohort studies using the VSD found no increase in risk of acute adverse reactions or adverse birth outcomes among those vaccinated with Tdap or influenza vaccines during pregnancy [556], as well as among those vaccinated with Tdap during pregnancy when comparing those who had received a tetanus toxoid containing vaccine relatively recently with those who had not [396]. In addition, no increase in risk of acute adverse reactions or adverse birth outcomes were found among those vaccinated concurrently with Tdap and influenza vaccines during pregnancy compared to those vaccinated sequentially [371].

A VSD nested case-control study of nearly half a million children found no significant difference in estimated cumulative vaccine antigen exposure through the first 23 months of life comparing children ages 2 to 4 years with infections not targeted by the vaccines versus children without such infections [557].

Conclusion: Certain combination vaccines or simultaneous administration of vaccines that are known to cause fever **can rarely cause** febrile seizures in infants and young children at rates that are higher than the rates from individually administered vaccines. The rate of febrile seizures in the 7-10 days after vaccination was approximately 2-3 times higher for children who received MMRV as compared to MMR and varicella vaccines administered separately on the same day, and 4 times higher as compared to MMR alone (resulting in 1 additional febrile seizure for every approximately 2300-4587 MMRV doses administered) [297]. When influenza and pneumococcal conjugate vaccines are given simultaneously as opposed to on separate visits in children 6-59 months of age, the risk of febrile seizures in the 24 hours after vaccination increases from roughly 10.2 to 17.5 per 100,000 doses [296].

Simultaneous administration of Tdap and influenza vaccines during pregnancy **does not increase the risk of** acute adverse reactions or adverse birth outcomes. Combination vaccines and

simultaneous administration of vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** any other adverse reactions at a greater rate than their individual vaccine components.

Discussion

This comprehensive systematic review provides strong evidence that vaccines are very safe. For some major AEFIs of concern to the public and clinicians such as autism, the evidence supports that vaccines do not cause the AEFI. For those where there is evidence that the vaccine causes the AEFI, the rate of the reaction is often rare (e.g., roughly 4 febrile seizures per 100,000 children vaccinated) or very rare (e.g., 1-3 cases of Guillain-Barré Syndrome (GBS) per million influenza vaccinations).

The causality conclusions of this review mostly align with those of the previous IOM and AHRQ reports. However, there are a few notable differences due to the emergence of new evidence since these reports' publication: The IOM concluded that the evidence was inadequate to accept or reject a causal relationship between influenza vaccine and GBS, and the AHRQ report concluded that strength of evidence (SoE) was high for an association between 2009 monovalent H1N1 vaccine and GBS; our review concluded that influenza vaccine can cause GBS very rarely in adults. The IOM report only assessed the relationship between immune thrombocytopenic purpura (ITP) and tetanus-, diphtheria- or pertussis-containing vaccines, and the AHRQ report concluded that SoE

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

was moderate for an association between MMR vaccine and thrombocytopenic purpura; our review concluded that MMR vaccine can very rarely cause ITP in children. The AHRQ report concluded that SoE was insufficient and the IOM report concluded that the evidence was inadequate to accept or reject a causal relationship between tetanus-, diphtheria- or pertussis-containing vaccines and SIDS, and neither report studied other vaccines and SIDS; our review concluded that both DTP and hepatitis B vaccines do not cause SIDS. The AHRQ report concluded that SoE was insufficient and the IOM report concluded that the evidence was inadequate to accept or reject a causal relationship between influenza vaccines and multiple sclerosis (MS); our review concluded that influenza vaccines do not cause MS in adults.

Our review has several limitations. Firstly, there is potential for misunderstanding or misrepresentation of our causality conclusion of "*vaccines* ***have not been shown to cause***", as evidence that the AEFI has not been evaluated and therefore likely based on personal anecdotes. In most of these instances, the specific condition in question is quite rare in the general population and there are no signals indicating the need for large scale expensive studies; in others there are limited studies indicating no evidence of increased risk associated with vaccines. In almost all cases where we reach this conclusion, if there were a risk greater than our category of 'very rare,' (<1:10,000), that risk would have been detected under existing surveillance systems.

Secondly, space limitations prevent us from sharing the entirety of the evidence used to derive each causality conclusion presented, and full evidence is provided for only 3 topics (autism, vaccine ingredients, and simultaneous vaccination). These topics were chosen as they are frequently raised by parents [501, 502]; however, they are not the only topics of interest for providers or the public. The evidence supporting all other conclusions is available in the *Full Vaccine Safety Review* section at the end of this thesis document and elsewhere [506, 507].

Conclusions

Although vaccines currently recommended for the general population in the U.S. do cause some adverse reactions, vaccines have an excellent safety profile overall and provide protection against infectious diseases to individuals and the general population.

Acknowledgements

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Figures and Tables

Table 1. Categories of Causality Conclusions[*]

Categories	Definitions
Vaccines **can cause** the event.	The evidence shows a clear association between the event and at least one vaccine routinely recommended in the U.S.
Vaccines **did cause** the event.	The evidence showed a clear association between the event and at least one previously recommended vaccine. However, these vaccine(s) are no longer used in the U.S., if they ever were.
Vaccines **have not been shown to cause** the event.	The evidence of an association between the event and vaccines currently routinely recommended to the general population in the United States is insufficient or non-existent.
Vaccines **do not cause** the event.	The evidence shows clear lack of association between the event and vaccines currently routinely recommended to the general population in the United States.

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Table 2. Standard Categories of Frequency for Adverse Drug Reactions (provided by "Guidelines for Preparing Core Clinical-Safety Information on Drugs" - Report of CIOMS Working Group III, 1995)

Categories	Definitions
Very common	≥ 1/10 (≥ 10%)
Common	≥ 1/100 and < 1/10 (~1%-10%)
Uncommon	≥ 1/1,000 and < 1/100 (~0.1-1%)
Rare	≥ 1/10,000 and < 1/1,000 (~0.01-0.1%)
Very rare	< 1/10,000 (< 0.01%)

Table 3. Causal Relationship Established between Adverse Event Following Immunization (AEFI) and at Least One Vaccine Currently Routinely Recommended for the General Population in the United States[*]

AEFI	Conclusion	Attributable risk (doses)	Evidence added to IOM/AHRQ reports
Anaphylaxis	Vaccine components can very rarely cause anaphylaxis.	1/100,000-1,000,000	McCarthy et al. 2013 Daley et al. 2014 Kawai et al. 2014 Turner et al. 2015b, 2015a Vichnin et al. 2015 McNeil et al. 2016 Baxter et al. 2017
Arthralgia/Arthritis (mild, acute, transient – not chronic)	Rubella-containing vaccines can cause mild, acute, transient arthralgia or arthritis, very commonly in adult women but rarely in children. Other U.S. vaccines have not been shown to cause arthralgia or arthritis. Vaccines have not been shown to cause chronic arthralgia/arthritis, as stated in the table below.	10-25/100 rubella-containing vaccine doses (adult females)	
Deltoid Bursitis	Incorrect administration of vaccines can cause deltoid bursitis.	n/a	
Disseminated Varicella Infection	Varicella vaccine can rarely cause disseminated varicella infection in immune deficient individuals for whom the vaccine is contraindicated.	n/a	
Encephalitis	Measles vaccine can very rarely cause encephalitis. Mumps vaccine used in other countries did cause encephalitis (but not the vaccine licensed in the U.S.).	IOM found one case with strong mechanistic evidence	Daley et al. 2014 Kawai et al. 2014 Klein et al. 2015 Hansen et al. 2016 Ghaderi et al. 2017
Febrile Seizures	Vaccines that induce fever in infants and young children, such as MMRV, influenza,	3.92/100,000 (all vaccines	Rowhani-Rahbar et al. 2013

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

	and PCV vaccines, can rarely cause febrile seizures.	given ages 3-5 months)	Daley et al. 2014 Hambidge et al. 2014 Klopfer et al. 2014 MacDonald et al. 2014 Schink et al. 2014 Bakken et al. 2015 Kawai et al. 2015 Li-Kim-Moy et al. 2015 Ma et al. 2015 Macartney et al. 2015 Duffy et al. 2016 Hansen et al. 2016 Kuter et al. 2016 Li et al. 2016 Duffy et al. 2017 Macartney et al. 2017
Guillain-Barré Syndrome (GBS)	Influenza vaccine can cause GBS very rarely in adults. An old formulation of rabies vaccine did cause GBS (but is no longer available). Other vaccines, including current rabies vaccine, have not been shown to cause GBS.	1-3/ 1,000,000	Dodd et al. 2013 Galeotti et al. 2013 Greene et al. 2013 Huang et al. 2013 Kwong et al. 2013 McCarthy et al. 2013 Kawai et al. 2014 Prestel et al. 2014 Vellozzi, Iqbal, and Broder 2014 Martin Arias et al. 2015 Vichnin et al. 2015 Hansen et al. 2016 Andrews, Stowe, and Miller 2017 Gee, Sukumaran, and Weintraub 2017

			Grimaldi-Bensouda et al. 2017 Miranda et al. 2017 Sandhu et al. 2017
Hepatitis	Varicella vaccine can rarely cause hepatitis if administered to persons with certain immune deficiencies. Vaccines given to immunocompetent persons do not cause hepatitis.	n/a	
Herpes Zoster	Varicella vaccine can rarely cause herpes zoster due to vaccine-strain viral reactivation.	IOM found several cases with strong mechanistic evidence	Prymula et al. 2014
Immune Thrombocytopenic Purpura (ITP)	MMR vaccine can very rarely cause ITP in children.	1-3/100,000	Huang et al. 2013 Villa et al. 2013 Hansen et al. 2016 Kharbanda et al. 2016
Meningitis	Reactivation of varicella vaccine can very rarely cause meningitis. Mumps vaccine used in other countries did cause meningitis (but not the vaccine licensed in the U.S.).	IOM found several cases with strong mechanistic evidence	Daley et al. 2014 Kawai et al. 2014 Klein et al. 2015 Hansen et al. 2016
Syncope	Vaccines (and other injections) can rarely cause syncope.	4.4-14.1/ 100,000	Armed Forces Health Surveillance Center 2013

Table 4. No Causal Relationship Established between Adverse Event Following Immunization (AEFI) and Vaccines Currently Routinely Recommended for the General Population in the United States[*]

AEFI	Conclusion	Evidence added to IOM/AHRQ reports

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Acute Disseminated Encephalomyelitis (ADEM)	An old formulation of rabies vaccine did cause ADEM (but is no longer available). Other vaccines, including current rabies vaccine, have not been shown to cause ADEM.	Langer-Gould et al. 2014 Persson et al. 2014 Scheller et al. 2015 Baxter, Lewis, Goddard, et al. 2016
Arthralgia/Arthritis (chronic)	Vaccines have not been shown to cause chronic arthralgia/arthritis.	
Asthma	Influenza vaccines do not cause asthma. Other vaccines have not been shown to cause asthma.	Halsey et al. 2015 Timmermann et al. 2015 Turner et al. 2015b, 2015a Baxter et al. 2017
Ataxia	Vaccines have not been shown to cause ataxia.	Klein et al. 2015
Autism	Childhood vaccines do not cause autism. Maternal vaccines have not been shown to cause autism.	Taylor, Swerdfeger, and Eslick 2014 Jain et al. 2015 Uno et al. 2015 Zerbo et al. 2017 Becerra-Culqui et al. 2018
Bell's Palsy	One influenza vaccine used in other countries did cause Bell's Palsy (but is no longer available). U.S. vaccines have not been shown to cause Bell's Palsy.	Tseng et al. 2017 Wijnans et al. 2017
Brachial Neuritis	Vaccines have not been shown to cause brachial neuritis.	
Chronic Fatigue Syndrome	Vaccines have not been shown to cause chronic fatigue syndrome.	Donegan et al. 2013 Magnus et al. 2015 Feiring et al. 2017
Chronic Inflammatory Disseminated Polyneuropathy (CIDP)	Vaccines have not been shown to cause CIDP.	

Chronic Urticaria	Vaccines have not been shown to cause chronic urticaria.	Bergfors et al. 2014 Hansen et al. 2016
Complex Regional Pain Syndrome (CRPS)	Vaccines have not been shown to cause CRPS.	Moreira et al. 2016
Diabetes	Vaccines do not cause diabetes.	Kharbanda et al. 2013 Naleway et al. 2014 Fabiani et al. 2015 Hansen et al. 2016 Karnchanasorn et al. 2016 Kharbanda et al. 2016 Morgan et al. 2016 Vaarala et al. 2017 Elding Larsson et al. 2018
Epilepsy	Vaccines have not been shown to cause epilepsy.	
Erythema Nodosum	Vaccines have not been shown to cause erythema nodosum.	
Fibromyalgia	Vaccines have not been shown to cause fibromyalgia.	
Hearing Loss	Vaccines have not been shown to cause hearing loss.	Baxter, Lewis, Bohrer, et al. 2016
Infantile Spasms	Vaccines have not been shown to cause infantile spasms.	
Multiple Sclerosis (MS)	Influenza vaccines do not cause MS in adults. Influenza vaccines have not been shown to cause MS in children. Other vaccines have not been shown to cause MS.	Langer-Gould et al. 2014 Persson et al. 2014 Halsey et al. 2015 Scheller et al. 2015 Vichnin et al. 2015 Mailand and Frederiksen 2016 Frederiksen and Mailand 2017
Myocardial Infarction (MI)	Vaccines have not been shown to cause MI.	Macintyre et al. 2013 Hebsur et al. 2014

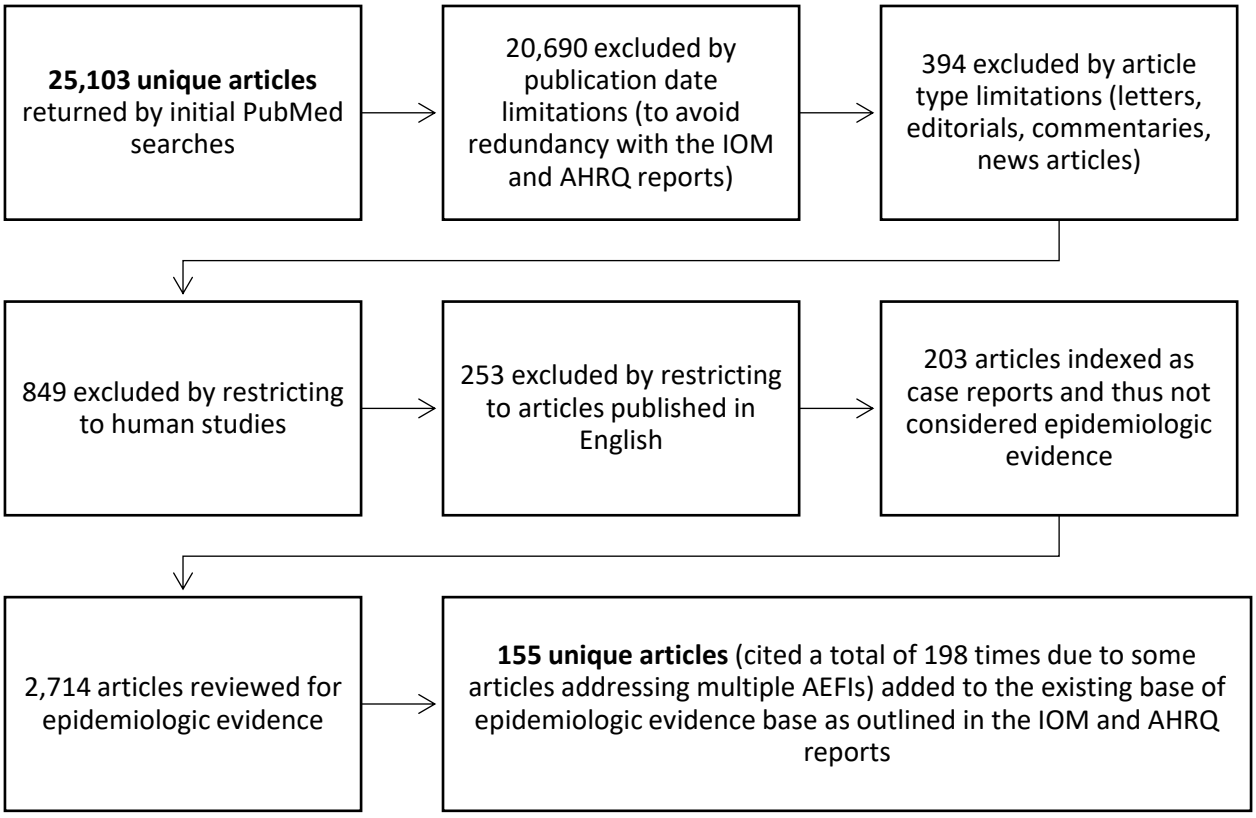
		Lavallee et al. 2014 Lin et al. 2014 Ochoa-Gondar et al. 2014 Clar et al. 2015 Vlachopoulos et al. 2015 Hsu et al. 2016 Chiang et al. 2017
Myocarditis	Smallpox vaccine can very rarely cause myocarditis, but is not routinely recommended to the general population in the U.S. Other vaccines have not been shown to cause myocarditis.	Engler et al. 2015 Kharbanda et al. 2016
Narcolepsy	Current vaccines have not been shown to cause narcolepsy. AS03-adjuvanted 2009 pandemic H1N1 influenza vaccine used in Europe did very rarely cause narcolepsy (but was not used in the U.S.).	Tsai et al. 2011 ECDC 2012 Nohynek et al. 2012 Partinen et al. 2012 Arnheim-Dahlström et al. 2013 Dauvilliers et al. 2013 Szakacs, Darin, and Hallbook 2013 Heier et al. 2013 McCarthy et al. 2013 Miller et al. 2013 Wijnans et al. 2013 Ahmed et al. 2014 Duffy et al. 2014 Johansen 2014 Montplaisir et al. 2014 O'Flanagan et al. 2014 Partinen et al. 2014 Persson et al. 2014 Feltelius et al. 2015 Stowe et al. 2016 Baxter et al. 2017

		Oberle et al. 2017 Sarkanen et al. 2018
Neuromyelitis Optica	Vaccines have not been shown to cause neuromyelitis optica.	Scheller et al. 2015
Oculorespiratory syndrome (ORS)	Two influenza vaccines used in Canada (but not used in the U.S.) did commonly cause ORS. Changes made to the formulation of these vaccines have resulted in a dramatic decrease in the risk of ORS.	
Opsoclonus Myoclonus Syndrome	Vaccines have not been shown to cause opsoclonus myoclonus syndrome.	
Optic Neuritis	Vaccines have not been shown to cause optic neuritis.	Scheller et al. 2015 Baxter, Lewis, Fireman, et al. 2016 Sridhar et al. 2017 Frederiksen and Topsoe Mailand 2017
Polyarteritis Nodosa	Vaccines have not been shown to cause polyarteritis nodosa.	
Primary Ovarian Insufficiency (POI)	Vaccines have not been shown to cause POI.	Naleway et al. 2018
Serum Sickness	Vaccines have not been shown to cause serum sickness.	
Small Fiber Neuropathy	Vaccines have not been shown to cause small fiber neuropathy.	
Spontaneous Abortion	Vaccines have not been shown to cause spontaneous abortion.	Tookey et al. 1991 Badilla et al. 2007 Dana et al. 2009 Garland et al. 2009 Wacholder et al. 2010 Forinash et al. 2011 Sato et al. 2011 Tavares et al. 2011 Bednarczyk, Adjaye-Gbewonyo, and Omer 2012

		Heikkinen et al. 2012 Makris et al. 2012 Oppermann et al. 2012 Pasternak et al. 2012 Sammon et al. 2012 Chambers et al. 2013 Chavant et al. 2013 Irving et al. 2013 Angelo et al. 2014 de Vries et al. 2014 Huang et al. 2014 Ma et al. 2014 Badell et al. 2015 Baril et al. 2015 Bratton et al. 2015 Goss et al. 2015 Ludvigsson et al. 2015 McMillan et al. 2015 Panagiotou et al. 2015 Vichnin et al. 2015 Bonde et al. 2016 Chambers et al. 2016 Donahue et al. 2017 Scheller et al. 2017 Steinhoff et al. 2017
Stroke	Vaccines have not been shown to cause stroke.	Daley et al. 2014 Lavallee et al. 2014 Lin et al. 2014 Siriwardena, Asghar, and Coupland 2014 Vila-Corcoles et al. 2014 Asghar, Coupland, and Siriwardena 2015

		Clar et al. 2015 Fullerton et al. 2015 Vichnin et al. 2015 Vlachopoulos et al. 2015 Hsu et al. 2016 Chiang et al. 2017 Lee et al. 2017
Sudden Infant Death Syndrome (SIDS)	DTP and hepatitis B vaccines do not cause SIDS. Other vaccines have not been shown to cause SIDS.	Hansen et al. 2016 Huang et al. 2017
Systemic Lupus Erythematosus (SLE)	Vaccines have not been shown to cause SLE.	Pellegrino, Radice, and Clementi 2015 Huang et al. 2016 Liao et al. 2016 Puges et al. 2016 Dhar et al. 2017
Transverse Myelitis	Vaccines have not been shown to cause transverse myelitis.	Nordin et al. 2014 Scheller et al. 2015
Vasculitis	Vaccines have not been shown to cause vasculitis.	Abrams et al. 2015 Jeffs et al. 2015 Da Dalt et al. 2016 Kerneis et al. 2016 Phuong et al. 2017

Figure 1. Literature Review Diagram



Manuscript Appendices

Appendix 1. General Search Terms

Type	Explanation	Terms
General Vaccine		("Vaccines"[Mesh] OR "Vaccination"[Mesh])
Date Limitation	If AE was included in 2014 AHRQ report, limited date to the end of their review.	("2013/08/01"[PDAT] : "3000/12/31"[PDAT])
Exclusion Criteria	No comments, editorials, letters, or news; human studies only; English language only; full text only	NOT (Comment[ptyp] OR Editorial[ptyp] OR Letter[ptyp] OR News[ptyp] OR Newspaper Article[ptyp]) NOT ("animals"[Mesh] NOT "humans"[Mesh]) AND English[lang] AND "loattrfull text"[sb]

Appendix 2. Adverse Event Following Immunization (AEFI) Search Terms

AEFI	Search Terms
Acute Disseminated Encephalomyelitis (ADEM)	(“Encephalomyelitis, Acute Disseminated”[Mesh] OR “acute disseminated encephalomyelitis”[tw] OR “acute disseminated encephalomyelitides”[tw] OR "ADEM"[tw])
Arthralgia, Arthritis	(“Arthritis”[Mesh] OR “Arthritis”[tw] OR “Arthritides”[tw] OR “Polyarthritis”[tw] OR “Polyarthritides”[tw] OR “arthrochondritis”[tw] OR “arthrosynovitis”[tw] OR “joint inflammation”[tw] OR “joint inflammations”[tw] OR “oligoarthritis”[tw] OR “Arthralgia”[Mesh] OR “Arthralgia”[tw] OR “Arthralgias”[tw] OR “Polyarthralgia”[tw] OR “Polyarthralgias”[tw] OR “joint pain”[tw] OR “joint pains”[tw])
Asthma	(“Asthma”[Mesh] OR “asthma”[tw] OR “asthmatic”[tw] OR “asthmas”[tw])
Ataxia	("Ataxia"[Mesh] OR "Ataxia"[tw] OR "Ataxias"[tw] OR "Ataxy"[tw] OR "Dyssynergia"[tw] OR "Coordination Impairment"[tw] OR "Coordination Impairments"[tw] OR "Lack of Coordination"[tw] OR "Incoordination"[tw] OR "Incoordinations"[tw])
Autism	("Autism Spectrum Disorder"[Mesh] OR "Autism"[tw] OR "Autistic"[tw] OR "Asperger"[tw])
Bell’s Palsy	(“Bell Palsy”[Mesh] OR “Bell Palsy”[tw] OR “Bells Palsy”[tw] OR “Bell's Palsy”[tw] OR “Bell Palsies”[tw] OR “Bells Palsies”[tw] OR “Bell's Palsies”[tw] OR “facial neuropathy”[tw] OR “facial paralysis”[tw] OR “facial paralyses”[tw] OR “facial palsy”[tw] OR “facial palsies”[tw])
Brachial Neuritis	(“Brachial Plexus Neuritis”[Mesh] OR “Neuralgia”[Mesh] OR “neuritis”[tw] OR “neuritides”[tw] OR “neuralgia”[tw] OR “neuralgias”[tw] OR “neuralgic”[tw] OR “neuropathy”[tw] OR “neuropathic”[tw] OR “Parsonage Aldren Turner Syndrome”[tw] OR “Parsonage-Aldren-Turner Syndrome”[tw] OR “Parsonage Turner Syndrome”[tw] OR “Parsonage-Turner Syndrome”[tw])
Chronic Inflammatory Disseminated Polyneuropathy (CIDP)	("Chronic Inflammatory Disseminated Polyneuropathy"[tw] OR "CIDP"[tw])
Complex Regional Pain Syndrome (CRPS)	("Complex Regional Pain Syndromes"[Mesh] OR "Complex Regional Pain Syndromes"[tw] OR "Complex Regional Pain Syndrome"[tw] OR "Causalgia"[tw] OR "Reflex Sympathetic Dystrophy"[tw])
Deltoid Bursitis	(“Bursitis”[Mesh] OR “Bursitis”[tw] OR “Bursitides”[tw] OR “Adhesive Capsulitis”[tw] OR “Adhesive Capsulitides”[tw] OR “Shoulder Impingement Syndrome”[Mesh] OR “Shoulder Impingement Syndrome”[tw] OR ((“periarthritis”[Mesh] OR “periarthritis”[tw] OR “tenosynovitus”[tw]) AND (“shoulder”[tw] OR “deltoid”[tw] OR “humeroscapular”[tw] OR “humeroscapularis”[tw] OR “scapulohumeral”[tw] OR “scapulohumeralis”[tw] OR “scapulo”[tw] OR “scapularis”[tw])) OR “UAIRVA”[tw] OR “frozen shoulder”[tw] OR “shoulder pain”[tw] OR “shoulder injury”[tw] OR “shoulder dysfunction”[tw] OR “shoulder stiffness”[tw] OR “stiff shoulder”[tw] OR “rigid shoulder”[tw] OR “shoulder rigidity”[tw])
Diabetes	("Diabetes Mellitus"[Mesh] OR "Diabetes"[tw])

Disseminated Varicella Infection	"Disseminated Varicella Infection"[tw]
Erythema Nodosum	("Erythema Nodosum"[Mesh] OR "Erythema Nodosum"[tw])
Fibromyalgia, Chronic Fatigue Syndrome	("Fatigue Syndrome, Chronic"[Mesh] OR "Fibromyalgia"[Mesh] OR "Chronic Fatigue"[tw] OR "Fibromyalgia"[tw] OR "Fibromyalgias"[tw] OR "Fibromyositis"[tw] OR "Fibrositis"[tw] OR "Fibrositides"[tw] OR "Diffuse Myofascial Pain Syndrome"[tw] OR "Myalgic Encephalomyelitis"[tw] OR "Postviral Fatigue Syndrome"[tw] OR "Postviral Fatigue Syndromes"[tw] OR "Royal Free Disease"[tw] OR "Systemic Exertion Intolerance Disease"[tw])
Guillain-Barré Syndrome (GBS)	(“Guillain-Barre Syndrome”[Mesh] OR “Guillain Barre”[tw] OR “Guillain-Barre”[tw] OR “Guillain-Barré”[tw] OR “Miller Fisher Syndrome”[Mesh] OR “Miller Fisher”[tw] OR“Miller-Fisher”[tw] OR “Fisher Syndrome”[tw] OR “Acute Inflammatory Polyneuropathy”[tw] OR “Acute Inflammatory Polyneuropathies”[tw] OR “Acute Inflammatory Demyelinating Polyneuropathy”[tw] OR “Acute Inflammatory Demyelinating Polyradiculoneuropathy”[tw] OR “Acute Inflammatory Polyradiculoneuropathy”[tw] OR“Acute Inflammatory Polyradiculoneuropathies”[tw] OR “Acute Inflammatory Demyelinating Polyradiculoneuropathy”[tw] OR “Acute Inflammatory Demyelinating Polyradiculoneuropathies”[tw] OR “Acute Autoimmune Neuropathy”[tw] OR “Acute Autoimmune Neuropathies”[tw])
Hearing Loss	("Hearing Loss"[Mesh] OR "Hearing Loss"[tw] OR "Hearing Impairment"[tw] OR "Hypoacusis"[tw] OR "Hypoacuses"[tw] OR "Deafness"[tw])
Hepatitis	(("Hepatitis"[Mesh] OR "Hepatitis"[tw] OR "Hepatitides"[tw]) AND "Viral Reactivation"[tw])
Herpes Zoster	(("Herpes Zoster" OR "Varicella") AND "Viral Reactivation"[tw])
Hypersensitivity Reactions (e.g., anaphylaxis, hives)	(“Anaphylaxis”[Mesh] OR “anaphylaxis”[tw] OR “anaphylactic”[tw] OR “Angioedema”[Mesh] OR “angioedema”[tw] OR “quincke edema”[tw] OR “quincke’s edema”[tw] OR “quinckes edema”[tw] OR “angioneurotic edema”[tw] OR “facial edema”[tw] OR “quincke oedema”[tw] OR “quincke’s oedema”[tw] OR “quinckes oedema”[tw] OR “angioneurotic oedema”[tw] OR “facial oedema”[tw] OR “Hypersensitivity”[Mesh] OR “hypersensitivity”[tw] OR “hypersensitivities”[tw] OR “allergy”[tw] OR “allergies”[tw] OR “allergic”[tw] OR “Urticaria”[Mesh] OR “urticaria”[tw] OR “urticarias”[tw] OR “hives”[tw])
Immune Thrombocytopenic Purpura (ITP)	(“Purpura, Thrombocytopenic, Idiopathic”[Mesh] OR “Thrombocytopenia”[Mesh] OR “Purpura”[Mesh] OR “ITP”[tw] OR “Werlhof's Disease”[tw] OR “Werlhofs Disease”[tw] OR “Werlhof Disease”[tw] OR “morbus werlhof”[tw] OR “thrombocytopenic”[tw] OR “thrombocytopenia”[tw] OR “thrombocytopenias”[tw] OR “thrombopenia”[tw] OR “thrombopenias”[tw] OR “macrothrombocytopenia”[tw] OR “macrothrombocytopenias”[tw] OR “platelet deficiency”[tw] OR “platelet deficiencies”[tw] OR “thrombocyte deficiency”[tw] OR “thrombocyte deficiencies”[tw] OR

	“thrombopenia”[tw] OR “thrombopenias”[tw] OR “purpura”[tw] OR “purpuras”[tw])
Meningitis, Encephalitis, Encephalopathy	("Encephalitis"[Mesh] OR "Encephalomyelitis"[Mesh] OR “encephalitis”[tw] OR “encephalitides”[tw] OR “encephalomyelitis”[tw] OR “encephalomyelitides”[tw] OR "Rasmussen Syndrome"[tw] OR "Rasmussen's Syndrome"[tw] OR "Rasmussens Syndrome"[tw] OR “encephalopathy”[tw] OR “encephalon”[tw] OR “encephalopathia”[tw] OR “panencephalopathy”[tw] OR “Leigh Disease”[Mesh] OR “leigh disease”[tw] OR “leigh's disease”[tw] OR “leighs disease”[tw] OR “leigh syndrome”[tw] OR “encephalomyopathy”[tw] OR “encephalomyopathies”[tw] OR “brain inflammation”[tw] OR “cerebritis”[tw] OR “Meningitis”[Mesh] OR “meningitis”[tw] OR “meningitides”[tw] OR “pachymeningitis”[tw] OR “pachymeningitides”[tw])
Multiple Sclerosis (MS)	(“Multiple Sclerosis”[Mesh] OR “multiple sclerosis”[tw] OR “disseminated sclerosis”[tw] OR “insular sclerosis”[tw])
Myocardial Infarction, Stroke	("Myocardial Infarction"[Mesh] OR "Myocardial Infarction"[tw] OR "Myocardial Infarctions"[tw] OR "Myocardial Infarct"[tw] OR "Myocardial Infarcts"[tw] OR "Heart Attack"[tw] OR "Heart Attacks"[tw] OR "Stroke"[tw] OR "Strokes"[tw])
Myocarditis, Myocardopathy, Cardiomyopathy	("Myocarditis"[Mesh] OR "Myocarditis"[tw] OR "Myocarditides"[tw] OR "Carditis"[tw] OR "Myocardopathy"[tw] OR "Myocardopathies"[tw] OR "Cardiomyopathies"[Mesh] OR "Cardiomyopathies"[tw] OR "Cardiomyopathy"[tw] OR "Myocardial Disease"[tw] OR "Myocardial Diseases"[tw])
Narcolepsy	(“Narcolepsy”[Mesh] OR “Cataplexy”[Mesh] OR “Narcolepsy”[tw] OR “Cataplexy”[tw] OR “Narcolepsy-Cataplexy”[tw] OR “Paroxysmal Sleep”[tw] OR “Gelineau Syndrome”[tw] OR “Gelineau's Syndrome”[tw] OR “Gelineaus Syndrome”[tw] OR “Gelineau Syndromes”[tw] OR “Gelineau's Syndromes”[tw] OR “Gelineaus Syndromes”[tw] OR “sleep epilepsy”[tw] OR “narcoleptic”[tw] OR “narcolepsis”[tw] OR “neurolepsy”[tw])
Oculorespiratory syndrome (ORS)	"Oculorespiratory syndrome"[tw]
Opsoclonus Myoclonus Syndrome	("Opsoclonus-Myoclonus Syndrome"[Mesh] OR "Opsoclonus-Myoclonus Syndrome"[tw] OR "Opsoclonus Myoclonus Syndrome"[tw] OR "Opsoclonus-Myoclonus Ataxia"[tw] OR "Opsoclonus Myoclonus Ataxia"[tw] OR "Dancing Eyes-Dancing Feet Syndrome"[tw] OR "Dancing Eyes Dancing Feet Syndrome"[tw] OR "Kinsbourne Syndrome"[tw] OR "Myoclonic Encephalopathies"[tw] OR "Myoclonic Encephalopathy"[tw])
Optic Neuritis, Neuromyelitis Optica	("Optic Neuritis"[Mesh] OR "Optic Neuritis"[tw] OR "Optic Neuritides"[tw] OR "Retrobulbar Neuritis"[tw] OR "Retrobulbar Neuritides"[tw] OR "Neuropapillitis"[tw] OR "Neuropapillitides"[tw] OR "Neuromyelitis Optica"[Mesh] OR "Neuromyelitis Optica"[tw] OR "NMO Spectrum"[tw] OR "Devic Disease"[tw] OR "Devic's Disease"[tw] OR "Devics Disease"[tw] OR "Devic Syndrome"[tw] OR "Devic's Syndrome"[tw] OR "Devics Syndrome"[tw])

Primary Ovarian Insufficiency (POI)	("Primary Ovarian Insufficiency"[Mesh] OR "Primary Ovarian Insufficiency"[tw] OR "Ovarian Failure"[tw] OR "Resistant Ovary Syndrome"[tw])
Seizures (e.g., Febrile, Epilepsy, Infantile Spasms)	("Seizures"[Mesh] OR "Seizures, Febrile"[Mesh] OR "Epilepsy"[Mesh] OR "Seizure"[tw] OR "Seizures"[tw] OR "Convulsion"[tw] OR "Convulsions"[tw] OR "Epilepsy"[tw] OR "Epilepsies"[tw])
Serum Sickness	("Serum Sickness"[Mesh] OR "Serum Sickness"[tw] OR "Serum Sicknesses"[tw])
Small Fiber Neuropathy	("Small Fiber Neuropathy"[Mesh] OR "Small Fiber Neuropathy"[tw] OR "Small Fiber Neuropathies"[tw] OR "Small Nerve Fiber Neuropathy"[tw] OR "Small Nerve Fiber Neuropathies"[tw] OR "Small Fibre Neuropathy"[tw] OR "Small Fibre Neuropathies"[tw] OR "Small Nerve Fibre Neuropathy"[tw] OR "Small Nerve Fibre Neuropathies"[tw])
Spontaneous Abortion	("Abortion, Spontaneous"[Mesh] OR "Spontaneous Abortion"[tw] OR "Spontaneous Abortions"[tw] OR "Miscarriage"[tw] OR "Miscarriages"[tw] OR "Early Pregnancy Loss"[tw] OR "Early Pregnancy Losses"[tw] OR "Tubal Abortion"[tw] OR "Tubal Abortions"[tw])
Sudden Infant Death Syndrome (SIDS)	("Sudden Infant Death"[Mesh] OR "Sudden Infant Death"[tw] OR "SIDS"[tw] OR "Crib Death"[tw] OR "Cot Death"[tw])
Syncope	("Syncope"[Mesh] OR "Syncope"[tw] OR "Syncopal"[tw] OR "Fainting"[tw] OR "Faints"[tw] OR "Syncopal"[tw] OR "Presyncope"[tw] OR "Presyncopes"[tw] OR "Drop Attack"[tw] OR "Drop Attacks"[tw])
Systemic Lupus Erythematosus (SLE)	("Lupus Erythematosus, Systemic"[Mesh] OR "Lupus Erythematosus"[tw] OR "Libman-Sacks Disease"[tw] OR "Libman Sacks Disease"[tw])
Transverse Myelitis	(“Myelitis, Transverse”[Mesh] OR “Myelitis”[tw] OR “Myelitides”[tw] OR “Myelopathy”[tw] OR “Myelopathies”[tw] OR “Spinal Cord Inflammation”[tw] OR “Spinal Cord Inflammations”[tw] OR “Spinal Inflammation”[tw] OR “Spinal Inflammations”[tw])
Vasculitis, Polyarteritis Nodosa	("Vasculitis"[Mesh] OR "Vasculitis"[tw] OR "Vasculitides"[tw] OR "Angiitis"[tw] OR "Angiitides"[tw] OR "Polyarteritis Nodosa"[Mesh] OR "Polyarteritis Nodosa"[tw] OR "Periarteritis Nodosa"[tw] OR "Necrotizing Arteritis"[tw] OR "Necrotizing Arteritides"[tw] OR "Essential Polyarteritis"[tw] OR "Essential Polyarteritides"[tw])

Appendix 3. Search results

Adverse Event Following Immunization (AEFI)	Initial results	Excluded (pub date)	Excluded (article type)	Excluded (not in humans)	Excluded (not in English)	Case report	Reviewed for Epi Evidence	Added to Epi Evidence
ADEM	698	653	10	1	5	16	13	4
Arthralgia, Arthritis	1566	1293	15	44	13	18	183	0
Asthma	1328	1111	14	28	10	4	161	5
Ataxia	135	117	1	4	0	4	9	1
Autism	677	583	17	1	5	0	71	5
Bell's Palsy	105	92	0	1	0	2	10	2
Brachial Neuritis	639	521	7	4	14	15	78	0
CIDP	5	4	0	0	0	1	0	0
CRPS	21	7	2	0	1	1	10	1
Deltoid Bursitis	25	17	1	0	0	6	1	0
Diabetes	1153	883	14	24	16	1	215	9
Disseminated Varicella Infection	3	3	0	0	0	0	0	0
Erythema Nodosum	48	45	0	0	0	0	3	0
Fibromyalgia, Chronic Fatigue Syndrome	73	51	3	0	1	0	18	3
GBS	512	405	12	2	5	8	80	17
Hearing Loss	203	169	3	2	1	4	24	1
Hepatitis	9	6	0	0	0	0	3	0
Herpes Zoster	8	4	0	0	1	0	3	1

Hypersensitivity Reactions (e.g., anaphylaxis, hives)	8752	7987	58	135	38	37	497	10
ITP	566	461	11	15	4	17	58	4
Meningitis, Encephalitis, Encephalopathy	9156	7735	115	190	86	50	980	5
Multiple Sclerosis	650	558	23	6	5	5	53	7
Myocardial Infarction, Stroke	285	215	7	2	4	3	54	16
Myocarditis, Myocardopathy, Cardiomyopathy	318	271	4	18	0	2	23	4
Narcolepsy	153	n/a	39	2	12	5	95	23
ORS	12	10	0	0	1	0	1	0
Opsoclonus Myoclonus Syndrome	2	2	0	0	0	0	0	0
Optic Neuritis, Neuromyelitis Optica	116	93	1	0	2	6	14	4
POI	15	n/a	5	2	0	2	6	1
Seizures	893	730	15	1	7	5	135	17
Serum Sickness	120	117	0	1	1	1	0	0
Small Fiber Neuropathy	5	1	0	0	0	1	3	0
Spontaneous Abortion	671	n/a	29	399	59	2	182	35
SIDS	126	116	1	0	0	0	9	2
Syncope	83	56	1	0	1	2	23	1
SLE	391	309	6	3	5	7	61	5
Transverse Myelitis	235	205	2	1	1	10	16	2

Vasculitis, Polyarteritis Nodosa	404	340	7	2	4	19	32	5
Total*	25103	20690	394	849	253	203	2714	155

**total calculated by combining all individual searches into one search, thus accounting for overlap of articles returned in multiple searches, not by adding raw numbers from each search together*

Appendix 4. Articles contributing to Adverse Event Following Immunization (AEFI) epidemiologic evidence not included in IOM or AHRQ reports

1. Persson I, Granath F, Askling J, Ludvigsson JF, Olsson T, Feltelius N. Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix: a population- and registry-based cohort study with over 2 years of follow-up. J Intern Med. 2014;275(2):172-190.
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15. Becerra-Culqui TA, Getahun D, Chiu V, Sy LS, Tseng HF. Prenatal Tetanus, Diphtheria, Acellular Pertussis Vaccination and Autism Spectrum Disorder. Pediatrics. 2018.
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Manuscript 2: Characterizing maternal vaccine attitudes and beliefs

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Key Points

Question

What are the baseline maternal and infant vaccine intentions, attitudes, beliefs, norms, and levels of trust among pregnant women in Georgia and Colorado?

Findings

Pregnant women demonstrated suboptimal maternal vaccine knowledge and intentions, and first-time pregnant women were substantially less certain in their vaccine knowledge and intentions than women with prior children. However, the vast majority of women trusted the information provided by their obstetrician or midwife about both maternal and infant vaccines.

Meaning

Obstetricians and midwives are in a unique position to provide accurate vaccine information to soon-to-be mothers and their partners before they make vaccine decisions for themselves and their children.

Abstract

Importance

Maternal vaccine coverage is poor and a substantial proportion of parents have concerns about vaccines. Most parents seek out vaccine information during and immediately after their first pregnancy. A better understanding of the vaccine attitudes and beliefs of pregnant women is needed to develop effective interventions to increase maternal and infant vaccine coverage. This article presents maternal and infant vaccine attitudes and beliefs of pregnant women.

Design

Pregnant women were surveyed to assess their maternal and infant vaccine intentions, attitudes, beliefs, norms, and levels of trust in information sources.

Setting

Pregnant women were recruited from a geographically and socio-demographically diverse obstetrician-gynecologist offices in Georgia and Colorado.

Participants

Two thousand two hundred and ten pregnant women were recruited to participate, roughly half from each state.

Results

Fifty-six percent of women intended to receive both influenza and Tdap vaccines while pregnant compared to 68% intending their infant to receive all recommended vaccines on time, although

this varied substantially by ethnicity and education. Women pregnant with their first child were less likely to intend to vaccinate themselves (52% versus 59%) and their children (62% versus 73%) and more likely to be unsure about both maternal (19% versus 8%) and infant (14% versus 4%) vaccines than women who had prior children (P<0.01). Of all constructs assessed, confidence in vaccine safety and efficacy were the most strongly associated with intention to receive maternal and infant vaccines. The vast majority (92-93%) of women trusted the information provided by their obstetrician or midwife about both maternal and infant vaccines.

Conclusions and Relevance

Pregnant women demonstrated suboptimal maternal vaccine knowledge and intentions. First-time pregnant women were substantially less certain in their vaccine knowledge and intentions than women with prior children, demonstrating the opportunity for vaccine education to increase vaccine confidence and informed decision making at this stage of life, especially coming from highly trusted sources of vaccine information for pregnant women such as obstetricians and gynecologists. Such educational interventions should be individually tailored and focus on improvements to constructs such as perceived susceptibility to and severity of VPDs as well as confidence in vaccine safety and efficacy.

Trial Registration

The survey informing this article was part of a randomized controlled trial funded by the National Institutes of Health [grant number R01AI110482].

Full Text

Introduction

Immunization is one of the most effective ways to prevent infectious diseases and their associated morbidity and mortality [13]. Vaccine coverage among children in the United States remains high [14]. However, vaccine hesitancy has emerged in recent decades as a threat to this high coverage [1-4], leading to the clustering of vaccine refusal and associated outbreaks of vaccine preventable diseases (VPDs) [5-9, 11, 558]. Vaccine coverage for maternal vaccines is poor, with only about half of pregnant women receiving influenza and pertussis vaccines [12].

Although most parents believe vaccines to be important, safe and effective, concerns are very prevalent [2, 10, 15, 82, 125-142]. There are substantial differences in vaccine knowledge, attitudes and beliefs by gender, education, socioeconomic status, ethnicity and race [133, 151, 159, 163, 166, 173-193]. Knowledge, attitudes and beliefs of pregnant women toward maternal vaccines also indicate ample room for improvement, though have not been as well characterized as parental attitudes and beliefs towards infant vaccines [22, 49, 194-210].

Most parents primarily seek out vaccine information during and immediately after their first pregnancy [211-214]. The first pregnancy may be a "teachable moment" – a key opportunity to provide accurate information about both maternal and infant vaccinations – since one's vaccine attitudes and beliefs may not be fully solidified at this point [24]. The vast majority of parents [16, 123, 129] and pregnant women [22, 195, 198, 200, 202, 204, 208] cite health care providers as

their most trusted source of vaccine information. However, many pregnant women do not receive information about infant vaccines directly from their obstetrician/gynecologist or midwife [207].

The objective of this study was to determine, among a diverse population of pregnant women: 1) knowledge, attitudes and beliefs regarding maternal and infant vaccines; 2) trust in vaccine information sources; 3) intention to vaccinate; 4) associations between vaccine intentions and vaccine knowledge, attitudes, beliefs and trust; and 5) differences by sociodemographic characteristics such as education, ethnicity, and having prior children. We also aimed to identify homogeneity among groups of pregnant women based on their vaccine attitudes and beliefs to facilitate audience segmentation and targeting of tailored educational interventions.

Methods

Data Collection

Survey data were collected as part of a large randomized controlled trial of a prenatal intervention to increase uptake of maternal and infant vaccines. Pregnant women were recruited by study staff from waiting rooms of a geographically and socio-demographically diverse set of obstetrician-gynecologist offices in Georgia and Colorado. Women were eligible for participation if they were 18-50 years old, 8-26 weeks pregnant, and had not yet received maternal vaccines during their current pregnancy. This paper examines the survey data collected from the participating pregnant women at baseline.

The baseline survey included 3 multiple choice questions assessing vaccine intentions and number of prior children and 58 Likert scale statements assessing attitudes and beliefs (Tables 2 and 3). Survey statements assessed constructs found in behavioral models such as the Health Belief Model (HBM) [498]. Response options were strongly agree, agree, disagree, and strongly disagree; knowledge and trust statements also included a "don't know" option; and trust statements regarding pediatricians and naturopathic/chiropractic doctors included options for "I don't have a pediatrician yet" and "I don't see this type of doctor", respectively. Specific vaccine safety concern statements were automatically administered only to participants who expressed a lack of confidence in the safety of a particular vaccine using survey skip logic. Twenty questions were randomly administered to about three quarters of the sample in order to keep surveys short to reduce respondent burden. Sociodemographic information such as state of residence, ethnicity and education was also collected.

Data Analysis

Responses to the survey questions were first explored through univariate analyses. Vaccine intention questions were dichotomized to represent those who intended to receive recommended maternal flu, Tdap, and all infant vaccines versus those who did not. Likert scale statements were dichotomized to represent those who agreed or strongly agreed versus those who did not. For statements that included an option for "don't know", dichotomous variables were also created representing those who disagreed or strongly disagreed with the survey statements versus those who did not, and those who chose "don't know" versus those who did not. Dichotomous variables both including and not including responses to the options for "I don't have a pediatrician yet" and

"I don't see this type of doctor" were created to represent trust statements regarding pediatricians and naturopathic/chiropractic doctors, respectively. Categorical variables representing the number of specific vaccine safety concern statements agreed or strongly agreed to were created. Ethnicity categories were collapsed to white, black, Hispanic, or other. Education categories were collapsed to having a graduate degree (Master's, Doctoral, or Professional), having an undergraduate degree (Bachelor's or Associate's), having at least an undergraduate degree, and not having a degree. Number of prior children was collapsed to having children prior to this pregnancy versus not.

Categorical and dichotomous variables for vaccine intentions and dichotomous variables for survey statements were stratified by sociodemographic characteristics. Pearson's chi-squared test for independence was used to assess differences in vaccine intentions by sociodemographic characteristics. McNemar's test was used to assess differences in frequency of agreement to survey statements. All P-values were two-sided and $P<0.05$ was considered statistically significant.

Simple logistic regressions were performed separately with dichotomous indicators for maternal flu, maternal Tdap, and infant vaccine intentions as the dependent variables and the dichotomous indicators for other survey items as independent variables. Odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated for all logistic regressions. 95%CIs that did not overlap 1 were considered statistically significant.

Three best-fit multiple logistic regression models (dependent variables: intention to receive maternal influenza vaccine, intention to receive maternal Tdap vaccine, intention to get baby all recommended vaccines on time) were created by backwards selection to include only those variables with statistical significance ($P<0.05$) in both the simple and multiple models. The categorical variable for number of vaccine safety concerns as well as individual vaccine safety concern variables were not included due to their collinearity with the confidence in vaccine safety

variables. Nested models were compared using the Bayesian information criterion and the likelihood ratio test.

Latent class analysis was performed to identify homogeneous groups of women based on their responses to the aforementioned survey items. The number of clusters was sequentially increased from two and the Lo-Mendell-Rubin likelihood ratio test was performed at each iteration to determine the number of classes that best fit the model while remaining as parsimonious as possible.

All analysis was performed using Stata/IC 12.1 (STATA Corp., College Station, TX, USA), except for the latent class analysis, which was performed using Mplus version 8 (Muthén & Muthén, Los Angeles, CA, USA).

Results

Study Population

The baseline survey was taken by 2210 pregnant women, about half from each state (Table 1 and Appendix 14). First-time pregnant women made up 46% of the sample. Of women who provided education information, 27% had an advanced degree and 45% had an associate's or bachelor's degree. Of women who provided their ethnicity, 63% were white, 17% were black and 11% were Hispanic.

Confidence in Vaccine Safety

Over three quarters of women were confident that getting influenza and Tdap vaccines during pregnancy was safe both for themselves (75% for flu, 80% for Tdap) and their unborn babies (77% for flu, 81% for Tdap) (Table 2). Eighty-six percent of women were confident that vaccines were safe for their babies after birth (Table 3). Confidence in vaccine safety was higher among white women, women with prior children, and women of higher education than non-white women, first-time pregnant women, and women of lower education, respectively (Appendix 6).

Specific Vaccine Safety Concerns

Sixty-nine percent of women were confident in both maternal and infant vaccine safety and thus identified no specific safety concerns. Of those who were not confident in vaccine safety, 33% identified 1-4 concerns, 30% identified 5-8 concerns, 23% identified 9-12 concerns, and 14% identified 13-16 concerns (Appendix 9). The most common vaccine safety concerns identified from these women were that vaccine ingredients were unsafe and unnatural, and that babies were better off receiving fewer vaccines within a short time span (Appendix 3). Concerns were fewer among white women, women with prior children, and women of higher education than non-white women, first-time pregnant women, and women of lower education, respectively (Appendix 10).

Other Vaccine Knowledge, Attitudes and Beliefs

Most women perceived influenza (86%) and whooping cough (76%) as dangerous for pregnant women (Table 2 and Appendix 4). Participants worried more about getting influenza (61%) than whooping cough (39%) while pregnant (P<0.01) (Appendix 15). Almost all women perceived whooping cough as dangerous for babies (92%); fewer worried about their baby getting whooping cough (61%) (P<0.01) (Table 3 and Appendix 4). More women perceived a reduction in disease risk for themselves (69% for flu, 75% for Tdap) than for their unborn baby (47% for flu, 62% for Tdap) by vaccinating during pregnancy (P<0.01); although 73% of women perceived a reduction in their baby's risk of whooping cough from the infant vaccine.

Nearly every woman considered getting vaccines for themselves during pregnancy (98%) or for their baby after birth (96%) as in their control. Most women thought that the majority of their friends and family would encourage her to get the vaccines recommended during pregnancy (72%) and the vaccines recommended for babies (81%). Most women thought they already had most of the important information they needed to make a decision about vaccines during pregnancy (83%) and for their babies (84%).

Vaccine knowledge, attitudes and beliefs varied by sociodemographic characteristics (Appendix 7). Of particular interest, first-time pregnant women were less likely than women with prior children to perceive having enough information about maternal (74% versus 90%, P<0.01) and infant (74% versus 93%, P<0.01) vaccines or know enough about maternal influenza (74% versus 89%, P<0.01), maternal Tdap (59% versus 81%, P<0.01) and infant DTaP (65% versus 87%, P<0.01) vaccine safety to make informed vaccine decisions. A substantial portion of this difference was due to less first-time pregnant women than women with prior children strongly agreeing to having enough information about maternal (21% versus 32%) and infant (22% versus 38%) vaccines and knowing enough about maternal influenza (24% versus 31%), maternal Tdap (18%

versus 26%) and infant DTaP (20% versus 33%) vaccine safety. First time pregnant women were also less likely to be confident in vaccine efficacy and perceive that the majority of their friends and family would get recommended vaccines than women with prior children.

Trust in Vaccine Information Sources

The vast majority of women trusted the information provided by their obstetrician or midwife about both maternal (92%) and infant (93%) vaccines (Table 2, Table 3 and Appendix 5). Among those who had already seen a pediatrician, the vast majority of women trusted the information they provided about maternal (92%) and infant (94%) vaccines. Over a third of women reported not seeing naturopathic and/or chiropractic doctors; 63-64% of the remaining women reported trusting vaccine information provided by naturopathic and/or chiropractic doctors. Most women trusted vaccine information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) (81%) and by scientists and doctors at universities and academic institutions (82%). Levels of trust in vaccine information sources varied by sociodemographic characteristics (Appendix 8).

Intentions to Vaccinate

Sixty-three percent of pregnant women intended to receive maternal influenza vaccine, and 65% intended to receive maternal Tdap vaccine (Table 1). Fifty-six percent of women intended to receive both maternal vaccines, 15% intended to receive neither vaccine, and 13% were unsure

(Appendix 1). Maternal vaccine intentions varied substantially by sociodemographic characteristics. Frequency of maternal vaccine intentions was higher among white women, women with prior children, women living in Colorado, and women of higher education, than non-white women, first-time pregnant women, women living in Georgia, and women of lower education, respectively. First-time pregnant women were more likely to be uncertain about maternal vaccines compared to women with prior children (8% vs. 19%, $P<0.01$).

Sixty-eight percent of women intended their baby to receive all recommended vaccines on time (Table 1). Twelve percent of women intended their baby to receive all recommended vaccines but spread out past the recommended ages. Five percent of women intended their baby to receive only some vaccines but on time, and 3% intended their baby to receive only some vaccines spread out past the recommended ages. Two percent intended their baby to receive no vaccines, and 9% were still unsure (Appendix 1). Frequency of infant vaccine intentions was again higher among white women, women with prior children, and women of higher education than non-white women, first-time pregnant women, and women of lower education, respectively. Fourteen percent of first-time pregnant women versus 4% with prior children had uncertain infant vaccine intentions ($P<0.01$).

Associations between Vaccine Intentions and Vaccine Knowledge, Attitudes, Beliefs and Trust

Maternal Vaccines

Confidence that maternal influenza vaccine is safe for the mother (OR: 37.11; 95%CI: 27.22-50.59) and for the unborn baby (OR: 26.41; 95%CI: 19.84-35.17) was strongly associated with intention to receive maternal influenza vaccine (Table 2 and Appendix 11). Likewise, confidence that maternal Tdap vaccine is safe for the mother (OR: 29.17; 95%CI: 21.23-40.09) and for the unborn baby (OR: 18.27; 95%CI: 13.72-24.32) was strongly associated with intention to receive maternal Tdap vaccine. Identifying maternal vaccine safety concerns was strongly negatively associated with intention to receive maternal vaccines.

Belief in maternal vaccine efficacy, high perceived susceptibility to and severity of maternal VPDs, perceived pro-maternal vaccine descriptive and injunctive norms, and high perception of maternal vaccine knowledge were all positively associated with intention to receive maternal vaccines. Of these, the largest effects were seen with belief in maternal vaccine efficacy: agreement with the statement "getting the flu vaccine will reduce my risk of getting the flu during my pregnancy" had 19.04 (95%CI: 14.63-24.80) times higher odds of intention to receive maternal influenza vaccine, and agreement with the statement "whooping cough vaccine will reduce my chances of getting whooping cough" had 11 (95%CI: 8.47-14.30) times higher odds of intention to receive maternal Tdap vaccine.

Trust in maternal vaccine information from obstetricians and midwives, pediatricians, the CDC and universities were all positively associated with intention to receive maternal vaccines. In contrast, trust in maternal vaccine information from naturopathic and/or chiropractic doctors was negatively associated with intention to receive maternal influenza vaccines, and not seeing

naturopathic and/or chiropractic doctors was positively associated with intention to receive maternal vaccines.

The best-fit model for intention to receive maternal influenza vaccine reduced to include the following as statistically significant predictors (Table 4): education, state (Colorado versus Georgia), number of maternal influenza vaccine safety concerns, perceived maternal susceptibility to flu, confidence in maternal influenza vaccine efficacy for both the mother and unborn baby, confidence in maternal influenza vaccine safety for the mother, pro-maternal vaccine descriptive and injunctive norms, and knowing enough about maternal influenza vaccine safety to make an informed decision. All predictors were positively associated with intention except for the number of concerns.

The best-fit model for intention to receive maternal Tdap vaccine reduced to include the following as statistically significant predictors (Table 4): ethnicity, prior children, number of maternal Tdap vaccine safety concerns, perceived susceptibility of baby contracting pertussis from the mother, confidence in maternal Tdap vaccine efficacy for the unborn baby, confidence in maternal Tdap vaccine safety for the mother, pro-maternal vaccine injunctive norms, and knowing enough about maternal Tdap vaccine safety to make an informed decision. All predictors were positively associated with intention except for ethnicity (black and Hispanic women had lower odds of intention than white women) and number of concerns.

Infant Vaccines

Confidence that vaccines are safe for babies after birth was strongly associated (OR: 16.90; 95%CI: 12.26-23.3) with intention to receive all recommended infant vaccines on time (Table 3

and Appendix 12). Identifying infant vaccine safety concerns was strongly negatively associated with intention to receive all infant vaccines on time.

Belief in infant vaccine efficacy, high perceived susceptibility to and severity of infant VPDs, perceived pro-infant vaccine descriptive and injunctive norms, and high perception of infant vaccine knowledge were all positively associated with intention to receive all infant vaccines on time. Agreement with the statement: "I believe it is better for my baby to develop their own immunity by getting sick rather than by getting a vaccine" corresponded with 74% lower odds of intention to receive all infant vaccines on time.

Trust in infant vaccine information from obstetricians and midwives, pediatricians, the CDC and universities were all positively associated with intention to receive infant vaccines. Not seeing naturopathic and/or chiropractic doctors was also positively associated with intention to receive infant vaccines.

The best-fit model for intention to get all recommended infant vaccines on time reduced to include the following as statistically significant predictors of referring contacts (Table 4): prior children, number of infant vaccine safety concerns, pro-infant vaccine injunctive norms, having enough information about infant vaccines to make an informed decision, and trust in vaccine information from pediatricians, naturopathic and/or chiropractic doctors, and academic institutions. All predictors were positively associated with intention except for number of concerns and trust in vaccine information from naturopathic and/or chiropractic doctors.

Latent Class Analysis

Three latent classes of pregnant women were found based on their vaccine intentions, knowledge, attitudes, beliefs, and trust (Appendix 13). The first class identified by this model, containing 36% of pregnant women, was characterized by **"vaccine enthusiasts"**, or women with strong positive attitudes towards vaccination. Eighty-one percent of women in this class intended to get both recommended maternal vaccines and 90% intended to get all recommended vaccines for their baby on time. The majority of vaccine enthusiasts chose "strongly agree" for statements assessing constructs such as confidence in vaccine safety, VPD severity, vaccine efficacy, self-efficacy, pro-vaccine norms, and having enough vaccine information, and for statements assessing trust in vaccine information from obstetricians or midwives, pediatricians, the CDC and universities.

The largest class (41%) was characterized by **"vaccine acceptors"**, or women with mostly positive attitudes towards vaccination but stated with less conviction and more variability. Sixty-two percent of women in this class intended to get both recommended maternal vaccines while 14% were not sure. Seventy-three percent intended to get all recommended vaccines for their baby on time, 16% intended to get their baby all recommended vaccines but some spread out past the recommended ages, and 4% were unsure. The majority of vaccine acceptors chose "agree" for statements assessing constructs such as confidence in vaccine safety, VPD severity, vaccine efficacy, self-efficacy, pro-vaccine descriptive and injunctive norms, and having enough vaccine information, and for statements assessing trust in vaccine information from obstetricians or midwives, pediatricians, the CDC and universities.

The smallest class (23%) was characterized by **"vaccine skeptics"**, or women with more common negative attitudes towards vaccination. Only 8% percent of women in this class intended to get both recommended maternal vaccines whereas 49% intended to get no maternal vaccines and 26% were unsure. Likewise, only 25% intended to get all recommended vaccines for their baby on time,

whereas 9% intended to get no vaccines for their baby and 29% were unsure. Vaccine skeptics most frequently chose “disagree” or “don’t know” for statements assessing constructs such as confidence in vaccine safety, VPD susceptibility, and vaccine efficacy, although many also chose “agree” for statements assessing constructs such as VPD severity and self-efficacy. Vaccine skeptics also demonstrated a variety of levels of trust in sources of vaccine information.

Discussion

Over half the pregnant women in our sample intended to receive all recommended maternal vaccines. This aligns with recent national data showing 49.1% coverage for maternal influenza and 54.4% for maternal Tdap vaccine [12]. Over two thirds intended for their baby to receive all recommended infant vaccines on time, which was also consistent with the most recent national data [2]. Although this shows vaccination is the norm, there were a substantial proportion of pregnant woman who did not intend to vaccinate themselves or their children according to the immunization schedule.

Most attitudinal constructs assessed were associated with vaccine intention, although confidence in vaccine safety and efficacy showed the strongest associations. The most consistent predictors of intention to receive vaccines when adjusted for other variables were confidence in vaccine safety, pro-vaccine norms, and feeling informed. This aligns with the findings of previous prospective cohort studies [200, 203, 206]. Since maternal vaccine acceptance is known to be influenced by perceived susceptibility to and severity of maternal VPDs [559, 560], educational

interventions focusing on these constructs along with maternal vaccine safety and efficacy may be best suited to impact maternal vaccine intention and coverage.

Considerable variation was apparent in maternal and infant vaccine intentions, knowledge, attitudes, beliefs, and trust when stratified by ethnicity, education, and having prior children. Women pregnant with their first child were less likely to intend to vaccinate themselves and their children and more likely to be unsure about both maternal and infant vaccines than women who had prior children. First-time pregnant women were also less likely to perceive having enough information to make informed maternal and infant vaccine decisions. This supports the idea that the first pregnancy is a "teachable moment" due to vaccine attitudes and beliefs not being as solidified at this point as they are after having a child [24]. However, among first-time pregnant women, only 19% reported being unsure about their decision to get maternal vaccines, only 14% reported being unsure about their decision to get infant vaccines, and only 26% reported not having enough information about maternal and infant vaccines. These data indicate the need for educational interventions before pregnancy as well, perhaps during adolescent vaccinations such as HPV.

The vast majority of women trusted the vaccine information provided by their and their baby's doctors, which is echoed throughout the literature [22, 195, 198, 200, 202, 204, 208]. The vast majority of women were also confident in the safety of both maternal and infant vaccines. However, about 20-25% were not confident in the safety of maternal vaccines, and about 14% were not confident in the safety of infant vaccines. Women recognized the severity of influenza and whooping cough much more frequently than they did their or their baby's own susceptibility to the disease. Women were also more likely to perceive the efficacy of maternal vaccines in protecting themselves from the disease than protecting their unborn baby. For whooping cough in

particular (due to its severity in infancy and the crucial protection provided by maternal antibodies during an otherwise vulnerable time), this demonstrates a gap in common knowledge and an opportunity for obstetricians and midwifes to educate their patients on the true purpose and importance of Tdap vaccination in pregnancy.

Our latent class analysis (LCA) produced three groups of pregnant women: those with strong positive vaccine attitudes (36% of women), those with moderately positive vaccine attitudes (41%), and those with negative vaccine attitudes (23%). This is a similar finding to the LCA performed by Weiss et al. among Swiss mothers which also identified three latent classes: positive attitudes (58%), fearful/uncertain attitudes (28%), and critical attitudes (14%) [218]. However, the description of the classes and the percentages in each do not align completely between the two analyses. This discrepancy could be due to many factors, including differences in nationality and culture, differences between current pregnant women and mothers of young children, and differences in the nature of the survey questions analyzed.

There are several limitations of this paper. Firstly, these data are not nationally generalizable. Although the study sites were chosen to capture as wide a range of demographics and vaccine hesitancy as possible, the sample consists solely of pregnant women from two states who were willing to participate in a randomized controlled trial over several years; participating pregnant women may be different than those who chose not to participate and pregnant women in general. Reasons for eligible women declining study participation include being too busy to screen (18%), not being interested in the study (40%), being wary of the study (5%), and not being able to communicate or read in English (13%). Our study population contained a higher proportion of educated, white women than indicated by CDC data on the demographics of U.S. births in 2016 in Colorado and Georgia [561]. In addition, some women in the sample did not complete the survey

and thus questions near the end of the survey had slightly lower response rates than questions towards the beginning. These data represent a cross-sectional snapshot of a specific population and trends over time cannot be analyzed. More surveys of vaccine intentions, attitudes and beliefs among all age groups and demographics are needed, especially nationally representative, standardized surveys administered regularly over time.

Despite these limitations, this paper provides useful insight into vaccine intentions, attitudes and beliefs of current U.S. pregnant women. Increasing perceived susceptibility to and severity of VPDs as well as confidence in vaccine safety and efficacy may also increase intention to receive maternal and infant vaccines. Tailored educational interventions targeting pregnant women, particularly first-time pregnant women, are needed.

Conclusion

Pregnant women demonstrated suboptimal maternal vaccine knowledge and intentions. First-time pregnant women were substantially less certain in their vaccine knowledge and intentions than women with prior children, demonstrating the opportunity for vaccine education to increase vaccine confidence and informed decision making at this stage of life, especially coming from highly trusted sources of vaccine information for pregnant women such as obstetricians and gynecologists. Such educational interventions should be individually tailored and focus on improvements to constructs such as perceived susceptibility to and severity of VPDs as well as confidence in vaccine safety and efficacy.

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Figures and Tables

Table 1. Frequency of Pregnant Women Intending to Receive Maternal and Infant Vaccines, Stratified by State, Education, Ethnicity and Number of Prior Children

Selected Characteristics	Total Sample, N (%)	Maternal Influenza Vaccine, N (%)	P*	Maternal Tdap Vaccine, N (%)	P*	All Infant Vaccines on Time, N (%)	P*
All	2210	1,388 (63)		1,434 (65)		1,502 (68)	
State							
Colorado	1104 (50)	736 (67)	**<0.01**	738 (67)	0.05	749 (68)	0.74
Georgia	1106 (50)	652 (59)		696 (63)		753 (69)	
total	2210	1,388 (63)		1,434 (65)		1,502 (68)	
Education**							
Graduate degree	485 (27)	377 (78)	**<0.01**	371 (76)	**<0.01**	389 (80)	**<0.01**
Undergraduate degree	817 (45)	521 (64)		552 (68)		569 (70)	
No college degree	520 (29)	261 (50)		297 (57)		311 (60)	
total	1,822	1,159 (64)		1,220 (67)		1,269 (70)	
Ethnicity							
Black/African American	314 (17)	149 (47)	**<0.01**	154 (49)	**<0.01**	173 (55)	**<0.01**
Hispanic/Latino	212 (11)	118 (56)		110 (52)		139 (66)	
White	1,181 (63)	821 (70)		882 (75)		867 (74)	
Other	166 (9)	99 (60)		97 (58)		111 (67)	
total	1,873	1,187 (63)		1,243 (66)		1,290 (69)	
Number of Prior Children							
0	1017 (46)	604 (59)	**<0.01**	606 (60)	**<0.01**	634 (62)	**<0.01**
1	785 (36)	542 (69)		571 (73)		587 (75)	
2	267 (12)	169 (63)		182 (68)		194 (73)	
3	92 (4)	47 (51)		46 (50)		59 (64)	
4+	45 (2)	25 (56)		28 (62)		28 (62)	
total	2206	1,387 (63)		1,433 (65)		1,502 (68)	

**P-value for the Pearson chi-squared proportion test at significance level of (α) 5%; bolded if significant*

***Graduate degree includes Master's, Doctoral, and Professional degrees; Undergraduate degree includes Bachelor's and Associate's degrees*

Table 2. Frequency of Pregnant Women Agreeing with Maternal Vaccine Related Statements, and Odds Ratios for those Women Intending to Receive Maternal Influenza and Tdap Vaccines

	Agree or Strongly Agree, N (%)	**Influenza, OR (95%CI)***	**Tdap, OR (95%CI)***
Total (N=2210)			
Number of Vaccine Safety Concerns Identified**			
Maternal influenza vaccine concerns (0-6)			
0 (reference)	1,639 (74)	1	
1-2	135 (6)	**0.08 (0.05-0.11)**	
3-4	199 (9)	**0.03 (0.02-0.04)**	
5-6	237 (11)	**0.01 (0.00-0.02)**	
Maternal Tdap vaccine concerns (0-6)			
0 (reference)	1,750 (79)		1
1-2	106 (5)		**0.08 (0.05-0.13)**
3-4	207 (9)		**0.04 (0.03-0.06)**
5-6	147 (7)		**0.02 (0.01-0.04)**
Confidence in Vaccine Safety Statements			
I am confident that getting the flu vaccine during my pregnancy is safe for me.	1670 (75)	**37.11 (27.22-50.59)**	
I am confident that getting the flu vaccine during my pregnancy is safe for my unborn baby.	1683 (77)	**26.41 (19.84-35.17)**	
I am confident that getting the whooping cough vaccine during my pregnancy is safe for me.	1762 (80)		**29.17 (21.23-40.09)**
I am confident that getting the whooping cough vaccine during my pregnancy is safe for my unborn baby.	1779 (81)		**18.27 (13.72-24.32)**
Vaccine Knowledge, Attitude and Belief Statements			
I worry that I could get the flu while I am pregnant.	1002 (61)	**4.74 (3.83-5.88)**	
The flu is dangerous for pregnant women.	1410 (86)	**2.54 (1.93-3.35)**	
The flu is more dangerous for pregnant women than for women who are not pregnant.	1304 (79)	**2.19 (1.73-2.79)**	
Getting the flu vaccine will reduce my risk of getting the flu during my pregnancy.	1142 (69)	**19.04 (14.63-24.80)**	

Getting the flu vaccine while I am pregnant will reduce my unborn baby's risk of getting the flu.	779 (47)	**6.20 (4.91-7.83)**	
I worry that I could get whooping cough while I am pregnant.	650 (39)		**3.60 (2.86-4.54)**
I worry that I could give whooping cough to my baby after birth.	937 (57)		**6.20 (4.96-7.75)**
Whooping cough is dangerous for pregnant women.	1260 (76)		**2.63 (2.09-3.31)**
Whooping cough vaccine will reduce my chances of getting whooping cough.	1241 (75)		**11.00 (8.47-14.30)**
Whooping cough vaccine will reduce the chance of me giving whooping cough to my unborn baby.	1150 (69)		**7.55 (5.98-9.53)**
Getting the whooping cough vaccine while I am pregnant will reduce my unborn baby's risk of getting whooping cough.	1021 (62)		**6.48 (5.19-8.10)**
It is in my control whether or not I get vaccines during my pregnancy.	1608 (98)	1.71 (0.93-3.13)	1.68 (0.92-3.09)
The majority of my friends and family would get the vaccines that are recommended during pregnancy.	1615 (74)	**7.99 (6.46-9.89)**	**6.14 (5.00-7.53)**
The majority of my friends and family would encourage me to get the vaccines that are recommended during pregnancy.	1584 (72)	**9.89 (7.97-12.26)**	**7.21 (5.87-8.85)**
I have most of the important information I need to make a decision about vaccines given during pregnancy.	1815 (83)	**4.16 (3.30-5.25)**	**3.92 (3.12-4.93)**
I know enough about the safety of the flu vaccine to make a decision about getting the vaccine for myself while pregnant.	1352 (81)	**4.62 (3.54-6.03)**	
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for myself while pregnant.	1176 (71)		**4.53 (3.61-5.68)**
Trust in Vaccine Information Source Statements			
I trust the information provided by my obstetrician or midwife about vaccines during pregnancy.	2042 (92)	**8.68 (5.78-13.04)**	**6.75 (4.66-9.80)**
I trust the information provided by my baby's doctor about vaccines during pregnancy.***	1880 (92)	**8.42 (5.61-12.62)**	**6.95 (4.77-10.11)**
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines during pregnancy.***	924 (64)	**0.65 (0.52-0.81)**	**0.72 (0.57-0.90)**
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines during pregnancy.	1776 (81)	**6.35 (5.03-8.03)**	**5.55 (4.42-6.97)**
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines during pregnancy.	1808 (82)	**3.86 (3.07-4.84)**	**3.56 (2.84-4.46)**

**Odds Ratio (95% Confidence Interval) for intention to receive maternal influenza or Tdap vaccine by agreement with survey statement; bolded if significant*

***specific safety concerns were only obtained from those who did not agree that the vaccine in question was safe*
****removed those who stated they hadn't yet seen this type of provider from this analysis*

Table 3. Frequency of Pregnant Women Agreeing with Infant Vaccine Related Statements, and Odds Ratios for those Women Intending to Get their Infant All Vaccines on Time

	Agree or Strongly Agree, N (%)*	**All Infant Vaccines on Time, OR (95%CI)***
Total (N=2203)		
Number of Infant Vaccine Safety Concerns Identified (0-4)**		
0 (reference)	1,916 (87)	1
1-2	94 (4)	**0.11 (0.07-0.18)**
3-4	200 (9)	**0.02 (0.01-0.04)**
Confidence in Vaccine Safety Statements		
I am confident that vaccines are safe for my baby after birth.	1894 (86)	**16.90 (12.26-23.30)**
Vaccine Knowledge, Attitude and Belief Statements		
I worry that my baby could get whooping cough after birth.	1012 (61)	**2.52 (2.04-3.11)**
Whooping cough is dangerous for babies.	1523 (92)	**2.43 (1.69-3.49)**
Whooping cough is more dangerous for babies than older children or adults.	1420 (86)	**2.46 (1.86-3.26)**
Getting the whooping cough vaccine for my baby after birth will reduce my baby's chances of getting whooping cough.	1201 (73)	**4.46 (3.54-5.61)**
It is in my control whether or not my baby gets his/her vaccines.	1590 (96)	1.58 (0.94-2.63)
I believe it is better for my baby to develop their own immunity by getting sick rather than by getting a vaccine.	475 (29)	**0.26 (0.20-0.32)**
The majority of my friends and family would get all of the vaccines recommended for their babies after birth.	1796 (82)	**4.73 (3.77-5.93)**
The majority of my friends and family would encourage me to get all of the vaccines recommended for my baby after birth.	1776 (81)	**5.85 (4.66-7.34)**
I have most of the important information I need to make a decision about vaccines for my baby after birth.	1852 (84)	**4.38 (3.45-5.56)**
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for my baby after birth.	1691 (77)	**3.12 (2.54-3.83)**
Trust in Vaccine Information Source Statements		
I trust the information provided by my obstetrician or midwife about vaccines for babies after birth.	2044 (93)	**15.33 (9.75-24.10)**

I trust the information provided by my baby's doctor about vaccines for babies after birth.***	1879 (94)	**26.75 (14.62-48.95)**
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines for babies after birth.***	869 (63)	0.87 (0.70-1.10)
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines for babies after birth.	1783 (81)	**7.29 (5.77-9.22)**
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines for babies after birth.	1816 (82)	**4.70 (3.73-5.91)**

**Odds Ratio (95% Confidence Interval) for intention to get infant all vaccines on time by agreement with survey statement; bolded if significant*

***specific safety concerns were only obtained from those who did not agree that the vaccine in question was safe*

****removed those who stated they hadn't yet seen this type of provider from this analysis*

Table 4. Frequency and Adjusted Odds Ratios of Pregnant Women Intending to Receive Maternal and Infant Vaccines by Associated Demographics and Vaccine Beliefs

Variables Associated with Intention to Vaccinate in MLR***	Intention to Vaccinate, N (%)*	aOR (95% CI)**
Intention to Receive Maternal Influenza Vaccine	1,388 (63)	
Having at least a college degree	898 (69)	2.05 (1.42-2.96)
State		1.51 (1.07-2.13)
Colorado	736 (67)	
Georgia	652 (59)	
Statements Agreed or Strongly Agreed to****		
I worry that I could get the flu while I am pregnant.	778 (78)	2.54 (1.80-3.59)
Getting the flu vaccine will reduce my risk of getting the flu during my pregnancy.	950 (83)	5.50 (3.66-8.27)
Getting the flu vaccine while I am pregnant will reduce my unborn baby's risk of getting the flu.	654 (84)	1.46 (1.01-2.11)
I am confident that getting the flu vaccine during my pregnancy is safe for me.	1,334 (80)	6.01 (3.35-10.76)
I am confident that getting the flu vaccine during my pregnancy is safe for my unborn baby.	1,323 (79)	2.59 (1.48-4.55)
The majority of my friends and family would get the vaccines that are recommended during pregnancy.	1,221 (76)	1.79 (1.12-2.86)
The majority of my friends and family would encourage me to get the vaccines that are recommended during pregnancy.	1,226 (77)	1.97 (1.23-3.13)
I have most of the important information I need to make a decision about vaccines given during pregnancy.	1,250 (69)	1.94 (1.22-3.08)
Intention to Receive Maternal Tdap Vaccine	1,434 (65)	
Ethnicity		
White (reference)	882 (75)	1
Black	154 (49)	0.49 (0.33-0.72)
Hispanic	110 (52)	0.51 (0.32-0.82)
Prior Children	827 (70)	1.39 (1.02-1.89)
Statements Agreed or Strongly Agreed to****		
I worry that I could give whooping cough to my baby after birth.	767 (82)	3.47 (2.57-4.67)
Whooping cough vaccine will reduce my chances of getting whooping cough.	969 (78)	2.68 (1.84-3.89)
I am confident that getting the whooping cough vaccine during my pregnancy is safe for me.	1,382 (78)	6.82 (4.44-10.48)
The majority of my friends and family would encourage me to get the vaccines that are recommended during pregnancy.	1,230 (78)	2.64 (1.89-3.68)

I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for myself while pregnant.	880 (75)	2.02 (1.46-2.80)
Intention to Get All Infant Vaccines on Time	1,502 (68)	
Prior Children	868 (73)	1.73 (1.27-2.36)
Statements Agreed or Strongly Agreed to****		
I am confident that vaccines are safe for my baby after birth.	1,451 (77)	5.19 (3.1-8.69)
I believe it is better for my baby to develop their own immunity by getting sick rather than by getting a vaccine.	223 (47)	0.59 (0.42-0.81)
The majority of my friends and family would encourage me to get all of the vaccines recommended for my baby after birth.	1,351 (76)	2.47 (1.67-3.66)
I trust the information provided by my baby's doctor about vaccines for babies after birth.*****	1,393 (74)	8.11 (3.39-19.4)
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines for babies after birth.*****	527 (61)	0.53 (0.37-0.75)
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines for babies after birth.	1,353 (75)	2.05 (1.29-3.28)

**number and percentage of those agreeing with survey statement who intend to vaccinate*

***adjusted Odds Ratio (95% Confidence Interval) for intention to vaccinate by agreement with survey statement*

****variables chosen for best-fit multiple logistic regression (MLR) model using backwards stepwise selection at significance level of $P<0.05$*

*****20 questions deemed non-essential were included in surveys for only ~75% of the sample (based on randomly assigned groups) in order to keep surveys short enough to obtain high completion rates*

******removed those who stated they hadn't yet seen this type of provider from this analysis*

Appendix 1. Frequency of All Categories of Pregnant Women's Maternal and Infant Vaccine Intentions, Stratified by First Child, State, Education and Ethnicity

Vaccine Intentions	Total N (%)	First Child, N (%)		Education*, N (%)		Ethnicity, N (%)			
		Yes	No	High	Low	Black	White	Hispanic	Other
Maternal	2210 (100)								
Flu and Tdap	1234 (56)	529 (52)	704 (59)	813 (62)	229 (44)	118 (38)	764 (65)	96 (45)	83 (50)
Flu not Tdap	154 (7)	75 (7)	79 (7)	85 (7)	32 (6)	31 (10)	57 (5)	22 (10)	16 (10)
Tdap not Flu	200 (9)	77 (8)	123 (10)	110 (8)	68 (13)	36 (11)	118 (10)	14 (7)	14 (8)
neither	328 (15)	139 (14)	187 (16)	148 (11)	100 (19)	67 (21)	122 (10)	43 (20)	27 (16)
unsure	294 (13)	197 (19)	96 (8)	146 (11)	91 (18)	62 (20)	120 (10)	37 (17)	26 (16)
P-value**		**<0.01**		**<0.01**			**<0.01**		
Infant	2203 (100)								
all on time	1502 (68)	634 (62)	868 (73)	958 (74)	311 (60)	173 (55)	867 (74)	139 (66)	111 (67)
all delayed	272 (12)	118 (12)	154 (13)	152 (12)	67 (13)	34 (11)	158 (13)	21 (10)	16 (10)
some on time	121 (5)	70 (7)	51 (4)	51 (4)	42 (8)	32 (10)	42 (4)	15 (7)	12 (7)
some delayed	68 (3)	36 (4)	32 (3)	36 (3)	17 (3)	10 (3)	31 (3)	6 (3)	4 (2)
none	48 (2)	14 (1)	34 (3)	19 (1)	18 (3)	9 (3)	21 (2)	9 (4)	3 (2)
unsure	192 (9)	144 (14)	48 (4)	82 (6)	65 (13)	56 (18)	60 (5)	21 (10)	20 (12)
P-value**		**<0.01**		**<0.01**			**<0.01**		

**Education=High for Doctoral or Professional degree, Master's degree, Bachelor's degree, Associate's degree; Education=Low for Postsecondary nondegree award, Some college no degree, High school diploma or equivalent, No formal educational credential*

***P-value for the Pearson chi-squared proportion test at significance level of (α) 5%; bolded if significant*

Appendix 2. Confidence in Vaccine Safety of Pregnant Women

Statement	Strongly Agree, N (%)	Agree, N (%)	Disagree, N (%)	Strongly Disagree, N (%)	Total
I am confident that getting the flu vaccine during my pregnancy is safe for me.	622 (28)	1048 (47)	414 (19)	124 (6)	2,208
I am confident that getting the flu vaccine during my pregnancy is safe for my unborn baby.	524 (24)	1159 (53)	432 (20)	92 (4)	2,207
I am confident that getting the whooping cough vaccine during my pregnancy is safe for me.	534 (24)	1228 (56)	372 (17)	70 (3)	2,204
I am confident that getting the whooping cough vaccine during my pregnancy is safe for my unborn baby.	498 (23)	1281 (58)	355 (16)	69 (3)	2,203
I am confident that vaccines are safe for my baby after birth.	773 (35)	1121 (51)	241 (11)	67 (3)	2,202

*Appendix 3. Specific Vaccine Safety Concerns Among Pregnant Women Not Confident in Vaccine Safety**

Statement	Strongly Agree, N (%)	Agree, N (%)	Disagree, N (%)	Strongly Disagree, N (%)	Don't Know**, N (%)	Total*
The flu vaccine is more likely to make me sick than protect me from getting the flu.	94 (17)	234 (43)	88 (16)	16 (3)	112 (21)	544
I worry that the ingredients in the flu vaccine are not safe for me to have while I am pregnant.	130 (24)	322 (60)	78 (15)	6 (1)		536
The flu vaccine is more likely to make me sick than protect my unborn baby from getting the flu.	54 (10)	216 (41)	88 (17)	11 (2)	155 (30)	524
I do not want to put the flu vaccine into my body when I am pregnant because I think it is unnatural.	116 (19)	347 (56)	139 (23)	15 (2)		617
I worry that the flu vaccine will cause birth defects.	53 (10)	193 (37)	262 (50)	16 (3)		524
I worry that the ingredients in the flu vaccine given to me during pregnancy are not safe for my unborn baby.	89 (17)	354 (68)	79 (15)	1 (0)		523
The whooping cough vaccine is more likely to cause me to get sick than protect me from getting whooping cough.	34 (8)	130 (29)	69 (16)	6 (1)	204 (46)	443
I worry that the ingredients in the whooping cough vaccine are not safe for me to have while I am pregnant.	81 (18)	303 (68)	55 (12)	4 (1)		443
The whooping cough vaccine is more likely to cause me to get sick than protect my unborn baby from getting whooping cough.	34 (8)	141 (33)	59 (14)	6 (1)	184 (43)	424
I do not want to put the whooping cough vaccine into my body when I am pregnant because I think it is unnatural.	92 (18)	295 (58)	108 (21)	10 (2)		505
I worry that the whooping cough vaccine will cause birth defects.	56 (13)	199 (47)	162 (38)	7 (2)		424
I worry that the ingredients in the whooping cough vaccine given to me during pregnancy are not safe for my unborn baby.	66 (16)	288 (68)	64 (15)	6 (1)		424
It is better for babies to get fewer vaccines at the same time.	76 (25)	162 (52)	65 (21)	6 (2)		309
Babies get more vaccines in their first two years of life than are good for them.	70 (23)	148 (48)	71 (23)	20 (6)		309
Vaccines often cause serious side effects in babies.	56 (18)	140 (45)	109 (35)	4 (1)		309
The ingredients in vaccines are not safe for my baby.	67 (22)	149 (48)	90 (29)	3 (1)		309

**specific safety concerns were only obtained from those who did not agree that the vaccine in question was safe*

***Don't Know; provided as an answer option only for knowledge-based questions*

*Appendix 4. Other Vaccine Knowledge, Attitudes and Beliefs of Pregnant Women**

Statement	Strongly Agree, N (%)	Agree, N (%)	Disagree, N (%)	Strongly Disagree, N (%)	Don't Know**, N (%)	Total *
I worry that I could get the flu while I am pregnant.	259 (16)	743 (45)	520 (31)	133 (8)		1,655
The flu is dangerous for pregnant women.	555 (34)	855 (52)	84 (5)	27 (2)	134 (8)	1,655
The flu is more dangerous for pregnant women than for women who are not pregnant.	512 (31)	792 (48)	139 (8)	27 (2)	186 (11)	1,656
Getting the flu vaccine will reduce my risk of getting the flu during my pregnancy.	385 (23)	757 (46)	247 (15)	79 (5)	188 (11)	1,656
Getting the flu vaccine while I am pregnant will reduce my unborn baby's risk of getting the flu.	235 (14)	544 (33)	298 (18)	73 (4)	503 (30)	1,653
I worry that I could get whooping cough while I am pregnant.	121 (7)	529 (32)	853 (52)	151 (9)		1,654
I worry that I could give whooping cough to my baby after birth.	263 (16)	674 (41)	605 (37)	112 (7)		1,654
Whooping cough is dangerous for pregnant women.	395 (24)	865 (52)	73 (4)	7 (0)	314 (19)	1,654
Whooping cough vaccine will reduce my chances of getting whooping cough.	423 (26)	818 (49)	110 (7)	30 (2)	273 (17)	1,654
Whooping cough vaccine will reduce the chance of me giving whooping cough to my unborn baby.	421 (25)	729 (44)	139 (8)	32 (2)	333 (20)	1,654
Getting the whooping cough vaccine while I am pregnant will reduce my unborn baby's risk of getting whooping cough.	347 (21)	674 (41)	166 (10)	40 (2)	426 (26)	1,653
It is in my control whether or not I get vaccines during my pregnancy.	884 (54)	724 (44)	28 (2)	15 (1)		1,651
The majority of my friends and family would get the vaccines that are recommended during pregnancy.	591 (27)	1024 (47)	190 (9)	47 (2)	350 (16)	2,202
The majority of my friends and family would encourage me to get the vaccines that are recommended during pregnancy.	572 (26)	1012 (46)	278 (13)	57 (3)	283 (13)	2,202
I have most of the important information I need to make a decision about vaccines given during pregnancy.	592 (27)	1223 (56)	334 (15)	52 (2)		2,201
I know enough about the safety of the flu vaccine to make a decision about getting the vaccine for myself while pregnant.	454 (27)	898 (54)	271 (16)	29 (2)		1,652
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for myself while pregnant.	369 (22)	807 (49)	417 (25)	60 (4)		1,653
I worry that my baby could get whooping cough after birth.	266 (16)	746 (45)	544 (33)	96 (6)		1,652
Whooping cough is dangerous for babies.	808 (49)	715 (43)	16 (1)	8 (0)	105 (6)	1,652

Whooping cough is more dangerous for babies than older children or adults.	770 (47)	650 (39)	31 (2)	7 (0)	195 (12)	1,653
Getting the whooping cough vaccine for my baby after birth will reduce my baby's chances of getting whooping cough.	465 (28)	736 (45)	99 (6)	23 (1)	329 (20)	1,652
It is in my control whether or not my baby gets his/her vaccines.	909 (55)	681 (41)	50 (3)	13 (1)		1,653
I believe it is better for my baby to develop their own immunity by getting sick rather than by getting a vaccine.	152 (9)	323 (20)	731 (44)	446 (27)		1,652
The majority of my friends and family would get all of the vaccines recommended for their babies after birth.	663 (30)	1133 (52)	131 (6)	30 (1)	243 (11)	2,200
The majority of my friends and family would encourage me to get all of the vaccines recommended for my baby after birth.	682 (31)	1094 (50)	155 (7)	35 (2)	236 (11)	2,202
I have most of the important information I need to make a decision about vaccines for my baby after birth.	676 (31)	1176 (53)	298 (14)	53 (2)		2,203
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for my baby after birth.	592 (27)	1099 (50)	456 (21)	56 (3)		2,203

**20 questions deemed non-essential were included in surveys for only ~75% of the sample (based on randomly assigned groups) in order to keep surveys short enough to obtain high completion rates*

***Don't Know; provided as an answer option only for knowledge-based questions*

Appendix 5. Trust in Vaccine Information Sources of Pregnant Women

Statement	Strongly Agree, N (%)	Agree, N (%)	Disagree, N (%)	Strongly Disagree, N (%)	Don't Know, N (%)	Not Seen*, N (%)	Total
I trust the information provided by…							
…my obstetrician or midwife about vaccines during pregnancy.	976 (44)	1066 (48)	54 (2)	13 (1)	95 (4)		2,204
…my obstetrician or midwife about vaccines for babies after birth.	949 (43)	1095 (50)	51 (2)	18 (1)	90 (4)		2,203
…my baby's doctor about vaccines during pregnancy.	906 (41)	974 (44)	64 (3)	18 (1)	74 (3)	168 (8)	2,204
…my baby's doctor about vaccines for babies after birth.	897 (41)	982 (45)	43 (2)	17 (1)	64 (3)	201 (9)	2,204
…naturopathic and/or chiropractic doctors about vaccines during pregnancy.	282 (13)	642 (29)	219 (10)	75 (3)	222 (10)	762 (35)	2,203
…naturopathic and/or chiropractic doctors about vaccines for babies after birth.	257 (12)	612 (28)	218 (10)	78 (4)	211 (10)	827 (38)	2,203
…federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines during pregnancy.	745 (34)	1031 (47)	132 (6)	69 (3)	227 (10)		2,204
…federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines for babies after birth.	748 (34)	1035 (47)	126 (6)	68 (3)	226 (10)		2,203
…scientists and doctors at universities and academic institutions about vaccines during pregnancy.	682 (31)	1126 (51)	102 (5)	22 (1)	271 (12)		2,203
…scientists and doctors at universities and academic institutions about vaccines for babies after birth.	670 (30)	1146 (52)	91 (4)	23 (1)	274 (12)		2,204

**Not Seen: for baby's doctor statements, answer option for "I don't have a pediatrician yet" included; for naturopathic and/or chiropractic doctor statements, answer option for "I don't see this type of doctor" included*

Appendix 6. Frequency of Pregnant Women Agreeing or Strongly Agreeing with Statements Assessing Confidence in Vaccine Safety, Stratified by First Child, State, Degree and Ethnicity

Total %	First Child, %			State*, %			Education*, %			Ethnicity*, %				
Agreed	**Yes**	**No**	**P****	**CO**	**GA**	**P****	**High**	**Low**	**P****	**Black**	**White**	**Hispanic**	**Other**	**P****
I am confident that getting the flu vaccine during my pregnancy is safe for me.														
76	74	78	**0.03**	78	73	**0.01**	78	70	**<0.01**	60	82	75	73	**<0.01**
I am confident that getting the flu vaccine during my pregnancy is safe for my unborn baby.														
76	73	79	**<0.01**	78	75	0.13	80	69	**<0.01**	61	82	73	75	**<0.01**
I am confident that getting the whooping cough vaccine during my pregnancy is safe for me.														
80	78	82	**0.04**	81	79	0.19	83	75	**<0.01**	66	86	75	79	**<0.01**
I am confident that getting the whooping cough vaccine during my pregnancy is safe for my unborn baby.														
81	78	83	**<0.01**	81	80	0.71	84	76	**<0.01**	70	86	73	78	**<0.01**
I am confident that vaccines are safe for my baby after birth.														
86	84	88	**0.01**	86	86	0.67	88	83	**<0.01**	78	90	84	83	**<0.01**

**State: CO=Colorado, GA=Georgia; Education=High for Doctoral or Professional degree, Master's degree, Bachelor's degree, Associate's degree; Education=Low for Postsecondary nondegree award, Some college no degree, High school diploma or equivalent, No formal educational credential*
***P-value for the Pearson chi-squared proportion test at significance level of (α) 5%; bolded if significant*

Appendix 7. Frequency of Pregnant Women Agreeing or Strongly Agreeing with Statements Assessing Vaccine Knowledge, Attitudes, and Beliefs, Stratified by First Child, State, Degree and Ethnicity

Total %	First Child, %			State*, %			Education*, %			Ethnicity*, %				
Agreed	**Yes**	**No**	**P****	**CO**	**GA**	**P****	**High**	**Low**	**P****	**Black**	**White**	**Hispanic**	**Other**	**P****
I worry that I could get the flu while I am pregnant.														
61	58	62	0.10	62	59	0.11	64	54	**<0.01**	43	66	59	59	**<0.01**
The flu is dangerous for pregnant women.														
85	85	85	0.75	83	87	0.05	88	81	**<0.01**	88	87	80	82	0.08
The flu is more dangerous for pregnant women than for women who are not pregnant.														
79	80	77	0.15	80	77	0.18	82	71	**<0.01**	76	82	71	74	**<0.01**
Getting the flu vaccine will reduce MY risk of getting the flu during my pregnancy.														
69	67	71	0.11	72	66	**0.01**	74	61	**<0.01**	54	77	61	61	**<0.01**
Getting the flu vaccine while I am pregnant will reduce my unborn baby's risk of getting the flu.														
47	44	50	**0.01**	50	44	**0.03**	50	41	**0.01**	40	52	39	44	**<0.01**
I worry that I could get whooping cough while I am pregnant.														
39	37	41	0.08	43	36	**<0.01**	42	37	0.10	25	43	44	40	**<0.01**
I worry that I could give whooping cough to my baby after birth.														
57	54	59	0.05	58	55	0.34	61	53	**<0.01**	43	64	56	51	**<0.01**
Whooping cough is dangerous for pregnant women.														
76	75	77	0.21	77	75	0.38	80	73	**0.01**	79	79	68	79	**0.04**
Whooping cough vaccine will reduce MY chances of getting whooping cough.														
75	72	77	**0.01**	77	73	0.07	80	68	**<0.01**	61	83	66	73	**<0.01**
Whooping cough vaccine will reduce the chance of me giving whooping cough to my unborn baby.														
70	67	72	0.05	72	67	**0.03**	74	62	**<0.01**	56	77	61	62	**<0.01**
Getting the whooping cough vaccine while I am pregnant will reduce my unborn baby's risk of getting whooping cough.														
62	57	66	**<0.01**	64	59	0.06	65	58	**0.02**	48	69	54	63	**<0.01**
It is in my control whether or not I get vaccines during my pregnancy.														
97	97	98	0.52	97	98	0.46	98	97	0.38	98	98	97	95	0.32
The majority of my friends and family would get the vaccines that are recommended during pregnancy.														
73	70	76	**<0.01**	76	71	**0.01**	79	64	**<0.01**	61	80	67	68	**<0.01**
The majority of my friends and family would encourage me to get the vaccines that are recommended during pregnancy.														
72	70	74	0.07	74	70	0.07	77	64	**<0.01**	61	79	64	67	**<0.01**
I have most of the important information I need to make a decision about vaccines given during pregnancy.														
82	74	90	**<0.01**	82	83	0.29	84	82	0.35	77	86	80	82	**<0.01**
I know enough about the safety of the flu vaccine to make a decision about getting the vaccine for myself while pregnant.														
82	74	89	**<0.01**	82	82	0.85	83	80	0.30	77	85	79	80	**0.01**

I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for myself while pregnant.														
71	59	81	**<0.01**	73	70	0.17	73	69	0.08	65	75	69	64	**<0.01**
I worry that my baby could get whooping cough after birth.														
61	62	61	0.77	66	56	**<0.01**	67	52	**<0.01**	36	70	60	58	**<0.01**
Whooping cough is dangerous for babies.														
92	91	93	0.14	93	91	0.14	94	90	**0.01**	88	95	88	91	**<0.01**
Whooping cough is more dangerous for babies than older children or adults.														
86	83	88	**0.01**	87	85	0.14	89	84	**0.01**	81	90	81	86	**<0.01**
Getting the whooping cough vaccine for my baby after birth will reduce my baby's chances of getting whooping cough.														
73	68	76	**<0.01**	76	69	**<0.01**	77	68	**<0.01**	63	79	66	73	**<0.01**
It is in my control whether or not my baby gets his/her vaccines.														
96	96	97	0.32	97	95	**0.01**	96	95	0.41	94	97	97	95	0.24
I believe it is better for my baby to develop their own immunity by getting sick rather than by getting a vaccine.														
29	30	27	0.19	29	29	0.88	24	38	**<0.01**	39	21	33	46	**<0.01**
The majority of my friends and family would get all of the vaccines recommended for their babies after birth.														
82	79	84	**<0.01**	82	81	0.53	86	74	**<0.01**	75	86	76	76	**<0.01**
The majority of my friends and family would encourage me to get all of the vaccines recommended for my baby after birth.														
81	79	82	0.10	81	81	0.95	84	74	**<0.01**	74	85	74	74	**<0.01**
I have most of the important information I need to make a decision about vaccines for my baby after birth.														
84	74	93	**<0.01**	84	84	0.63	85	82	0.10	80	87	82	85	**0.02**
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for my baby after birth.														
77	65	87	**<0.01**	77	77	0.80	78	75	0.27	71	80	74	73	**<0.01**

**State: CO=Colorado, GA=Georgia; Education=High for Doctoral or Professional degree, Master's degree, Bachelor's degree, Associate's degree; Education=Low for Postsecondary nondegree award, Some college no degree, High school diploma or equivalent, No formal educational credential*
***P-value for the Pearson chi-squared proportion test at significance level of (α) 5%; bolded if significant*

Appendix 8. Frequency of Pregnant Women Agreeing or Strongly Agreeing with Statements Assessing Trust in Vaccine Information Sources, Stratified by First Child, State, Degree and Ethnicity

Total %	First Child, %			State*, %			Education*, %			Ethnicity*, %				
Agreed	**Yes**	**No**	**P****	**CO**	**GA**	**P****	**High**	**Low**	**P****	**Black**	**White**	**Hispanic**	**Other**	**P****
I trust the information provided by my obstetrician or midwife about vaccines during pregnancy.														
93	92	93	0.13	92	93	0.76	95	89	**<0.01**	90	95	91	90	**0.01**
I trust the information provided by my obstetrician or midwife about vaccines for babies after birth.														
93	92	93	0.21	93	92	0.35	94	90	**<0.01**	90	94	94	90	**0.02**
I trust the information provided by my baby's doctor about vaccines during pregnancy.***														
92	93	92	0.26	93	91	0.07	94	89	**<0.01**	89	94	91	88	**<0.01**
I trust the information provided by my baby's doctor about vaccines for babies after birth.***														
94	94	93	0.34	94	93	0.28	95	91	**<0.01**	91	95	95	92	0.06
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines during pregnancy.***														
64	61	67	**0.04**	63	65	0.58	56	80	**<0.01**	73	60	78	57	**<0.01**
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines for babies after birth.***														
63	60	66	**0.05**	64	63	0.67	55	79	**<0.01**	74	59	76	57	**<0.01**
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines during pregnancy.														
81	80	81	0.36	81	80	0.37	85	73	**<0.01**	74	85	77	74	**<0.01**
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines for babies after birth.														
81	80	82	0.32	81	81	0.71	85	74	**<0.01**	75	85	76	78	**<0.01**
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines during pregnancy.														
82	82	82	0.68	86	78	**<0.01**	87	76	**<0.01**	75	87	80	79	**<0.01**
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines for babies after birth.														
82	82	83	0.37	86	79	**<0.01**	87	77	**<0.01**	75	87	82	80	**<0.01**

**State: CO=Colorado, GA=Georgia; Education=High for Doctoral or Professional degree, Master's degree, Bachelor's degree, Associate's degree; Education=Low for Postsecondary nondegree award, Some college no degree, High school diploma or equivalent, No formal educational credential*

***P-value for the Pearson chi-squared proportion test at significance level of (α) 5%; bolded if significant*

****removed those who stated they hadn't yet seen this type of provider from the stratified analysis*

*Appendix 9. Number of Specific Vaccine Safety Concerns Identified Per Pregnant Woman**

Number of concerns	N	% of total	% of those with at least one concern
0	1,532	69	0
1	39	2	6
2	71	3	10
3	64	3	9
4	57	3	8
5	67	3	10
6	62	3	9
7	35	2	5
8	39	2	6
9	38	2	6
10	33	1	5
11	37	2	5
12	45	2	7
13	18	1	3
14	26	1	4
15	24	1	4
16	23	1	3
total	2,210	100	100

**specific safety concerns were only obtained from those who did not agree that the vaccine in question was safe*

Appendix 10. Number of Specific Vaccine Safety Concerns Identified, Stratified by First Child, State, Degree and Ethnicity

Number of Concerns	Total N (%)	First Child, N (%)		Education*, N (%)		Ethnicity, N (%)			
		Yes	No	High	Low	Black	White	Hispanic	Other
0	1,532 (69)	666 (65)	865 (73)	953 (73)	325 (63)	160 (51)	905 (77)	138 (65)	108 (65)
1-4	231 (10)	116 (11)	113 (10)	122 (9)	65 (13)	43 (14)	105 (9)	25 (12)	19 (11)
5-8	203 (9)	113 (11)	89 (7)	110 (8)	53 (10)	53 (17)	84 (7)	17 (8)	18 (11)
9-12	153 (7)	80 (8)	73 (6)	72 (6)	48 (9)	37 (12)	52 (4)	20 (9)	16 (10)
13-16	91 (4)	42 (4)	49 (4)	45 (3)	29 (6)	21 (7)	35 (3)	12 (6)	5 (3)
P-value**		**<0.01**		**<0.01**			**<0.01**		

**Education=High for Doctoral or Professional degree, Master's degree, Bachelor's degree, Associate's degree; Education=Low for Postsecondary nondegree award, Some college no degree, High school diploma or equivalent, No formal educational credential*

***P-value for the Pearson chi-squared proportion test at significance level of (α) 5%; bolded if significant*

Appendix 11. Odds Ratios Assessing Associations between Pregnant Women's Maternal Vaccine Intentions and their Maternal Vaccine Knowledge, Attitudes, Beliefs and Trust

Survey Statement	OR (95%CI) with Maternal Vaccine Intentions**				
	Influenza Vaccine	**NO Influenza Vaccine**	**Tdap Vaccine**	**NO Tdap Vaccine**	**Unsure**
Confidence in Vaccine Safety					
I am confident that getting the flu vaccine during my pregnancy is safe for me.					
*Agree**	**37.11 (27.22-50.59)**	**0.06 (0.04-0.07)**			**0.37 (0.28-0.47)**
I am confident that getting the flu vaccine during my pregnancy is safe for my unborn baby.					
*Agree**	**26.41 (19.84-35.17)**	**0.07 (0.06-0.09)**			**0.34 (0.26-0.44)**
I am confident that getting the whooping cough vaccine during my pregnancy is safe for me.					
*Agree**			**29.17 (21.23-40.09)**	**0.08 (0.06-0.10)**	**0.30 (0.23-0.39)**
I am confident that getting the whooping cough vaccine during my pregnancy is safe for my unborn baby.					
*Agree**			**18.27 (13.72-24.32)**	**0.10 (0.08-0.13)**	**0.34 (0.26-0.44)**
Specific Vaccine Safety Concerns***					
The flu vaccine is more likely to make me sick than protect me from getting the flu.					
*Agree**	**0.14 (0.07-0.26)**	**2.22 (1.54-3.19)**			1.01 (0.67-1.52)
*Disagree**	**8.79 (4.93-15.68)**	**0.52 (0.33-0.80)**			**0.42 (0.23-0.79)**
*Unsure**	0.98 (0.50-1.92)	**0.61 (0.40-0.93)**			**1.85 (1.17-2.93)**
I do not want to put the flu vaccine into my body when I am pregnant because I think it is unnatural.					
*Agree**	**0.17 (0.10-0.28)**	**3.14 (2.13-4.61)**			0.88 (0.57-1.35)
I worry that the ingredients in the flu vaccine are not safe for me to have while I am pregnant.					
*Agree**	**0.30 (0.16-0.56)**	**2.37 (1.48-3.81)**			0.71 (0.42-1.20)
The flu vaccine is more likely to make me sick than protect my unborn baby from getting the flu.					
*Agree**	**0.22 (0.12-0.41)**	**2.51 (1.74-3.62)**			0.70 (0.47-1.05)
*Disagree**	**3.93 (2.25-6.86)**	**0.54 (0.35-0.84)**			0.81 (0.48-1.38)
*Unsure**	1.39 (0.80-2.41)	**0.55 (0.37-0.81)**			**1.72 (1.13-2.63)**
I worry that the flu vaccine will cause birth defects.					
*Agree**	**0.28 (0.15-0.51)**	**1.69 (1.18-2.43)**			1.02 (0.68-1.52)
I worry that the ingredients in the flu vaccine given to me during pregnancy are not safe for my unborn baby.					
*Agree**	**0.44 (0.24-0.81)**	1.52 (0.94-2.46)			1.04 (0.59-1.81)
The whooping cough vaccine is more likely to cause me to get sick than protect me from getting whooping cough.					
*Agree**			0.52 (0.26-1.02)	**2.63 (1.71-4.03)**	**0.43 (0.26-0.69)**
*Disagree**			**2.18 (1.11-4.30)**	0.69 (0.42-1.14)	0.99 (0.56-1.73)
*Unsure**			1.04 (0.57-1.89)	**0.52 (0.36-0.77)**	**2.12 (1.38-3.26)**

I do not want to put the whooping cough vaccine into my body when I am pregnant because I think it is unnatural.				
*Agree**		**0.16 (0.09-0.27)**	**5.30 (3.30-8.51)**	0.64 (0.40-1.01)
I worry that the ingredients in the whooping cough vaccine are not safe for me to have while I am pregnant.				
*Agree**		**0.42 (0.20-0.86)**	**2.54 (1.45-4.43)**	0.57 (0.32-1.01)
The whooping cough vaccine is more likely to cause me to get sick than protect my unborn baby from getting whooping cough.				
*Agree**		**0.34 (0.18-0.63)**	**3.69 (2.40-5.66)**	**0.38 (0.23-0.62)**
*Disagree**		**4.13 (2.26-7.54)**	**0.50 (0.29-0.85)**	0.69 (0.36-1.33)
*Unsure**		0.98 (0.58-1.68)	**0.43 (0.29-0.64)**	**2.93 (1.86-4.61)**
I worry that the whooping cough vaccine will cause birth defects.				
*Agree**		0.92 (0.54-1.58)	1.28 (0.86-1.90)	0.78 (0.50-1.21)
I worry that the ingredients in the whooping cough vaccine given to me during pregnancy are not safe for my unborn baby.				
*Agree**		**0.36 (0.20-0.67)**	**2.74 (1.62-4.65)**	0.65 (0.37-1.12)
Other Vaccine Knowledge, Attitudes and Beliefs				
I worry that I could get the flu while I am pregnant.				
*Agree**	**4.74 (3.83-5.88)**	**0.18 (0.14-0.23)**		**0.67 (0.50-0.89)**
The flu is dangerous for pregnant women.				
*Agree**	**2.54 (1.93-3.35)**	**0.47 (0.35-0.63)**		**0.56 (0.39-0.80)**
*Disagree**	**0.49 (0.34-0.73)**	**2.60 (1.75-3.86)**		0.73 (0.39-1.39)
*Unsure**	**0.38 (0.26-0.54)**	**1.56 (1.06-2.29)**		**2.79 (1.85-4.22)**
The flu is more dangerous for pregnant women than for women who are not pregnant.				
*Agree**	**2.19 (1.73-2.79)**	**0.53 (0.41-0.69)**		**0.58 (0.42-0.81)**
*Disagree**	**0.5 (0.37-0.70)**	**2.55 (1.83-3.55)**		0.75 (0.44-1.26)
*Unsure**	**0.50 (0.37-0.68)**	1.16 (0.82-1.65)		**2.64 (1.83-3.81)**
Getting the flu vaccine will reduce my risk of getting the flu during my pregnancy.				
*Agree**	**19.04 (14.63-24.8)**	**0.07 (0.06-0.10)**		**0.29 (0.22-0.40)**
*Disagree**	**0.06 (0.04-0.08)**	**16.53 (12.40-22.03)**		1.37 (0.97-1.92)
*Unsure**	**0.21 (0.15-0.29)**	**1.74 (1.25-2.41)**		**5.13 (3.64-7.23)**
Getting the flu vaccine while I am pregnant will reduce my unborn baby's risk of getting the flu.				
*Agree**	**6.20 (4.91-7.83)**	**0.17 (0.13-0.22)**		**0.36 (0.26-0.50)**
*Disagree**	**0.22 (0.17-0.28)**	**5.92 (4.59-7.63)**		1.01 (0.71-1.42)
*Unsure**	**0.53 (0.43-0.65)**	1.16 (0.91-1.48)		**2.72 (2.03-3.65)**
I worry that I could get whooping cough while I am pregnant.				
*Agree**		**3.6 (2.86-4.54)**	**0.19 (0.14-0.26)**	0.74 (0.55-1.00)
I worry that I could give whooping cough to my baby after birth.				
*Agree**		**6.20 (4.96-7.75)**	**0.12 (0.09-0.17)**	**0.55 (0.41-0.73)**

Whooping cough is dangerous for pregnant women.					
*Agree**			**2.63 (2.09-3.31)**	**0.52 (0.41-0.68)**	**0.43 (0.32-0.58)**
*Disagree**			0.73 (0.46-1.15)	**1.98 (1.23-3.18)**	0.52 (0.22-1.21)
*Unsure**			**0.35 (0.28-0.46)**	**1.72 (1.31-2.26)**	**2.88 (2.12-3.93)**
Whooping cough vaccine will reduce my chances of getting whooping cough.					
*Agree**			**11.00 (8.47-14.30)**	**0.16 (0.12-0.21)**	**0.26 (0.19-0.35)**
*Disagree**			**0.11 (0.07-0.17)**	**9.37 (6.43-13.66)**	1.03 (0.62-1.71)
*Unsure**			**0.14 (0.11-0.19)**	**2.81 (2.12-3.71)**	**5.02 (3.68-6.84)**
Whooping cough vaccine will reduce the chance of me giving whooping cough to my unborn baby.					
*Agree**			**7.55 (5.98-9.53)**	**0.17 (0.13-0.22)**	**0.35 (0.26-0.47)**
*Disagree**			**0.21 (0.15-0.29)**	**7.45 (5.32-10.42)**	**0.51 (0.28-0.91)**
*Unsure**			**0.19 (0.15-0.25)**	**2.51 (1.93-3.26)**	**4.34 (3.21-5.86)**
Getting the whooping cough vaccine while I am pregnant will reduce my unborn baby's risk of getting whooping cough.					
*Agree**			**6.48 (5.19-8.10)**	**0.19 (0.15-0.25)**	**0.33 (0.25-0.44)**
*Disagree**			**0.23 (0.17-0.31)**	**6.17 (4.54-8.39)**	0.72 (0.45-1.15)
*Unsure**			**0.27 (0.21-0.34)**	**2.00 (1.56-2.57)**	**3.9 (2.91-5.24)**
It is in my control whether or not I get vaccines during my pregnancy.					
*Agree**	1.71 (0.93-3.13)	**0.46 (0.24-0.85)**	1.68 (0.92-3.09)	**0.45 (0.24-0.85)**	1.45 (0.51-4.1)
The majority of my friends and family would get the vaccines that are recommended during pregnancy.					
*Agree**	**7.99 (6.46-9.89)**	**0.21 (0.17-0.25)**	**6.14 (5.00-7.53)**	**0.25 (0.21-0.31)**	**0.30 (0.23-0.38)**
*Disagree**	**0.15 (0.11-0.21)**	**5.92 (4.47-7.85)**	**0.19 (0.14-0.26)**	**5.18 (3.92-6.86)**	1.38 (0.96-1.99)
*Unsure**	**0.20 (0.15-0.25)**	**2.39 (1.88-3.05)**	**0.25 (0.20-0.32)**	**1.94 (1.51-2.49)**	**3.97 (3.02-5.22)**
The majority of my friends and family would encourage me to get the vaccines that are recommended during pregnancy.					
*Agree**	**9.89 (7.97-12.26)**	**0.15 (0.12-0.19)**	**7.21 (5.87-8.85)**	**0.20 (0.16-0.24)**	**0.32 (0.25-0.41)**
*Disagree**	**0.10 (0.07-0.13)**	**8.45 (6.56-10.88)**	**0.14 (0.10-0.18)**	**7.07 (5.51-9.07)**	**1.49 (1.09-2.04)**
*Unsure**	**0.24 (0.19-0.32)**	**1.93 (1.48-2.52)**	**0.31 (0.24-0.40)**	**1.51 (1.14-2.00)**	**3.86 (2.89-5.15)**
I have most of the important information I need to make a decision about vaccines given during pregnancy.					
*Agree**	**4.16 (3.30-5.25)**	**0.54 (0.43-0.69)**	**3.92 (3.12-4.93)**	**0.56 (0.44-0.72)**	**0.23 (0.17-0.30)**
I know enough about the safety of the flu vaccine to make a decision about getting the vaccine for myself while pregnant.					
*Agree**	**4.62 (3.54-6.03)**	**0.62 (0.47-0.81)**			**0.16 (0.12-0.22)**
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for myself while pregnant.					
*Agree**			**4.53 (3.61-5.68)**	**0.50 (0.39-0.63)**	**0.18 (0.13-0.24)**
Trust in Vaccine Information Sources					
I trust the information provided by my obstetrician or midwife about vaccines during pregnancy.					
*Agree**	**8.68 (5.78-13.04)**	**0.19 (0.14-0.26)**	**6.75 (4.66-9.80)**	**0.21 (0.15-0.29)**	**0.48 (0.33-0.71)**

*Disagree**	**0.11 (0.06-0.21)**	**8.13 (4.77-13.86)**	**0.13 (0.07-0.24)**	**7.46 (4.46-12.49)**	1.01 (0.50-2.07)
*Unsure**	**0.14 (0.08-0.23)**	**3.48 (2.30-5.28)**	**0.18 (0.11-0.28)**	**3.02 (1.99-4.59)**	**2.91 (1.84-4.60)**
I trust the information provided by my baby's doctor about vaccines during pregnancy.					
*Agree**	**3.84 (3.00-4.92)**	**0.31 (0.24-0.40)**	**4.04 (3.16-5.17)**	**0.28 (0.22-0.36)**	**0.56 (0.41-0.77)**
*Disagree**	**0.12 (0.07-0.22)**	**7.57 (4.70-12.19)**	**0.15 (0.09-0.26)**	**6.86 (4.32-10.89)**	1.01 (0.53-1.93)
*Unsure**	**0.15 (0.09-0.27)**	**3.36 (2.10-5.35)**	**0.19 (0.11-0.32)**	**3.03 (1.89-4.85)**	**2.71 (1.61-4.56)**
*Unseen**	**0.55 (0.40-0.75)**	**1.52 (1.08-2.14)**	**0.45 (0.33-0.62)**	**1.96 (1.40-2.74)**	**1.60 (1.07-2.40)**
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines during pregnancy.					
*Agree**	**0.55 (0.46-0.65)**	**1.81 (1.48-2.20)**	**0.63 (0.53-0.75)**	**1.53 (1.25-1.88)**	**1.31 (1.03-1.68)**
*Disagree**	**1.40 (1.08-1.83)**	0.79 (0.59-1.07)	**1.41 (1.08-1.85)**	0.78 (0.57-1.07)	0.71 (0.48-1.06)
*Unsure**	0.84 (0.63-1.11)	1.11 (0.81-1.53)	0.79 (0.59-1.05)	1.21 (0.87-1.66)	1.20 (0.82-1.77)
*Unseen**	**1.77 (1.47-2.14)**	**0.54 (0.43-0.68)**	**1.55 (1.28-1.87)**	**0.64 (0.51-0.80)**	0.80 (0.61-1.05)
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines during pregnancy.					
*Agree**	**6.35 (5.03-8.03)**	**0.19 (0.15-0.23)**	**5.55 (4.42-6.97)**	**0.20 (0.16-0.25)**	**0.55 (0.41-0.72)**
*Disagree**	**0.12 (0.08-0.17)**	**8.43 (6.16-11.55)**	**0.13 (0.09-0.19)**	**8.22 (6.03-11.21)**	1.01 (0.66-1.55)
*Unsure**	**0.29 (0.21-0.38)**	**2.27 (1.71-3.03)**	**0.33 (0.25-0.44)**	**2.00 (1.49-2.69)**	**2.47 (1.78-3.44)**
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines during pregnancy.					
*Agree**	**3.86 (3.07-4.84)**	**0.28 (0.22-0.35)**	**3.56 (2.84-4.46)**	**0.29 (0.23-0.37)**	**0.64 (0.48-0.86)**
*Disagree**	**0.13 (0.09-0.21)**	**6.66 (4.54-9.76)**	**0.18 (0.12-0.27)**	**5.67 (3.91-8.23)**	1.19 (0.72-1.97)
*Unsure**	**0.41 (0.31-0.53)**	**2.11 (1.61-2.76)**	**0.41 (0.32-0.53)**	**2.13 (1.62-2.80)**	**1.67 (1.20-2.32)**

**Agree indicates a response of either Agree or Strongly Agree; Disagree indicates a response of either Disagree or Strongly Disagree, Unsure indicates a response of Don't Know (provided as an answer option only for knowledge- and trust-based questions), and Unseen indicates a response of "I don't have a pediatrician yet" or "I don't see this type of doctor" for the trust in in baby's doctor and naturopathic/chiropractic doctors, respectively*

***OR: Odds Ratio; 95%CI: 95% Confidence Interval; bolded if statistically significant*

****specific safety concerns were only obtained from those who did not agree that the vaccine in question was safe*

Appendix 12. Odds Ratios Assessing Associations between Pregnant Women's Vaccine Intentions for their Baby and their Infant Vaccine Knowledge, Attitudes, Beliefs and Trust

	OR (95%CI) with Infant Vaccine Intentions**					
Survey Statement	**All On Time**	**All But Spread Out**	**Some But On Time**	**Some and Spread Out**	**None**	**Unsure**
Confidence in Vaccine Safety						
I am confident that vaccines are safe for my baby after birth.						
*Agree**	**16.90 (12.26-23.30)**	1.20 (0.82-1.77)	**0.30 (0.20-0.45)**	**0.06 (0.04-0.11)**	**0.01 (0.00-0.04)**	**0.12 (0.09-0.17)**
Specific Vaccine Safety Concerns* **						
It is better for babies to get fewer vaccines at the same time.						
*Agree**	**0.47 (0.25-0.91)**	2.32 (0.79-6.85)	1.22 (0.54-2.79)	2.25 (0.92-5.55)	1.40 (0.62-3.18)	0.64 (0.37-1.11)
Babies get more vaccines in their first two years of life than are good for them.						
*Agree**	**0.36 (0.19-0.66)**	**7.38 (1.73-31.51)**	1.29 (0.60-2.77)	**2.70 (1.16-6.27)**	0.69 (0.35-1.35)	0.79 (0.47-1.33)
Vaccines often cause serious side effects in babies.						
*Agree**	**0.18 (0.09-0.34)**	0.66 (0.32-1.37)	1.40 (0.68-2.88)	1.14 (0.59-2.19)	**5.37 (2.05-14.05)**	1.44 (0.86-2.41)
The ingredients in vaccines are not safe for my baby.						
*Agree**	**0.15 (0.08-0.28)**	0.99 (0.45-2.17)	1.01 (0.49-2.08)	1.99 (0.92-4.31)	**7.03 (2.12-23.32)**	1.28 (0.74-2.19)
Other Vaccine Knowledge, Attitudes and Beliefs						
I worry that my baby could get whooping cough after birth.						
*Agree**	**2.52 (2.04-3.11)**	0.74 (0.55-1.00)	**0.39 (0.25-0.59)**	**0.48 (0.28-0.82)**	**0.26 (0.13-0.52)**	**0.47 (0.33-0.66)**
Whooping cough is dangerous for babies.						
*Agree**	**2.43 (1.69-3.49)**	1.93 (0.97-3.87)	**0.38 (0.22-0.67)**	0.68 (0.29-1.62)	0.47 (0.19-1.14)	**0.27 (0.17-0.42)**
*Disagree**	**0.40 (0.18-0.90)**	n/a	**4.55 (1.66-12.47)**	2.7 (0.62-11.79)	**8.84 (2.88-27.19)**	0.94 (0.22-4.06)
*Unsure**	**0.43 (0.29-0.64)**	0.66 (0.33-1.32)	**2.06 (1.06-4.00)**	1.16 (0.41-3.28)	0.77 (0.18-3.24)	**4.44 (2.77-7.12)**
Whooping cough is more dangerous for babies than older children or adults.						
*Agree**	**2.46 (1.86-3.26)**	1.32 (0.83-2.08)	**0.45 (0.28-0.73)**	**0.42 (0.23-0.78)**	0.48 (0.23-1.00)	**0.30 (0.21-0.45)**
*Disagree**	**0.42 (0.22-0.81)**	0.61 (0.19-2.00)	1.99 (0.69-5.74)	**3.61 (1.23-10.55)**	**3.66 (1.08-12.42)**	1.99 (0.82-4.84)
*Unsure**	**0.43 (0.31-0.58)**	0.80 (0.49-1.31)	**2.14 (1.27-3.59)**	1.92 (0.97-3.79)	1.61 (0.70-3.69)	**3.33 (2.23-4.96)**
Getting the whooping cough vaccine for my baby after birth will reduce my baby's chances of getting whooping cough.						
*Agree**	**4.46 (3.54-5.61)**	1.16 (0.83-1.63)	**0.35 (0.23-0.53)**	**0.26 (0.15-0.44)**	**0.04 (0.01-0.11)**	**0.17 (0.12-0.25)**

Disagree *	**0.14 (0.09-0.21)**	1.27 (0.75-2.14)	**2.57 (1.43-4.63)**	**5.22 (2.80-9.76)**	**67.64 (30.29-151.06)**	1.04 (0.55-1.98)
*Unsure**	**0.37 (0.29-0.48)**	0.73 (0.49-1.09)	**2.19 (1.40-3.42)**	**1.84 (1.03-3.31)**	0.44 (0.16-1.25)	**6.75 (4.73-9.65)**
It is in my control whether or not my baby gets his/her vaccines.						
*Agree**	1.58 (0.94-2.63)	1.06 (0.48-2.36)	0.87 (0.31-2.46)	**0.33 (0.13-0.86)**	n/a	0.50 (0.25-1.00)
I believe it is better for my baby to develop their own immunity by getting sick rather than by getting a vaccine.						
*Agree**	**0.26 (0.20-0.32)**	1.27 (0.92-1.74)	**2.46 (1.61-3.75)**	**4.11 (2.29-7.37)**	**12.69 (5.23-30.77)**	**3.86 (2.73-5.47)**
The majority of my friends and family would get all of the vaccines recommended for their babies after birth.						
*Agree**	**4.73 (3.77-5.93)**	1.15 (0.82-1.62)	**0.34 (0.23-0.50)**	**0.40 (0.24-0.66)**	**0.11 (0.06-0.21)**	**0.15 (0.11-0.21)**
Disagree *	**0.16 (0.11-0.23)**	1.20 (0.76-1.90)	**3.72 (2.32-5.97)**	**4.60 (2.59-8.17)**	**12.25 (6.77-22.18)**	**2.42 (1.56-3.75)**
*Unsure**	**0.34 (0.26-0.44)**	0.68 (0.43-1.07)	**1.76 (1.08-2.87)**	0.92 (0.42-2.04)	1.89 (0.90-3.95)	**6.89 (4.95-9.59)**
The majority of my friends and family would encourage me to get all of the vaccines recommended for my baby after birth.						
*Agree**	**5.85 (4.66-7.34)**	0.99 (0.72-1.36)	**0.29 (0.20-0.42)**	**0.31 (0.19-0.50)**	**0.07 (0.04-0.14)**	**0.15 (0.11-0.21)**
Disagree *	**0.12 (0.09-0.17)**	1.50 (1.00-2.24)	**4.16 (2.68-6.46)**	**4.81 (2.79-8.3)**	**15.70 (8.69-28.39)**	**2.56 (1.71-3.83)**
*Unsure**	**0.32 (0.24-0.42)**	0.67 (0.42-1.06)	**1.82 (1.12-2.98)**	1.28 (0.63-2.62)	1.96 (0.94-4.10)	**6.75 (4.84-9.42)**
I have most of the important information I need to make a decision about vaccines for my baby after birth.						
*Agree**	**4.38 (3.45-5.56)**	0.92 (0.66-1.29)	**0.42 (0.28-0.63)**	**0.44 (0.26-0.75)**	2.11 (0.75-5.91)	**0.11 (0.08-0.15)**
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for my baby after birth.						
*Agree**	**3.12 (2.54-3.83)**	0.96 (0.71-1.29)	**0.45 (0.31-0.66)**	**0.42 (0.26-0.69)**	2.15 (0.91-5.08)	**0.15 (0.11-0.20)**
Trust in Vaccine Information Sources						
I trust the information provided by my obstetrician or midwife about vaccines for babies after birth.						
*Agree**	**15.33 (9.75-24.10)**	1.27 (0.75-2.17)	**0.44 (0.26-0.76)**	**0.11 (0.07-0.19)**	**0.06 (0.03-0.11)**	**0.15 (0.10-0.22)**
Disagree *	**0.09 (0.05-0.17)**	0.67 (0.29-1.56)	1.67 (0.71-3.94)	**10.90 (5.78-20.54)**	**30.69 (16.18-58.19)**	1.82 (0.91-3.61)
*Unsure**	**0.06 (0.03-0.11)**	0.89 (0.46-1.75)	**2.57 (1.33-4.97)**	**4.48 (2.21-9.10)**	**2.87 (1.11-7.42)**	**11.69 (7.47-18.31)**
I trust the information provided by my baby's doctor about vaccines for babies after birth.						
*Agree**	**5.65 (4.39-7.28)**	1.34 (0.91-1.97)	**0.48 (0.31-0.73)**	**0.14 (0.08-0.23)**	**0.10 (0.06-0.19)**	**0.16 (0.12-0.22)**
Disagree *	**0.04 (0.02-0.10)**	1.09 (0.51-2.33)	1.96 (0.83-4.65)	**11.77 (6.11-22.70)**	**37.77 (19.65-72.60)**	1.40 (0.63-3.12)
*Unsure**	**0.05 (0.02-0.12)**	0.47 (0.17-1.29)	**4.30 (2.23-8.29)**	**3.47 (1.44-8.34)**	**4.13 (1.58-10.81)**	**10.77 (6.42-18.05)**
*Unseen**	**0.40 (0.30-0.54)**	0.77 (0.48-1.25)	1.22 (0.67-2.21)	**3.26 (1.83-5.83)**	0.91 (0.32-2.56)	**4.37 (3.04-6.28)**
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines for babies after birth.						
*Agree**	**0.57 (0.47-0.68)**	**2.14 (1.66-2.77)**	1.34 (0.93-1.94)	1.30 (0.80-2.10)	1.69 (0.95-2.99)	1.05 (0.78-1.43)

*Disagree**	1.08 (0.83-1.41)	1.09 (0.76-1.57)	0.91 (0.52-1.58)	0.98 (0.48-2.00)	1.72 (0.85-3.49)	0.60 (0.36-1.01)
*Unsure**	**0.55 (0.41-0.74)**	1.10 (0.72-1.68)	1.15 (0.64-2.08)	1.67 (0.84-3.31)	1.37 (0.57-3.25)	**2.44 (1.64-3.61)**
*Unseen**	**2.28 (1.87-2.79)**	**0.36 (0.26-0.49)**	0.72 (0.48-1.07)	0.59 (0.34-1.02)	**0.28 (0.12-0.62)**	0.76 (0.55-1.04)
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines for babies after birth.						
*Agree**	**7.29 (5.77-9.22)**	1.11 (0.80-1.55)	**0.37 (0.25-0.54)**	**0.09 (0.05-0.15)**	**0.03 (0.01-0.07)**	**0.15 (0.11-0.21)**
*Disagree**	**0.10 (0.07-0.14)**	1.05 (0.68-1.64)	**2.95 (1.85-4.70)**	**14.07 (8.51-23.27)**	**30.27 (15.91-57.57)**	**2.38 (1.58-3.58)**
*Unsure**	**0.27 (0.20-0.36)**	0.79 (0.50-1.24)	**1.81 (1.10-2.99)**	**1.93 (1.02-3.66)**	1.79 (0.82-3.86)	**7.28 (5.21-10.19)**
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines for babies after birth.						
*Agree**	**4.70 (3.73-5.91)**	1.03 (0.73-1.44)	**0.37 (0.25-0.55)**	**0.33 (0.20-0.54)**	**0.06 (0.03-0.11)**	**0.21 (0.16-0.29)**
*Disagree**	**0.09 (0.06-0.15)**	0.99 (0.56-1.76)	**2.83 (1.59-5.05)**	**9.05 (5.16-15.86)**	**22.94 (12.54-41.97)**	**2.37 (1.43-3.94)**
*Unsure**	**0.35 (0.27-0.46)**	0.97 (0.66-1.43)	**2.13 (1.36-3.34)**	0.67 (0.29-1.57)	**2.70 (1.41-5.16)**	**4.67 (3.36-6.50)**

**Agree indicates a response of either Agree or Strongly Agree; Disagree indicates a response of either Disagree or Strongly Disagree, Unsure indicates a response of Don't Know (provided as an answer option only for knowledge- and trust-based questions), and Unseen indicates a response of "I don't have a pediatrician yet" or "I don't see this type of doctor" for the trust in in baby's doctor and naturopathic/chiropractic doctors, respectively*

***OR: Odds Ratio; 95%CI: 95% Confidence Interval; bolded if statistically significant*

****specific safety concerns were only obtained from those who did not agree that the vaccine in question was safe*

Appendix 13. Latent Classes of Pregnant Women Based on their Vaccine Intentions, Knowledge, Attitudes, Beliefs, and Trust

Survey Responses	"Vaccine Enthusiasts" %	"Vaccine Acceptors" %	"Vaccine Skeptics" %
Total	36	41	23
Vaccine Intentions			
Current guidelines suggest pregnant women to receive two vaccines while pregnant, flu and whooping cough. I intend to get:			
both flu and whooping cough vaccines	81	62	7
flu but not whooping cough vaccine	5	9	6
whooping cough but not flu vaccine	6	11	12
not sure	5	14	25
no vaccines	3	5	49
Current guidelines suggest babies receive several vaccines. Regarding the vaccinations my doctor recommends for my baby after birth, I intend to get my baby:			
all recommended vaccines on time	91	73	25
all recommended vaccines but some spread out past the recommended ages	7	16	14
some recommended vaccines but each on time	1	5	13
some recommended vaccines spread out past the recommended ages	0	2	10
I'm not sure yet	1	4	29
no vaccines	0	0	9
Confidence in Vaccine Safety			
Number of Specific Vaccine Safety Concerns Identified			
0	93	85	6
1-4	4	11	20
5-8	3	4	27
9-12	0	0	29
13-16	0	0	18
I am confident that getting the flu vaccine during my pregnancy is safe for me.			
strongly agree	66	11	2

agree	30	80	19
disagree	3	9	59
strongly disagree	2	1	21
I am confident that getting the flu vaccine during my pregnancy is safe for my unborn baby.			
strongly agree	58	7	2
agree	38	84	20
disagree	4	9	62
strongly disagree	1	0	16
I am confident that getting the whooping cough vaccine during my pregnancy is safe for me.			
strongly agree	62	4	1
agree	34	92	25
disagree	3	4	61
strongly disagree	1	0	13
I am confident that getting the whooping cough vaccine during my pregnancy is safe for my unborn baby.			
strongly agree	59	3	2
agree	38	93	28
disagree	3	4	57
strongly disagree	0	0	13
I am confident that vaccines are safe for my baby after birth.			
strongly agree	80	13	6
agree	20	84	41
disagree	1	3	41
strongly disagree	0	0	13
Other Vaccine Knowledge, Attitudes and Beliefs*			
I worry that I could get the flu while I am pregnant.			
strongly agree	31	8	6
agree	43	57	27
disagree	20	33	46
strongly disagree	5	3	21
The flu is dangerous for pregnant women.			

strongly agree	56	21	20
agree	36	65	52
*don't know***	4	8	15
disagree	3	4	11
strongly disagree	1	2	2
The flu is more dangerous for pregnant women than for women who are not pregnant.			
strongly agree	54	19	15
agree	32	60	50
*don't know***	6	13	17
disagree	6	7	15
strongly disagree	1	1	3
Getting the flu vaccine will reduce my risk of getting the flu during my pregnancy.			
strongly agree	53	9	2
agree	37	69	18
*don't know***	4	11	23
disagree	5	9	41
strongly disagree	1	1	17
Getting the flu vaccine while I am pregnant will reduce my unborn baby's risk of getting the flu.			
strongly agree	35	4	0
agree	31	47	11
*don't know***	22	33	40
disagree	9	16	36
strongly disagree	3	1	13
I worry that I could get whooping cough while I am pregnant.			
strongly agree	17	2	2
agree	38	37	15
disagree	36	58	64
strongly disagree	9	3	19
I worry that I could give whooping cough to my baby after birth.			
strongly agree	38	5	3
agree	40	53	21

disagree	16	40	60
strongly disagree	6	2	16
Whooping cough is dangerous for pregnant women.			
strongly agree	47	11	12
agree	39	67	47
*don't know***	10	18	34
disagree	3	4	6
strongly disagree	0	0	1
Whooping cough vaccine will reduce my chances of getting whooping cough.			
strongly agree	62	8	2
agree	31	78	28
*don't know***	5	12	41
disagree	1	3	22
strongly disagree	1	0	7
Whooping cough vaccine will reduce the chance of me giving whooping cough to my unborn baby.			
strongly agree	61	9	2
agree	27	70	24
*don't know***	8	16	45
disagree	3	4	23
strongly disagree	1	1	6
Getting the whooping cough vaccine while I am pregnant will reduce my unborn baby's risk of getting whooping cough.			
strongly agree	54	5	0
agree	29	65	16
*don't know***	13	23	50
disagree	4	7	25
strongly disagree	0	1	8
It is in my control whether or not I get vaccines during my pregnancy.			
strongly agree	80	33	48
agree	19	64	48
disagree	1	2	3
strongly disagree	0	1	2

The majority of my friends and family would get the vaccines that are recommended during pregnancy.			
strongly agree	61	9	6
agree	31	70	30
*don't know***	5	15	35
disagree	3	6	22
strongly disagree	1	1	7
The majority of my friends and family would encourage me to get the vaccines that are recommended during pregnancy.			
strongly agree	60	9	5
agree	32	69	26
*don't know***	5	14	24
disagree	3	8	35
strongly disagree	1	0	10
I have most of the important information I need to make a decision about vaccines given during pregnancy.			
strongly agree	60	6	13
agree	34	80	47
disagree	5	14	32
strongly disagree	1	0	8
I know enough about the safety of the flu vaccine to make a decision about getting the vaccine for myself while pregnant.			
strongly agree	62	4	15
agree	32	80	44
disagree	5	16	35
strongly disagree	1	1	5
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for myself while pregnant.			
strongly agree	55	2	10
agree	35	70	34
disagree	9	27	47
strongly disagree	1	2	10
I worry that my baby could get whooping cough after birth.			
strongly agree	38	5	3
agree	41	57	30
disagree	15	36	54

strongly disagree	5	2	14
Whooping cough is dangerous for babies.			
strongly agree	86	33	22
agree	13	60	59
*don't know***	2	5	16
disagree	0	1	2
strongly disagree	0	1	1
Whooping cough is more dangerous for babies than older children or adults.			
strongly agree	81	31	23
agree	14	56	48
*don't know***	5	11	24
disagree	0	2	5
strongly disagree	0	1	1
Getting the whooping cough vaccine for my baby after birth will reduce my baby's chances of getting whooping cough.			
strongly agree	65	10	5
agree	25	70	31
*don't know***	9	17	41
disagree	1	3	18
strongly disagree	0	0	5
It is in my control whether or not my baby gets his/her vaccines.			
strongly agree	86	35	42
agree	13	61	50
disagree	1	3	6
strongly disagree	0	1	1
I believe it is better for my baby to develop their own immunity by getting sick rather than by getting a vaccine.			
strongly agree	16	2	11
agree	4	20	42
disagree	28	61	41
strongly disagree	52	17	6
The majority of my friends and family would get all of the vaccines recommended for their babies after birth.			
strongly agree	65	10	12

agree	29	76	42
*don't know***	3	10	24
disagree	2	4	17
strongly disagree	1	0	5
The majority of my friends and family would encourage me to get all of the vaccines recommended for my baby after birth.			
strongly agree	67	11	11
agree	28	76	38
*don't know***	3	9	25
disagree	2	4	21
strongly disagree	1	0	6
I have most of the important information I need to make a decision about vaccines for my baby after birth.			
strongly agree	69	6	15
agree	27	81	46
disagree	3	13	31
strongly disagree	1	0	9
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for my baby after birth.			
strongly agree	65	3	11
agree	29	75	38
disagree	6	22	42
strongly disagree	1	1	9
Trust in Vaccine Information Sources			
I trust the information provided by my obstetrician or midwife about vaccines during pregnancy.			
strongly agree	93	18	15
agree	7	80	57
*don't know***	0	1	17
disagree	0	1	10
strongly disagree	0	0	2
I trust the information provided by my obstetrician or midwife about vaccines for babies after birth.			
strongly agree	92	17	15
agree	8	81	58

*don't know***	0	1	16
disagree	0	1	9
strongly disagree	0	0	3
I trust the information provided by my baby's doctor about vaccines during pregnancy.			
strongly agree	88	16	12
agree	8	76	45
*don't know***	0	1	13
I don't have a pediatrician yet	3	6	17
disagree	0	1	10
strongly disagree	0	0	3
I trust the information provided by my baby's doctor about vaccines for babies after birth.			
strongly agree	88	16	12
agree	7	75	48
*don't know***	0	0	11
I don't have a pediatrician yet	4	8	18
disagree	0	0	8
strongly disagree	0	0	3
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines during pregnancy.			
strongly agree	26	3	9
agree	11	41	38
*don't know***	7	10	15
I don't see this type of doctor	41	34	26
disagree	10	10	10
strongly disagree	6	2	3
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines for babies after birth.			
strongly agree	24	3	9
agree	11	38	37
*don't know***	6	10	15
I don't see this type of doctor	45	37	27
disagree	9	10	10
strongly disagree	6	2	3

I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines during pregnancy.			
strongly agree	80	10	5
agree	18	80	34
*don't know***	2	9	26
disagree	0	2	22
strongly disagree	0	0	13
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines for babies after birth.			
strongly agree	81	9	5
agree	17	80	36
*don't know***	2	9	26
disagree	0	2	21
strongly disagree	0	0	12
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines during pregnancy.			
strongly agree	74	8	6
agree	22	79	47
*don't know***	4	12	27
disagree	1	2	16
strongly disagree	0	0	4
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines for babies after birth.			
strongly agree	72	8	6
agree	23	79	48
*don't know***	4	12	27
disagree	1	2	14
strongly disagree	0	0	4

**20 questions deemed non-essential were included in surveys for only ~75% of the sample (based on randomly assigned groups) in order to keep surveys short enough to obtain high completion rates*

***DK=Don't Know; provided as an answer option only for knowledge- and trust-based questions*

Appendix 14. First Child, Degree and Ethnicity Stratified by State

State	Total N (%)	First Child, N (%)		Education*, N (%)		Ethnicity, N (%)			
		Yes	No	High	Low	Black	White	Hispanic	Other
GA	1,106 (50)	504 (46)	598 (54)	661 (72)	258 (28)	257 (27)	534 (57)	61 (7)	85 (9)
CO	1,104 (50)	513 (46)	591 (54)	641 (71)	262 (29)	57 (6)	647 (69)	151 (16)	81 (9)
P-value**		0.73		0.66		**<0.01**			

**Education=High for Doctoral or Professional degree, Master's degree, Bachelor's degree, Associate's degree; Education=Low for Postsecondary nondegree award, Some college no degree, High school diploma or equivalent, No formal educational credential*

***P-value for the Pearson chi-squared proportion test at significance level of (α) 5%; bolded if significant*

Appendix 15. Comparisons of Constructs by Vaccine

Agreement with Survey Constructs	Maternal Influenza Vaccine, N (%)	Maternal Tdap Vaccine, N (%)	P*	Maternal Vaccines, N (%)	Infant Vaccines, N (%)	P**
Confidence in Vaccine Safety						
Confidence in Vaccine Safety (for the mother)	1670 (75)	1762 (80)	**<0.01**			
Confidence in Vaccine Safety (for the infant)	1683 (77)	1779 (81)	**<0.01**		1894 (86)	**<0.01**
Disease Susceptibility	1002 (61)	650 (39)	**<0.01**		1012 (61)	**<0.01**
Disease Severity	1410 (86)	1260 (76)	**<0.01**		1523 (92)	**<0.01**
Vaccine Efficacy (for the mother)	1142 (69)	1241 (75)	**<0.01**			
Vaccine Efficacy (for the infant)	779 (47)	1021 (62)	**<0.01**		1201 (73)	**<0.01**
Self-Efficacy	1608 (98)				1590 (96)	**0.03**
Descriptive Norms	1615 (74)				1796 (82)	**<0.01**
Injunctive Norms	1584 (72)				1776 (81)	**<0.01**
Perception of Vaccine Knowledge				1815 (83)	1852 (84)	**0.02**
Perception of Vaccine Safety Knowledge	1352 (81)	1176 (71)	**<0.01**		1691 (77)	**<0.01**
Trust in Vaccine Information Sources						
Trust in obstetricians, midwives				2042 (92)	2044 (93)	0.66
Trust in pediatricians				1880 (92)	1879 (94)	**<0.01**
Trust in naturopaths, chiropractors				924 (64)	869 (63)	**0.02**
Trust in CDC				1776 (81)	1783 (81)	0.27
Trust in academia				1808 (82)	1816 (82)	0.36

**P-value for McNemar's test comparing maternal influenza vaccine to maternal Tdap vaccine at significance level of (α) 5%; bolded if significant*

***P-value for McNemar's test comparing maternal vaccines (either maternal vaccines in general or just maternal Tdap vaccine, depending on statement) to infant vaccines at significance level of (α) 5%; bolded if significant*

Appendix 16. Comparing Frequency of Agreement with Maternal Vaccine Related Statements between Pregnant Women Intending to Receive Only Maternal Influenza Vaccine and Pregnant Women Intending to Receive Only Tdap Vaccine

Maternal Vaccine Related Survey Statements	Agree or Strongly Agree, N (%) – Total	Agree or Strongly Agree, N (%) – Influenza Only*	Agree or Strongly Agree, N (%) – Tdap Only**	P***
Confidence in Vaccine Safety Statements				
I am confident that getting the flu vaccine during my pregnancy is safe for me.	1670 (75)	142 (92)	93 (47)	**<0.01**
I am confident that getting the flu vaccine during my pregnancy is safe for my unborn baby.	1683 (77)	140 (91)	105 (53)	**<0.01**
I am confident that getting the whooping cough vaccine during my pregnancy is safe for me.	1762 (80)	110 (71)	179 (90)	**<0.01**
I am confident that getting the whooping cough vaccine during my pregnancy is safe for my unborn baby.	1779 (81)	113 (73)	169 (85)	**0.01**
Vaccine Knowledge, Attitude and Belief Statements				
I worry that I could get the flu while I am pregnant.	1002 (61)	70 (62)	47 (33)	**<0.01**
The flu is dangerous for pregnant women.	1410 (86)	96 (85)	116 (81)	0.36
The flu is more dangerous for pregnant women than for women who are not pregnant.	1304 (79)	97 (86)	108 (75)	**0.03**
Getting the flu vaccine will reduce my risk of getting the flu during my pregnancy.	1142 (69)	87 (76)	47 (33)	**<0.01**
Getting the flu vaccine while I am pregnant will reduce my unborn baby's risk of getting the flu.	779 (47)	58 (51)	34 (24)	**<0.01**
I worry that I could get whooping cough while I am pregnant.	650 (39)	20 (18)	56 (38)	**<0.01**
I worry that I could give whooping cough to my baby after birth.	937 (57)	28 (25)	97 (65)	**<0.01**
Whooping cough is dangerous for pregnant women.	1260 (76)	78 (70)	114 (77)	0.21
Whooping cough vaccine will reduce my chances of getting whooping cough.	1241 (75)	77 (69)	122 (82)	**0.01**
Whooping cough vaccine will reduce the chance of me giving whooping cough to my unborn baby.	1150 (69)	68 (60)	118 (79)	**<0.01**
Getting the whooping cough vaccine while I am pregnant will reduce my unborn baby's risk of getting whooping cough.	1021 (62)	59 (52)	100 (68)	**0.01**

It is in my control whether or not I get vaccines during my pregnancy.	1608 (98)	108 (95)	137 (95)	0.88
The majority of my friends and family would get the vaccines that are recommended during pregnancy.	1615 (74)	124 (81)	133 (67)	**<0.01**
The majority of my friends and family would encourage me to get the vaccines that are recommended during pregnancy.	1584 (72)	121 (79)	125 (63)	**<0.01**
I have most of the important information I need to make a decision about vaccines given during pregnancy.	1815 (83)	121 (79)	154 (77)	0.73
I know enough about the safety of the flu vaccine to make a decision about getting the vaccine for myself while pregnant.	1352 (81)	101 (89)	109 (76)	**<0.01**
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for myself while pregnant.	1176 (71)	60 (53)	115 (77)	**<0.01**
Trust in Vaccine Information Source Statements				
I trust the information provided by my obstetrician or midwife about vaccines during pregnancy.	2042 (92)	144 (94)	181 (91)	0.31
I trust the information provided by my baby's doctor about vaccines during pregnancy.****	1880 (92)	130 (84)	172 (86)	0.68
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines during pregnancy.****	924 (64)	61 (40)	99 (50)	0.06
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines during pregnancy.	1776 (81)	123 (80)	150 (75)	0.28
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines during pregnancy.	1808 (82)	123 (80)	154 (77)	0.52

**number and percentage of those agreeing with survey statement who intend to receive maternal influenza vaccine only*

***number and percentage of those agreeing with survey statement who intend to receive maternal Tdap vaccine only*

****P-value for the Pearson chi-squared proportion test comparing those who intend to receive maternal influenza vaccine only and those who intend to receive maternal Tdap vaccine only at significance level of (α) 5%; bolded if significant*

*****removed those who stated they hadn't yet seen this type of provider from this analysis*

Manuscript 3: Factors associated with referring close contacts to an app with individually-tailored vaccine information

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Key Points

Question

What makes a pregnant woman more or less likely to refer friends and family for vaccine information?

Findings

Pregnant women were more likely to refer an educational app about vaccines to their close friends and family if they trusted vaccine information from academic institutions, perceived influenza as dangerous for pregnant women, perceived maternal vaccines as safe and effective, or perceived their friends and family to be pro-maternal vaccines.

Meaning

Pregnant women who recognize the importance of maternal vaccines are willing to refer an educational app about vaccines to their close friends and family.

Abstract

Importance

Vaccine hesitancy is a threat to high vaccine coverage and controlling diseases. Maternal vaccine coverage is substantially lower than infant vaccine coverage, leaving young infants vulnerable to influenza and pertussis infections. Cocooning is a strategy to limit risk of infection among vulnerable infants by vaccinating those who will come into contact with the infant. Perceived norms have been shown to affect vaccine intentions and coverage. Distribution of accurate and accessible vaccine information through existing social networks could be an important tool in increasing vaccine confidence and coverage. This article presents data on factors associated with pregnant women referring their close friends and family to an educational app about vaccines.

Design

Pregnant women were given a 71-question survey to assess their vaccine intentions, attitudes, beliefs, norms, and levels of trust and provided educational videos about vaccines through an electronic tablet application. Information on ethnicity, education, and number of prior children was also collected by the app. Pregnant women were then given the opportunity to refer up to six contacts to enroll in the app.

Setting

Pregnant women were recruited from a geographically and socio-demographically diverse set of obstetrician-gynecologist offices in Georgia and Colorado.

Participants

One thousand one hundred and five pregnant women (545 from Colorado and 560 from Georgia) provided survey data and were given the opportunity to refer up to 6 contacts to the app.

Results

Two hundred and eighty of these women (25%) chose to refer contacts, for an average of 2.75 contacts per referring woman. The vast majority referred by pregnant women were their partners, parents, siblings, relatives, or close friends. Constructs associated with increased likelihood of referring contacts included: perceived safety and efficacy of maternal vaccines, perceived susceptibility to and severity of influenza; pro-maternal vaccine descriptive norms, and trust in vaccine information from the CDC and academic institutions. Belief that babies are better off developing immunity through natural illness rather than vaccination was associated with decreased likelihood of referring contacts.

Conclusions and Relevance

Pregnant women who valued vaccination and perceived their social network to value vaccination were more likely to refer an educational app about vaccines to their close friends and family. Further research is needed to determine the potential impact of this app referral strategy on vaccine coverage when implemented on a large scale.

Trial Registration

The survey informing this article was part of a randomized controlled trial funded by the National Institutes of Health [grant number R01AI110482].

Full Text

Introduction

Immunization is one of the most effective ways to prevent infectious diseases and their associated morbidity and mortality [13]. Vaccine hesitancy is a threat to high vaccine coverage and controlling diseases [1-11]. Although vaccine coverage among children in the United States remains high [14], maternal vaccine coverage is substantially lower [12], leaving infants too young to receive their own vaccines vulnerable to potentially deadly influenza and pertussis infections [28, 38-40].

Cocooning, or vaccinating close contacts of the incoming newborn, is strategy to limit risk of infection among vulnerable infants [46-48]. Factors derived from the Health Belief Model (HBM) [498] such as high perceived benefits of vaccine, high perceived susceptibility to disease, and low perceived barriers to vaccination have been associated with higher rates of cocooning [49]. Distribution of vaccine information and financial incentives for vaccination are potential interventions to influence these factors.

Vaccine decisions, like many other types of decisions, have been shown to be influenced by one's peers within their social network [200, 562-564], especially among those with vaccine concerns [565]. Thus, changes in vaccine confidence and decisions of individuals within in a social network may also impact the vaccine confidence and decisions of other individuals within that social network.

As part of an NIH-funded large randomized controlled trial of a prenatal intervention to increase uptake of maternal and infant vaccines (referred to as P3+), we developed an application for pregnant women called MomsTalkShots that can be used on smartphones, tablets and computers. The app collects survey data on vaccine knowledge, attitudes and beliefs and then delivers educational videos about vaccines tailored to the individual's survey responses. Videos were designed to present information in a scientifically accurate yet engaging manner with easily understandable language and a broad range of ethnicities represented. This was done so that the app would have broad appeal to a variety of ethnicities and levels of education. Upon conclusion of the videos, the app encouraged a selection of pregnant women in P3+ to refer their close friends and family to the app so they could receive the individually-tailored educational videos as well as a small financial incentive for receiving cocooning vaccinations at Walgreens.

This study used Social Cognitive Theory (SCT), which examines the influence of one's social environment on health behavior at the interpersonal level [500]. Access to the MomsTalkShots app alters the environment of cocooning vaccinations by providing financial incentives and more convenient pharmacy access to vaccination, while concurrently influencing personal vaccine knowledge and attitudes via the educational videos, aligning with SCT's concept of reciprocal determinism. The study also takes advantage of the interpersonal influence on behavior, by empowering pregnant women to share vaccine knowledge and opinions with their close contacts and vice versa with increased self-efficacy due to increased knowledge of the benefits and importance of vaccination.

This article examines which factors (e.g., vaccine intentions, knowledge, attitudes, beliefs, perceived norms, trust in information sources, and demographics) were associated with an

increased likelihood of pregnant women referring contacts, as well as what types of contacts were predominantly referred and then successfully enrolled in the app.

Methods

Data Collection

Survey data was collected through the MomsTalkShots app as part of the P3+ study. Pregnant women were recruited for the study from a geographically and socio-demographically diverse set of obstetrician-gynecologist offices in Georgia (GA) and Colorado (CO). Women entering these offices for regularly scheduled appointments were approached to be screened by study staff, and were eligible for participation if they were between 18 and 50 years old, between 8 and 26 weeks pregnant, and had not yet received influenza or Tdap vaccine during their current pregnancy. At first, only first-time pregnant women were recruited for the study, although recruitment was eventually expanded to include all pregnant women in order to increase the sample size. Sample size calculations were based on maternal Tdap vaccine coverage, and were thus recalculated to account for the increase in coverage between the time of the study proposal and study initiation.

The baseline survey included 71 total questions: 3 multiple choice questions assessing vaccine intentions and number of prior children, 60 statements with Likert scale answer options, and 8 open-ended questions with an optional free form answer box which were not analyzed in this paper. Likert scale options were limited to strongly agree, agree, disagree, and strongly disagree for most statements; knowledge and trust statements also included a “don’t know” option, and trust

statements regarding pediatricians and naturopathic/chiropractic doctors included options for “I don’t have a pediatrician yet” and “I don't see this type of doctor”, respectively. Response options for the question assessing maternal vaccine intentions were: “both flu and whooping cough vaccines”, “flu but not whooping cough vaccine”, “whooping cough but not flu vaccine”, “no vaccines”, and “not sure”. Response options for the question assessing infant vaccine intentions were: “all recommended vaccines on time”, “all recommended vaccines but some spread out past the recommended ages”, “some recommended vaccines but each on time”, “some recommended vaccines spread out past the recommended ages”, “no vaccines”, and “not sure yet”. Twenty-nine of these questions were deemed essential and administered to all participants; these included the 3 multiple choice questions, statements assessing belief in vaccine safety and efficacy, and statements assessing constructs such as descriptive norms, injunctive norms, perception of vaccine knowledge, and trust in vaccine information sources. Twenty-three questions were specific vaccine safety concern questions which were automatically administered only to participants who expressed a lack of confidence in the safety of a particular vaccine based on their responses to the vaccine safety questions. Two of these specific vaccine safety concern questions were potentially administered to survey participants twice due to this skip logic (“I do not want to put the flu vaccine into my body when I am pregnant because I think it is unnatural” and “I do not want to put the whooping cough vaccine into my body when I am pregnant because I think it is unnatural”). Twenty questions were deemed non-essential and administered to about three quarters of the sample (based on randomly assigned groups) in order to keep surveys short enough to obtain high completion rates; these questions covered constructs including perceived susceptibility to VPDs, perceived severity of VPDs, response efficacy, and self-efficacy. Demographic information such as state of residence, ethnicity and education was collected.

Half of all participants selected at random were given the opportunity to refer up to 6 friends and family members to be invited to enroll in the app for a related study. Those who referred at least one contact received a $10 gift card. A subset of roughly two thirds of the referred contacts selected at random were then sent up to 10 emails each spaced out by at least a week inviting them to join the study by enrolling in the app, for which a link was provided.

Data Analysis

Vaccine intention questions were dichotomized to represent those who intended to receive recommended maternal flu, Tdap, and all infant vaccines versus those who did not, and Likert scale statements were dichotomized to represent those who agreed or strongly agreed versus those who did not. Responses to the two specific vaccine safety concern questions that were potentially administered to survey participants twice due to skip logic were combined to each form one variable in the dataset. A categorical variable representing the number of specific vaccine safety concern statements agreed or strongly agreed to (0-16) per woman was created. Ethnicity categories were collapsed to white, black, Hispanic, or other; education categories were collapsed to having a graduate degree (Master's, Doctoral, or Professional), having an undergraduate degree (Bachelor's or Associate's), and not having a degree; and number of prior children was collapsed to having children prior to this pregnancy versus not.

Sociodemographic characteristics and survey responses were each analyzed as independent variables in simple logistic regressions with a dichotomous variable for having referred contacts versus not having referred contacts as the dependent variable, and odds ratios (ORs) were

calculated. A best-fit multiple logistic regression model was then created by backwards selection to include only those variables with statistical significance ($P<0.05$) in both the simple and multiple models. The categorical variable for number of vaccine safety concerns as well as individual vaccine safety concern variables were not included due to their collinearity with the confidence in vaccine safety variables. Nested models were compared using the Akaike information criterion (AIC), the Bayesian information criterion (BIC), and the likelihood ratio test.

Percentages of contacts referred and enrolled in the app by type of relationship to the referrer were calculated. Pearson's chi-squared test for independence was used to assess differences in enrollment rates by relationship type.

All P-values were two-sided and $P<0.05$ was considered statistically significant. Analysis was performed using Stata/IC 12.1 (STATA Corp., College Station, TX, USA).

Results

One thousand one hundred and five pregnant women (545 from Colorado and 560 from Georgia) provided survey data and were given the opportunity to refer up to 6 contacts to the app (Table 1). Twenty-six percent of women who provided education information had an advanced degree and 44% had an associate's or bachelor's degree. Sixty-two percent of women who provided their ethnicity identified as white; 17% identified as black and 12% as Hispanic or Latino. Forty-eight percent of women were pregnant for the first time. No statistically significant associations between likelihood of referring contacts to the app and ethnicity, education, state, or having prior children were found.

Two hundred and eighty women (25%) referred at least one contact to the app. Of these women, 37% referred one contact, 21% referred two contacts, 12% referred three contacts, 6% referred four contacts, 4% referred five contacts, and 19% referred the maximum of six contacts (Table 2).

A total of 772 contacts were referred, or an average of 2.75 contacts per referring woman (Table 3). Nineteen percent of referred contacts were listed as partners; 25% as parents; 16% as siblings; 15% as other relatives; 20% as close friends; 2% as casual friends, 2% as caregivers to the infant; and 2% as other.

Several statistically significant associations were found between pregnant women who referred contacts and their vaccine intentions, knowledge, attitudes, beliefs and trust (Table 4). Women who were unsure about their infant vaccine intentions were less likely to refer contacts to the app (OR: 0.45; P=0.01). Women were more likely to refer contacts to the app if they were confident in the safety and efficacy of maternal vaccines, had high perceived susceptibility to and severity of influenza during pregnancy, reported pro-maternal vaccine descriptive norms, and reported trust in vaccine information from the CDC and academic institutions. Conversely, women were less likely to refer contacts to the app if they agreed with the statement "I believe it is better for my baby to develop their own immunity by getting sick rather than by getting a vaccine" (OR: 0.58; P=0.03).

Other associations were suggested albeit not statistically significantly (Appendix 1). For example, pregnant women who intended to receive maternal influenza (OR: 1.29; P=0.08) and Tdap (OR: 1.29; P=0.09) vaccines appeared slightly more likely to refer contacts to the app than women without such intention. Although associations varied somewhat by relationships to referred contacts, no statistically significant contrasting effects between relationship types were found.

The best-fit model reduced to include agreement with only two survey statements as statistically significant predictors of referring contacts: “the flu is more dangerous for pregnant women than for women who are not pregnant” (OR: 2.07; P=0.01); and “getting the flu vaccine will reduce my risk of getting the flu during my pregnancy” (OR: 1.61; P=0.04).

Four hundred twenty-two (55%) of the contacts referred were randomly selected to be invited by email to join the study and enroll in the app (Table 5). Of these, 274 enrolled in the app (65% response rate). No statistically significant difference in enrollment rates by type of relationship to the referring pregnant woman was found (P=0.36).

Discussion

Pregnant women were more likely to refer their friends and family to an educational app about vaccines if they were confident in the safety and efficacy of maternal vaccines, perceived themselves susceptible to influenza during pregnancy and recognized its severity, reported pro-vaccine norms, and trusted vaccine information from the CDC and academic institutions. The most consistent predictors of referring friends and family when adjusted for other variables were perceiving VPD severity and vaccine efficacy.

The vast majority of contacts referred to an educational app about vaccines by pregnant women were their partners, parents, siblings, relatives, or close friends. Very few users referred casual friends or caregivers. No difference was seen in the likelihood of the referred contact enrolling in the app based on the type of relationship with the referring pregnant woman.

The positive association between referring contacts to the app and trust in vaccine information from academic institutions makes sense, as the app was clearly labeled as a product of the three universities collaborating on this study (Emory University, University of Colorado Anschutz Medical Campus, and Johns Hopkins Bloomberg School of Public Health).

Perceived pro-vaccine attitudes of women's friends and family was positively associated with referring them to an educational app about vaccines, indicating that women were more comfortable sharing information with their family and friends that they knew would resonate with their pre-existing beliefs; or perhaps that some were hesitant to share information they thought would be contradictory to their family and friends' pre-existing beliefs. This may limit the ability of this referral strategy to decrease vaccine hesitancy if most referred contacts are already confident in vaccines; however, it could still have an impact on cocooning vaccine coverage through the reinforcement of the importance of vaccination to an audience predisposed to agree with this message.

A belief that babies are better off developing immunity through natural illness rather than vaccination was significantly associated with decreased likelihood of referring contacts. This indicates that perceived lack of severity of disease or benefit of vaccination (or both) may decrease desire to share an educational app about vaccines with friends and family. If women who already value vaccination are substantially more likely to refer their friends and family to the app than women who do not, that would limit the amount of improvement in women's vaccine attitudes and beliefs possible through this strategy.

In addition, women with uncertain infant vaccine intentions were less likely to refer contacts to the app than those who had already made up their mind, which limits the potential of this strategy to influence women's vaccine intentions for their children through educating her social network.

However, no statistically significant effect was seen for women with uncertain maternal vaccine intentions, for which much greater frequency of uncertainty existed, implying that this strategy could still have an impact on maternal vaccine intentions.

The ethnicity, education and state of residence (CO vs GA) of the pregnant women using the MomsTalkShots app did not appear to impact their likelihood of referring contacts, nor did having prior children. These data may indicate the broad appeal of this app and referral strategy to the general population regardless of ethnicity or education level.

There are several limitations of this study. Firstly, these data are not nationally generalizable. This study was embedded into an existing clinical trial analyzing a comprehensive intervention to increase vaccination among pregnant women; thus, the pregnant women who chose to enroll in the preexisting trial and thus were available to participate in this study may be different than those who did not and pregnant women in general. Reasons for eligible women declining study participation include being too busy to screen (18%), not being interested in the study (40%), being wary of the study (5%), and not being able to communicate or read in English (13%). Our study population contained a higher proportion of educated, white women than indicated by CDC data on the demographics of U.S. births in 2016 in Colorado and Georgia [561]. In addition, the income level of pregnant women participating in this trial was not collected, so we are unable to properly control for this in our analysis. Because pregnant women were offered a $10 gift card as an incentive for referring contacts to the app, they may have been primarily motivated to do so because of the financial incentive, instead of because of any of the factors we measured and analyzed. Somewhat reassuring is that having at least a college degree was not statistically significantly associated with referring contacts to the app, as education is associated with income. Whether a referred contact enrolled in the app or not may have been impacted by email habits and

spam filters, which may explain why no statistically significant difference was seen in likelihood of enrolling in the app by type of relationship with the referring pregnant woman.

As providing financial incentives for referring contacts would likely be impractical on a large scale, further research into the impact and sustainability of this type of app referral strategy without incentives is needed. Further research is also needed to assess whether vaccination attitudes, intentions and uptake are impacted among referred contacts, and whether this in turn has any effect on the referring pregnant woman. If successful, such a strategy could increase vaccine confidence and maternal and cocooning vaccine coverage for very little cost, by spreading accurate, individually tailored vaccine information through existing social networks of pregnant women. This app referral strategy could then also be refined for populations other than pregnant women, to widen and diversify its potential impact on vaccine coverage and disease prevention.

Conclusion

Pregnant women who valued vaccination and perceived their social network to value vaccination were more likely to refer an educational app about vaccines to their close friends and family. Further research is needed to determine the potential impact of this app referral strategy on vaccine coverage when implemented on a large scale.

Acknowledgements

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Figures and Tables

Table 1. Percentage of Pregnant Women who Referred Contacts to Educational App about Vaccines, Stratified by State, Education, Ethnicity and First Child

Selected Characteristics	Total, N (%)	Referred Contacts, N (%)*	P**
All	1105	280 (25)	
State			
Colorado	545 (49)	145 (27)	0.34
Georgia	560 (51)	135 (24)	
total	1,105	280 (25)	
Education			
Graduate degree***	230 (26)	74 (32)	0.10
Undergraduate degree***	392 (44)	97 (25)	
No college degree	279 (31)	70 (25)	
total	901	241 (27)	
Ethnicity			
Black or African American	159 (17)	34 (21)	0.24
Hispanic or Latino	116 (12)	32 (28)	
White	574 (62)	150 (26)	
Other	84 (9)	28 (33)	
total	933	244 (26)	
First Child			
Yes	525 (48)	137 (26)	0.62
No	577 (52)	143 (25)	
total	1,102	280 (25)	

**number and percentage in each sociodemographic group who referred contacts to app*

***P-value for the Pearson chi-squared proportion test at significance level of (α) 5%; bolded if significant*

****Graduate degree includes Master's, Doctoral, and Professional degrees; Undergraduate degree includes Bachelor's and Associate's degrees*

Table 2. Number of Contacts Referred to Educational App about Vaccines per Pregnant Woman

Number of Contacts Referred	**N (%)**
0	825 (75)
1+	280 (25)
1	104 (9)
2	60 (5)
3	34 (3)
4	18 (2)
5	10 (1)
6 (maximum allowed)	54 (5)
total	1105 (100)

Table 3. Contacts Referred to Educational App about Vaccines by Relationship to Pregnant Women Who Referred Them

Relationship	Referred, N (%)
Partner	142 (19)
Parent	189 (25)
Sibling	124 (16)
Other Relative	114 (15)
Close Friend	152 (20)
Casual Friend	16 (2)
Caregiver	13 (2)
Other	14 (2)
*total**	764 (100)

**Relationship type was not collected for 8 participants*

Table 4. Odds Ratios for Vaccine Intentions, Knowledge, Attitudes, Beliefs and Trust Found to be Associated with Pregnant Women Referring Contacts to Educational App about Vaccines

Survey Items	Contacts Referred, OR (95%CI)*
Vaccine Intentions	
Uncertain Infant Vaccine Intentions	0.45 (0.25, 0.83)
Survey Statements - Agreed or Strongly Agreed	
Confidence in Vaccine Safety	
I am confident that getting the whooping cough vaccine during my pregnancy is safe for me.	1.59 (1.09, 2.33)
Other Vaccine Knowledge, Attitudes and Beliefs	
I worry that I could get the flu while I am pregnant.	1.51 (1.02, 2.25)
The flu is more dangerous for pregnant women than for women who are not pregnant.	2.25 (1.29, 3.92)
Getting the flu vaccine will reduce my risk of getting the flu during my pregnancy.	1.75 (1.11, 2.77)
Getting the whooping cough vaccine while I am pregnant will reduce my unborn baby's risk of getting whooping cough.	1.60 (1.05, 2.45)
The majority of my friends and family would get the vaccines that are recommended during pregnancy.	1.44 (1.04, 1.98)
I believe it is better for my baby to develop their own immunity by getting sick rather than by getting a vaccine.	0.58 (0.36, 0.94)
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines during pregnancy.	1.50 (1.05, 2.14)
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines for babies after birth.	1.53 (1.06, 2.20)
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines during pregnancy.	1.60 (1.10, 2.34)
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines for babies after birth.	1.86 (1.25, 2.77)

**Odds Ratio (95% Confidence Interval) for referring contacts to app by agreement with survey statement*

*Table 5. Contacts Who Chose to Enroll in Educational App about Vaccines by Relationship to Pregnant Women Who Referred Them***

Relationship	Not Enrolled, N (%)	Enrolled, N (%)	Total*
Partner	31 (38)	50 (62)	81
Parent	29 (31)	64 (69)	93
Sibling	18 (27)	48 (73)	66
Other Relative	25 (36)	45 (64)	70
Close Friend	36 (41)	52 (59)	88
Casual Friend	4 (67)	2 (33)	6
Caregiver	3 (38)	5 (63)	8
Other	2 (20)	8 (80)	10
*total**	148 (35)	274 (65)	422

**Only 422 of 772 referred contacts (55%) invited to enroll*

***Pearson chi-squared (7) = 7.7229 ; P-value = 0.358*

Appendix 1. Odds Ratios for Pregnant Women Referring Various Types of Contacts to Educational App about Vaccines Based on their Vaccine Intentions, Knowledge, Attitudes, Beliefs and Trust

Survey Items	Any Contact Referred, OR (95%CI)*	Partner Referred, OR (95%CI)*	Parent Referred, OR (95%CI)*	Sibling Referred, OR (95%CI)*	Other Relative Referred, OR (95%CI)*	Close Friend Referred, OR (95%CI)*
Vaccine Intentions						
Maternal Vaccines						
Intention to receive maternal flu vaccine	1.29 (0.97, 1.72)	1.28 (0.89, 1.84)	1.13 (0.78, 1.63)	0.86 (0.57, 1.30)	0.93 (0.57, 1.50)	1.17 (0.75, 1.82)
Intention to not receive maternal flu vaccine	0.77 (0.56, 1.08)	0.79 (0.52, 1.20)	0.94 (0.62, 1.42)	0.89 (0.54, 1.45)	1.06 (0.62, 1.83)	0.71 (0.42, 1.22)
Intention to receive maternal Tdap vaccine	1.29 (0.96, 1.72)	1.13 (0.79, 1.61)	**1.54 (1.04, 2.28)**	0.86 (0.56, 1.31)	1.02 (0.62, 1.67)	0.84 (0.54, 1.28)
Intention to not receive maternal Tdap vaccine	0.77 (0.55, 1.09)	0.94 (0.62, 1.42)	**0.60 (0.37, 0.98)**	0.88 (0.53, 1.47)	0.94 (0.53, 1.68)	1.13 (0.69, 1.85)
Not sure	0.88 (0.59, 1.32)	0.86 (0.51, 1.46)	0.86 (0.50, 1.47)	1.54 (0.91, 2.61)	1.05 (0.53, 2.08)	1.18 (0.66, 2.11)
Infant Vaccines						
Intention to get baby all recommended vaccines on time	1.16 (0.87, 1.57)	1.28 (0.87, 1.86)	1.13 (0.77, 1.65)	0.70 (0.46, 1.07)	0.93 (0.57, 1.53)	0.77 (0.50, 1.19)
Intention to get baby all recommended vaccines but some spread out past the recommended ages	1.05 (0.71, 1.56)	0.88 (0.52, 1.50)	1.09 (0.65, 1.82)	**1.94 (1.16, 3.23)**	1.29 (0.67, 2.49)	1.67 (0.97, 2.88)
Intention to get baby some recommended vaccines but each on time	1.46 (0.82, 2.61)	1.01 (0.48, 2.12)	0.64 (0.26, 1.60)	0.74 (0.27, 2.05)	1.59 (0.68, 3.75)	0.58 (0.18, 1.85)

Intention to get baby some recommended vaccines spread out past the recommended ages	0.98 (0.44, 2.21)	0.89 (0.32, 2.48)	0.95 (0.34, 2.64)	1.39 (0.49, 3.89)	0.89 (0.21, 3.72)	1.89 (0.74, 4.82)
Intention to get baby no vaccines	0.69 (0.23, 2.06)	0.95 (0.29, 3.10)	1.01 (0.31, 3.30)	0.46 (0.06, 3.38)	0.62 (0.08, 4.59)	1.57 (0.48, 5.14)
Not sure yet	**0.45 (0.25, 0.83)**	0.6 (0.29, 1.24)	0.82 (0.42, 1.59)	1.09 (0.54, 2.20)	0.61 (0.22, 1.69)	0.73 (0.32, 1.70)
Survey Statements - Agreed or Strongly Agreed						
Confidence in Vaccine Safety						
I am confident that getting the flu vaccine during my pregnancy is safe for me.	1.26 (0.91, 1.75)	1.36 (0.89, 2.08)	1.05 (0.70, 1.58)	0.73 (0.47, 1.15)	1.35 (0.75, 2.43)	1.56 (0.90, 2.69)
I am confident that getting the flu vaccine during my pregnancy is safe for my unborn baby.	1.04 (0.75, 1.44)	1.31 (0.86, 2.01)	0.97 (0.65, 1.45)	0.79 (0.50, 1.24)	0.86 (0.51, 1.47)	1.29 (0.77, 2.18)
I am confident that getting the whooping cough vaccine during my pregnancy is safe for me.	**1.59 (1.09, 2.33)**	1.6 (0.98, 2.59)	**1.81 (1.08, 3.04)**	1.49 (0.84, 2.66)	1.26 (0.67, 2.37)	1.18 (0.68, 2.05)
I am confident that getting the whooping cough vaccine during my pregnancy is safe for my unborn baby.	1.31 (0.90, 1.89)	**1.72 (1.04, 2.85)**	1.50 (0.91, 2.47)	1.11 (0.65, 1.90)	0.90 (0.51, 1.61)	1.04 (0.61, 1.78)
I am confident that vaccines are safe for my baby after birth.	1.08 (0.71, 1.65)	1.32 (0.78, 2.26)	1.33 (0.77, 2.31)	1.14 (0.62, 2.12)	0.90 (0.47, 1.73)	1.07 (0.58, 1.99)
Total number of specific vaccine safety concern						

statements agreed or strongly agreed to (0-16)						
0 (reference)	1	1	1	1	1	1
1-4	0.74 (0.46-1.19)	0.58 (0.30-1.13)	0.74 (0.39-1.40)	1.04 (0.53-2.05)	1.40 (0.70-2.81)	0.99 (0.50-1.95)
5-8	0.84 (0.52-1.37)	0.96 (0.54-1.70)	1.44 (0.85-2.44)	1.57 (0.85-2.90)	1.10 (0.49-2.47)	1.13 (0.57-2.24)
9-12	0.79 (0.45-1.39)	0.62 (0.28-1.36)	1.03 (0.53-2.03)	1.10 (0.49-2.44)	1.48 (0.66-3.34)	0.59 (0.21-1.63)
13-16	0.45 (0.19-1.09)	0.44 (0.14-1.42)	1 (n/a)**	0.52 (0.12-2.14)	1 (n/a)**	0.24 (0.03-1.77)
Other Vaccine Knowledge, Attitudes and Beliefs						
I worry that I could get the flu while I am pregnant.	**1.51 (1.02, 2.25)**	1.29 (0.79, 2.11)	1.53 (0.89, 2.65)	0.89 (0.49, 1.62)	2.06 (0.92, 4.60)	0.91 (0.51, 1.63)
The flu is dangerous for pregnant women.	1.15 (0.65, 2.02)	0.99 (0.52, 1.92)	1.20 (0.57, 2.56)	1.37 (0.53, 3.50)	5.67 (0.77, 41.66)	0.75 (0.36, 1.56)
The flu is more dangerous for pregnant women than for women who are not pregnant.	**2.25 (1.29, 3.92)**	**3.17 (1.37, 7.37)**	**2.64 (1.13, 6.16)**	1.26 (0.58, 2.72)	**4.26 (1.01, 17.89)**	0.80 (0.41, 1.56)
Getting the flu vaccine will reduce my risk of getting the flu during my pregnancy.	**1.75 (1.11, 2.77)**	**1.98 (1.10, 3.58)**	1.46 (0.81, 2.63)	0.81 (0.44, 1.51)	2.56 (0.98, 6.66)	1.49 (0.75, 2.95)
Getting the flu vaccine while I am pregnant will reduce my unborn baby's risk of getting the flu.	1.35 (0.92, 1.98)	1.50 (0.94, 2.40)	1.24 (0.75, 2.06)	1.03 (0.56, 1.87)	1.20 (0.60, 2.38)	0.87 (0.49, 1.55)
I worry that I could get whooping cough while I am pregnant.	0.92 (0.61, 1.40)	0.68 (0.41, 1.14)	0.92 (0.57, 1.50)	0.96 (0.55, 1.70)	0.86 (0.44, 1.67)	0.69 (0.36, 1.31)

I worry that I could give whooping cough to my baby after birth.	1.07 (0.73, 1.58)	0.99 (0.61, 1.59)	1.07 (0.67, 1.73)	0.96 (0.55, 1.68)	0.52 (0.27, 1.00)	0.87 (0.48, 1.58)
Whooping cough is dangerous for pregnant women.	0.88 (0.57, 1.35)	0.85 (0.50, 1.46)	0.82 (0.48, 1.39)	0.76 (0.41, 1.41)	**0.49 (0.25, 0.94)**	0.97 (0.48, 1.92)
Whooping cough vaccine will reduce my chances of getting whooping cough.	1.10 (0.70, 1.72)	0.91 (0.53, 1.55)	1.02 (0.59, 1.75)	1.00 (0.53, 1.89)	0.74 (0.37, 1.48)	1.34 (0.64, 2.81)
Whooping cough vaccine will reduce the chance of me giving whooping cough to my unborn baby.	1.59 (1.00, 2.53)	1.53 (0.87, 2.70)	**2.30 (1.23, 4.30)**	1.66 (0.84, 3.25)	1.12 (0.55, 2.26)	1.55 (0.76, 3.16)
Getting the whooping cough vaccine while I am pregnant will reduce my unborn baby's risk of getting whooping cough.	**1.60 (1.05, 2.45)**	1.40 (0.84, 2.33)	2.10 (1.21, 3.65)	1.18 (0.66, 2.10)	0.72 (0.38, 1.36)	1.54 (0.80, 2.96)
It is in my control whether or not I get vaccines during my pregnancy.	0.80 (0.20, 3.13)	2.00 (0.27, 14.71)	1 (n/a)**	1 (n/a)**	0.40 (0.09, 1.74)	1.24 (0.17, 9.18)
The majority of my friends and family would get the vaccines that are recommended during pregnancy.	**1.44 (1.04, 1.98)**	1.41 (0.93, 2.13)	1.37 (0.90, 2.08)	1.08 (0.67, 1.73)	1.09 (0.64, 1.88)	**1.88 (1.07, 3.3)**
The majority of my friends and family would encourage me to get the vaccines that are recommended during pregnancy.	1.34 (0.97, 1.84)	1.39 (0.93, 2.09)	1.29 (0.86, 1.93)	1.18 (0.74, 1.89)	1.27 (0.73, 2.21)	1.61 (0.95, 2.72)
I have most of the important information I need to make a	1.27 (0.89, 1.83)	1.34 (0.83, 2.18)	1.05 (0.66, 1.66)	0.65 (0.40, 1.06)	0.68 (0.39, 1.18)	0.70 (0.42, 1.15)

decision about vaccines given during pregnancy.						
I know enough about the safety of the flu vaccine to make a decision about getting the vaccine for myself while pregnant.	1.26 (0.75, 2.12)	1.28 (0.67, 2.47)	1.35 (0.66, 2.76)	1.42 (0.59, 3.38)	2.25 (0.68, 7.41)	1.08 (0.50, 2.34)
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for myself while pregnant.	1.19 (0.78, 1.82)	1.20 (0.70, 2.08)	1.00 (0.60, 1.69)	0.64 (0.36, 1.13)	**0.42 (0.22, 0.79)**	0.90 (0.47, 1.70)
I worry that my baby could get whooping cough after birth.	0.95 (0.64, 1.40)	0.81 (0.50, 1.31)	1.06 (0.65, 1.72)	0.86 (0.49, 1.50)	0.53 (0.28, 1.01)	1.04 (0.57, 1.92)
Whooping cough is dangerous for babies.	0.78 (0.39, 1.53)	1.44 (0.52, 4.01)	0.66 (0.31, 1.42)	0.64 (0.27, 1.52)	0.57 (0.22, 1.47)	1.19 (0.36, 3.90)
Whooping cough is more dangerous for babies than older children or adults.	1.16 (0.66, 2.04)	1.14 (0.56, 2.32)	1.04 (0.52, 2.05)	0.90 (0.42, 1.94)	0.54 (0.25, 1.15)	1.32 (0.52, 3.38)
Getting the whooping cough vaccine for my baby after birth will reduce my baby's chances of getting whooping cough.	1.36 (0.86, 2.15)	**1.89 (1.01, 3.55)**	1.35 (0.77, 2.38)	2.11 (0.98, 4.51)	0.95 (0.47, 1.93)	1.32 (0.65, 2.70)
It is in my control whether or not my baby gets his/her vaccines.	0.56 (0.24, 1.31)	0.93 (0.29, 3.05)	0.78 (0.24, 2.57)	0.85 (0.20, 3.58)	0.38 (0.11, 1.30)	0.57 (0.17, 1.89)
I believe it is better for my baby to develop their own immunity by getting sick	**0.58 (0.36, 0.94)**	**0.33 (0.16, 0.67)**	**0.40 (0.20, 0.82)**	0.45 (0.20, 1.01)	0.66 (0.29, 1.54)	0.66 (0.33, 1.34)

rather than by getting a vaccine.						
The majority of my friends and family would get all of the vaccines recommended for their babies after birth.	1.02 (0.71, 1.46)	0.97 (0.63, 1.50)	0.81 (0.53, 1.24)	1.05 (0.61, 1.79)	0.62 (0.36, 1.05)	1.06 (0.61, 1.83)
The majority of my friends and family would encourage me to get all of the vaccines recommended for my baby after birth.	0.93 (0.66, 1.32)	1.15 (0.74, 1.80)	0.79 (0.52, 1.20)	0.97 (0.58, 1.62)	0.77 (0.44, 1.34)	1.61 (0.87, 2.98)
I have most of the important information I need to make a decision about vaccines for my baby after birth.	1.23 (0.85, 1.80)	1.55 (0.91, 2.65)	1.18 (0.72, 1.94)	1.02 (0.58, 1.80)	0.78 (0.43, 1.41)	0.96 (0.54, 1.69)
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for my baby after birth.	1.17 (0.84, 1.62)	1.16 (0.77, 1.76)	1.24 (0.80, 1.91)	0.90 (0.56, 1.45)	0.73 (0.43, 1.22)	0.71 (0.45, 1.12)
Trust in Vaccine Information Sources						
I trust the information provided by my obstetrician or midwife about vaccines during pregnancy.	0.95 (0.57, 1.60)	1.20 (0.60, 2.41)	0.90 (0.47, 1.69)	0.76 (0.37, 1.53)	1.36 (0.49, 3.78)	0.72 (0.36, 1.46)
I trust the information provided by my obstetrician or midwife about vaccines for babies after birth.	1.15 (0.67, 1.98)	1.35 (0.65, 2.80)	0.98 (0.50, 1.90)	0.85 (0.40, 1.78)	1.82 (0.57, 5.84)	0.71 (0.35, 1.43)

I trust the information provided by my baby's doctor about vaccines during pregnancy.	0.89 (0.60, 1.30)	1.01 (0.63, 1.63)	1.00 (0.61, 1.63)	0.79 (0.46, 1.36)	1.21 (0.60, 2.46)	0.75 (0.44, 1.29)
I trust the information provided by my baby's doctor about vaccines for babies after birth.	0.99 (0.67, 1.45)	0.96 (0.60, 1.53)	0.84 (0.53, 1.34)	0.74 (0.44, 1.25)	1.40 (0.66, 2.94)	0.75 (0.44, 1.29)
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines during pregnancy.	0.76 (0.57, 1.00)	**0.63 (0.44, 0.91)**	0.91 (0.64, 1.29)	0.79 (0.51, 1.20)	0.93 (0.58, 1.50)	0.80 (0.52, 1.24)
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines for babies after birth.	0.82 (0.62, 1.09)	0.70 (0.49, 1.01)	0.98 (0.69, 1.40)	0.92 (0.60, 1.40)	0.98 (0.60, 1.58)	0.90 (0.58, 1.38)
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines during pregnancy.	**1.50 (1.05, 2.14)**	1.29 (0.81, 2.04)	1.07 (0.69, 1.68)	1.05 (0.62, 1.77)	0.84 (0.48, 1.48)	1.15 (0.66, 1.99)
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines for babies after birth.	**1.53 (1.06, 2.20)**	1.41 (0.88, 2.26)	1.11 (0.70, 1.74)	1.10 (0.64, 1.88)	0.89 (0.50, 1.59)	1.12 (0.65, 1.95)
I trust the information provided by scientists and doctors at universities and	**1.60 (1.10, 2.34)**	1.57 (0.95, 2.60)	1.46 (0.88, 2.43)	1.19 (0.68, 2.08)	1.10 (0.58, 2.06)	1.34 (0.74, 2.44)

academic institutions about vaccines during pregnancy.						
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines for babies after birth.	**1.86 (1.25, 2.77)**	**1.90 (1.10, 3.28)**	**2.10 (1.17, 3.75)**	1.38 (0.76, 2.51)	1.07 (0.57, 2.01)	1.20 (0.67, 2.14)
App Usability						
This app provided me information that was helpful.	1.02 (0.39-2.66)	0.71 (0.23-2.16)	0.57 (0.20-1.59)	0.65 (0.19-2.30)	**0.26 (0.09-0.75)**	2.17 (0.28-16.52)
I trust the information provided about vaccines in this app.	1.89 (0.71-5.07)	1.41 (0.42-4.81)	1.52 (0.45-5.17)	1.45 (0.33-6.33)	0.72 (0.21-2.51)	1 (n/a)**
The vaccine information in this app was interesting.	0.35 (0.12-1.03)	0.55 (0.15-2.04)	**0.26 (0.08-0.85)**	0.52 (0.11-2.42)	0.93 (0.12-7.32)	0.54 (0.12-2.49)
The vaccine information in this app was clear to understand.	1 (n/a)**	1 (n/a)**	1 (n/a)**	1 (n/a)**	1 (n/a)**	1 (n/a)**

**OR=Odds Ratio of Referring Contacts, 95%CI=95% Confidence Interval, bolded if statistically significant*
***n/a indicates failure to fit logistic model due to independent variable value of 0 perfectly predicting failure*

Appendix 2. Pregnant Women's Vaccine Intentions, Knowledge, Attitudes, Beliefs and Trust Associated with Number of Contacts Referred to Educational App about Vaccines (Regression Coefficient and P-value)

Survey Items	RC*	P*
Vaccine Intentions		
Current guidelines suggest pregnant women to receive two vaccines while pregnant, flu and whooping cough. I intend to get both flu and whooping cough vaccines.	0.07	0.43
Current guidelines suggest babies receive several vaccines. Regarding the vaccinations my doctor recommends for my baby after birth, I intend to get my baby all recommended vaccines on time.	0.03	0.73
Confidence in Vaccine Safety		
I am confident that getting the flu vaccine during my pregnancy is safe for me.	0.08	0.48
I am confident that getting the flu vaccine during my pregnancy is safe for my unborn baby.	-0.01	0.95
I am confident that getting the whooping cough vaccine during my pregnancy is safe for me.	0.17	0.15
I am confident that getting the whooping cough vaccine during my pregnancy is safe for my unborn baby.	0.11	0.36
I am confident that vaccines are safe for my baby after birth.	-0.01	0.96
Other Vaccine Knowledge, Attitudes and Beliefs		
I worry that I could get the flu while I am pregnant.	**0.28**	**0.03**
The flu is dangerous for pregnant women.	0.12	0.53
The flu is more dangerous for pregnant women than for women who are not pregnant.	**0.36**	**0.02**
Getting the flu vaccine will reduce my risk of getting the flu during my pregnancy.	0.17	0.23
Getting the flu vaccine while I am pregnant will reduce my unborn baby's risk of getting the flu.	0.15	0.23
I worry that I could get whooping cough while I am pregnant.	-0.01	0.97
I worry that I could give whooping cough to my baby after birth.	-0.02	0.87
Whooping cough is dangerous for pregnant women.	-0.08	0.60
Whooping cough vaccine will reduce my chances of getting whooping cough.	-0.04	0.77
Whooping cough vaccine will reduce the chance of me giving whooping cough to my unborn baby.	0.14	0.35
Getting the whooping cough vaccine while I am pregnant will reduce my unborn baby's risk of getting whooping cough.	0.11	0.42
It is in my control whether or not I get vaccines during my pregnancy.	-0.22	0.65
The majority of my friends and family would get the vaccines that are recommended during pregnancy.	**0.27**	**0.01**
The majority of my friends and family would encourage me to get the vaccines that are recommended during pregnancy.	0.20	0.06
I have most of the important information I need to make a decision about vaccines given during pregnancy.	-0.08	0.48
I know enough about the safety of the flu vaccine to make a decision about getting the vaccine for myself while pregnant.	0.12	0.49
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for myself while pregnant.	-0.07	0.61

I worry that my baby could get whooping cough after birth.	-0.05	0.69
Whooping cough is dangerous for babies.	-0.16	0.51
Whooping cough is more dangerous for babies than older children or adults.	-0.07	0.73
Getting the whooping cough vaccine for my baby after birth will reduce my baby's chances of getting whooping cough.	0.24	0.11
It is in my control whether or not my baby gets his/her vaccines.	-0.33	0.30
I believe it is better for my baby to develop their own immunity by getting sick rather than by getting a vaccine.	**-0.39**	**0.01**
The majority of my friends and family would get all of the vaccines recommended for their babies after birth.	-0.07	0.55
The majority of my friends and family would encourage me to get all of the vaccines recommended for my baby after birth.	0.01	0.92
I have most of the important information I need to make a decision about vaccines for my baby after birth.	0.06	0.61
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for my baby after birth.	-0.03	0.77
Trust in Vaccine Information Sources		
I trust the information provided by my obstetrician or midwife about vaccines during pregnancy.	-0.07	0.71
I trust the information provided by my obstetrician or midwife about vaccines for babies after birth.	0.01	0.96
I trust the information provided by my baby's doctor about vaccines during pregnancy.	-0.11	0.58
I trust the information provided by my baby's doctor about vaccines for babies after birth.	-0.20	0.34
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines during pregnancy.	-0.17	0.07
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines for babies after birth.	-0.14	0.15
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines during pregnancy.	0.17	0.15
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines for babies after birth.	0.18	0.12
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines during pregnancy.	**0.30**	**0.01**
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines for babies after birth.	**0.34**	**0.01**
I trust the information provided about vaccines in this app.	0.10	0.75

**RC=Regression Coefficient; considered significant if P-value <.05; bolded if statistically significant*

Appendix 3. Specific Vaccine Concerns Among Pregnant Women Not Confident in Vaccine Safety Associated with Referring Contacts to Educational App about Vaccines (Odds Ratios and P-values)

Specific Vaccine Safety Concern Statements**	OR*	P*
The flu vaccine is more likely to make me sick than protect me from getting the flu.	0.64	0.14
I worry that the ingredients in the flu vaccine are not safe for me to have while I am pregnant.	0.81	0.62
The flu vaccine is more likely to make me sick than protect my unborn baby from getting the flu.	**0.52**	**0.02**
I do not want to put the flu vaccine into my body when I am pregnant because I think it is unnatural.	0.62	0.12
I worry that the flu vaccine will cause birth defects.	1.19	0.54
I worry that the ingredients in the flu vaccine given to me during pregnancy are not safe for my unborn baby.	1.03	0.93
The whooping cough vaccine is more likely to cause me to get sick than protect me from getting whooping cough.	0.50	0.08
I worry that the ingredients in the whooping cough vaccine are not safe for me to have while I am pregnant.	0.44	0.07
The whooping cough vaccine is more likely to cause me to get sick than protect my unborn baby from getting whooping cough.	0.59	0.15
I do not want to put the whooping cough vaccine into my body when I am pregnant because I think it is unnatural.	0.52	0.09
I worry that the whooping cough vaccine will cause birth defects.	1.45	0.31
I worry that the ingredients in the whooping cough vaccine given to me during pregnancy are not safe for my unborn baby.	1.05	0.92
It is better for babies to get fewer vaccines at the same time.	0.83	0.70
Babies get more vaccines in their first two years of life than are good for them.	0.76	0.54
Vaccines often cause serious side effects in babies.	0.68	0.35
The ingredients in vaccines are not safe for my baby.	0.80	0.62

** OR: Odds Ratio of Referring Contacts; P-value considered significant if <.05; bolded if statistically significant*
***specific safety concerns were only obtained from those who did not agree that the vaccine in question was safe*

Appendix 4. Odds Ratios for Vaccine Intentions, Knowledge, Attitudes, Beliefs and Trust Found to be Associated with Pregnant Women Referring Contacts to Educational App about Vaccines, Adjusted by Norms

Survey Items	Contacts Referred, aOR (95%CI)*
Vaccine Intentions	
Uncertain Infant Vaccine Intentions	**0.50 (0.27-0.93)**
Survey Statements - Agreed or Strongly Agreed	
Confidence in Vaccine Safety	
I am confident that getting the whooping cough vaccine during my pregnancy is safe for me.	1.43 (0.96-2.14)
Other Vaccine Knowledge, Attitudes and Beliefs	
I worry that I could get the flu while I am pregnant.	1.46 (0.97-2.18)
The flu is more dangerous for pregnant women than for women who are not pregnant.	**2.18 (1.24-3.82)**
Getting the flu vaccine will reduce my risk of getting the flu during my pregnancy.	**1.72 (1.06-2.78)**
Getting the whooping cough vaccine while I am pregnant will reduce my unborn baby's risk of getting whooping cough.	1.41 (0.90-2.21)
The majority of my friends and family would get the vaccines that are recommended during pregnancy.	**0.60 (0.37-0.98)**
I believe it is better for my baby to develop their own immunity by getting sick rather than by getting a vaccine.	1.40 (0.96-2.04)
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines during pregnancy.	1.45 (0.99-2.11)
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines for babies after birth.	1.48 (1.00-2.18)
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines during pregnancy.	**1.73 (1.16-2.59)**
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines for babies after birth.	1.46 (0.97-2.18)

**aOR=Adjusted Odds Ratio of Referring Contacts (multiple logistic regression including independent variable of interest along with variable for descriptive norms indicating agreement with the statement "the majority of my friends and family would get the vaccines that are recommended during pregnancy"), 95%CI=95% Confidence Interval (bolded if significant)*

Results of Hypotheses Testing

The results for the hypothesis testing performed for each research question is summarized below.

Manuscript 2: Characterizing pregnant women's vaccine attitudes and beliefs

Secondary Research Question 1: Do these intentions, attitudes, beliefs, norms, and levels of trust differ by state, ethnicity, education, and having prior children?

$H1_0$: Pregnant women's vaccine intentions, attitudes, beliefs, norms, and levels of trust do not differ by state, ethnicity, education, or having prior children.

$H1_A$: Pregnant women's vaccine intentions, attitudes, beliefs, norms, and levels of trust do differ by state, ethnicity, education, or having prior children.

Result: $H1_0$ rejected, $H1_A$ accepted.

Secondary Research Question 2: Which attitudes, beliefs, norms, and levels of trust affect vaccine intentions?

$H1_0$: Pregnant women's vaccine attitudes, beliefs, norms, and levels of trust do not affect their vaccine intentions.

$H1_A$: Pregnant women's vaccine attitudes, beliefs, norms, and levels of trust do affect their vaccine intentions.

Result: $H1_0$ rejected, $H1_A$ accepted.

Secondary Research Question 3: Which demographics, attitudes, beliefs, norms, and levels of trust are the best predictors of vaccine intentions?

$H1_0$: Pregnant women's demographics and vaccine attitudes, beliefs, norms, and levels of trust do not affect their vaccine intentions when adjusted for each other.

$H1_A$: Pregnant women's demographics and vaccine attitudes, beliefs, norms, and levels of trust do affect their vaccine intentions when adjusted for each other.

Result: $H1_0$ rejected, $H1_A$ accepted.

Secondary Research Question 4: How many groups of pregnant women with distinct patterns of vaccine intentions, attitudes, beliefs, norms, and levels of trust can be identified, and how are they characterized?

$H1_0$: Pregnant women's vaccine intentions, attitudes, beliefs, norms, and levels of trust are best characterized by one homogenous group.

$H1_A$: Pregnant women's vaccine intentions, attitudes, beliefs, norms, and levels of trust are best characterized by multiple homogenous groups.

Result: $H1_0$ rejected, $H1_A$ accepted.

Manuscript 3: Factors associated with referring close contacts to an app with individually-tailored vaccine information

Primary Research Question: Which demographics and vaccine intentions, attitudes, beliefs, norms, and levels of trust are associated with higher likelihood of a pregnant woman referring friends and family to an educational app about vaccines?

$H1_0$: Pregnant women's demographics and vaccine attitudes, beliefs, norms, and levels of trust are not associated with likelihood of referring contacts to app.

$H1_A$: Pregnant women's demographics and vaccine attitudes, beliefs, norms, and levels of trust are associated with likelihood of referring contacts to app.

Result: $H1_0$ rejected, $H1_A$ accepted.

Secondary Research Question 2: Which types of contacts based on relationship to the referring pregnant woman are more likely to enroll in such an app upon invitation to do so?

$H1_0$: Contacts who enroll in app do not differ from contacts who do not enroll in app based on relationship to the referring pregnant woman.

$H1_A$: Contacts who enroll in app do differ from contacts who do not enroll in app based on relationship to the referring pregnant woman.

Result: Fail to reject $H1_0$.

Thesis Appendices

Thesis Appendix 1: Baseline Survey for Pregnant Women in P3+

Note: The survey provided in this Appendix was drafted by Rupali J. Limaye, PhD, Assistant Scientist at Johns Hopkins Bloomberg School of Public Health, in tandem with Matthew Dudley.

Question	Construct
Current guidelines suggest pregnant women to receive two vaccines while pregnant, flu and whooping cough. I intend to get:	vaccine intentions-maternal
I worry that I could get the flu (influenza) while I am pregnant.	susceptibility-maternal
The flu is dangerous for pregnant women.	severity-maternal
The flu is more dangerous for pregnant women than for women who are not pregnant.	severity-maternal
Getting the flu vaccine will reduce MY risk of getting the flu during my pregnancy.	response efficacy-maternal
Getting the flu vaccine while I am pregnant will reduce MY UNBORN BABY'S risk of getting the flu.	response efficacy-pediatric
I am confident that getting the flu vaccine during my pregnancy is safe for ME.	beliefs in vaccine safety-maternal
The flu vaccine is more likely to make me sick than protect ME from getting the flu.	specific concern-maternal
I do not want to put the flu vaccine into my body when I am pregnant because I think it is unnatural.	specific concern-maternal
I worry that the ingredients in the flu vaccine are not safe for ME to have while I am pregnant.	specific concern-maternal
Please let us know why else you believe that the flu vaccine is not safe for YOU:	specific concern-maternal
I am confident that getting the flu vaccine during my pregnancy is safe for MY UNBORN BABY.	beliefs in vaccine safety-maternal
The flu vaccine is more likely to make me sick than protect MY UNBORN BABY from getting the flu.	specific concern-maternal
I do not want to put the flu vaccine into my body when I am pregnant because I think it is unnatural.	specific concern-maternal
I worry that the flu vaccine will cause birth defects.	specific concern-maternal
I worry that the ingredients in the flu vaccine given to me during pregnancy are not safe for MY UNBORN BABY.	specific concern-maternal
Please let us know why else you believe that the flu vaccine is not safe for YOUR UNBORN BABY:	specific concern-maternal
I worry that I could get whooping cough (pertussis) while I am pregnant.	susceptibility-maternal
I worry that I could give whooping cough to MY BABY AFTER BIRTH.	susceptibility-maternal
Whooping cough is dangerous for pregnant women.	severity-maternal

Whooping cough vaccine will reduce MY chances of getting whooping cough.	response efficacy-maternal
Whooping cough vaccine will reduce the chance of me giving whooping cough to MY UNBORN BABY.	response efficacy-maternal
Getting the whooping cough vaccine while I am pregnant will reduce MY UNBORN BABY'S risk of getting whooping cough.	response efficacy-maternal
I am confident that getting the whooping cough vaccine during my pregnancy is safe for ME.	beliefs in vaccine safety-maternal
The whooping cough vaccine is more likely to cause me to get sick than protect ME from getting whooping cough.	specific concern-maternal
I do not want to put the whooping cough vaccine into my body when I am pregnant because I think it is unnatural.	specific concern-maternal
I worry that the ingredients in the whooping cough vaccine are not safe for ME to have while I am pregnant.	specific concern-maternal
Please let us know why else you believe that the whooping cough vaccine is not safe for YOU:	specific concern-maternal
I am confident that getting the whooping cough vaccine during my pregnancy is safe for MY UNBORN BABY.	beliefs in vaccine safety-maternal
The whooping cough vaccine is more likely to cause me to get sick than protect MY UNBORN BABY from getting whooping cough.	specific concern-maternal
I do not want to put the whooping cough vaccine into my body when I am pregnant because I think it is unnatural.	specific concern-maternal
I worry that the whooping cough vaccine will cause birth defects.	specific concern-maternal
I worry that the ingredients in the whooping cough vaccine given to me during pregnancy are not safe for MY UNBORN BABY.	specific concern-maternal
Please let us know why else you believe that the whooping cough vaccine is not safe for YOUR UNBORN BABY:	specific concern-maternal
It is in my control whether or not I get vaccines during my pregnancy.	self-efficacy-maternal
The majority of my friends and family would get the vaccines that are recommended during pregnancy.	descriptive norm-maternal
The majority of my friends and family would encourage me to get the vaccines that are recommended during pregnancy.	injunctive norm-maternal
I have most of the important information I need to make a decision about vaccines given during pregnancy.	perception of knowledge
I know enough about the safety of the flu vaccine to make a decision about getting the vaccine for myself while pregnant.	perception of knowledge
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for myself while pregnant.	perception of knowledge
Most of the information about vaccines during pregnancy that I trust, I receive from:	additional sources of information
Current guidelines suggest babies receive several vaccines. Regarding the vaccinations my doctor recommends for MY BABY AFTER BIRTH, I intend to get my baby:	vaccine intentions-pediatric
Please let us know which vaccines you plan not to get:	vaccine intentions-pediatric
I worry that my baby could get whooping cough after birth.	susceptibility-pediatric
Whooping cough is dangerous for babies.	severity-pediatric

Whooping cough is more dangerous for babies than older children or adults.	severity-pediatric
Getting the whooping cough vaccine for MY BABY AFTER BIRTH will reduce my baby's chances of getting whooping cough.	response efficacy-pediatric
I am confident that vaccines are safe for MY BABY AFTER BIRTH.	beliefs in vaccine safety-pediatric
It is better for babies to get fewer vaccines at the same time.	specific concern-pediatric
Babies get more vaccines in their first two years of life than are good for them.	specific concern-pediatric
Vaccines often cause serious side effects in babies.	specific concern-pediatric
The ingredients in vaccines are not safe for my baby.	specific concern-pediatric
Please let us know why else you believe that vaccines are not safe for YOUR BABY AFTER BIRTH:	specific concern-pediatric
It is in my control whether or not my baby gets his/her vaccines.	self-efficacy-pediatric
Vaccines improve immunity. I believe it is better for my baby to develop their own immunity by getting sick rather than by getting a vaccine.	self-efficacy-pediatric
The majority of my friends and family would get all of the vaccines recommended for THEIR BABIES AFTER BIRTH.	descriptive norm-pediatric
The majority of my friends and family would encourage me to get all of the vaccines recommended for MY BABY AFTER BIRTH.	injunctive norm-pediatric
I have most of the important information I need to make a decision about vaccines for MY BABY AFTER BIRTH.	perception of knowledge
I know enough about the safety of the whooping cough vaccine to make a decision about getting the vaccine for MY BABY AFTER BIRTH.	perception of knowledge
I trust the information provided by my obstetrician or midwife about vaccines during pregnancy.	information source
I trust the information provided by my obstetrician or midwife about vaccines for babies after birth.	information source
I trust the information provided by my baby's doctor about vaccines during pregnancy.	information source
I trust the information provided by my baby's doctor about vaccines for babies after birth.	information source
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines during pregnancy.	information source
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines for babies after birth.	information source
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines during pregnancy.	information source
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines for babies after birth.	information source
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines during pregnancy.	information source
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines for babies after birth.	information source
Most of the information about vaccines for babies after birth that I trust, I receive from:	information source
Do you already have any children?	

Thesis Appendix 2: Email to Invite Close Contacts to Join the Cocooning Study

Note: The email provided in this Appendix was drafted by Matthew Dudley and edited by Rupali J. Limaye, PhD, Assistant Scientist at Johns Hopkins Bloomberg School of Public Health.

Subject: Invitation to participate in the MomsTalkShots project

Text: (referred contact name),

(referring user name) has invited you to participate in a research project on the topic of maternal and childhood vaccines. MomsTalkShots, an app that helps mothers and family members make decisions about immunizations during pregnancy and after giving birth, would like to hear your thoughts about these vaccines. If you choose to participate, you will be asked to enroll in the app and complete a brief survey, for which you will receive a $20 gift card upon completion to thank you for your time. You will also receive a $10 gift card upon completion of a very brief follow-up survey. If you then choose to receive flu and/or whooping cough vaccinations at a Walgreens, you will receive $10 worth of Walgreens Balance Rewards points for each vaccine received. If you choose to participate, please access the app by clicking here: (INSERT LINK).

Thank you for your consideration!

Sincerely,

Matthew Z. Dudley, MSPH
Project Coordinator
Johns Hopkins Bloomberg School of Public Health

Thesis Appendix 3: Intervention Contact Registration Survey

Note: The survey provided in this Appendix was drafted by Matthew Dudley in tandem with Rupali J. Limaye, PhD, Assistant Scientist at Johns Hopkins Bloomberg School of Public Health.

Question	Construct
Current guidelines suggest close friends and family members of pregnant women to receive two vaccines, flu and whooping cough. I intend to get:	vaccine intentions-contact
I worry that the woman who referred me to this study could get the flu (influenza) while pregnant.	susceptibility-maternal
The flu is dangerous for pregnant women.	severity-maternal
The flu is more dangerous for pregnant women than for women who are not pregnant.	severity-maternal
Getting the flu vaccine will reduce the chance of me giving the flu to both the pregnant woman who referred me to this study and to her baby.	response efficacy-maternal
I am confident that getting the flu vaccine is safe.	beliefs in vaccine safety-maternal
The flu vaccine is more likely to make me sick than protect me from getting the flu.	specific concern-maternal
I do not want to put the flu vaccine into my body because I think it is unnatural.	specific concern-maternal
I worry that the ingredients in the flu vaccine are not safe.	specific concern-maternal
Please let us know why else you believe that the flu vaccine is not safe:	specific concern-maternal
I worry that the woman who referred me to this study could get whooping cough (pertussis) while pregnant.	susceptibility-maternal
I worry that the baby of the woman who referred me to this study could get whooping cough after birth.	susceptibility-maternal
Whooping cough is dangerous for pregnant women.	severity-maternal
Getting the whooping cough vaccine will reduce the chance of me giving whooping cough to both the pregnant woman who referred me to this study and to her baby.	response efficacy-maternal
I am confident that getting the whooping cough vaccine is safe.	beliefs in vaccine safety-maternal
The whooping cough vaccine is more likely to cause me to get sick than protect me from getting whooping cough.	specific concern-maternal
I do not want to put the whooping cough vaccine into my body because I think it is unnatural.	specific concern-maternal
I worry that the ingredients in the whooping cough vaccine are not safe.	specific concern-maternal
Please let us know why else you believe that the whooping cough vaccine is not safe:	specific concern-maternal
It is in my control whether or not I get vaccines.	self-efficacy-maternal
The majority of my friends and family, IF THEY GOT PREGNANT TODAY, would get the vaccines that are recommended during pregnancy.	descriptive norm-maternal

IF I OR MY PARTNER GOT PREGNANT TODAY, the majority of my friends and family would encourage us to get the vaccines that are recommended during pregnancy.	injunctive norm-maternal
I know enough about the flu vaccine to make a decision about getting the vaccine.	perception of knowledge
I know enough about the whooping cough vaccine to make a decision about getting the vaccine.	perception of knowledge
Whooping cough is dangerous for babies.	severity-pediatric
Whooping cough is more dangerous for babies than older children or adults.	severity-pediatric
I am confident that vaccines are safe for babies.	beliefs in vaccine safety-pediatric
It is better for babies to get fewer vaccines at the same time.	specific concern-pediatric
Babies get more vaccines in their first two years of life than are good for them.	specific concern-pediatric
Vaccines often cause serious side effects in babies.	specific concern-pediatric
The ingredients in vaccines are not safe for babies.	specific concern-pediatric
Please let us know why else you believe that vaccines are not safe for babies:	specific concern-pediatric
Vaccines improve immunity. I believe it is better to develop immunity by getting sick rather than by getting a vaccine.	self-efficacy-pediatric
The majority of my friends and family, IF THEY OR THEIR PARTNER GOT PREGNANT TODAY, would get all of the vaccines recommended for their baby after birth.	descriptive norm-pediatric
IF I OR MY PARTNER GOT PREGNANT TODAY, the majority of my friends and family would encourage US to get all of the vaccines recommended for our baby after birth.	injunctive norm-pediatric
I trust the information provided by my doctor about vaccines.	information source
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines.	information source
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines.	information source
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines.	information source
Most of the information about vaccines that I trust, I receive from:	information source
I am comfortable receiving vaccines at a pharmacy instead of a doctor's office.	
Do you have any children?	
How old is your youngest child?	
What is your age?	
What is your gender?	
What is your annual income?	
What is your relationship to the pregnant woman who referred you to this study?	
On average, how often do you speak with her (the pregnant woman who referred you to this study)?	
On average, how often do you see her in person?	
I would encourage her to get the DTaP vaccine for her new baby.	

I would encourage her to get the flu vaccine for her new baby.
I got (or will get) the DTaP vaccine for my youngest child.
Most years, I got (or will get) the flu vaccine for my youngest child.

Thesis Appendix 4: Intervention Contact Post-Video Survey

Note: The survey provided in this Appendix was drafted by Matthew Dudley in tandem with Rupali J. Limaye, PhD, Assistant Scientist at Johns Hopkins Bloomberg School of Public Health.

The vaccine information in this app was interesting.
The vaccine information in this app was clear to understand.
This app provided me information that was helpful.
I trust the information provided about vaccines in this app.
I know enough about the flu vaccine to make a decision about getting the vaccine.
I know enough about the whooping cough vaccine to make a decision about getting the vaccine.
Current guidelines suggest close friends and family members of pregnant women to receive two vaccines, flu and whooping cough. I intend to get:
What do you think would make the app more useful to you?

Thesis Appendix 5: Intervention Contact 60 Day Post-Birth Survey

Note: The survey provided in this Appendix was drafted by Matthew Dudley in tandem with Rupali J. Limaye, PhD, Assistant Scientist at Johns Hopkins Bloomberg School of Public Health.

Question	Construct
During the past year, I received:	vaccine intentions-contact
Did you receive either vaccine at Walgreens?	vaccine intentions-contact
Please enter the approximate date you received the flu vaccine.	vaccine intentions-contact
Where did you receive your flu vaccine?	vaccine intentions-contact
Please enter the approximate date you received the whooping cough vaccine.	vaccine intentions-contact
Where did you receive your whooping cough vaccine?	vaccine intentions-contact
I was satisfied with my experience receiving vaccines at Walgreens.	
I was satisfied with the Walgreens Balance Rewards Program.	
What did you like best about your experience at Walgreens?	
What could have been done to make this experience better?	
I am comfortable receiving vaccines at a pharmacy instead of a doctor's office.	
The flu is dangerous for pregnant women.	severity-maternal
The flu is more dangerous for pregnant women than for women who are not pregnant.	severity-maternal
Getting the flu vaccine (would have) reduced the chance of me giving the flu to both the pregnant woman who referred me to this study and to her baby.	response efficacy-maternal
I am confident that getting the flu vaccine is safe.	beliefs in vaccine safety-maternal
The flu vaccine is more likely to make me sick than protect me from getting the flu.	specific concern-maternal
I do not want to put the flu vaccine into my body because I think it is unnatural.	specific concern-maternal
I worry that the ingredients in the flu vaccine are not safe.	specific concern-maternal
Please let us know why else you believe that the flu vaccine is not safe:	specific concern-maternal
Whooping cough is dangerous for pregnant women.	severity-maternal
Getting the whooping cough vaccine (would have) reduced the chance of me giving whooping cough to both the pregnant woman who referred me to this study and to her baby.	response efficacy-maternal
I am confident that getting the whooping cough vaccine is safe.	beliefs in vaccine safety-maternal
The whooping cough vaccine is more likely to cause me to get sick than protect me from getting whooping cough.	specific concern-maternal

I do not want to put the whooping cough vaccine into my body because I think it is unnatural.	specific concern-maternal
I worry that the ingredients in the whooping cough vaccine are not safe.	specific concern-maternal
Please let us know why else you believe that the whooping cough vaccine is not safe:	specific concern-maternal
It is in my control whether or not I get vaccines.	self-efficacy-maternal
The majority of my friends and family, IF THEY GOT PREGNANT TODAY, would get the vaccines that are recommended during pregnancy.	descriptive norm-maternal
IF I OR MY PARTNER GOT PREGNANT TODAY, the majority of my friends and family would encourage us to get the vaccines that are recommended during pregnancy.	injunctive norm-maternal
I know enough about the flu vaccine to make a decision about getting the vaccine.	perception of knowledge
I know enough about the whooping cough vaccine to make a decision about getting the vaccine.	perception of knowledge
Whooping cough is dangerous for babies.	severity-pediatric
Whooping cough is more dangerous for babies than older children or adults.	severity-pediatric
I am confident that vaccines are safe for babies.	beliefs in vaccine safety-pediatric
It is better for babies to get fewer vaccines at the same time.	specific concern-pediatric
Babies get more vaccines in their first two years of life than are good for them.	specific concern-pediatric
Vaccines often cause serious side effects in babies.	specific concern-pediatric
The ingredients in vaccines are not safe for babies.	specific concern-pediatric
Please let us know why else you believe that vaccines are not safe for babies:	specific concern-pediatric
Vaccines improve immunity. I believe it is better to develop immunity by getting sick rather than by getting a vaccine.	self-efficacy-pediatric
The majority of my friends and family, IF THEY OR THEIR PARTNER GOT PREGNANT TODAY, would get all of the vaccines recommended for their baby after birth.	descriptive norm-pediatric
IF I OR MY PARTNER GOT PREGNANT TODAY, the majority of my friends and family would encourage US to get all of the vaccines recommended for our baby after birth.	injunctive norm-pediatric
I trust the information provided by my doctor about vaccines.	information source
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines.	information source
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines.	information source
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines.	information source
Most of the information about vaccines that I trust, I receive from:	information source

Thesis Appendix 6: Control Contact 60 Day Post-Birth Survey

Note: The survey provided in this Appendix was drafted by Matthew Dudley in tandem with Rupali J. Limaye, PhD, Assistant Scientist at Johns Hopkins Bloomberg School of Public Health.

Question	Construct
During the past year, I received:	vaccine intentions-contact
Did you receive either vaccine at Walgreens?	vaccine intentions-contact
Please enter the approximate date you received the flu vaccine.	vaccine intentions-contact
Where did you receive your flu vaccine?	vaccine intentions-contact
Please enter the approximate date you received the whooping cough vaccine.	vaccine intentions-contact
Where did you receive your whooping cough vaccine?	vaccine intentions-contact
I was satisfied with my experience receiving vaccines at Walgreens.	cocooning
I was satisfied with the Walgreens Balance Rewards Program.	cocooning
What did you like best about your experience at Walgreens?	cocooning
What could have been done to make this experience better?	cocooning
I am comfortable receiving vaccines at a pharmacy instead of a doctor's office.	cocooning
The flu is dangerous for pregnant women.	severity-maternal
The flu is more dangerous for pregnant women than for women who are not pregnant.	severity-maternal
Getting the flu vaccine (would have) reduced the chance of me giving the flu to both the pregnant woman who referred me to this study and to her baby.	response efficacy-maternal
I am confident that getting the flu vaccine is safe.	beliefs in vaccine safety-maternal
The flu vaccine is more likely to make me sick than protect me from getting the flu.	specific concern-maternal
I do not want to put the flu vaccine into my body because I think it is unnatural.	specific concern-maternal
I worry that the ingredients in the flu vaccine are not safe.	specific concern-maternal
Please let us know why else you believe that the flu vaccine is not safe:	specific concern-maternal
Whooping cough is dangerous for pregnant women.	severity-maternal
Getting the whooping cough vaccine (would have) reduced the chance of me giving whooping cough to both the pregnant woman who referred me to this study and to her baby.	response efficacy-maternal
I am confident that getting the whooping cough vaccine is safe.	beliefs in vaccine safety-maternal
The whooping cough vaccine is more likely to cause me to get sick than protect me from getting whooping cough.	specific concern-maternal

I do not want to put the whooping cough vaccine into my body because I think it is unnatural.	specific concern-maternal
I worry that the ingredients in the whooping cough vaccine are not safe.	specific concern-maternal
Please let us know why else you believe that the whooping cough vaccine is not safe:	specific concern-maternal
It is in my control whether or not I get vaccines.	self-efficacy-maternal
The majority of my friends and family, IF THEY GOT PREGNANT TODAY, would get the vaccines that are recommended during pregnancy.	descriptive norm-maternal
IF I OR MY PARTNER GOT PREGNANT TODAY, the majority of my friends and family would encourage us to get the vaccines that are recommended during pregnancy.	injunctive norm-maternal
I know enough about the flu vaccine to make a decision about getting the vaccine.	perception of knowledge
I know enough about the whooping cough vaccine to make a decision about getting the vaccine.	perception of knowledge
Whooping cough is dangerous for babies.	severity-pediatric
Whooping cough is more dangerous for babies than older children or adults.	severity-pediatric
I am confident that vaccines are safe for babies.	beliefs in vaccine safety-pediatric
It is better for babies to get fewer vaccines at the same time.	specific concern-pediatric
Babies get more vaccines in their first two years of life than are good for them.	specific concern-pediatric
Vaccines often cause serious side effects in babies.	specific concern-pediatric
The ingredients in vaccines are not safe for babies.	specific concern-pediatric
Please let us know why else you believe that vaccines are not safe for babies:	specific concern-pediatric
Vaccines improve immunity. I believe it is better to develop immunity by getting sick rather than by getting a vaccine.	self-efficacy-pediatric
The majority of my friends and family, IF THEY OR THEIR PARTNER GOT PREGNANT TODAY, would get all of the vaccines recommended for their baby after birth.	descriptive norm-pediatric
IF I OR MY PARTNER GOT PREGNANT TODAY, the majority of my friends and family would encourage US to get all of the vaccines recommended for our baby after birth.	injunctive norm-pediatric
I trust the information provided by my doctor about vaccines.	information source
I trust the information provided by naturopathic and/or chiropractic doctors about vaccines.	information source
I trust the information provided by federal agencies such as the Centers for Disease Control and Prevention (CDC) about vaccines.	information source
I trust the information provided by scientists and doctors at universities and academic institutions about vaccines.	information source
Most of the information about vaccines that I trust, I receive from:	information source
Do you have any children?	
How old is your youngest child?	
What is your age?	

What is your gender?
What is your annual income?
What is your relationship to the pregnant woman who referred you to this study?
On average, how often do you speak with her (the pregnant woman who referred you to this study)?
On average, how often do you see her in person?
I would encourage her to get the DTaP vaccine for her new baby.
I would encourage her to get the flu vaccine for her new baby.
I got (or will get) the DTaP vaccine for my youngest child.
Most years, I got (or will get) the flu vaccine for my youngest child.

Full Vaccine Safety Review

This section includes the full evidence supporting conclusions from Tables 3 and 4 of Manuscript 1 (*The State of Vaccine Safety Science: Systematic Reviews of the Evidence*). It is included here instead of within Manuscript 1 to keep the manuscript at a publishable length. The contents of this section are also found on the website for the Johns Hopkins Institute for Vaccine Safety (IVS), http://www.vaccinesafety.edu/, and in the book entitled *The Clinician's Vaccine Safety Resource Guide: Optimizing Prevention of Vaccine-Preventable Diseases Across the Lifespan*, written by the authors of this Manuscript 1 (with Matthew Dudley as first author) and published by Springer Publishing Company [506, 507].

All content in this section was drafted by Matthew Dudley but reviewed and edited at length by the other book authors. Additional feedback on some of this content was given by other non-author reviewers, including: Kevin Ault, Steven Black, Allison Chamberlain, Robert Chen, Mindy Christianson, Kathryn Edwards, Laura Riley, Kawsar Talaat, Oladeji Oloko, Tina Proveaux, and the members of the Brighton Collaboration (Nick Andrews, Jim Buttery, Yolanda Guerra Mendoza, Jyoti Joshi, Daniel Keene, Bettina Klug, Philipp Lambach, Barbara Law, Noni MacDonald, Giuseppe Monaco, David Nalin, James M. Oleske, Helen Petousis-Harris, Fernanda Tavares Da Silva, Nicoline van der Maas). Many thanks are due to all who contributed.

Do Combination Vaccines or Simultaneous Vaccination Increase the Risk of Adverse Events?

Conclusion: Certain combination vaccines or simultaneous administration of vaccines that are known to cause fever **can rarely cause** febrile seizures in infants and young children beyond the risk presented by individually administered vaccines. Specifically, the rate of febrile seizures in the 7-10 days after vaccination was approximately 2-3 times higher for children who received MMRV as compared to MMR and varicella vaccines administered separately on the same day and 4 times higher as compared to MMR alone, and when influenza and pneumococcal conjugate vaccines are given simultaneously as opposed to separately in children 6-59 months of age, the risk of febrile seizures in the 24 hours after vaccination increases from roughly 5 to 17.5 per 100,000 doses.

Simultaneous administration of Tdap and influenza vaccines during pregnancy **does not increase the risk of** acute adverse events or adverse birth outcomes. Combination vaccines and simultaneous administration of vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** any other adverse events at a greater rate than their individual vaccine components.

Why this is an issue: Prior to 1985, vaccines protecting against seven diseases total were recommended for children under two years of age. As new vaccines have been developed, the

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

number of vaccines that are recommended for children and the number of diseases they protect against have increased correspondingly. According to the 2018 Immunization Schedule, available on the website of the Centers for Disease Control and Prevention (CDC) at **http://www.cdc.gov/vaccines/schedules/**, the vaccinations recommended by the Advisory Committee on Immunization Practices (ACIP) for children under two has now increased to protect against 14 different diseases. This is good news; it means our children are protected against more serious diseases than before possible. However, it is understandable that this increase has raised some concern regarding the safety of vaccinating infants and young children with multiple immunizations in a short period of time.

Nonetheless, these concerns are unfounded. The immune systems of infants and children encounter millions of antigens in their environment every day; vaccines only contain a tiny fraction of a typical child's daily exposure to antigens. New vaccines are tested extensively for safety and effectiveness at the recommended ages and with other recommended vaccines for years prior to introduction in the U.S. as part of the rigorous FDA requirements for licensure. The recommended schedule for children is then carefully constructed by the ACIP in collaboration with major physician organizations including the American Academy of Pediatrics and the American Academy of Family Physicians in order to provide the greatest possible safety and protection against disease. Refusing or delaying vaccines, or following alternative schedules, has been shown to increase risk of disease [6, 59, 93, 566-574].

Epidemiological evidence: Vaccines which may induce fever may also rarely induce febrile seizures. Febrile seizures are a common and typically benign childhood condition, occurring in 2-

5% of children at some point during their first five years of life. Febrile seizures have an estimated background incidence of 240–480 per 100,000 person-years in children under five years, although this varies considerably by age, genetics, co-morbidities and environmental risk factors. There are no long-term effects of simple febrile seizures, [293-296]. See the *Do Vaccines Cause Seizures?* summary for more details.

Febrile seizures occurred at a rate of 26.4 per 1000 person-years after MMR and 84.6 per 1,000 person-years after MMRV (ProQuad®) in the 7-10 days after vaccination [297]. Several studies have confirmed that MMRV combination vaccine has a higher risk of febrile convulsions than simultaneous yet separate administration of the first dose of MMR and varicella vaccine (Varivax®) [297, 543-547]. There is no increased risk of fever or febrile seizures in children receiving their second dose of measles-containing vaccine at 4 to 6 years of age, whether given MMR or MMRV [40, 220]. Delaying MMR or MMRV vaccines past 15 months of age results in a higher risk of seizures than vaccinating according to the recommended schedule [548, 549].

Febrile seizures were estimated to occur at a rate of 17.5 per 100,000 doses in children aged 6-59 months after receiving concomitant trivalent inactivated influenza vaccine (abbreviation: TIV) and 13-valent pneumococcal conjugate vaccine (abbreviation: PCV13; trade name: Prevnar13®); lower rates of 4.9 per 100,000 doses and 5.3 per 100,000 doses were estimated in children who received TIV without concomitant PCV13 and in children who received PCV13 without concomitant TIV, respectively. However, these risk differences varied substantially with age due to the age-dependent background rates of febrile seizures, with the highest estimates at 16 months and the lowest at 59 months [296].

A large cohort study found a small increased risk of febrile seizures after the first two doses of the DTaP-IPV-Hib combination vaccine in Denmark, with an absolute risk of less than 4 per 100,000 vaccinations [550]. A large Vaccine Safety Datalink (VSD) study found no association between seizures and the DTaP-IPV combination vaccine (Kinrix®) among children 4 to 6 years of age [551].

Two methodologically sound, controlled epidemiological studies found no association between autism spectrum disorder (ASD) and simultaneous vaccination with multiple vaccines [513, 514], as well as a meta-analysis [118]. See the *Do Vaccines Cause Autism?* summary for more details.

A 2002 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), entitled *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction*, found that the evidence favors rejection of a causal relationship between multiple immunizations and increased risk for infections and for type I diabetes [224].

A 2013 IOM report entitled *The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies*, the most comprehensive examination of the immunization schedule to date, uncovered no evidence of major safety concerns associated with adherence to the childhood immunization schedule [552].

A randomized trial in France and Belgium during the 2014–2015 influenza season found no difference in rates of symptoms among older adults comparing co-administration of IIV4 and

PPV23 with separate administration, with the exception of injection site pain which occurred more frequently in the co-administration group [553]. A 2016 report summarizing ten phase 3 and 4 studies found no impact on vaccine reactogenicity or safety when co-administering routine vaccines with MenACWY-CRM [554]. A phase II randomized study found that co-administration of bivalent meningococcal B vaccine and DTaP/IPV was safe and well tolerated [555].

Retrospective cohort studies using the VSD found no increase in risk of acute adverse events or adverse birth outcomes among those vaccinated with Tdap or influenza vaccines during pregnancy [556], as well as among those vaccinated with Tdap during pregnancy when comparing those who had received a tetanus toxoid containing vaccine relatively recently with those who had not [396]. In addition, no increase in risk of acute adverse events or adverse birth outcomes were found among those vaccinated concurrently with Tdap and influenza vaccines during pregnancy compared to those vaccinated sequentially [371].

A VSD nested case-control study of nearly half a million children found no significant difference in estimated cumulative vaccine antigen exposure through the first 23 months of life comparing children ages 2 to 4 years with infections not targeted by the vaccines versus children without such infections [557].

Do Vaccine Ingredients Cause Adverse Events?

Conclusion: Certain ingredients that are present in some vaccines (other than disease-specific antigens), such as gelatin or neomycin, **can very rarely cause** severe hypersensitivity reactions (e.g. anaphylaxis) in vaccinees with those specific allergies. In addition, some adjuvants **can cause** increased rates of local reactions, and alum containing adjuvants **can cause** nodules at the injection site.

Vaccine ingredients, including the preservative thimerosal, **do not cause** autism**.** Ingredients in vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** any other adverse events.

Why this is an issue: As part of the Food and Drug Administration (FDA) Modernization Act of 1997, the FDA conducted an analysis on exposure to mercury in children. This led them to examine the risk of thimerosal, an ethylmercury containing preservative that was present in some vaccines at the time. The FDA risk assessment revealed no evidence of harm caused by the doses of thimerosal in vaccines other than local hypersensitivity reactions [120]. However, the exposure exceeded the United States Environmental Protection Agency (EPA) guidelines for methylmercury exposure; there were no available guidelines for ethylmercury, which is now known to have a shorter half-life than methylmercury. Long term follow-up of children to evaluate the risk of mild neurologic effects from ethylmercury had not been conducted at that time. Because

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

of the uncertainty in the risk assessment, as a precautionary measure thimerosal was removed as a preservative from most vaccines administered to children (small amounts of thimerosal are still present in multi-dose vials of influenza vaccine).

Around this time, concern about autism and MMR vaccine had also begun to increase (see the *Do Vaccines Cause Autism?* summary for more details). As evidence mounted that MMR vaccine was not associated with autism, some autism interest groups shifted their hypothesis from MMR vaccine to the belief that thimerosal was causing autism in children. This theory was based upon observed similarities in some features of autism spectrum disorder (ASD) and mercury poisoning [119]. The plausibility of this suspected association was refuted by neurologists and several large studies have documented that thimerosal was not associated with an increased risk of autism spectrum disorder [121]. More information is available on the website of the Centers for Disease Control and Prevention (CDC) at **http://www.cdc.gov/vaccinesafety/concerns/ thimerosal.**

Other vaccine ingredients including preservatives, adjuvants, or manufacturing residuals, can sound scary to the general public, especially when they are poorly understood. This has caused some understandable, albeit unfounded, concerns regarding the safety of these ingredients. Examples of this are aluminum and formaldehyde, which are known toxins for humans when consumed in large quantities. However, one must always keep the dosage in mind, as a great many things can be toxic with a high enough exposure. In the case of these vaccine ingredients, they present no danger in the miniscule quantities in which they are used in vaccines (which is typically much less than is found naturally in the body, common food or the environment), and serve only to stabilize the vaccine or enhance the immune response [542]. More information is available on

the FDA website at the following link: **http://www.fda.gov/BiologicsBloodVaccines/ SafetyAvailability/VaccineSafety/ucm187810.htm.** A full list of components by vaccine can be found at the Johns Hopkins Institute for Vaccine Safety website at the following link: **http://www.vaccinesafety.edu/components.htm.**

Epidemiological evidence: Six methodologically sound, controlled epidemiological studies found no association between autism spectrum disorder (ASD) and thimerosal in vaccines [112, 508-512], as well as the relevant systematic reviews [115, 116] and a meta-analysis [118]. The Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), concluded that the body of evidence favors rejection of a causal relationship between autism and thimerosal-containing vaccines [114]. See the *Do Vaccines Cause Autism?* summary for more details.

A few studies have reported an association between vaccines containing aluminum adjuvants and persistent nodules at the injection site, at an estimated rate of 0.03-0.83% [533-536]. Two studies examining infant exposure to aluminum from both diet and vaccines concluded that aluminum adjuvants at the levels of in vaccines are well below the calculated safe body burden [537, 538]. A 2017 review found that current data do not support a causal relationship between aluminum containing vaccines and a variety of autoimmune disorders [539]. A meta-analysis of clinical trials of 25,056 children under 10 years of age who received vaccines with newer adjuvants AS01, AS02, AS03 or MF59 found no safety concerns [540].

A review of data on substances sometimes found in certain vaccines in very small quantities, such as thimerosal, aluminum, gelatin, human serum albumin, formaldehyde, antibiotics, egg proteins,

and yeast proteins, found no evidence of harm other than rare instances of hypersensitivity reactions such as anaphylaxis in those with severe allergies to either gelatin or egg proteins [542]. See the *Do Vaccines Cause Hypersensitivity Reactions* summary for more details.

Do Vaccines Cause Acute Disseminated Encephalomyelitis (ADEM)?

Conclusion: Older formulations of rabies vaccine **did cause** Acute Disseminated Encephalomyelitis (ADEM), but newer formulations of rabies vaccine **have not been shown to cause** ADEM, and rabies vaccine is not routinely recommended to the general population in the United States. Other vaccines that are currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** ADEM.

Epidemiological evidence: The Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing an association between vaccination and ADEM, since the only applicable studies available used passive surveillance systems and therefore lacked an unvaccinated comparison group [222]. Studies published since the 2012 IOM report have found no association between ADEM and the pandemic H1N1 influenza vaccine Pandremix [575], quadrivalent HPV vaccine (Gardasil®) [576-578] or hepatitis B vaccine [577]. However, one recent Vaccine Safety Datalink study did find a possible association between ADEM and Tdap vaccine estimated at no more than 1.16 excess cases per million vaccines administered [579].

Proposed biological mechanism: ADEM has been reported very rarely after natural infections with wild-type measles, mumps, rubella, varicella, influenza, hepatitis A, and other viruses [222]. However, the pathophysiology of ADEM is not fully understood. Also, ADEM has been reported

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very rarely after immunizations, but in most instances infections with other agents have not been ruled out and there is no available test to determine a causal association with a particular infection or vaccine. Biological mechanisms proposed to explain the immunogenic etiology of ADEM following infection or immunization include direct destruction [580] and molecular mimicry [581, 582], which refers to the possibility that similar epitopes shared between self-peptides and foreign peptides (introduced via infection or immunization) inadvertently cause the activation of autoreactive T or B cells, leading to autoimmunity. In the case of ADEM, this abnormal immune response would be directed against the host's myelin protein [583]. Although a temporal association with ADEM has been described for vaccines such as Japanese encephalitis, yellow fever, measles, influenza, varicella, and hepatitis [584-586], the only clear pathological association ever demonstrated was with the Semple rabies vaccine [587].

The 2012 IOM report described two cases of ADEM after administration of the Engerix-B® hepatitis B vaccine showing a reoccurrence of symptoms after vaccine rechallenge [588, 589]; however, these were insufficient to conclude a causal association [222]. The report also described one case of ADEM after tetanus toxoid vaccination [590]; however, even after considering knowledge about the aforementioned natural infection, the IOM concluded that this mechanistic evidence was weak. The IOM concluded that the only mechanistic evidence for an association between ADEM and MMR, varicella or influenza vaccines was knowledge about the natural infections, and that there was no mechanistic evidence for all other vaccines, as the publications reviewed provided no evidence beyond a temporal association [222].

Do Vaccines Cause Arthralgia or Arthritis?

Conclusion: Infections may trigger or contribute to the pathogenesis of arthritis. Thus, vaccines may prevent arthritis by protecting against natural infections. Rubella-containing vaccines (e.g. MMR) **can cause** mild, acute, transient arthralgia or arthritis, rarely in children but commonly in certain adult women (between 10-25% of adult female vaccinees without preexisting rubella immunity), usually beginning 1-3 weeks after vaccination and then persisting up to 3 weeks. Other vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** chronic arthralgia or arthritis.

Epidemiological evidence: Mild, acute, transient arthralgia occurs in approximately 25% of adult women without preexisting rubella immunity after rubella vaccination, and mild, acute, transient arthritis occurs in approximately 10%, usually beginning 1-3 weeks after vaccination and then persisting up to 3 weeks. Both are less common in men and rare in children [40].

The 2012 report by the Institute of Medicine (IOM) [222], now called the National Academy of Medicine (NAM), described four studies in women [591-594] and seven studies in children [595-601] that generally reported an increased risk of transient arthralgia after rubella or MMR vaccination. Also described are two studies assessing chronic arthralgia and arthritis in women [593, 594] and two studies assessing arthropathy in men [602, 603] after rubella or MMR vaccination; one study assessing the association between HPV vaccine and transient arthralgia

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

[604]; one study assessing the association between hepatitis B vaccination and exacerbation of rheumatoid arthritis [605]; and two studies assessing the association between diphtheria or tetanus toxoid vaccination and chronic arthritis [603, 606]; however, these studies did not provide convincing evidence due to a lack of validity and precision. The IOM found no relevant studies of quality in the literature providing evidence of an association between any other vaccines and chronic arthropathy [222].

Most studies published since the 2012 IOM report did not show a statistically significant association between influenza and HPV vaccines and arthralgia [607-610]. One study found a relative risk of arthralgia of 2.0 (95% CI: 1.6-2.5) after receipt of a vero-cell culture-derived trivalent influenza vaccine [611], and another study found an odds ratio of grade 3 arthralgias of 2.68 (95% CI: 1.29-5.59) after receipt of the AS04-adjuvanted HPV-16/18 vaccine (Cervarix®) among women in Korea [612]. No association has been found between vaccination and arthritis [576, 613-616]. Studies in patients with autoimmune inflammatory arthritis showed no change in disease severity or relapse rates after influenza vaccination [617-623].

Proposed biological mechanism: Environmental factors such as infections may trigger or contribute to the pathogenesis of arthritis; however, the exact mechanisms are still unclear [624-627].

Based on both cases reviewed and knowledge about the natural infection, the IOM concluded that there was some mechanistic evidence in support of a causal relationship between rubella vaccine in women and arthralgia [591, 628-630]; however, there was less evidence for a relationship

between rubella vaccine in women and chronic arthralgia [630-632] or arthritis [629, 632]. There was little evidence for a relationship between rubella vaccine and arthropathy in men, transient arthralgia in children or chronic arthropathy in children [633, 634], for influenza vaccine and onset or exacerbation of arthropathy [635], or for hepatitis B vaccine and onset or exacerbation of arthritis [636, 637]. The IOM also concluded that there was no mechanistic evidence for an association between all other vaccines and arthralgia, arthritis or arthropathy.

Do Vaccines Cause Asthma?

Conclusion: Natural infection with influenza can contribute to asthma exacerbation. Thus, influenza vaccine prevents asthma exacerbation by protecting against natural infection. Influenza vaccines **do not cause** asthma or asthma exacerbation. Other vaccines currently routinely recommended to the general population in the U.S.* **have not been shown to cause** asthma or asthma exacerbation.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM) [222], now called the National Academy of Medicine (NAM), described a number of studies with sufficient validity and precision that all reported no association between inactivated influenza vaccination and asthma exacerbation [638-646]. The report described several studies with sufficient validity and precision that generally reported no association between live attenuated influenza vaccination (LAIV) and asthma exacerbation as well [275, 647-652]. However, a 2015 white paper on the safety of influenza vaccines concluded that LAIV was associated with an increase in wheezing in children ages 18 to 35 months who had a history of wheezing [653]. Two studies of the 2013-2014 and 2014-2015 flu seasons in the United Kingdom study found that LAIV was well tolerated among those with well-controlled asthma or recurrent wheezing [654, 655]. A prospective observational cohort study found an increased risk of wheezing among California children 2-4 years of age during the 42-day risk interval after receiving quadrivalent LAIV during the 2013–2014 influenza

* These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

season [656]. One study published in 2015 suggests a possible protective effect of MMR vaccination against asthma [657].

Proposed biological mechanism: Influenza, along with other natural viral respiratory infections, can contribute to asthma exacerbation, as these viruses enter and replicate within airway epithelial cells, initiating an immune response. Natural influenza infection also causes greater morbidity in asthmatic subjects than in the general population, perhaps due to a difference in the antiviral response of asthmatics [658].

The 2012 IOM report described cases of asthma exacerbation after both inactivated and live attenuated influenza vaccination [659]; however, even after considering knowledge about the aforementioned natural infection, the IOM concluded that this mechanistic evidence was weak [222].

Do Vaccines Cause Ataxia?

Conclusion: Natural mumps and varicella infections are associated with acute cerebellar ataxia. Thus, mumps and varicella vaccines prevent ataxia by protecting against natural infection. Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** ataxia.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing an association between ataxia and measles, mumps, rubella, varicella, diphtheria, tetanus or pertussis vaccines, since the only applicable studies available either had serious methodological limitations or used passive surveillance systems and therefore lacked an unvaccinated comparison group [222].

A Vaccine Safety Datalink study published since the 2012 IOM report found a lowered risk of ataxia in the interval shortly after both MMR and MMRV (ProQuad®) vaccination versus the comparison interval of 57 to 180 days after vaccination [660]. Per the 2007 ACIP recommendations, acute cerebellar ataxia has been previously described as potentially associated with single-antigen varicella vaccine (Varivax®); however, available data are insufficient to determine a causal association [319].

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Proposed biological mechanism: Wild-type mumps and varicella infections are associated with cerebellar ataxia, and wild-type measles virus is known to invade the central nervous system [222]. MMR and varicella vaccines are live attenuated viral vaccines, and are therefore able to replicate in the body. Although it is biologically possible for these live vaccines to cause ataxia, the available evidence has not demonstrated an increased risk. For more information, see the *Measles, Mumps and Rubella* and *Varicella* summaries.

The 2012 IOM report described one case of ataxia after measles vaccination [661]; however, even after considering knowledge about natural measles, mumps and varicella infections, the IOM concluded that this mechanistic evidence was weak. The IOM also concluded that there was no mechanistic evidence for an association between ataxia and rubella, diphtheria, tetanus or pertussis vaccines, as the publications reviewed provided no evidence beyond a temporal association [222].

Do Vaccines Cause Autism?

Conclusion: Childhood vaccines **do not cause** autism. Maternal vaccines **have not been shown to cause** autism.

The Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), concluded that the body of evidence favors rejection of a causal relationship between autism and MMR vaccine and thimerosal-containing vaccines [114, 222]. MMR vaccine also prevents rubella disease, thus preventing congenital rubella syndrome and its associated cases of autism.

Why this is an issue: Andrew Wakefield, a gastroenterologist at the Royal Free Hospital in England, published a case series in the medical journal *The Lancet* in 1998. In this article he described 12 children with pervasive developmental disorder associated with gastrointestinal symptoms, 8 of whom had behavioral issues temporally associated with MMR vaccination via retrospective accounts by their parents or physicians [96]. Despite study authors acknowledging that this did not prove an association between the vaccine and autism, the lead author went far beyond the paper's conclusions in a press release and ongoing interactions with the media [97, 98]. Public concern on the topic grew quickly. In 2010, Dr. Wakefield's license to practice medicine in the UK was revoked by the British General Medical Council and his study was retracted by *The Lancet* as evidence of serious professional misconduct mounted. Among other infractions, Wakefield was found to have ordered unnecessary invasive procedures on children without approval of the hospital ethics committee and received undeclared financial considerations from the Legal Aid Board, a group pursuing multiparty legal action for allegedly vaccine-damaged

children [99-104]. In addition, he had applied for patents for vaccines to rival MMR vaccine. It was also revealed that, for most of the children in the original study, their symptoms either started well before or long after MMR vaccination. Despite the complete refutation of Wakefield's fraudulent findings by the scientific community, concern still exists among some parents.

Vaccines of interest: While the initial vaccine targeted by Dr. Wakefield was MMR, the target has shifted over time, especially as epidemiological evidence accumulated that the MMR vaccine was not associated with autism spectrum disorder (ASD). Other targets have included the preservative thimerosal as well as simultaneous vaccination with multiple vaccines. See the *Do Vaccine Ingredients Cause Adverse Events?* and the *Do Combination Vaccines or Simultaneous Vaccination Increase the Risk of Adverse Events?* summaries for more details.

Epidemiological evidence: There have been 15 methodologically sound, controlled epidemiological studies exploring an association between ASD and receipt of MMR vaccine [105-112], thimerosal in vaccines [112, 508-512], and simultaneous vaccination with multiple vaccines [513, 514], in addition to the relevant systematic reviews [113-117] and one meta-analysis [118]. Together, these studies included more than 1.8 million children. Notwithstanding 11 studies from another pair of authors [515-525], all of which had substantial methodological flaws [114-116, 526], the epidemiological evidence consistently shows no association between MMR vaccine, thimerosal in vaccines, or simultaneous vaccination and ASD.

One recent study suggested a possible increased risk of ASD among children whose mothers received an influenza vaccination during their first trimester of pregnancy, although this

association was not statistically significant after a post hoc analysis adjusting for multiple comparisons, and there was no association between ASD and influenza vaccination received during any trimester [527]. Another recent study showed that receiving Tdap vaccine during pregnancy is not associated with increased risk of ASD in the child [528].

Proposed biological mechanism: The overlapping times of childhood vaccine administration and usual onset of ASD symptoms have led to speculations about a possible causal pathway; however, the proposed links have been unsubstantiated [529]. Several different theories were proposed to attribute the cause of ASD to vaccines. Wakefield suggested that a dysregulated immune response to measles antigen in the MMR vaccine led to persistent intestinal infection, allowing "toxins" to enter the blood stream and enter the central nervous system leading to developmental regression in children. He claimed support for this because of his alleged detection of measles virus RNA in bowel specimens of several children with ASD [96]. However, his referenced study was found to be fraudulent, and no evidence of persistent infection has been shown in studies that used appropriate methods [530-532]. Another proposed trigger for ASD was thimerosal, an ethylmercury-containing preservative that used to be present in some vaccines, although not in the MMR vaccine. This theory was based on observed similarities in some features of ASD and mercury poisoning [119]; however, the degree of these similarities and the plausibility of this suspected association was refuted by neurologists [121]. The IOM found no valid mechanistic evidence connecting MMR or thimerosal-containing vaccines and ASD [114, 222].

Do Vaccines Cause Bell's Palsy?

Conclusion: Natural infections with varicella, tetanus and diphtheria have each been associated with Bell's Palsy. Thus, varicella, tetanus and diphtheria vaccines prevent Bell's Palsy by protecting against these natural infections. Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** Bell's Palsy.

Epidemiological evidence: The only vaccine ever confirmed to cause Bell's Palsy was Berna Biotech's Nasalflu®, an inactivated intranasal influenza vaccine adjuvanted with *E. coli* heat-labile toxin which is no longer being produced. This vaccine was licensed for the 2000-2001 flu season in Switzerland and then permanently withdrawn from the market upon detection of the Bell's Palsy caused by the vaccine [662]. It was never used in the United States.

The 2012 report by the Institute of Medicine (IOM) [222], now called the National Academy of Medicine (NAM), described two studies with sufficient validity and precision that both reported no association between inactivated influenza vaccine and Bell's Palsy [663, 664]. The report also described one study assessing an association between acellular pertussis vaccination and Bell's Palsy [665]; however, this study did not provide convincing evidence due to a lack of validity and precision [222]. Most studies published since the 2012 IOM report have also reported no association between vaccination and Bell's Palsy [666-668]; however, one study did find a

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

temporal association between receipt of meningococcal conjugate vaccine concomitantly with other vaccines and Bell's Palsy [669].

Proposed biological mechanism: Known causes of Bell's Palsy include infections due to *Borrelia burgdorferi*, the agent of Lyme disease, and zoster virus in Ramsay-Hunt syndrome. Infections with *Clostridium tetani* or *Corynebacterium diphtheria* have been associated with facial nerve palsy as well, albeit very rarely [222]. Although other viral infections such as herpes simplex virus (HSV) and varicella zoster virus (VZV) have also been associated with Bell's Palsy [670-673], the pathogenesis of Bell's Palsy remains poorly understood. Hypotheses include reactivation of latent viral infections in facial nerve ganglia [674] or an autoimmune mechanism possibly with segmental demyelination [675]. Regarding the association of Bell's Palsy with Nasalflu®, an influenza vaccine adjuvanted with *E. coli* heat-labile toxin, the most likely hypothesis is that the *E. coli* enterotoxin resulted in inflammation and entrapment of the facial nerve in the facial canal [653, 676].

The IOM concluded that the only mechanistic evidence for an association between Bell's Palsy and tetanus or diphtheria vaccines was knowledge about the natural infection, and that there was no mechanistic evidence for hepatitis A, hepatitis B and influenza vaccines causing Bell's palsy [222].

Do Vaccines Cause Brachial Neuritis?

Conclusion: Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** brachial neuritis.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing an association between vaccination and brachial neuritis [222]. No relevant studies of quality have been published since this report.

Proposed biological mechanism: Although the etiology of brachial neuritis is still uncertain, it is generally considered to be an immune-mediated inflammatory reaction against nerve fibers in the brachial plexus. One possible mechanism is activation of the complement system, in which a cascade of proteolysis and successive release of cytokines functions to amplify the immune response but can damage host cells if not properly regulated. Other mechanisms for such a reaction include anti-peripheral nerve myelin antibodies or T cells [677].

The IOM concluded that there was no mechanistic evidence for an association between vaccination and brachial neuritis, as the publications reviewed provided no evidence beyond a temporal association [222].

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Do Vaccines Cause Chronic Inflammatory Disseminated Polyneuropathy?

Conclusion: Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** chronic inflammatory disseminated polyneuropathy (CIDP).

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing CIDP and MMR, diphtheria, tetanus, pertussis, influenza, hepatitis A, hepatitis B, or meningococcal conjugate vaccines [222]. No relevant studies of quality have been published since this report.

Proposed biological mechanism: One potential mechanism that could contribute to CIDP is molecular mimicry [222], which refers to the possibility that similar epitopes shared between self-peptides and foreign peptides (introduced via infection or immunization) inadvertently cause the activation of autoreactive T or B cells, leading to autoimmunity.

The 2012 IOM report described three reports of CIDP after influenza vaccine, in two of which development of CIDP occurred in the patients after vaccine administration in two separate years [678]. However, the publication provided no evidence beyond a temporal association and the IOM concluded that this mechanistic evidence was weak. The IOM also concluded that there was no mechanistic evidence for an association between CIDP and MMR, diphtheria, tetanus, pertussis,

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

hepatitis A, hepatitis B, HPV or meningococcal conjugate vaccines, as the publications reviewed provided no evidence beyond a temporal association [222].

Do Vaccines Cause Complex Regional Pain Syndrome?

Conclusion: Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** complex regional pain syndrome (CRPS).

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing CRPS and vaccination [222]. A combined analysis of seven phase III clinical trials of 9-valent HPV vaccine published since this report found no association between the vaccine and CRPS [679].

Proposed biological mechanism: Previous controlled studies have shown an association between pain and injection of norepinephrine and phenylephrine [680, 681]. About half of patients with CRPS have documented trauma to the affected area prior to injection [222].

The 2012 IOM report described one case of CRPS after hepatitis B vaccination showing a reoccurrence of symptoms after vaccine re-challenge [682]. However, the rest of the publications reviewed provided little evidence beyond a temporal association [222].

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Do Vaccines Cause Deltoid Bursitis?

Conclusion: Vaccines **can cause** deltoid bursitis when administered incorrectly.

Resources pertaining to correct administration of vaccines, including a printable infographic, are provided by the Centers for Disease Control and Prevention (CDC) at the following link: **https://www.cdc.gov/vaccines/hcp/infographics/call-the-shots.html**.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), described one study assessing an association between the injection of a vaccine and deltoid bursitis [683]; however, this study did not provide convincing evidence due to a lack of validity and precision [222].

Proposed biological mechanism: A vaccine that is unintentionally injected into the synovial tissue structures underlying the deltoid muscle can induce a prolonged immune-mediated inflammatory response [684-686]. Such an error in vaccine administration could occur due to inappropriate needle length or improper injection technique involving administration in the upper one-third of the muscle [687-691]. The 2012 IOM report described several cases providing strong clinical evidence that vaccine injection was a contributing cause of the rapid development of deltoid bursitis [678, 692].

Do Vaccines Cause Diabetes?

Conclusion: Vaccines currently routinely recommended to the general population in the U.S.[*] **do not cause** diabetes.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM) [222], now called the National Academy of Medicine (NAM), described a number of studies with sufficient validity and precision that all reported a lack of an association between MMR, DTaP or Tdap vaccines and type 1 diabetes [693-698]. Studies published since this report also reported a null, or in some cases even protective, association between vaccination and type 1 diabetes [576, 699-704]. This includes a meta-analysis of 23 observational studies investigating 16 different vaccines [705]. Studies examining inactivated seasonal influenza and Tdap vaccinations in pregnancy reported either no association with, or even a possible protective effect against, gestational diabetes [366, 394, 706, 707]. National Health and Nutrition Examination Survey (NHANES) data from 2005-2010 suggested a possible protective effect of hepatitis B vaccination against diabetes as well [708]. A retrospective observational study of California infants found no cases of type 1 diabetes during the 30-day risk interval after 46,486 doses of DTaP-IPV/Hib vaccine administered [709].

Persons with chronic illnesses such as type 1 or type 2 diabetes have high morbidity and mortality associated with common infectious diseases such as influenza, hepatitis b, and pneumococcal disease. Thus, routine vaccination per current ACIP recommendations is also strongly

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

recommended for all persons with diabetes by the American Diabetes Association [710, 711]. In addition, the ACIP recommends the administration of hepatitis b vaccine to all unvaccinated adults with diabetes mellitus aged 19 through 59 [712].

Proposed biological mechanism: Mechanisms that may induce type 1 diabetes include activation of the complement system, in which a cascade of proteolysis and successive release of cytokines functions to amplify the immune response but can damage host cells if not properly regulated, as well as molecular mimicry, which refers to the possibility that similar epitopes shared between self-peptides and foreign peptides (introduced via infection or immunization) inadvertently cause the activation of autoreactive T or B cells, leading to autoimmunity. However, the IOM concluded that there was no mechanistic evidence for an association between vaccination and type 1 diabetes, as the publications reviewed provided no evidence beyond a temporal association [222].

Do Vaccines Cause Disseminated Varicella Infection?

Conclusion: Disseminated varicella infection is a serious potential complication of natural infection with varicella virus, particularly among immunodeficient persons. Thus, varicella vaccine prevents disseminated varicella infection by protecting against natural infection. However, varicella vaccines **can rarely cause** disseminated varicella infection in patients with severe immune deficiency, for whom the vaccine is contraindicated. Other vaccines currently routinely recommended to the general population in the U.S.[*] **do not cause** disseminated varicella infection.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), described one study assessing varicella vaccination with disseminated varicella infection [713]; however, it did not provide convincing evidence due to a lack of validity and precision [222].

Proposed biological mechanism: Varicella vaccines are live attenuated viral vaccines, and are therefore able to replicate in the body. Generalized rash is reported in 4-6% of recipients. Systemic reactions are uncommon but possible. Mild zoster illness (shingles) resulting from a latent infection with varicella vaccine virus has been reported. Immunodeficiency is a contraindication for most live vaccines, including varicella vaccine. For more information, see the *Varicella* summary.

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

The 2012 IOM report described cases of disseminated varicella infection after varicella vaccination [714-733], and concluded that these cases together presented strong mechanistic evidence supporting an association [222]. In immunodeficient persons, disseminated varicella infection can also result in pneumonia [714-716, 725-727], meningitis [718], or hepatitis [714-716, 720, 722].

There have been several deaths due to disseminated varicella in children who had undiagnosed severe combined immunodeficiency (SCID) at the time of vaccination. However, it is extremely rare for children with SCID to remain undiagnosed at the age of varicella vaccination [734-737].

Do Vaccines Cause Erythema Nodosum?

Conclusion: Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** erythema nodosum (EN).

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing EN and hepatitis B vaccine [222]. No relevant studies of quality have been published since this report.

Proposed biological mechanism: The most common cause of EN is infection [738]. Although the pathogenesis of EN is not fully understood, it is thought to be caused by an influx of immune complexes into the subcutaneous fat [739]. Another possible mechanism is activation of the complement system, in which a cascade of proteolysis and successive release of cytokines functions to amplify the immune response but can damage host cells if not properly regulated. Other mechanisms that could contribute to the development of EN include autoantibodies or T cells [222].

The 2012 IOM report described one case of EN after hepatitis B vaccination [740]; however, the IOM concluded that this mechanistic evidence was weak.

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Do Vaccines Cause Fibromyalgia or Chronic Fatigue Syndrome?

Conclusion: Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** fibromyalgia or chronic fatigue syndrome (CFS).

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing an association between fibromyalgia and MMR, influenza, hepatitis B or DTaP vaccines, or between CFS and MMR vaccine [222]. One self-controlled case series published since this report found no association between CFS and bivalent HPV vaccine (Cervarix®) [741]. Two Norwegian register-based studies found no increased risk of CFS following pH1N1 vaccination [742] or HPV vaccination [743], respectively.

Proposed biological mechanism: The etiological causes and underlying pathogenic mechanisms of fibromyalgia and CFS are still unclear and the subject of much debate [744-746]. Theories that attempt to explain the mechanisms behind the development of these two disorders generally focus on sympathetic nervous system dysfunction, the inflammatory and oxidative stress pathways and the neuroendocrine system. Symptoms such as pain and fatigue have been associated with chronic inflammation, raised levels of oxidative stress and mitochondrial dysfunction. It has also been suggested that the hypothalamic-pituitary-adrenal axis and cortisol also have a role in the pathogenesis of fibromyalgia and CFS; however, it is still unclear whether these pathways are

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

causes or just byproducts of these syndromes [747, 748]. Environmental stimuli such as stress or viral infection are thought to be able to trigger the pathogenesis of these disorders in genetically predisposed individuals [745, 749].

The IOM concluded that there was no mechanistic evidence for an association between fibromyalgia and MMR, influenza, hepatitis B or DTaP vaccines, or between CFS and MMR vaccine [222].

Do Vaccines Cause Guillain-Barré Syndrome?

Conclusion: Influenza vaccines reduce the risk of influenza infection, which causes Guillain-Barré syndrome (GBS). Thus, influenza vaccines prevent GBS by protecting against natural influenza infection. However, influenza vaccines **can very rarely cause** GBS within 6 weeks of vaccination in adults, at an estimated rate of 1-3 cases per million vaccinations. Influenza vaccines **have not been shown to cause** GBS in children. Older formulations of rabies vaccine **did cause** GBS, but newer formulations of rabies vaccine **have not been shown to cause** GBS, and rabies vaccine is not routinely recommended to the general population in the United States. Other vaccines that are currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** GBS.

In most years when influenza vaccine strains are a good match for the circulating wild type viruses, influenza vaccines prevent much more GBS than the vaccines cause [286, 653]. **Therefore, the very small risk of GBS from influenza vaccines pales in comparison to the benefits of the vaccine.**

Why this is an issue: In 1976, a new strain of influenza emerged that bore similarities to the strain that caused the deadly 1918 flu pandemic. A vaccine consisting of the inactivated strain was prepared and administered to mitigate the impact of a pandemic if it were to occur. Fortunately, the feared pandemic never occurred. However, safety surveillance installed and expanded as part

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

of this program picked up clusters of GBS in the recently vaccinated. Although this adverse event was quite rare, it was shown to be significantly associated with this particular vaccine, and the program was terminated in late 1976 amid much public criticism. Enhanced surveillance for GBS after influenza vaccination has been conducted since this time [286, 750].

Epidemiological evidence: The incidence of GBS due to all causes has been estimated as 0.4–4.0 cases per 100,000 person-years [286]. Clinical trials do not approach the size necessary to examine a potential causal association between vaccines and a rare adverse event like GBS [751]. A systematic literature review identified 24 relevant controlled studies with unduplicated data, including 9 cohort [663, 750, 752-758], 3 case-control [759-761] and 12 self-controlled studies [287, 762-772].

Adults who received the 1976-77 swine flu vaccine were 9.5 (95% Confidence Interval: 8.2-10.3) times more likely to develop GBS compared to those who did not receive the vaccine [750]. This increased risk was primarily in the six weeks following vaccination, translating into about one excess cases per 100,000 vaccinations. Without the widespread pandemic of swine influenza anticipated in 1976, this risk of GBS led to the cessation of the 1976-77 flu vaccine campaign.

Since the 1976-77 influenza season, safety surveillance has monitored GBS after influenza vaccination closely. The level of risk seen in 1976-77 has been ruled out in these studies. A meta-analysis of 6 active surveillance systems in the U.S. in the 2009-10 influenza season showed a small statistically significant increased risk of GBS in the 42 days after pandemic H1N1 influenza vaccination (incident rate ratio 2.35; 95% CI 1.53-3.68) [287]. An international collaboration in

the 2009-10 influenza season combining data from Australia, Canada, China, Denmark, Finland, the Netherlands, Singapore, Spain, the UK, and the U.S. found a similarly small but significant increase in risk during the 42 days post pandemic H1N1 vaccination (relative incidence 2.42; 95% CI 1.58-3.72) [767]. A 2015 meta-analysis also found a small but significant increase in risk of GBS following influenza vaccination (relative risk 1.41; 95% CI 1.20-1.66), although the risk was higher for pandemic vaccines (RR 1.84; 95% CI 1.36-2.50) than for seasonal vaccines (RR 1.22; 95% CI 1.01-1.48) [773]. These three meta-analyses indicate an approximate doubling of risk of GBS in the six weeks following pandemic H1N1 influenza vaccination. This is also consistent with estimates of risk of GBS in many studies of seasonal influenza vaccine, many of which were underpowered to show such a small increase in risk with statistical significance [287, 663, 750, 752-772, 774]. This doubling of risk translates into only 1-3 excess cases of GBS per million persons vaccinated, with a higher attributable risk among older populations due to a higher background rate of GBS among older populations. The evidence for post-influenza vaccine GBS among children is inadequate to draw definitive conclusions. The risk for GBS post-influenza vaccine is much less than the estimated risk after wild-type influenza infection, providing further evidence that the benefits of influenza vaccination greatly outweigh the risks [286].

Other than influenza vaccines, vaccines routinely used in the U.S. have not been shown to cause GBS. A retrospective observational study of California infants found no cases of GBS during the 30-day risk interval after 46,486 doses of DTaP-IPV/Hib vaccine administered [709]. A review of quadrivalent HPV vaccine safety data published between 2006 and 2015 found no increase in incidence of GBS compared to background rates [775]. Most studies published since this 2006-2015 review have also found no increased risk of GBS following HPV vaccine [776-778], with

the exception of one large cohort study in France [779], which found a positive association between HPV vaccine and GBS (adjusted hazard ratio 3.78; 95% CI 1.79-7.98), resulting in an attributable risk of 1-2 GBS cases per 100,000 girls vaccinated against HPV. One rabies vaccine that contained sheep brain tissue was associated with GBS, but this vaccine is no longer used in the U.S. [780].

Proposed biological mechanism: Most GBS cases are preceded by a recent respiratory or gastrointestinal infection. *Campylobacter jejuni,* which causes gastrointestinal infections, is the most common specific infectious agent identified through molecular mimicry. [781]. *Campylobacter jejuni* induces antibodies that react against GM1 gangliosides in human neurons due to shared antigenic and epitopic features with lipo-oligosaccharide moieties on the cell wall of the *Campylobacter* bacterium [782, 783]. The mechanism for other infectious agents associated with GBS has not been identified [286, 762, 784].

Do Vaccines Cause Hearing Loss?

Conclusion: Natural infections with viruses such as measles and mumps have been associated with both transient and permanent hearing loss. Thus, measles and mumps vaccines prevent such hearing loss by protecting against natural infection. Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** hearing loss.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing hearing loss and MMR vaccine, since the only applicable study available used a passive surveillance system and therefore lacked an unvaccinated comparison group [222]. A large case-centered analysis published since the IOM report found no association between hearing loss and vaccination [785].

Proposed biological mechanism: Natural infection with wild-type mumps virus has been associated with transient high-frequency deafness in 4.4% of cases among members of the military, as well as with permanent unilateral deafness approximately once every 20,000 cases [222]. Prior to the use of mumps vaccine, mumps was the most common cause of acquired hearing loss in children in the United States and other countries [786-788]. Direct viral infection has been implicated as the mechanism in such cases of hearing loss. Measles infection can also cause hearing loss, most likely as a result of encephalitis [222, 789].

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

The 2012 IOM report described several cases [790-792] and some experimental evidence [793, 794] of hearing loss after measles or mumps vaccines. The IOM concluded that there was no mechanistic evidence for an association between hearing loss and rubella vaccine [222]. Although spontaneous hearing loss does rarely occur after these vaccinations, the causes are unknown, and the data available has not demonstrated an increased risk.

Do Vaccines Cause Hepatitis?

Conclusion: Natural infection with hepatitis viruses is known to cause hepatitis disease. Natural infection with measles, mumps, rubella and varicella viruses have also been associated with hepatitis, albeit rarely. Thus, measles, mumps, rubella and varicella vaccines, and especially hepatitis A and hepatitis B vaccines, prevent hepatitis disease by protecting against natural infection. Vaccines currently routinely recommended to the general population in the U.S.[*] **do not cause** hepatitis when administered to immunocompetent persons.

Varicella is a live virus vaccine that is contraindicated for most patients with underlying immune deficiencies. If the vaccine is mistakenly administered to severely immune deficient individuals, it **can cause** hepatitis as well as other complications. For more information, see the *Varicella*, the *Do Vaccines Cause Disseminated Varicella Infection?* and the *Do Vaccines Cause Herpes Zoster?* summaries.

Patients with chronic hepatic diseases such as chronic hepatitis B or hepatitis C infection can and should receive all routine vaccinations as recommended by the ACIP. Hepatitis A and hepatitis B vaccines are specifically recommended for such individuals to protect them from these natural infections leading to more severe disease [795].

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing an association between hepatitis and either MMR or Hepatitis A vaccines [222]. No relevant studies of quality have been published since this report.

Proposed biological mechanism: Infection with wild-type hepatitis viruses can cause both acute and chronic hepatitis disease. However, hepatitis A vaccine is formalin-inactivated and hepatitis B vaccine is a yeast-derived recombinant vaccine; neither are live vaccines [40]. For more information, please see the *Hepatitis A* and *Hepatitis B* summaries.

Infection with wild-type measles, mumps, rubella and varicella viruses have on rare occasions been associated with hepatitis. Potential mechanisms in which general viral infection could contribute to symptoms of hepatitis include activation of the complement system, in which a cascade of proteolysis and successive release of cytokines functions to amplify the immune response but can damage host cells if not properly regulated, as well as autoantibodies or T cells [222]. MMR and varicella vaccines are live attenuated viral vaccines, and are therefore able to replicate in the body. For more information, see the *Measles, Mumps and Rubella* and *Varicella* summaries.

The IOM found only weak mechanistic evidence for an association between hepatitis and either MMR or Hepatitis A vaccines, even when considering knowledge about the natural infection, as the only post-vaccination cases documented provided little evidence beyond a temporal association [222].

Do Vaccines Cause Herpes Zoster?

Conclusion: Varicella vaccines **can rarely cause** herpes zoster due to vaccine-strain viral reactivation. Other vaccines currently routinely recommended to the general population in the U.S.[*] **do not cause** vaccine-strain viral reactivation.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), described one study assessing varicella vaccination with vaccine-strain viral reactivation [796]; however, it did not provide convincing evidence due to a lack of validity and precision [222]. One large randomized controlled trial published since the 2012 IOM report and conducted in ten European countries found one unconfirmed case of herpes zoster infection and one papular rash out of 4976 recipients of either the MMR vaccine Priorix® and the varicella vaccine Varilrix® or the combination MMRV vaccine Priorix-Tetra®, all vaccines not used in the U.S. Both of these serious adverse events[1] were reported as recovered or resolved [797].

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

[1] A serious adverse event is defined by the Food and Drug Administration (FDA) as resulting "in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition." This definition is found in Title 21, §312.32 of the Electronic Code of Federal Regulations, which can be accessed at the following link: http://www.ecfr.gov/cgi-bin/text-idx?SID=6b68426ec6d55c78a6799d161ba 6754c&mc=true&node=se21.5.312_132&rgn=div8

Proposed biological mechanism: Varicella vaccines are live attenuated viral vaccines, and are therefore able to replicate in the body. Generalized rash is reported in 4-6% of recipients. Systemic reactions are uncommon but possible. Mild zoster illness (shingles) resulting from a latent infection with varicella vaccine virus has been reported. Some cases of herpes zoster after vaccination are due to reactivation of wild type varicella virus from a prior (usually unrecognized) primary varicella infection [714]. Immunodeficiency is a contraindication for most live vaccines, including varicella vaccine. For more information, see the *Varicella* summary.

The 2012 IOM report described cases of vaccine-strain viral reactivation after varicella vaccination [714-733], and concluded that these cases together presented strong mechanistic evidence supporting an association [222]. A laboratory-documented case of herpes zoster caused by the vaccine-strain varicella zoster virus in an immunocompetent recipient of zoster vaccine was reported in 2014 [798]. In immunodeficient persons, vaccine-strain viral reactivation can result in meningitis [714, 719, 731-733] or encephalitis [721, 730].

Do Vaccines Cause Hypersensitivity Reactions (e.g. anaphylaxis, hives)?

Conclusion: Vaccines **can very rarely cause** immediate hypersensitivity reactions (i.e. anaphylaxis, angioedema, and/or hives) usually within minutes, but up to several hours of vaccination in persons with allergy to a vaccine component. Also, vaccines **can cause** large local swelling reactions or nodules at the injection site due to delayed-type hypersensitivity reactions.

International consensus for evaluation and management of allergic reactions to vaccines can be found at the following link: **https://waojournal.biomedcentral.com/articles/10.1186/s40413-016-0120-5** [272].

Epidemiological evidence: Allergic reactions to vaccines (including immediate hypersensitivity reactions) have been estimated to occur approximately once per 50,000-1,000,000 doses. Anaphylaxis, the most concerning type of such reactions, has been estimated to occur approximately once per 100,000-1,000,000 doses for most commonly administered vaccines [272]. Rates of anaphylaxis can differ depending on the vaccine, age of the recipient, and gender; for example, adult females are at a relatively higher risk of hypersensitivity reactions including anaphylaxis than males. However, anaphylaxis is very rare [541]. Hives occurs more commonly, but no precise rate is available.

The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), described one study assessing influenza vaccination and anaphylaxis [663]; however, this study did not provide convincing evidence of an association due to a lack of validity and precision.

The IOM found no relevant studies of quality in the literature assessing any other vaccines and anaphylaxis, since the only applicable studies available used passive surveillance systems and therefore lacked an unvaccinated comparison group [222]. However, numerous case studies have provided strong mechanistic evidence, as described in the Proposed Biological Mechanism section below.

Most studies published since the 2012 IOM report have not found a statistically significant association between vaccination and anaphylaxis [551, 758, 772, 775], but this is unsurprising considering the rarity of this adverse event and possibility of misclassification; prospective cohort studies are usually too small to detect the small increased risk of anaphylaxis following vaccines [541]. A recent Vaccine Safety Datalink study identified 33 confirmed vaccine-triggered anaphylaxis cases among 25,173,965 vaccine doses, which corresponds to a rate of 1.3 cases of anaphylaxis per million vaccine doses [799]. Two studies of the 2013-2014 and 2014-2015 flu seasons in the United Kingdom study found no occurrences of systemic allergic reactions following LAIV in young people with egg allergy, even among those who had previously experienced anaphylaxis to eggs [654, 655]. A prospective observational cohort study of California children and adults 2-49 years of age found no significantly increased risk of hypersensitivity during the 3-day risk interval for 62,040 quadrivalent LAIV recipients during the 2013–2014 influenza season overall; although when restricting the analysis to recipients 5-8 years of age, a significantly higher risk of hypersensitivity was observed [656].

The IOM found no relevant studies of quality in the literature assessing chronic urticaria and diphtheria, tetanus or pertussis vaccines [222]. Since the publication of the 2012 IOM report,

randomized controlled trials in Hong Kong and Korea found no increased risk of urticaria in recipients of the AS04-adjuvanted HPV-16/18 vaccine (Cervarix®) [610, 612]. A randomized controlled trial in the U.S. found no association between localized or systemic urticaria and the inactivated influenza vaccine Fluzone® [269]. A randomized controlled trial in the U.S. and South America found no association between quadrivalent meningococcal conjugate vaccine and urticaria in young infants in the year following vaccination [800]. A retrospective observational study of California infants had 3 cases of urticaria considered related to vaccine receipt out of 46,486 doses of DTaP-IPV/Hib vaccine administered [709].

A few studies have reported an association between vaccines containing aluminum adjuvants and persistent nodules at the injection site, at an estimated rate of 0.03-0.83% [533-536]. Extensive swelling reactions in the injected limb after vaccination with DTaP has also been reported [801-803].

Proposed biological mechanism: Vaccines have been shown to incite immediate hypersensitivity reactions, including anaphylaxis, usually mediated through IgE antibody. These reactions are more likely due to potential allergens among the vaccine constituents rather than to the active ingredients, but often the direct cause of the reaction is not discovered [804]. Chronic urticaria involves different pathogenic mechanisms [272]. A full list of potential allergens within vaccines can be found at the Johns Hopkins Institute for Vaccine Safety website at the following link: **http://www.vaccinesafety.edu/components-Allergens.htm**.

The 2012 IOM report provides case reports of anaphylaxis after MMR [805-816], varicella [715, 716, 817-822], influenza [817, 823-829], hepatitis B [817], meningococcal conjugate [830] and tetanus toxoid vaccines [831-834], which together present strong mechanistic evidence for a rare causal association with these vaccines. The report also provides several reports for HPV [835, 836] and hepatitis A vaccines [828], for which the mechanistic evidence is less conclusive [222].

Development of acute urticaria is associated with natural infections, including viral hepatitis and many different bacteria [837-839]. One mechanism that could contribute to the development of chronic urticaria is IgE hypersensitivity. Other possible mechanisms include activation of the complement system, in which a cascade of proteolysis and successive release of cytokines functions to amplify the immune response but can damage host cells if not properly regulated. However, the IOM concluded that there was no mechanistic evidence for an association between chronic urticaria and diphtheria, tetanus or pertussis vaccines [222].

Do Vaccines Cause Immune Thrombocytopenic Purpura?

Conclusion: Natural viral infections such as influenza, varicella, measles, mumps and rubella are associated with immune thrombocytopenic purpura (ITP). Thus, influenza, varicella, measles, mumps and rubella vaccines prevent ITP by protecting against natural infection. Measles-containing vaccines **can very rarely cause** ITP within 6 weeks of vaccination in children. However, **these vaccines prevent many more cases of ITP than they cause.** Influenza vaccines **do not cause** ITP. Other vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** ITP.

Epidemiological evidence: Rates of ITP after MMR vaccination have been estimated at 1-3 cases per 100,000 doses [40, 840, 841]. However, this is significantly lower than rates of ITP after natural infection otherwise prevented by the vaccine; the incidence of ITP after natural rubella infection is an estimated 1 per 3,000, and incidence after natural measles infection is estimated to be even higher [841].

The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing an association between ITP and diphtheria, tetanus, pertussis and varicella vaccines, since the only applicable studies available used passive surveillance systems and therefore lacked an unvaccinated comparison group [222].

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Studies published since this report have consistently shown an increased risk of thrombocytopenic purpura in children within 6 weeks of measles-containing vaccination [840-843]. However, several studies published since this report have found no association between influenza vaccines and ITP [768, 844, 845], and early childhood vaccines other than MMR or MMRV (ProQuad®) have not been shown to cause ITP [840, 841]. One study examining the safety of trivalent inactivated seasonal influenza vaccination in pregnant women reported a null association with thrombocytopenia [846]. A VSD study of 438,487 live births between 2007 and 2013 found slightly decreased rates of venous thromboembolic events and thrombocytopenia among pregnant women receiving Tdap vaccination [394]. A retrospective observational study of California infants found no cases of ITP during the 30-day risk interval after 46,486 doses of DTaP-IPV/Hib vaccine administered [709].

Proposed biological mechanism: ITP has been associated with natural viral infections such as influenza, varicella, measles, mumps and rubella [841, 847]. Patients with ITP have antibodies to platelets. Measles virus has an affinity for platelets and measles vaccine results in a transient decrease in platelet counts in the first few days following vaccination. ITP occurs later, within the first 6 weeks following vaccination. The most likely pathogenesis for ITP involves altered immune processing of the measles virus-platelet aggregations and induction of anti-platelet antibodies [848]. The IOM found only weak mechanistic evidence for an association between ITP and varicella vaccine, even when considering knowledge about the natural infection, as the only post-vaccination case documented provided little evidence beyond recurrence of symptoms after vaccine re-challenge [716]. The IOM also concluded that there was no mechanistic evidence for an association between ITP and diphtheria, tetanus or pertussis vaccines [222].

Do Vaccines Cause Meningitis or Encephalitis/Encephalopathy?

Conclusion: Varicella vaccine in routine use in the United States* **can very rarely cause** viral meningitis. Measles-containing vaccines **can very rarely cause** measles inclusion body encephalitis (MIBE). Mumps vaccines used in other countries have caused meningitis and encephalitis. However, the mumps vaccine in routine use in the United States* is made from a different strain of vaccine virus and has not been shown to cause meningitis or encephalitis. **The benefit of vaccination in preventing neurologic diseases such as meningitis and encephalitis greatly outweighs the minimal risk of vaccine complications.**

Natural infections with measles, mumps, rubella and varicella viruses can cause encephalitis and meningitis. Thus, measles, mumps, rubella and varicella vaccines protect against encephalitis and meningitis caused by these agents. These vaccines are made from attenuated versions of the wild-type viruses, and do not cause central nervous system infections in normal hosts. However, these attenuated vaccine viruses can cause disease in persons with certain immune deficiencies, and are therefore contraindicated in these populations. For instance, varicella vaccine virus can persist and cause reactivation zoster, which has been very rarely associated with viral meningitis, although affected patients without immune deficiencies recover fully without any lasting effects. In addition, very rare cases of measles inclusion body encephalitis (MIBE) have occurred following administration of measles-containing vaccines.

* These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Natural infections with *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* type b (Hib) can cause severe bacterial meningitis. Pneumococcal, Hib, and meningococcal vaccines protect against meningitis caused by these agents. The vaccines that protect against these infections do not cause meningitis; the vaccines are made from only the outer capsule and/or bacterial proteins so they cannot cause infections like the naturally occurring bacteria [40, 849-854].

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM) [222], now called the National Academy of Medicine (NAM), described three studies with sufficient validity and precision that reported null associations between MMR vaccine and meningitis [110, 855, 856]. The report also described several studies assessing meningitis, encephalitis or encephalopathy and MMR [110, 857, 858], DTaP [665, 859] or meningococcal [858] vaccines, but these studies did not provide convincing evidence due to a lack of validity and precision. The IOM found no relevant studies of quality in the literature assessing encephalitis or encephalopathy and varicella, influenza or hepatitis B vaccines, since the only applicable studies available either had serious methodological limitations or used passive surveillance systems and therefore lacked an unvaccinated comparison group [222].

Since the publication of the 2012 IOM report, one large post-licensure study found no association between herpes zoster vaccination and meningitis, encephalitis or encephalopathy [860]. A case-centered analysis of 110 childhood encephalitis cases from California found no association between vaccination and encephalitis [861]. Large Vaccine Safety Datalink studies found no association between meningitis/encephalitis and either 2012-2013 influenza vaccines [758], the

DTaP-IPV combination vaccine (Kinrix®) [551], or MMR, MMRV (ProQuad®) and varicella vaccine (Varivax®) [660]. A retrospective observational study of California infants found no cases of encephalitis or meningitis during the 30-day risk interval after 46,486 doses of DTaP-IPV/Hib vaccine administered [709]. A 2017 Norwegian registry study found no increased risk of encephalitis following pH1N1 vaccine [862].

The IOM found no relevant epidemiologic studies of quality in the literature assessing an association between vaccination and MIBE [222].

Proposed biological mechanism: An estimated 1-10% of persons naturally infected with wild-type mumps virus develop meningitis. Natural infection with wild-type measles, mumps or rubella viruses occasionally leads to development of encephalitis, at estimated rates of one case per 1000-2000 patients infected with measles, 400-6000 patients infected with mumps, or 5000 patients infected with rubella, respectively [222]. Measles can also cause a persistent infection of the brain resulting in subacute sclerosing panencephalitis (SSPE), which occurs at a rate of approximately 22 cases of SSPE per 100,000 reported cases of measles [863]. Natural infection with wild-type influenza has also been associated with encephalitis, albeit rarely [222, 864-866].

In early-onset encephalitis after infection with mumps virus, neuronal damage is suspected to result from direct viral invasion. Natural viral infection can cause meningitis or encephalitis via either direct viral invasion or a viral-induced autoimmune reaction. Mechanisms proposed for the development of meningitis or encephalitis after viral vaccination include direct viral infection, autoimmune mechanisms resulting in post-infectious encephalitis (such as ADEM), varicella vaccine-strain viral reactivation, and persistent viral infection [222]. For more information, see the

Do Vaccines Cause Acute Disseminated Encephalomyelitis (ADEM)? and the *Do Vaccines Cause Herpes Zoster?* summaries.

Encephalitis and encephalopathy have even been reported as complications of some bacterial infections such as diphtheria and pertussis. There is also some evidence that pertussis-specific antigens can traverse the blood-brain barrier and thereby directly affect the central nervous system [222]. Historically, the whole cell pertussis vaccine (no longer used in the US) was associated with encephalopathy within 7 days of vaccination by the IOM in 1994. However, subsequent studies have failed to show such an association [857, 867], and a landmark study from 2006 showed that 11 of 14 children with alleged vaccine encephalopathy actually had a specific de novo mutation explaining their encephalopathy (SCN1A encephalopathy, also known as Dravet Syndrome) [868].

The IOM also concluded that there was no mechanistic evidence of quality showing an association between encephalitis or encephalopathy and varicella, hepatitis b and meningococcal vaccines, nor for an association between meningitis and measles or rubella vaccines, as the publications reviewed provided no evidence beyond a temporal association [222]. The 2012 IOM report described several cases of encephalitis or encephalopathy after MMR [869-871], influenza [872] and DTaP [873] vaccines, and four cases of meningitis after mumps vaccine [869, 874, 875], but when considering knowledge about the natural infection the IOM concluded this mechanistic evidence was weak [222]. However, there is one well documented case of measles vaccine virus isolated from the cerebrospinal fluid of a patient with encephalitis in Canada [876], as well as documented cases of meningitis following reactivation of vaccine-type varicella zoster virus [731, 877, 878].

MMR and varicella vaccines are live attenuated viral vaccines which replicate in the body. Severe immunosuppression is a contraindication for MMR, MMRV, and varicella vaccine [40]. For more information, see the *Measles, Mumps and Rubella* and *Varicella* summaries.

In immunodeficient persons, persistent infection with live vaccine viruses is possible. Measles vaccine virus can lead to central nervous system infection and MIBE [222]. The 2012 IOM report described several cases of MIBE after measles vaccination in immunodeficient persons [876, 879, 880], and concluded that these cases together presented strong mechanistic evidence supporting an association [222].

Do Vaccines Cause Multiple Sclerosis?

Conclusion: Influenza vaccines **do not cause** multiple sclerosis (MS). Other vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** MS.

Epidemiological evidence: Most studies described in the 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no association between vaccination and MS, whether assessing onset [881-885] or relapse [886, 887] in adults, or onset [881, 888] or relapse [889] in children; however, these studies did not provide convincing evidence due to a lack of validity and precision [222]. Studies published since the 2012 IOM report focusing on the pandemic H1N1 influenza vaccine Pandremix [575, 614, 890], quadrivalent HPV vaccine (Gardasil®) [576-578, 775] and hepatitis B vaccine [577] have also found no association with MS. A white paper on influenza vaccine safety published in 2015 concluded that while each individual study had relatively low power, as a group they provide consistent evidence against a causal association between influenza vaccine in adults and MS onset or relapse; although the data are more limited in children, there is no signal to indicate concern [653]. A recent systematic review found no increase in risk of development of MS after vaccination against hepatitis B, HPV, influenza, MMR, tetanus, diphtheria, polio, smallpox, or BCG vaccines [891]. Another recent literature review also found no increase in risk of onset or relapse of MS after vaccination [892].

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Proposed biological mechanism: Hypersensitivity reactions triggered by autoimmunity, genetics or environmental factors such as viral infection are often incriminated in the destruction of the host's myelin basic protein (MBP) and other antigens [893]. Similarities in features of MS and other demyelinating disorders have been described and some subjects with the diagnosis of Acute Disseminated Encephalomyelitis (ADEM) have had recurrences and progressed to MS [585, 894]. One possible mechanism is molecular mimicry, which refers to the possibility that similar epitopes shared between self-peptides and foreign peptides (introduced via infection or immunization) inadvertently cause the activation of autoreactive T or B cells, leading to autoimmunity. Of the many vaccines assessed for a possible association with MS, the hepatitis B vaccine has captured the most interest, because molecular mimicry has been demonstrated in rabbits between hepatitis B viral polymerase and the part of the MBP that leads to encephalitis [895]. This suggests that infection with a virus showing similarities with MBP regions associated with the development of encephalitis could induce MS through molecular mimicry. However, the IOM concluded that there was no mechanistic evidence for an association between vaccination and MS, as the publications reviewed provided no evidence beyond a temporal association [222].

Do Vaccines Cause Myocardial Infarction or Stroke?

Conclusion: Myocardial infarction (MI) has been associated with natural influenza infection, and stroke has been associated with natural varicella infection, albeit both very rarely. Thus, influenza vaccine prevents MI and varicella vaccine prevents stroke by protecting against natural infection. Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** myocardial infarction or stroke. Influenza vaccine has been associated with a reduced risk of stroke.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), described one study with sufficient validity and precision that reported a decreased risk of both MI and stroke within the first month after influenza vaccine [896]. The report also described one study assessing stroke and varicella vaccine (Varivax®) [796], but this study did not provide convincing evidence due to a lack of validity and precision [222].

A matched case-control study of 78,706 persons published since the 2012 IOM report found that receipt of seasonal influenza vaccine within the previous year was significantly associated with lower odds of MI (adjusted odds ratio: 0.81; 95% confidence interval: 0.77-0.85) and receipt of pneumococcal vaccine was not associated with a change in odds of MI in adults [897]. Another matched case-control study of 94,022 persons found that receipt of seasonal influenza vaccine

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

within-season was significantly associated with lower odds of stroke (aOR: 0.76; 95% CI: 0.72-0.80) and receipt of pneumococcal vaccine was not associated with a change in odds of stroke [898]. A self-controlled case-series study of 17,853 persons found a reduction in incidence of stroke after receipt of influenza vaccine [899]. In all three of these studies, early seasonal influenza vaccination (before mid-November) was much more beneficial than later seasonal influenza vaccination. A 2017 meta-analysis also concluded that influenza vaccine was associated with a reduced risk of stroke (OR: 0.82; 95% CI: 0.75-0.91) [900]. A self-controlled case series found a decreased incidence of MI up to 60 days after seasonal influenza vaccination, ranging from a 32% reduction within the first 14 days (incidence rate ratio: 0.68; 95% CI: 0.60-0.78) to a 18% reduction within 29-59 days (IRR: 0.82; 95% CI: 0.75-0.90) [901]. A case-control study of 559 Australian patients also found decreased odds of MI after influenza vaccination (aOR: 0.55; 95% CI 0.35-0.85) [902]. Pooled data from several studies examining adults with recent ischemic stroke found no association between influenza vaccination and MI or stroke [903]. Two case-control studies and one population study of Taiwanese patients over 65 years of age found decreased odds of cardiovascular events such as MI and stroke after influenza vaccination [904-906]. Prospective cohorts of older adults found that receipt of pneumococcal polysaccharide vaccine was either not associated with MI or stroke [907, 908] or associated with a decreased risk of acute coronary syndrome events in general [909, 910]. A prospective cohort of 27,204 Spanish individuals initially found a decreased risk of stroke in individuals receiving 23-valent pneumococcal polysaccharide vaccine [911]; however, this association was later refuted by the authors [912]. This study did show that influenza vaccine was associated with reduced risk of death from stroke [913], and that pneumococcal vaccine was not associated with MI [914]. A study in 193,083 adults over 50 years of age found no association between varicella zoster vaccine and MI using both case-

centered and self-controlled case series analyses [860]. Two large Vaccine Safety Datalink studies found no association between stroke and receipt of quadrivalent HPV vaccine (Gardasil®) in females age 9 to 26 [915] or receipt of the DTaP-IPV combination vaccine (Kinrix®) in children age 4 to 6 [551], respectively. A review of quadrivalent HPV vaccine safety data published between 2006 and 2015 found no increase in incidence of stroke compared to background rates [775]. Herpes zoster vaccine was not associated with an increased risk of stroke or cardiovascular events in numerous safety studies [916]. A 2015 international case-control study concluded that routine vaccinations in childhood appear to be protective against stroke [917]. A 2015 Cochrane review determined that influenza vaccination may reduce cardiovascular mortality and combined cardiovascular events among patients with cardiovascular disease, although not enough evidence was available to establish whether influenza vaccination prevented primary cardiovascular disease [918].

Proposed biological mechanism: Potential mechanisms for MI include viral infection and alterations in the coagulation cascade [222]. MI has been associated with natural influenza infection, albeit very rarely [919]. Potential mechanisms for stroke include direct viral infection, viral reactivation, and alterations in the coagulation cascade [222]. Stroke has been associated with natural varicella infection, at an incidence of about 1 in 15,000 cases [920].

The IOM concluded that the only mechanistic evidence for an association between MI and live attenuated influenza vaccine or between stroke and varicella vaccine was knowledge about the natural infections. The IOM also concluded that there was no mechanistic evidence for an

association between stroke and influenza vaccine or between MI and inactivated influenza vaccine, as the publications reviewed provided little evidence beyond a temporal association [222].

Do Vaccines Cause Myocarditis or Myocardopathy/Cardiomyopathy?

Conclusion: Myocarditis can be induced by either viral or bacterial infection, most notably developing in up to two thirds of persons infected with diphtheria. Thus, diphtheria vaccine prevents myocarditis by protecting against natural infection. Smallpox vaccine **does very rarely cause** myocarditis and myocardopathy/cardiomyopathy, but is not routinely recommended to the general population in the United States. Other vaccines that are currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** myocarditis or myocardopathy/cardiomyopathy.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing myocarditis and diphtheria, tetanus or pertussis vaccines [222].

One study published since this report of 193,083 adults over 50 years of age found no association between zoster vaccine and myocarditis using both case-centered and self-controlled case series analyses [860]. A VSD study of 438,487 live births between 2007 and 2013 found no increased risk of cardiac events such as cardiomyopathy, myocarditis, pericarditis, or heart failure among pregnant women receiving Tdap vaccination [394].

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

U.S. military personnel administered smallpox vaccine had almost 7.5 times higher incidence of myopericarditis in the 30 days post vaccination than non-vaccinated active duty military personnel (16.11 per 100,000 vaccinees versus 2.16 per 100,000 non-vaccinees) [921]. A 2015 prospective cohort study also found an increased risk of myocarditis/pericarditis after smallpox vaccine, but no cases of myocarditis after receipt of trivalent inactivated influenza vaccine [922].

Proposed biological mechanism: Myocarditis often results from a prolonged immune response induced by viral infection [923]. In particular, myocardopathy/cardiomyopathy develops in up to two thirds of persons infected with *Corynebacterium diphtheria*, due to the effects of the exotoxin released by the bacteria. However, the diphtheria vaccine does not contain active toxin. Other mechanisms that could contribute to myocarditis include autoantibodies or T cells [222].

The IOM concluded that there was no mechanistic evidence for an association between myocarditis and tetanus or pertussis containing vaccines [222].

Do Vaccines Cause Narcolepsy?

Conclusion: The AS03-adjuvanted 2009 pandemic H1N1 influenza vaccine (trade name: Pandemrix™) was associated with an increased risk of narcolepsy in several northern European countries. In other countries where there is a lower prevalence of genetic factors associated with narcolepsy, studies did not find an increase in risk with this vaccine or other influenza vaccines. The vaccine in question (Pandemrix™) was not licensed in the United States, and vaccines in routine use in the United States[*] **have not been shown to cause** narcolepsy.

Why this is an issue: A sharp increase in the number of narcolepsy diagnoses in children was noticed shortly after immunization campaigns for the pandemic 2009 H1N1 vaccines in Finland and Sweden. Subsequent analysis confirmed an association between the European AS03-adjuvanted pandemic 2009 H1N1 vaccine (Pandemrix™) and narcolepsy onset in several northern European countries. Immunization with this vaccine is thus no longer recommended in children [924-926]. This vaccine was not used in the United States, and no increase in narcolepsy has been found with any vaccine routinely used in the United States.

Epidemiological evidence: Multiple studies have consistently documented an increased risk of narcolepsy associated with AS03-adjuvanted influenza vaccines, primarily in the childhood populations of northern European countries [575, 924-936]. The estimated rate was 1 case per 16,000 persons vaccinated between 4 and 19 years of age in Finland [924]. The strength of this

[*] These conclusions do not consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

association varied depending on the country studied, with an intermediate association in the rest of Europe and a possible association in Canada [930, 937]. This could be explained by differences in population genetics [938]. Studies have not shown any association between narcolepsy and other influenza vaccines, either MF59-adjuvanted or without an adjuvant [656, 772, 939-941]. A cohort study of almost one million adolescent girls in Denmark and Sweden found no association between quadrivalent HPV vaccine and narcolepsy [942]. A 2018 meta-analysis found that during the first year after vaccination with Pandemrix^{TM} the relative risk of narcolepsy increased 5 to 14-fold in children and adolescents and 2 to 7-fold in adults, and the vaccine attributable risk in children and adolescents was approximately 1 per 18,400 doses of vaccine [943].

Proposed biological mechanism: The 1918 pandemic of influenza infection was associated with an illness consistent with narcolepsy. The 2009-10 pandemic influenza may have been associated with an increase in narcolepsy in China, but no increase was observed in many other countries [944]. Almost all patients with narcolepsy have HLA DQB1*0602, a genetic marker for predisposition to the disorder [945, 946]. Recent studies have provided further evidence that infections may serve as a potential trigger for the pathogenesis of narcolepsy [947]. A number of mechanisms have been postulated to explain the association with the ASO3-adjuvanted vaccine in several European countries, but many of these hypotheses have been found to be lacking. One recent hypothesis includes the possibility that a combination of infection with the 2009 pandemic H1N1 influenza virus followed by the ASO3-adjuvanted vaccine could have resulted in narcolepsy in genetically predisposed individuals [948].

Do Vaccines Cause Oculorespiratory Syndrome?

Conclusion: The Fluviral S/F® and Vaxigrip® vaccines used in Canada between 2000 and 2003 (but never used in the United States) **did commonly cause** oculorespiratory syndrome (ORS) within 24 hours of vaccination, at an estimated rate of up to 2.9 cases per 100 vaccinations. Changes have been made in the formulation of these vaccines that have resulted in a dramatic decrease in the risk of ORS.

There have been reports of ORS-like symptoms after receipt of inactivated influenza vaccines (IIV) in routine use in the United States. However, these reports are rare, and symptoms are generally mild and transient.

Why this is an issue: ORS is an adverse event associated with influenza vaccine that was first described in Canada during the 2000-2001 influenza season. It is characterized by conjunctivitis, facial swelling, and upper respiratory symptoms that develop within 24 hours of vaccination. ORS is generally mild, resolving within 48 to 72 hours [31].

Epidemiological evidence: 96% of the ORS cases reported in Canada during the 2000–2001 influenza season occurred after vaccination with Fluviral S/F® [949]. The attributable risk of ORS for the 2001-2002 formulation of Fluviral S/F® was estimated to be 2.9 cases per 100 vaccinees [950]. The 2012 report by the Institute of Medicine (IOM) [222], now called the National Academy of Medicine (NAM), described three studies with sufficient validity and precision that demonstrated an association between ORS and the aforementioned influenza vaccine [950-952].

Most studies have not demonstrated a causal relationship between ORS and influenza vaccines used in the U.S. [641]. However, according to the 2012 IOM report, this could be due to underreporting of the typically mild symptoms of ORS as well as the annual variance in influenza vaccine formulation [222]. The ACIP recommendations for influenza vaccines in 2013-2014 noted several investigations that identified persons with symptoms meeting an ORS case definition in safety monitoring systems and trials that had been conducted before 2000 in Canada, the United States, and Europe [953].

Proposed biological mechanism: The clinical presentation of ORS indicates that its pathogenesis is most likely immune-based [31]. One mechanism suggested for the development of ORS after influenza vaccination is activation of the complement system, in which a cascade of proteolysis and successive release of cytokines functions to amplify the immune response but can damage host cells if not properly regulated [222]. Possible mechanisms of complement activation by influenza viruses include direct binding of the matrix (M1) protein [954] and immune complex formation with preformed nonprotective antibodies leading to tissue pathology [955]. Host factors involving cytokine production may also predispose some individuals to develop ORS after influenza vaccination [956].

The presence of numerous microaggregates of unsplit viruses in the 2000-2001 Canadian formulation has been proposed as an important factor behind that season's high rates of ORS, and an improved formulation in following years brought decreased rates [950].

The 2012 IOM report described both experimental and clinical evidence [951, 952, 957-960] supporting a causal relationship between ORS and the aforementioned influenza vaccine [222].

Do Vaccines Cause Opsoclonus Myoclonus Syndrome?

Conclusion: Opsoclonus myoclonus syndrome (OMS) is a very rare neurological condition that generally begins at one to two years of age and is characterized by uncontrolled, irregular and rapid movements of the muscles and eyes [54].

Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** OMS.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing OMS and measles, mumps, rubella, diphtheria, tetanus or pertussis vaccines [222]. No relevant studies of quality have been published since this report.

Proposed biological mechanism: OMS is generally caused by either a tumor or a viral infection [961-964]. Potential mechanisms for OMS include activation of the complement system, in which a cascade of proteolysis and successive release of cytokines functions to amplify the immune response but can damage host cells if not properly regulated, as well as molecular mimicry, which refers to the possibility that similar epitopes shared between self-peptides and foreign peptides (introduced via infection or immunization) inadvertently cause the activation of autoreactive T or B cells, leading to autoimmunity.

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

The IOM concluded that there was no mechanistic evidence for an association between OMS and measles, mumps, rubella, diphtheria, tetanus or pertussis vaccines, as the publications reviewed provided no evidence beyond a temporal association [222].

Do Vaccines Cause Optic Neuritis or Neuromyelitis Optica?

Conclusion: Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** optic neuritis or neuromyelitis optica (NMO).

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM) [222], now called the National Academy of Medicine (NAM), described two studies assessing optic neuritis and MMR, influenza, hepatitis B, diphtheria and tetanus vaccines [883, 965], but these studies did not provide convincing evidence due to a lack of validity and precision. The IOM found no relevant studies of quality in the literature assessing optic neuritis and pertussis vaccine or NMO and MMR, influenza, hepatitis B or HPV vaccines [222].

Studies published since the 2012 IOM report have not found evidence of an association between vaccination and optic neuritis. A prospective cohort study of 189,629 females receiving quadrivalent HPV vaccine (Gardasil®) in California did not find a statistically significant association with optic neuritis [576]. A Vaccine Safety Datalink study found no cases of optic neuritis in over 200,000 pregnant women within 42 days after receiving trivalent inactivated influenza vaccine [846]. A claims-based retrospective matched cohort analysis of females 9-26 years of age did not find an association between HPV vaccine and optic neuritis [966]. A cohort study of 3,983,824 females 10-44 years of age in Denmark and Sweden found no association between quadrivalent HPV vaccine and demyelinating diseases including optic neuritis and

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

neuromyelitis optica [578]. A case-centered analysis in a large integrated Californian health plan population did not find an association between vaccines and optic neuritis [967]. A recent literature review found no increase in risk of optic neuritis after vaccination [892].

Proposed biological mechanism: Anti-phosphatidylcholine antibodies have been suggested as a potential cause of optic neuritis [968]. A highly specific immunoglobulin G autoantibody that targets aquaporin-4 is present in up to 80% of patients with NMO [969, 970]. One possible mechanism for this is molecular mimicry, which refers to the possibility that similar epitopes shared between self-peptides and foreign peptides (introduced via infection or immunization) inadvertently cause the activation of autoreactive T or B cells, leading to autoimmunity. Another possible mechanism is activation of the complement system, in which a cascade of proteolysis and successive release of cytokines functions to amplify the immune response but can damage host cells if not properly regulated. Other mechanisms that could contribute to optic neuritis or NMO include formation of immune complexes, as well as direct or persistent viral infection. Natural infection with wild-type measles, mumps or rubella viruses has been associated with optic neuritis, albeit very rarely [222].

The 2012 IOM report described two cases of optic neuritis after MMR [971, 972], two cases of optic neuritis after influenza vaccine showing a reoccurrence of symptoms after vaccine rechallenge [678, 973], and one case of NMO after rubella vaccine [974]; however, even when considering knowledge about the aforementioned natural infections, the IOM concluded that this mechanistic evidence was weak. The IOM also concluded that there was no mechanistic evidence

for an association between optic neuritis and hepatitis B, diphtheria, tetanus or pertussis vaccines, or between NMO and influenza, hepatitis B, HPV, measles or mumps vaccines [222].

Do Vaccines Cause Primary Ovarian Insufficiency?

Conclusion: Vaccines in routine use in the United States[*] **have not been shown to cause** primary ovarian insufficiency (POI, formerly called primary ovarian failure), and the available evidence does not support a causal relationship.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), did not assess POI as a potential outcome of vaccination [222]. A recent VSD retrospective cohort study of nearly 200,000 young women in Oregon and Washington found no association between HPV, Tdap, or MenACWY vaccines and POI [249]. Publications of case series include a combined six total case reports of POI that may have had onset at varying times after HPV vaccination [975-977]. Other publications are mostly limited to commentaries about the reports, and preliminary analyses from passive surveillance or ecological data.

Proposed biological mechanism: The cause of POI is not known for most affected patients and only a very small proportion of cases are due to autoimmunity [978]. Mechanisms proposed by authors of case reports for HPV to be involved with the pathogenesis involve either toxic effects or autoimmune responses to the vaccine [979, 980]. However, questions have been raised regarding the validity of the arguments put forth in these publications in several letters to the editor [981, 982] and a special editorial [983]. Major problems with the proposed associations include

[*] These conclusions do not consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

the inconsistent time intervals between vaccination and onset, the plausibility of the proposed mechanism, the lack of population-level or passive surveillance changes in rates, and potential conflicts of interest of several of the authors. A systematic review and critical appraisal of the proposed mechanism found no evidence to suggest it is a viable explanation for autoimmunity [984].

Conclusion: Fever is a common symptom of many natural infections, including bacteria such as diphtheria, pertussis, meningococcus and pneumococcus, and viruses such as hepatitis A, hepatitis B, influenza, measles mumps, rubella, polio, rotavirus and varicella. Fever is associated with febrile seizures in infants. Thus, many vaccines prevent fever and febrile seizures by protecting against natural infections.

However, all vaccines that cause fever in young children also have a small inherent risk of causing febrile seizures**.** The first dose of measles-containing vaccines **can rarely cause** febrile seizures in infants and young children 7-10 days after vaccination, at an estimated rate of 26.4 per 1000 person-years after MMR and 84.6 per 1,000 person-years after MMRV (ProQuad®). Influenza and pneumococcal conjugate vaccines when administered separately **can very rarely cause** febrile seizures in infants and young children in the 24 hours after vaccination, at an estimated rate of 5 events per 100,000 doses in the U.S. The risk of febrile seizures is increased when influenza and pneumococcal conjugate vaccines are given simultaneously, to an estimated rate of 17.5 per 100,000 doses. The DTaP-IPV-Hib combination vaccine in use in Denmark **can very rarely cause** febrile seizures in infants and young children, at an estimated rate of less than 4 per 100,000 doses. Whole-cell DTP vaccine **did cause** febrile seizures, but is no longer used in the United States. Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** persistent epilepsy or infantile spasms.

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Febrile seizures are a common and typically benign childhood condition, occurring in 2-5% of children at some point during their first five years of life. Febrile seizures have an estimated background incidence of 240–480 per 100,000 person-years in children under five years, although this varies considerably by age, genetics, co-morbidities and environmental risk factors. There are no long-term effects of simple febrile seizures, with the possible exception of an increased risk of recurrence [293-296].

Considering the benign nature of simple febrile seizures, the rarity of vaccine-induced febrile seizures and the relative frequency of fever related to natural infection particularly among young children, **the benefits of vaccination greatly outweigh the minimal risk of vaccine complications.**

Epidemiological evidence: Between 5% and 15% of children receiving the first dose of measles-containing vaccines develop a transient fever ≥ 103°F, 7-12 days after the first dose. Nine methodologically sound, controlled epidemiological studies have all found an increased risk of seizures 7-14 days after MMR vaccination [858, 985-992]. A 2016 summary of 23 post-licensure clinical trials and a 2015 meta-analysis both confirmed these findings [993, 994]. The MMRV combination vaccine (ProQuad®) has a higher risk of febrile convulsions than simultaneous yet separate administration of MMR and varicella vaccine (Varivax®) [297, 543-547]. Febrile seizures occurred at a rate of 26.4 per 1000 person-years after MMR and 84.6 per 1,000 person-years after MMRV in the 7-10 days after vaccination [297]. There is no increased risk of fever or febrile seizures in children receiving their second dose of measles-containing vaccine at 4 to 6 years of

age, whether given MMR or MMRV [40, 220, 995]. Delaying MMR or MMRV vaccines past 15 months of age results in a higher risk of seizures than vaccinating according to the recommended schedule [548, 549].

Febrile seizures were estimated to occur at a rate of 17.5 per 100,000 doses in children aged 6-59 months after receiving concomitant trivalent inactivated influenza vaccine (TIV) and 13-valent pneumococcal conjugate vaccine (abbreviation: PCV13; trade name: Prevnar13®); lower rates of 4.9 per 100,000 doses and 5.3 per 100,000 doses were estimated in children who received TIV without concomitant PCV13 and in children who received PCV13 without concomitant TIV, respectively. However, these risk differences varied substantially with age due to the age-dependent background rates of febrile seizures, with the highest estimates at 16 months and the lowest at 59 months [296].

Aside from the CSL Biotherapies trivalent vaccine licensed in Australia in 2010 [996-998], influenza vaccines have generally not been associated with seizures. Six methodologically sound, controlled epidemiological studies found no statistically significant association between seizures and influenza vaccination [640, 641, 999-1002]. However, a large Vaccine Safety Datalink (VSD) study of children under 5 years of age did find a small increased risk of seizures after TIV (incidence rate ratio 2.4; 95% CI 1.2-4.7), as well as a similar increased risk after PCV13 (IRR 2.5; 95% CI 1.3-4.7) and an even further increased risk after receiving both vaccines simultaneously (IRR 5.9; 95% CI 3.1-11.3) [296]. Another VSD study found an increased risk of febrile seizures following concomitant administration of TIV and PCV13 (relative risk 5.3; 95% CI 1.87-14.75) [1003]. A self-controlled risk interval analysis found that although TIV

administered by itself had no increased risk of febrile seizures, risk of febrile seizures on the two days following vaccination increased when TIV was administered simultaneously with either PCV (IRR 3.50; 95% CI 1.13-10.85) or DTaP-containing vaccines (IRR 3.50; 95% CI 1.52-8.07). This concomitant administration led to a small absolute risk of 30 excess febrile seizures per 100,000 persons vaccinated [1004]. In addition, a study of 226,889 Norwegian children found a twofold increased risk of febrile seizures in the 1-3 days after pH1N1 vaccination [1005]. However, the same study also found a tenfold increased risk of febrile seizures in the 1-3 days after diagnosis of pH1N1 infection.

The 2012 report by the Institute of Medicine (IOM) [222], now called the National Academy of Medicine (NAM), did not find convincing evidence of an association between seizures and varicella, DTaP or hepatitis B vaccines [665, 713, 990, 1006, 1007]. A large cohort study published since this report found a small increased risk of febrile seizure after the first two doses of the DTaP-IPV-Hib combination vaccine in Denmark, with an absolute risk of less than 4 per 100,000 vaccinations [550]. Two large VSD studies published since the 2012 IOM report found no association between seizures and the DTaP-IPV combination vaccine (Kinrix®) [551] or quadrivalent HPV vaccine (Gardasil®) [915]. A retrospective observational study of California infants had 5 cases of seizures considered related to vaccine receipt out of 46,486 doses of DTaP-IPV/Hib vaccine administered [709]. A large VSD study found that vaccination in children 3-5 months of age was associated with increased risk of febrile seizures (incidence rate ratio: 23; 95% CI 5.13-100.8) on the day of and the day after vaccination, leading to a small attributable risk of 3.92 febrile seizures per 100,000 children vaccinated [1008].

A case-control study reviewed in the 2012 IOM report did not find convincing evidence of an association between infantile spasms and the tetanus and diphtheria toxoid vaccines [1009], and the report found no relevant studies of quality in the literature assessing an association between infantile spasms and pertussis vaccine [222]. No relevant studies of quality examining infantile spasms and vaccination have been published since this report.

Proposed biological mechanism: Immunization may induce fever through the release of cytokines from inflammatory cells, and fever is associated with febrile seizures [222]. Although an interaction of genetics, brain maturity, and fever is hypothesized, the pathophysiology of febrile seizures is largely unknown [295]. The pathogenesis may be explained by alteration of brain ion channel function due to change in temperature [1010, 1011], modification of neuronal excitability [1012] or fever-induced respiratory alkalosis [1013]. Studies have shown that genetic susceptibility plays an important role in the pathogenesis of febrile seizures, and various loci have been mapped on different chromosomes in individuals with febrile seizures [1014-1027]. For well-studied vaccines such as influenza vaccines, increases in reactogenicity have been shown to be associated with differences in manufacturing procedures [1028-1030].

Do Vaccines Cause Serum Sickness?

Conclusion: Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** serum sickness.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing serum sickness and diphtheria, tetanus or pertussis vaccines [222]. No relevant studies of quality have been published since this report.

Proposed biological mechanism: Formation of immune complexes is a known mechanism in the development of serum sickness. Another mechanism that could potentially contribute to development of serum sickness is activation of the complement system, in which a cascade of proteolysis and successive release of cytokines functions to amplify the immune response but can damage host cells if not properly regulated [222].

The 2012 IOM report described one case of serum sickness after a diphtheria and tetanus vaccine [1031]; however, the IOM concluded that this mechanistic evidence was weak. The IOM also concluded that there was no mechanistic evidence for an association between serum sickness and pertussis vaccine [222]. Since publication of the 2012 IOM report, a case of serum sickness after H1N1 pandemic influenza vaccine was also described in the literature [1032].

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Do Vaccines Cause Small Fiber Neuropathy?

Conclusion: Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** small fiber neuropathy (SFN).

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing SFN and varicella or influenza vaccines [222]. No relevant studies of quality have been published since this report.

Proposed biological mechanism: SFN encompasses the heterogeneous group of disorders that damage the small subsets of sensory and autonomic nerve fibers with little to no large fiber involvement [1033]. One mechanism that could contribute to SFN is molecular mimicry, which refers to the possibility that similar epitopes shared between self-peptides and foreign peptides (introduced via infection or immunization) inadvertently cause the activation of autoreactive T or B cells, leading to autoimmunity. However, the IOM concluded that there was no mechanistic evidence for an association between SFN and varicella or influenza vaccines, as the publication reviewed provided no evidence beyond a temporal association [222].

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Do Vaccines Cause Spontaneous Abortion?

Conclusion: Vaccines currently routinely recommended for pregnant women in the U.S. **have not been shown to cause** spontaneous abortion (SAb). Although one study has suggested a possible increase in risk of SAb early in pregnancy following inactivated influenza vaccine (IIV), other studies have not found an association and the results are not conclusive.

Why this is an issue: The Advisory Committee on Immunization Practices (ACIP) recommends that "all women who are pregnant or who might be pregnant in the influenza season receive influenza vaccine. Any licensed, recommended, and age-appropriate influenza vaccine may be used. Influenza vaccine can be administered at any time during pregnancy, before and during the influenza season." Live attenuated influenza vaccine (LAIV) has never been recommended for use in pregnancy in the U.S. [262].

The recommendation for IIV in pregnancy was based upon the benefits of the vaccine for prevention of influenza in the mother and infants born to women immunized in pregnancy, and the overall excellent safety profile of IIV among children and adults [325]. SAb is defined in the United States as the loss of a fetus before 20 weeks of gestation (before 24 weeks in some other countries), and occurs in roughly 15-20% of clinically recognized pregnancies [1034].

Donahue et al. recently reported results from a case-control study examining the risk of SAb following receipt of inactivated influenza vaccines containing A/H1N1pdm2009 antigen in the 2010-11 and 2011-12 seasons [372]. The odds of vaccine receipt in the 28-day exposure window

were double among women who had an SAb compared with the control women who had live births or stillbirths (adjusted odds ratio: 2.0; 95% Confidence Interval: 1.1–3.6). This association was mostly seen in the 2010-11 season (aOR: 3.7; 95%CI: 1.4-9.4) rather than the 2011-12 season (aOR: 1.4; 95%CI: 0.6–3.3). In a post-hoc analysis, the study found the risk was almost entirely attributed to women who had received vaccines containing pandemic H1N1 (pH1N1) antigen in the previous year (aOR: 7.7; 95%CI: 2.2–27.3) compared to women unvaccinated in the previous year (aOR: 1.3; 95%CI: 0.7–2.7) [372].

As pointed out by Chambers et al. in an accompanying commentary, SAb is one of the most challenging birth outcomes to study using observational studies. Many clinically unrecognized pregnancies occur and retrospective studies have a difficult time capturing these pregnancies and SAbs [373]. Limitations of the Donahue et al. study include ascertainment of SAb date, the potential that healthcare seeking for SAb care was associated with vaccination, preferential vaccination among women with comorbidities or other risk factors for SAb, the potential that cases had greater opportunity for vaccination because they sought care for symptoms foreshadowing SAb diagnosis, and others discussed in the paper and commentary [372, 373].

Epidemiological evidence: The Donahue et al. findings need to be interpreted in the context of other epidemiological data. Studies of IIV conducted in pregnant women prior to this recommendation had not revealed an increase in risk of SAb, but most did not assess the risk in the first trimester or were underpowered to detect a small increased risk. One recent randomized trial recruiting women at 17-34 weeks gestation [374], thirteen other observational studies [375-387], two systematic reviews [364, 388], and one meta-analysis [355] have assessed the potential

association between influenza vaccine and SAb or a related outcome, and none have found an association.

Steinhoff et al. enrolled 3,693 women in a randomized, placebo-controlled trial of influenza immunization during pregnancy in Nepal. Three participants in the placebo group (0.2%) and 5 in the vaccine group (0.3%) experienced miscarriage (risk ratio: 1.67; 95%CI: 0.40-6.98). 31 participants in the placebo group (1.7%) and 33 in the vaccine group (1.8%) experienced stillbirth (RR: 1.07; 95%CI: 0.66-1.73) [374]. SAb was uncommon in this study given the age of study enrollment (17-34 weeks).

Chambers et al. followed 1,032 American and Canadian women between 2009 and 2012 in a prospective cohort study. 841 of these women received a pH1N1-containing vaccine during pregnancy. No increased risk of SAb was found (adjusted hazard ratio: 0.92; 95%CI: 0.31-2.72). 184 women vaccinated during the first trimester were included in an analysis that showed no increased risk of SAb (aHR: 0.84; 95%CI: 0.27–2.64) [375].

Chambers et al. also recruited 1,730 American and Canadian women between 2010 to 2014 as part of the cohort arm of the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS). 1,263 of these women were exposed to an influenza vaccine during pregnancy. There was no overall increase in risk of spontaneous abortion in first trimester exposure compared to the unexposed (aHR: 1.12; 95%CI: 0.47-2.65). Additionally, women who were vaccinated in the first trimester or any trimester were more likely than unvaccinated women to deliver a live born child (HR: 1.09; 95%CI 1.05, 1.13) [376].

Chavant et al. included 2,415 pregnant women vaccinated between November 2009 and March 2010 in France in a prospective cohort study. 97.6% of these women received a vaccine without adjuvant and 2.4% received an adjuvanted vaccine. They found that exposure to pH1N1-containing vaccines during pregnancy did not increase the risk of adverse pregnancy outcomes. 12 of the 2,246 pregnancies with known outcomes ended in spontaneous abortion. This 0.5% rate is below the base rate in the general population, observed at 10-15%; however, this is probably because only 3.9% of women in this study were vaccinated during their first trimester. Of the 92 women who were vaccinated during their first trimester, 5 experienced SAb [377].

Ma et al. included 226 pregnant women in China in a prospective cohort study. 122 of these women were immunized with pH1N1 vaccine. They found no difference in rates of spontaneous abortion between the vaccinated and unvaccinated group (0.8% vs 1.9%, respectively; P=0.470). However, the trimester of vaccination is not reported [380].

Oppermann et al. included 1,652 pregnant women in Germany in a prospective cohort study. 323 of these women were immunized with pH1N1 vaccine between September 2009 and March 2010. No increased risk of SAb was found (HR: 0.89; 95%CI: 0.36–2.19), although this was reported for all trimesters instead of just first trimester due to the limited number of first trimester vaccinations (n=55) and inability to adjust fully for confounders. The study also showed a higher rate of live births in vaccinated versus unvaccinated cohorts (97.2% vs. 87.9%) [381].

Pasternak et al. studied SAb among 35,408 Danish women using a national register based cohort study. 2,736 of these women were immunized with pH1N1 vaccine. No increased risk of SAb was found (HR: 1.11; 95%CI: 0.71-1.73). The risk of SAb specific to first trimester vaccinations was not reported. No increased risk of fetal death (either spontaneous abortion or stillbirth) was found among all vaccinated (HR: 0.79; 95%CI: 0.53-1.16) or first-trimester vaccinated women (HR: 0.96; 95%CI: 0.63-1.47) [382].

Tavares et al. included 267 pregnant women vaccinated in Britain during the 2009 flu season in a prospective cohort study. Of the 41 (15.4%) women vaccinated during the first trimester with known pregnancy outcomes, 3 ended in SAbs. They reported that this and all adverse events were consistent with the expected rates in their population [383].

De Vries et al. recruited 295 pregnant women who received pH1N1 vaccine for a cohort study in the Netherlands, of which 23 were vaccinated in their first trimester, and reported no increased risk of spontaneous abortions compared with the background rate [387].

Eaton et al. surveyed 5,365 pregnant women in Northern California by telephone, 40.7% of whom were vaccinated in the first trimester, and found no difference in SAb between pH1N1 and seasonal influenza vaccines. The risk of SAb specific to first trimester vaccinations was not reported [1035].

Irving et al. found in a 2005-2006 case-control study in the U.S. no association with SAb during the 28 days after receipt of IIV (adjusted matched odds ratio: 1.23; 95%CI: 0.53-2.89). The study included 243 women with SAbs and 243 matched control women. 16 (7%) women with SAb and

15 (6%) matched control group women received influenza vaccine within the 28-day exposure window, all women included in the study were vaccinated before conception or in the first trimester [384].

Sammon et al. found in a retrospective cohort study in the U.K. a reduced risk of SAb and fetal death among pregnant women vaccinated against pandemic influenza. However, this may have been due to residual confounding that was unable to be measured, as suggested by sensitivity analyses [385].

Heikkinen et al. analyzed 4,508 pregnancy outcomes in a mixed prospective and retrospective cohort study in Argentina, Italy, and the Netherlands. Of the cohort, 2,295 (50.9%) women were vaccinated, 92 (4%) in their first trimester. They found no spontaneous abortions among women vaccinated against pandemic influenza, although this was attributed to the high average gestational age at enrollment [386].

Bratton et al. conducted a systematic review and meta-analysis. Their pooled estimate for SAb was not significant (relative risk: 0.91; 95%CI: 0.68-1.22). They did find that women who received influenza vaccine had a lower likelihood of stillbirth (RR: 0.73; 95%CI: 0.55-.96); even when restricted to pH1N1 vaccine (RR, 0.69; 95% CI, 0.53-0.90) [355].

The only study that investigated the effect of previous season vaccination history was Donahue et al. The epidemiological evidence of a possible association between SAb and a second dose of

inactivated influenza vaccine between 5-20 gestational weeks is inconclusive and requires additional study.

Studies of HPV [775, 1036-1045] and rubella [1046-1048] vaccines inadvertently given during pregnancy have not found an association with SAb or miscarriage. A systematic review of hepatitis B, pneumococcal polysaccharide and meningococcal polysaccharide vaccines in pregnancy [1049] and a meta-analysis of smallpox vaccination in pregnancy [1050] also found no association with SAb. Studies examining a potential association with SAb among other vaccines are lacking.

Proposed biological mechanism: Infection with wild-type influenza virus during pregnancy can cause life-threatening illness in pregnant women and increases the risk of SAb, as demonstrated during the 2009 influenza pandemic [1051, 1052].

No clear biological mechanism explains the observations in the Donahue et al. study. The authors hypothesized that an increased inflammatory response following a second (or booster) dose of pandemic influenza vaccine may increase the risk of SAb in early pregnancy [372]. They point out that studies have demonstrated a relationship between vaccination and inflammation, and between inflammation and pregnancy loss [1053-1055]. It has been shown that influenza vaccine can trigger a brief inflammatory response in pregnant women that is similar to that seen in non-pregnant women [1056, 1057]. Other studies found that infection with or vaccination against pandemic influenza virus induced an expansion of T helper type 1 (Th1) cells, which are thought to be pro-inflammatory [1058, 1059]. Significant associations between an increased Th1 response and miscarriage have been reported [1053, 1054]. The observation of the increase in SAb in those

who had been vaccinated the previous year (especially during the 2010-2011 season) is perplexing and is not explainable by just inflammation. No studies have demonstrated an increase in inflammation in those with previous vaccination. In fact, repeat vaccination has been shown to result in lower antibody response [1060-1062]. It may be that the observation noted by Donahue is unique to the 2010-2011 season due to the pandemic of 2009, that it was attributable to one of the aforementioned limitations of the study, or that the finding was due to chance. Ongoing studies in subsequent seasons are investigating this question.

Do Vaccines Cause Sudden Infant Death Syndrome (SIDS)?

Conclusion: DTP and hepatitis B vaccines **do not cause** sudden infant death syndrome (SIDS). Other vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** SIDS.

Epidemiological evidence: In a 2003 report entitled *Immunization Safety Review: Vaccinations and Sudden Unexpected Death in Infancy*, the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), concluded that the evidence favored rejection of a causal relationship between DTP vaccine or exposure to multiple vaccines and SIDS [223]. The 2012 IOM report found no new relevant studies of quality in the literature assessing SIDS and DTaP vaccination [222]. Two large randomized controlled trials found no association between SIDS and pentavalent rotavirus vaccine [1063, 1064]. No increase in the risk of SIDS after immunization with the DTP vaccine was found among a cohort of 129,834 U.S. children born between 1974 and 1984 [1065]. A Vaccine Safety Datalink study of more than 350,000 live births between 1993 and 1998 found no association between hepatitis B birth immunization and neonatal death [1066]. A meta-analysis found that immunizations are actually associated with a reduced risk of SIDS; however, this may be attributable to the healthy vaccinee effect [1067]. A reanalysis of three case-control studies included in this meta-analysis using the self-controlled case series method found neither an increased nor reduced risk of SIDS during the period after vaccination [1068]. A retrospective observational study of California infants found no cases of SIDS that were considered

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

to be related to the administration of 46,486 doses of DTaP-IPV/Hib vaccine [709]. Case-control and self-controlled case series analyses of the Taiwanese death registration databases found no association between SIDS and DTaP vaccine [1069].

Proposed biological mechanism: The IOM concluded that there was no mechanistic evidence for an association between SIDS and diphtheria, tetanus or pertussis vaccination, as the publications reviewed provided no evidence beyond a temporal association [222].

Do Vaccines Cause Syncope?

Conclusion: Vaccines currently routinely recommended to the general population in the U.S.[*] **can rarely cause** syncope up to an hour after vaccination, most frequently among adolescents, and especially among females 11-18 years of age.

Potential injury from syncope after vaccination can be prevented by careful monitoring of vaccine recipients and having them sit or lay down if symptoms develop [246]. The ACIP recommends that recipients always receive the vaccine while sitting and that providers observe adolescent and adult patients for 15 minutes after vaccination [244, 245]. To avoid a hysterical reaction among peers to a post-vaccination syncope case, it is also recommended that adolescents are vaccinated out of sight of others awaiting vaccination [247].

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing an association between vaccination and syncope, since the only applicable studies available either had limited power or serious methodological limitations, or used passive surveillance systems and therefore lacked an unvaccinated comparison group [222]. However, numerous case studies have provided strong mechanistic evidence, as described in the proposed biological mechanism section below.

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

A study by the U.S. Armed Forces published since the 2012 IOM report estimated annual rates of syncope associated with immunization to be between 4.4 and 14.1 events per 100,000 immunizations [1070].

Proposed biological mechanism: Syncope is usually caused by a vasovagal reaction in which sympathetic nervous system stimulation brings a sudden onset of hypotension. Potential stimuli for a vasovagal reaction include invasive medical procedures such as venipuncture, as well as simply the sight of blood in some persons [246].

The 2012 IOM report described a number of cases of syncope after vaccination [246, 678, 836, 1071-1078]. Due to the consistency of the prodromal symptoms, such as dizziness and pallor, and that most cases had a latency of 15 minutes or less between vaccine injection and the development of vasovagal syncope, the IOM concluded that this mechanistic evidence was strong and presented definitive clinical evidence [222]. Syncope following vaccination has also occasionally been reported via passive surveillance systems [541].

Do Vaccines Cause Systemic Lupus Erythematosus?

Conclusion: Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** systemic lupus erythematosus (SLE).

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM) [222], now called the National Academy of Medicine (NAM), described four studies assessing exacerbation of SLE and influenza vaccine [1079-1082] and one study assessing onset of SLE and hepatitis B vaccine [1083]; however, these studies did not provide convincing evidence due to a lack of validity and precision. The IOM found no relevant studies of quality in the literature assessing either exacerbation of SLE and hepatitis B vaccine or onset of SLE and influenza vaccine [222].

Two cohort studies published since the 2012 IOM report, a retrospective cohort of people over 60 years of age who received the herpes zoster vaccine (Zostavax®) [1084] and a prospective cohort of women receiving quadrivalent HPV vaccine (Gardasil®) [576], found no association between vaccination and SLE. A controlled trial in Brazil randomized 54 SLE patients to receive either varicella vaccine or placebo and vaccinated 28 healthy matched controls, and found no difference in adverse event frequency between groups [1085]. A 2017 clinical trial found that quadrivalent HPV vaccine was safe and well tolerated in patients with SLE [1086]. Two 2016 meta-analyses found no difference in adverse event rates after influenza vaccination between SLE patients and healthy controls [1087, 1088]. A 2015 systematic review did not find an increased risk of SLE

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

exacerbation following HPV vaccination [1089]. A 2016 meta-analysis found that influenza and pneumococcal vaccines had no impact on SLE disease activity [1090].

Proposed biological mechanism: There is evidence that natural infection may exacerbate symptoms in SLE patients [1091]. Inflammation is present both during SLE exacerbations and during immune responses to infection or vaccination. One possible mechanism is activation of the complement system, in which a cascade of proteolysis and successive release of cytokines functions to amplify the immune response but can damage host cells if not properly regulated. Other mechanisms that could contribute to onset or exacerbation of SLE include autoantibodies or T cells, and formation of immune complexes.

The 2012 IOM report described some experimental evidence and one case of SLE after hepatitis B vaccination [1092]; however, the IOM concluded that this mechanistic evidence was weak. The IOM also concluded that there was no mechanistic evidence for an association between SLE and influenza vaccine, as the publications reviewed provided little evidence beyond a temporal association [222].

Do Vaccines Cause Transverse Myelitis?

Conclusion: Natural viral infections with influenza, hepatitis A, measles, mumps and rubella and varicella have all been associated with transverse myelitis, albeit rarely. Thus, these viral vaccines may prevent transverse myelitis by protecting against natural infection. Vaccines currently routinely recommended to the general population in the U.S.[*] **have not been shown to cause** transverse myelitis.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing an association between transverse myelitis and MMR, varicella, influenza, hepatitis A, hepatitis B, HPV, meningococcal conjugate, diphtheria, tetanus or pertussis vaccines, since the only applicable studies available either had serious methodological limitations or used passive surveillance systems and therefore lacked an unvaccinated comparison group [222].

Two Vaccine Safety Datalink studies published since the 2012 IOM report found no cases of transverse myelitis in over 200,000 pregnant women within 42 days after receiving trivalent inactivated influenza vaccine [846] and in over 9,000 pregnant women within 42 days after receiving 2009 H1N1 pandemic influenza vaccine [1093]. A cohort study of 3,983,824 females 10-44 years of age in Denmark and Sweden found no association between quadrivalent HPV vaccine and demyelinating diseases, including transverse myelitis [578].

[*] These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Proposed biological mechanism: Natural infection with wild-type influenza, hepatitis A, measles, mumps and rubella viruses, as well as herpes zoster and reactivation of latent wild-type varicella virus, have all been associated with transverse myelitis, albeit rarely. Mechanisms that could contribute to transverse myelitis include viral reactivation [222], as well as molecular mimicry, which refers to the possibility that similar epitopes shared between self-peptides and foreign peptides (introduced via infection or immunization) inadvertently cause the activation of autoreactive T or B cells, leading to autoimmunity.

The 2012 IOM report described a few cases of transverse myelitis after MMR [1094-1096], varicella [1097], and hepatitis B vaccines [1098], but even when also considering knowledge about the aforementioned natural infections the IOM concluded this mechanistic evidence was weak. The IOM also concluded that there was no mechanistic evidence for an association between transverse myelitis and HPV, meningococcal conjugate, diphtheria, tetanus and pertussis vaccines [222].

Do Vaccines Cause Vasculitis or Polyarteritis Nodosa?

Conclusion: Polyarteritis nodosa (PAN) has been reported as a rare complication of natural infection with hepatitis B virus. Thus, hepatitis B vaccine prevents PAN by protecting against natural infection. Vaccines currently routinely recommended to the general population in the U.S.* **have not been shown to cause** vasculitis or PAN.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM) [222], now called the National Academy of Medicine (NAM), described two studies assessing exacerbation of vasculitis and influenza vaccine [1099, 1100], but these studies did not provide convincing evidence due to a lack of validity and precision. The IOM found no relevant studies of quality in the literature assessing onset of vasculitis or PAN and influenza or hepatitis B vaccines, or exacerbation of vasculitis and hepatitis B vaccine [222].

Since the IOM report, a randomized trial found that influenza vaccine was safe for patients in remission with anti-neutrophil cytoplasmic antibody-associated vasculitis [1101], and a prospective observational study found that vaccinations had no significant clinical impact on patients with systemic necrotising vasculitis [1102]. An Italian case-control study found an increased risk of Henoch-Schonlein purpura, a common childhood vasculitis, within 12 weeks of MMR vaccination (odds ratio 3.4; 95% CI 1.2-10.0) [1103]. A large VSD study found that vaccination was associated with a decrease in incidence of the vascular disorder known as

* These conclusions do not necessarily consider vaccines recommended only for special populations in the United States such as Yellow Fever vaccine (international travelers) or Smallpox vaccine (military personnel).

Kawasaki disease [1104], and a 2017 systematic review concluded that evidence is lacking for a causal relationship between immunization and Kawasaki disease [1105].

Proposed biological mechanism: PAN has been reported as a rare complication of natural infection with hepatitis B virus. Formation of immune complexes has been suggested as a potential mechanism for vasculitis or PAN after hepatitis B vaccine. Another possible mechanism is activation of the complement system, in which a cascade of proteolysis and successive release of cytokines functions to amplify the immune response but can damage host cells if not properly regulated. Other mechanisms that could contribute to vasculitis include autoantibodies or T cells [222].

The 2012 IOM report described two cases of exacerbation of vasculitis after influenza vaccine that showed recurrence of symptoms after vaccine re-challenge [678], and three cases of PAN after hepatitis B vaccine [1106-1109]; however, even when considering knowledge about the aforementioned natural infections, the IOM concluded that this mechanistic evidence was weak. The IOM also concluded that there was no mechanistic evidence for an association between PAN and influenza vaccine, between exacerbation of vasculitis and hepatitis B vaccine, or between onset of vasculitis and influenza vaccine or hepatitis B vaccine [222].

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Curriculum Vitae

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PERSONAL DATA

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EDUCATION AND TRAINING

Degree	**Year**	**Institution**	**Field**
PhD	2018	Johns Hopkins Bloomberg School of Public Health	International Health - Concentration in Global Disease Epidemiology and Control - GPA: 4.0 Dissertation: *How Pregnant Women in the United States Perceive Vaccines for Themselves, their Close Contacts and their Children*
MSPH	2014	Johns Hopkins Bloomberg School of Public Health	International Health - Concentration in Global Disease Epidemiology and Control - Certificate in Vaccine Science and Policy - GPA: 4.0 MSPH Essay: *The effects of separating HIV and TB patients in April 2001 on outbreaks of spoligotyped drug resistant TB strains in Lima, Peru's Hospital Dos de Mayo*
BA	2009	Emory University	- Concentration in Chemistry - Secondary concentration in French Studies

PROFESSIONAL EXPERIENCE

Position	Dates	Institution
Epidemiologist	8/14 – present	Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health
Research Associate	8/14 – 8/15	Johns Hopkins Bloomberg School of Public Health
Project Coordinator, Norovirus	8/13 – 5/14	Asociación Benefica PRISMA, Lima Peru
AmeriCorps Health Educator	9/11 – 7/12	Erie Family Health Center, Amundsen High School, Chicago IL
Registration Specialist	8/10 – 2/11	Piedmont Heart Institute, Atlanta GA
Teaching Assistant	9/09 - 5/10	Ecoles élémentaires Michelet, La Forêt, Juliot Curie, and Maxime Marchand, Evreux France

PROFESSIONAL ACTIVITIES

Consultations

- World Health Organization, Geneva, Switzerland. August-December 2014

HONORS AND AWARDS

Honors

- Member of Delta Omega Public Health Honor Society - Alpha Chapter
- Rank of Eagle Scout - Boy Scouts of America

PUBLICATIONS

Journal Articles

1. Dudley MZ, Sheen P, Gilman RH, et al. Detecting Mutations in the Mycobacterium tuberculosis Pyrazinamidase Gene pncA to Improve Infection Control and Decrease Drug Resistance Rates in Human Immunodeficiency Virus Coinfection. Am J Trop Med Hyg. 2016 Dec 7;95(6):1239-1246. Epub 2016 Oct 24. PubMed PMID: 27928075; PubMed Central PMCID: PMC5154434.
2. Salmon DA, Dudley MZ, Glanz JM, Omer SB. Vaccine hesitancy: Causes, consequences, and a call to action. Vaccine. 2015 Nov 27;33 Suppl 4:D66-71. doi:

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3. Halsey NA, Talaat KR, Greenbaum A, Mensah E, Dudley MZ, Proveaux T, Salmon DA. The safety of influenza vaccines in children: An Institute for Vaccine Safety white paper. Vaccine. 2015 Dec 30;33 Suppl 5:F1-F67. doi: 10.1016/j.vaccine.2015.10.080. Review. PubMed PMID: 26822822.
4. Frew PM, Randall LA, Malik F, Limaye RJ, Wilson A, O'Leary ST, Salmon D, Donnelly M, Ault K, Dudley MZ, Fenimore VL, Omer SB. Clinician perspectives on strategies to improve patient maternal immunization acceptability in obstetrics and gynecology practice settings. Hum Vaccin Immunother. 2018 Jul 3;14(7):1548-1557. doi: 10.1080/21645515.2018.1425116. Epub 2018 Feb 15. PubMed PMID: 29313458; PubMed Central PMCID: PMC6067872.
5. Ellingson MK, Dudley MZ, Limaye RJ, Salmon DA, O'Leary ST, Omer SB. Enhancing uptake of influenza maternal vaccine. Expert Rev Vaccines. 2018 Dec 27. doi: 10.1080/14760584.2019.1562907. PubMed PMID: 30587042.