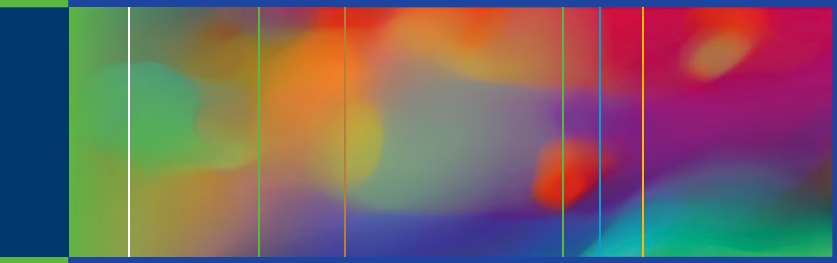
Matthew Z. Dudley · Daniel A. Salmon
Neal A. Halsey · Walter A. Orenstein
Rupali J. Limaye · Sean T. O'Leary · Saad B. Omer



The Clinician's Vaccine Safety Resource Guide

Optimizing Prevention of Vaccine-Preventable Diseases Across the Lifespan

Springer

The Clinician's Vaccine Safety Resource Guide

Matthew Z. Dudley
Daniel A. Salmon
Neal A. Halsey
Walter A. Orenstein
Rupali J. Limaye
Sean T. O'Leary
Saad B. Omer

The Clinician's Vaccine Safety Resource Guide

Optimizing Prevention of Vaccine-Preventable Diseases Across the Lifespan

Springer

Matthew Z. Dudley, PhD, MSPH
Epidemiologist, Institute for Vaccine Safety
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD, USA

Neal A. Halsey, MD
Professor Emeritus, Department of International Health
Johns Hopkins Bloomberg School of Public Health
Professor Emeritus, Department of Pediatrics
Johns Hopkins School of Medicine
Director Emeritus, Institute for Vaccine Safety
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD, USA

Rupali J. Limaye, PhD, MPH, MA
Associate Director for Behavioral Research, Institute for Vaccine Safety
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD, USA

Saad B. Omer, MBBS, PhD, MPH
William H. Foege Professor of Global Health
Professor of Epidemiology and Pediatrics, Emory University
Atlanta, GA, USA

Daniel A. Salmon, PhD, MPH
Professor, Departments of International Health and Health, Behavior and Society
Director, Institute for Vaccine Safety
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD, USA

Walter A. Orenstein, MD, DSc (Hon)
Professor of Medicine, Pediatrics, Global Health, and Epidemiology
Emory University
Associate Director, Emory Vaccine Center
Director, Center of Excellence for Influenza Research and Surveillance (Emory-UGA CEIRS)
Former President, National Foundation for Infectious Diseases (NFID)
Atlanta, GA, USA

Sean T. O'Leary, MD, MPH
Associate Professor, Pediatrics-Infectious Diseases
University of Colorado School of Medicine
Denver, CO, USA

ISBN 978-3-319-94693-1 ISBN 978-3-319-94694-8 (eBook)
https://doi.org/10.1007/978-3-319-94694-8

Library of Congress Control Number: 2018952079

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

Immunizations have had an enormous impact on public health. However, over the past decade, vaccine acceptance has been challenged by individuals and groups who question their benefit [1]. Increasing numbers of people are requesting alternative vaccination schedules [2, 3] or postponing or declining vaccination [4]. One of the main drivers for vaccine hesitancy has been concern over vaccine safety. In one survey of parents reporting concerns about vaccines, 26% worried about the development of autism or other potential learning difficulties after receiving vaccines, 13.5% expressed concern that vaccines could lead to chronic illnesses, and 13.2% stated that vaccines were not tested enough for safety prior to their use [5]. In another online survey of several thousand parents [6], most surveyed participants agreed that vaccines protected their children from diseases; however, more than half expressed concerns regarding serious adverse effects of vaccines. Overall, 11.5% of the parents had refused at least 1 recommended vaccine and the development of autism was often cited as the reason.

Therefore this book "The Clinician's Safety Resource Guide: Optimizing Prevention of Vaccine Preventable Diseases Across the Lifespan" comes as a welcome publication to assist the healthcare provider in addressing vaccine safety concerns. The book is organized into a number of sections to aid in retrieving the needed information for routine

immunizations in the United States over the entire age spectrum including, children, adolescents, adults and pregnant women. The document also provides "evidence-based strategies for talking with patients about vaccines", succinctly describes the vaccine safety system, and summarizes each of the recommended vaccines, the clinical manifestations and impact of the diseases they prevent, the official immunization recommendations, contraindications and precautions, information on vaccine effectiveness and safety, and standardized talking points for use with patients. The final section contains information on specific vaccine concerns and the scientific data to address these concerns.

The book leaves the reader with an understanding that vaccines are comprehensively evaluated prior to their licensure. They are developed, tested, and regulated in a very similar manner to other drugs, but usually in much larger numbers of subjects and with comprehensive surveillance systems to assess any increase in adverse events after licensure. In addition the final section outlining the specific vaccine concerns, highlights that not all parents and patients have the same questions about vaccine safety and that the information must be tailored to the question. Addressing vaccine safety concerns is a time and effort consuming process [7]. With the assistance of this book, this task can be made more efficient and productive. We owe the authors our great appreciation for their work.

References

1. Opel, D.J., et al., *The architecture of provider-parent vaccine discussions at health supervision visits.* Pediatrics, 2013. **132**(6): p. 1037-46.
2. Brewer, N.T., et al., *Announcements Versus Conversations to Improve HPV Vaccination Coverage: A Randomized Trial.* Pediatrics, 2017. **139**(1).
3. Nyhan, B., et al., *Effective messages in vaccine promotion: a randomized trial.* Pediatrics, 2014. **133**(4): p. e835-42.

4. Heritage, J. and D. Maynard, *Communication in Medical Care: Interaction Between Primary Care Physicians and Patients*. 2006.
5. Horne, Z., et al., *Countering antivaccination attitudes.* Proc Natl Acad Sci U S A, 2015. **112**(33): p. 10321-4.
6. Barnett, D.J., et al., *Assessment of local public health workers' willingness to respond to pandemic influenza through application of the extended parallel process model.* PLoS One, 2009. **4**(7): p. e6365.
7. Department of Health and Human Services (HHS), Department of Veterans Affairs, and Department of Defense, *A Comprehensive Review of Federal Vaccine Safety Programs and Public Health Activities*. 2008.

Kathryn M. Edwards, MD
Sarah H. Sell and Cornelius Vanderbilt Chair
Professor of Pediatrics
Vanderbilt University Medical Center
Nashville, TN, USA

Acknowledgements

Partial funding support was provided by the National Institutes of Health (NIH) via an R01 grant (1R01AI11048201A; mPIs: Salmon, Omer).

We would like to thank everyone who contributed to or reviewed some or all of this content, 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).

Contents

Authors

Matthew Z. Dudley, PhD, MSPH Epidemiologist, Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Daniel A. Salmon, PhD, MPH Professor, Departments of International Health and Health, Behavior and Society, Director, Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Neal A. Halsey, MD Professor Emeritus, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Professor Emeritus, Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, MD, USA

Director Emeritus, Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Walter A. Orenstein, MD, DSc (Hon) Professor of Medicine, Pediatrics, Global Health, and Epidemiology, Emory University, Atlanta, GA, USA

Associate Director, Emory Vaccine Center, Director, Center of Excellence for Influenza Research and Surveillance (Emory-UGA CEIRS), Atlanta, GA, USA

Former President, National Foundation for Infectious Diseases (NFID), Atlanta, GA, USA

Rupali J. Limaye, PhD, MPH, MA Associate Director for Behavioral Research, Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Sean T. O'Leary, MD, MPH Associate Professor, Pediatrics-Infectious Diseases, University of Colorado School of Medicine, Denver, CO, USA

Saad B. Omer, MBBS, PhD, MPH William H. Foege Professor of Global Health, Professor of Epidemiology and Pediatrics, Emory University, Atlanta, GA, USA

Abbreviations

95%CI	95% Confidence Interval
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
ACIP	Advisory Committee on Immunization Practice
ACNM	American College of Nurse-Midwives
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ADEM	Acute Disseminated Encephalomyelitis
AEFI	Adverse events following immunization
aHR	Adjusted hazard ratio
AHRQ	Agency for Healthcare Research and Quality
AMA	American Medical Association
aOR	Adjusted odds ratio
ASD	Autism spectrum disorder
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CFS	Chronic fatigue syndrome
cGMP	Current Good Manufacturing Practice

CIDP	Chronic Inflammatory Disseminated Polyneuropathy
CIN	Cervical Intraepithelial Neoplasia
CISA	Clinical Immunization Safety Assessment network
CMS	Centers for Medicare and Medicaid Services
CPSTF	Community Preventive Services Task Force
CRPS	Complex regional pain syndrome
CRS	Congenital Rubella Syndrome
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria, Tetanus and acellular Pertussis combination vaccine
DTP	Diphtheria, Tetanus and whole-cell Pertussis combination vaccine
EN	Erythema nodosum
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
H, as in H1N1	Hemagglutinin
HAV	Hepatitis A Virus
HBeAg	Hepatitis B e antigen
HBIG	Hepatitis B immune globulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HHS	Department of Health and Human Services
Hib	*Haemophilus influenzae* type b
HPV	Human Papillomavirus
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
HSV	Herpes simplex virus
ID	Intradermal
IHS	Indian Health Services
IIV	Inactivated Influenza Vaccine
IM	Intramuscular
IND	Investigational New Drug
IOM	Institute of Medicine

IPV	Inactivated Polio Vaccine
IRB	Institutional Review Board
IRR	Incidence rate ratio
ITP	Immune thrombocytopenia purpura
IVS	Johns Hopkins Institute for Vaccine Safety
LAIV	Live Attenuated Influenza Vaccine
MBP	Myelin basic protein
MCO	Managed care organizations
MCV	Meningococcal conjugate vaccine
MI	Myocardial infarction
MIBE	Measles inclusion body encephalitis
mL	Milliliter
MMR	Measles, Mumps and Rubella vaccine
MMRV	Measles, Mumps, Rubella and Varicella combination vaccine
MPSV	Meningococcal polysaccharide vaccine
MS	Multiple sclerosis
N, as in H1N1	Neuraminidase
NAM	National Academy of Medicine
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NMO	Neuromyelitis optica
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OMS	Opsoclonus myoclonus syndrome
OPV	Oral poliovirus vaccine
OR	Odds ratio
ORS	Oculorespiratory syndrome
PAN	Polyarteritis nodosa
PCV	Pneumococcal conjugate vaccine
pH1N1	Pandemic H1N1 influenza
POI	Primary ovarian insufficiency
PRISM	Post-Licensure Rapid Immunization Safety Monitoring Network
RIV	Recombinant influenza vaccine
RR	Relative risk/risk ratio
RV	Rotavirus vaccine

RZV	Recombinant zoster vaccine
SAb	Spontaneous abortion
SCID	Severe combined immunodeficiency
SFN	Small fiber neuropathy
SGA	Small for gestational age
SIDS	Sudden Infant Death Syndrome
SLE	Systemic lupus erythematosus
SSPE	Subacute sclerosing panencephalitis
Tdap	Tetanus, Diphtheria and acellular Pertussis booster vaccine
Th1	T helper type 1 cells
TIV	Trivalent inactivated influenza vaccine
US	United States
VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Events Reporting System
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System
VICP	National Vaccine Injury Compensation Program
VIP	Vaccine in Pregnancy Registry
VLP	Virus-like particles
VSD	Vaccine Safety Datalink
VZV	Varicella Zoster Virus
WHO	World Health Organization
ZVL	Zoster Vaccine, Live attenuated

Part I
Introduction

Chapter 1
Introduction

This book contains useful information on vaccines that are routinely recommended for most children, adolescents, adults and pregnant women in the United States. This information has been compiled and tailored for all vaccine providers and their staff.

First, evidence-based strategies for talking with patients about vaccines are described. Then, the vaccine safety system is discussed. The following section contains summaries of recommended vaccines along with the diseases they prevent. These summaries include official recommendations, contraindications and precautions, information on vaccine effectiveness and safety, and standardized talking points for use with patients. The final section contains summaries and talking points covering numerous potential vaccine adverse events and the current scientific evidence for associations (or non-associations) with vaccines.

Much of the information contained herein will be made available on the website for the Institute for Vaccine Safety at Johns Hopkins Bloomberg School of Public Health, found at the following link: **http://www.vaccinesafety.edu**. This content will also be available as an electronic searchable database in the associated app for smartphones, tablets and computers.

The website and app will be updated after each meeting of the Advisory Committee on Immunization Practices (ACIP),

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_1

to reflect any changes in recommendations made. The entire book will be updated regularly to incorporate new evidence as it arises. Feedback on the content of this book is encouraged and appreciated. To provide your feedback, please contact the authors at **info@hopkinsvaccine.org**.

We hope that having this information succinctly summarized and readily available will help providers and their staff be more comfortable and confident when answering questions and recommending vaccines to their patients.

Chapter 2
How to Talk with Patients About Vaccines

Conversations about vaccines with many patients can be easy. For some patients, vaccines can be a difficult topic. Talking with patients about uncomfortable topics can be challenging. However, it is part of providers' everyday interactions with patients. Within these interactions, the uneasiness surrounding certain topics more often emanates from the patient than the provider. In many cases, providers are able to overcome patients' uneasiness, as they have dealt with a particular topic frequently and are thus comfortable addressing it.

Talking about vaccines with patients who have concerns or questions can be difficult, given the unfortunate and abundant misinformation surrounding vaccines in the media and communicated by peers. Uneasiness can be more mutual when discussing vaccines. In this book, we provide many of the facts you will need to address both simple and complicated questions, including Advisory Committee on Immunization Practice (ACIP) recommendations, a description of the disease(s) being prevented, the vaccine(s) available, contraindications, vaccine effectiveness, and an overview of safety for the particular vaccine or combined vaccine. We include a section on important information for obstetric providers and considerations in pregnancy.

A presumptive approach to vaccinating on time should be the framework you use when you approach vaccination.

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_2

Getting vaccines according to the ACIP schedule should be the default choice for your patients. The way physicians introduce vaccination can be very influential on patients' willingness to vaccinate [1, 2]. Instead of asking patients, "Would you like to get your influenza vaccine today?" changing that simple question into the statement, "It's time to get your influenza vaccine today" can make a dramatic difference. The latter phrasing presumes that vaccination will occur, and therefore frames vaccination as the default. Framing vaccine receipt as a routine procedure indicates to the patient that vaccination is expected, and it is the standard of care in your practice. It sets getting vaccinated on time as the default for the patient in the decision-making process. This phrasing does not take a patient's choice away. A patient always has the final say in deciding whether or not to vaccinate. The advantage to presuming vaccination is that it clearly and confidently indicates to the patient that vaccination is important and is the standard of care that you endorse for them.

While the majority of patients that you encounter may be accepting of the vaccines you recommend, some may be more reluctant. This reluctance can exist for a variety of reasons and may not always be due to a lack of awareness or knowledge of the recommended vaccines. Vaccine hesitancy often involves deeply held world views, misperceptions formed over time, or beliefs adopted from others in their family or social circles. When you encounter a patient who is hesitant about receiving vaccines, whether he/she has just a few specific questions or seems more reluctant overall, *how* you discuss vaccines is very important. Listen to the patient to understand what they believe and why.

Vaccine conversations can be broken down into message framing and message content. It is often intuitive when a patient has a misperception to attempt to counter or debunk that myth or misperception. However, correcting misinformation alone can, in fact, reinforce the misperception or backfire [3].

We provide a five-step strategy to work with vaccine hesitant patients:

1) Establish empathy and credibility
2) Briefly address specific concerns, if any
3) Pivot to disease risk
4) Convey vaccine effectiveness
5) Give a strong and personalized recommendation.

Establishing empathy and credibility with the patient is very important. This is especially important for patients with specific concerns that may stem from popular myths or claims from invalid research, as this approach allows you to connect on a broader sentiment or value that you both find important [4]. With this said, you must be very careful to not affirm a myth or misperception while attempting to make that connection. For example, if a patient says that he/she is concerned about getting a flu shot because the flu shot will cause the flu, don't attempt to connect with the patient by affirming this misconception with, "I understand why you are worried the flu vaccine might cause the flu". Restating the concern, even if later addressed in an effort to overcome it, can ultimately reinforce the false belief. Instead, connect first with the deeper desire to stay healthy since the patient is clearly interested in staying healthy. An empathetic and credible response to this concern might start with, "So what I hear you saying is that you want to avoid the flu and stay healthy". By connecting with the value or sentiment underpinning a misguided concern, you are likely to find common ground on the topic without affirming or confirming misguided beliefs.

For patients with specific concerns, it may be helpful to begin by borrowing a technique from the field of Motivational Interviewing – that is, asking permission to share. "I've looked into this a great deal. Would it be okay if I shared with you what I've found out about this?" By doing this, assuming the patient says yes, which most will, you have made the patient more receptive to your next statements.

After establishing an empathetic and credible conversation and obtaining permission to share, there is now an opportunity to discuss the specific concern or concerns originally

raised by the patient. The detail of your response may should need to be tailored to the educational level of the patient and how much evidence they desire. You may find yourself walking a fine line between providing information and lecturing, which can be off-putting. Be careful about bringing up potential concerns the patient didn't raise in the first place, and in general, keep explanations simple. A simple myth is more cognitively attractive than an overcomplicated correction. Remember: "less is more."

Once you have respectfully acknowledged a patient's concern, the next important approach of message framing is pivoting to the disease. Instead of persisting in an attempt to dissuade them from a misguided belief, turn instead to emphasizing the susceptibility to and severity of the diseases vaccines protect against, since the risk of contracting a vaccine-preventable disease is much greater than the risk of suffering a severe adverse reaction from a vaccine [5]. This allows you to steer the conversation in an educational direction around a common enemy (i.e. the diseases) instead of toward a potentially adversarial back and forth about a specific vaccine or vaccine components. Because overall childhood vaccination rates are high in the US and have been for some time, patients are often not familiar with how dangerous some of these diseases can be for themselves and/or their children. Instead, they may be more familiar with, and more fearful of, highly publicized reports of rare adverse events or myths. It is important to emphasize that diseases like influenza and pertussis have not been eradicated and continue to pose a substantial risk. When pivoting to the disease, there is a fine line between informing a patient and intimidating or scaring a patient. The goal is not to scare patients into getting vaccinated but rather to shift the focus of the conversation from myths about vaccines to facts about the diseases they prevent.

Emphasize what can be done to protect from these diseases. Provide the patient with the fact that vaccination is a highly effective and very safe way to prevent these diseases.

The immunization schedule for children recommended by the ACIP begins providing protection to infants as young as they can safely and adequately respond to the vaccine. Protecting infants as young as possible, rather than delaying vaccines or using an alternative schedule, protects these very vulnerable babies when they are often at increased risk of serious complications from vaccine-preventable diseases. Waiting to vaccinate leaves the patient or child at risk of disease.

Those with lower perceptions of risk or lower perceptions of efficacy are significantly less likely to take action [6]. Translating these concepts to vaccine acceptance means that individuals with the greatest understanding of disease risk as well as the greatest awareness that the act of vaccinating will protect them from that disease risk will be more likely to vaccinate. Discussions of disease risk must always be paired with self-efficacy and a call to action to be effective. Follow discussions about disease risk with the message that vaccination is the single best decision a patient can make to protect himself, herself or their child. By doing this, a patient will have a clearer understanding that his or her conscious decision to vaccinate will indeed help protect from disease.

Close the conversation with a strong and personalized recommendation. Offer that you strongly recommend vaccination to your friends and family in addition to your patients. If you have children and they are vaccinated (or will be vaccinated), mentioning this as well can help increase patient trust in your recommendation.

While all healthcare providers want the best care and education for their patients, time and resources are limited. In this book, you will find an organized repository of the most salient information about vaccination. Consisting of a compilation of brief summaries about vaccines that are recommended (and not recommended) for their patients, you will be able to quickly find useful, evidence-based answers to safety and effectiveness questions that you or your patients have. Summaries include systematically-developed reviews of the scientific literature around a broad range of vaccine

safety issues and talking points to help guide you through some of the more challenging provider-patient discussions you may encounter.

The framework of the talking points provided in each summary is based on the five-step strategy detailed above. All five steps will be included in each set of talking points. This means there will be some redundancy between the talking points in different summaries, especially in the first and last steps. However, it also means that each set of talking points will be able to stand on its own without this explanation. In some, there will be talking points for Step 2 to address common concerns (such as influenza vaccine causing influenza). In other cases, this section is left blank and is left to the provider to determine the answer based on the specific concern. In some of these talking points, we have given suggested wording while in others, we simply provide the facts for the provider to adapt to his or her own personal communication style. The framework to be used for each set of talking points is demonstrated in the below example.

Framework for Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family, and my friends about this topic?
Step 2: Briefly address specific concerns, if any
•
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and dangerous.

(continued)

Step 4: Convey vaccine effectiveness
• The good news is that there are vaccines that prevent these diseases. • Vaccines have been shown to be very safe and effective.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

To further reinforce these messages, we have developed an individually-tailored app for smartphones, tablets, and computers that surveys patients and then provides vaccine information. Vaccine information is provided in the form of video content that is tailored to the specific vaccine attitudes and beliefs of the patient, and messages are presented in a manner consistent with the framework described in this chapter. The vast majority of patients who have used the app found it interesting, clear to understand, helpful, and trustworthy.

There are many evidence-based strategies for increasing vaccination rates beyond conversations with patients. While not the focus of this book, providers should consider which of these strategies may be practical for implementation in their offices. Many of these are fairly straightforward, such as standing orders for vaccination, and can markedly increase vaccination uptake in an office (standing orders can be thought of as the ultimate 'presumptive' recommendation). The Community Preventive Services Task Force (CPSTF) has reviewed many of these strategies, and their findings can be accessed at their website: **https://www.thecommunityguide.org/topic/vaccination**.

We hope you find this book useful in your conversations with patients. As one of their most trusted sources for medical advice, the more confident you are in promoting vaccines, the more confident they will be in accepting them for themselves or their children.

Contributions to this chapter were made by Allison Chamberlain, PhD, MS (Emory University Rollins School of Public Health).

References

1. Opel, D.J., et al., *The architecture of provider-parent vaccine discussions at health supervision visits*. Pediatrics, 2013. **132**(6): p. 1037–46.
2. Brewer, N.T., et al., *Announcements Versus Conversations to Improve HPV Vaccination Coverage: A Randomized Trial*. Pediatrics, 2017. **139**(1).
3. Nyhan, B., et al., *Effective messages in vaccine promotion: a randomized trial*. Pediatrics, 2014. **133**(4): p. e835–42.
4. Heritage, J. and D. Maynard, *Communication in Medical Care: Interaction Between Primary Care Physicians and Patients*. 2006.
5. Horne, Z., et al., *Countering antivaccination attitudes*. Proc Natl Acad Sci U S A, 2015. **112**(33): p. 10321–4.
6. Barnett, D.J., et al., *Assessment of local public health workers' willingness to respond to pandemic influenza through application of the extended parallel process model*. PLoS One, 2009. **4**(7): p. e6365.

Chapter 3
Monitoring Vaccine Safety

Safety standards for vaccines are very high given they are used among healthy persons for prevention rather than treatment and it is often difficult to predict who will be exposed to and develop a particular disease if they are not immune. Additionally, vaccines often target vulnerable populations such as infants and pregnant women. Vaccines can be required for day care, school entrance and attendance, and certain professions such as healthcare workers, increasing the government's burden to monitor and ensure safety. Lastly, vaccines are often used among a very large proportion of the population, such as all children, and consequently a rare risk of adverse reactions may impact a significant number of people. There are a broad range of activities conducted by the federal government, the private sector and academic investigators to optimize the safety of vaccines and identify, characterize and minimize vaccine adverse reactions when they occur. These activities are described below, largely summarizing a more detailed review [1].

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_3

Pre-Licensure

Pre-clinical Studies

Pre-clinical safety assessments are laboratory and animal studies that do not include humans. These studies characterize products by physical, chemical and biological methods, control of the manufacturing process, and lot release tests for safety, purity, and potency [2]. As vaccine candidates are developed, they are examined for possible adverse events. Ingredients in vaccines such as any adjuvants, which are substances that boost the body's immune response to vaccines, are evaluated. Nonclinical studies are carried out in animal models where potential toxicity is assessed in regard to dosage, route of administration, number of doses and other characteristics. Vaccines targeting pregnant women or females of reproductive age include assessment of adverse effects on fetal development in animals.

After nonclinical assessments have provided evidence that the vaccine is safe to test in humans, the sponsor (academic institution, organization or manufacturer developing the vaccine) submits an Investigational New Drug (IND) application to the Food and Drug Administration (FDA). The FDA evaluates the information on vaccine toxicology, manufacturing and quality control, plans for clinical studies, and the investigators' clinical trials expertise. After review, the FDA grants permission to initiate clinical trials in humans; however, the FDA has the authority to stop the study at any time if safety concerns arise [3].

Clinical Trials

Following FDA approval, the investigator must obtain Institutional Review Board (IRB) approval to ensure that appropriate safeguards are put in place to protect all study subjects during the trial. Clinical trials are then conducted in four phases:

Phase I: 20-100 healthy subjects are included to assess dose-related toxicity and immunogenicity.

Phase II: 50-1,000 healthy subjects are divided into control and intervention groups to assess vaccine responses, safety, and sometimes clinical efficacy. Also, dose-related immune responses are usually assessed.

Phase III: 1,000-50,000 or more subjects. Similar to Phase II trial but with greater power to assess safety due to the larger study size. Most Phase III trials assess actual clinical efficacy or an immune correlate of protection, if known, and the proportion of vaccinees who develop that immune protection level. Phase III trials are also used to collect data on vaccine production consistency and manufacturing scale up. Data generated from Phase III trials are the major trials upon which FDA evaluates products for safety and effectiveness to determine if a license is warranted.

Phase IV: These are conducted after licensure and are more likely to be able to detect delayed onset and rarer adverse events.

Clinical trials are phased to maximize the information gained while minimizing the risks to human subjects. Phase I and II trials usually include only healthy volunteers and may include only a restricted age range. Phase III trials target populations for the use of the vaccine post-licensure and may include individuals with underlying health conditions. Each trial usually has a Data and Safety Monitoring Board (DSMB) composed of an independent panel of experts who review safety data and can call for the end of the trial due to unacceptable risks or because it is deemed unethical to not provide the vaccine to those in the control group as the data conclusively show the vaccine is both effective and safe. Clinical trials in each phase may involve a true placebo or the experimental vaccine may be compared to an existing licensed vaccine.

Regulatory Approval and Vaccine Licensure

The sponsor, usually the manufacturer, submits a Biologics License Application (BLA) to the FDA for vaccine licensure. A BLA includes biological and chemical compositions of the

vaccine, results from clinical trials, description of the manufacturing facility, proposed product labeling, and post-licensure surveillance plans. The FDA inspects manufacturing sites to evaluate compliance with current Good Manufacturing Practice (cGMP) and other industry standards to ensure purity, potency, safety and consistency in manufacturing. The decision to approve a BLA is based on disease epidemiology, vaccine safety and efficacy [3].

Vaccine Manufacturing

After the approval of a BLA, the licensed vaccine and its manufacturing processes are monitored by the FDA. In addition to the safety tests carried out before licensure, each batch of vaccines, called a lot, undergoes testing for purity, potency, and sterility. Any changes to the vaccine, its label, or manufacturing process must be submitted to the FDA for approval prior to product distribution. Before approving the change, the FDA may require further testing to confirm continued safety of the vaccine [3].

Post-Licensure

Vaccine Recommendations

Following licensure, the Advisory Committee on Immunization Practices (ACIP) makes recommendations to the Centers for Disease Control and Prevention (CDC) about the optimal use of the vaccine. The ACIP consists of fifteen members who are experts in relevant fields such as immunology, vaccine research and development, internal medicine, pediatric care, nursing, infectious diseases, public health, and social aspects of immunization programs. The committee also includes eight non-voting ex officio members who represent federal government agencies with immunization responsibilities in the United States. Representatives from professional medical

associations such as the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), the American College of Obstetricians and Gynecologists (ACOG), and the American Medical Association (AMA) participate in these discussions as liaisons, and vaccine recommendations are coordinated or harmonized with AAP, AAFP and ACOG.

Taking into consideration risks, benefits and costs of the vaccine, and disease epidemiology, the ACIP makes a recommendation to CDC including guidelines on which persons should be vaccinated, number of doses, timing, age of administration, and also provides information on adverse events, contraindications and precautions. The ACIP recommendations, once accepted by CDC, may lead to changes in the national immunization schedule which in turn may lead to widespread use of the vaccine. However, the speed of uptake of a new vaccine even after ACIP recommendation can depend on other factors including provider knowledge, costs and financing mechanisms (e.g. if insurance companies cover the cost), and public acceptance [4].

Post-Licensure Safety Surveillance

Clinical trials determine the safety and efficacy of vaccines and the ACIP guidelines are intended to ensure that the benefits outweigh the risks of vaccines. However, clinical trials have limitations. They are usually conducted with strict inclusion criteria, usually in healthy subjects within a certain age group, and therefore results may not be generalizable to all of the populations the vaccine is actually used in after licensure. Trials may not be large enough to detect rare adverse events. For example, if an adverse event occurs at a population baseline rate of 1 in 1,000 people and the vaccine doubles this risk, a clinical trial would need 50,000 subjects (which is larger than most clinical trials) to statistically detect an increased risk posed by the vaccine. Given the near universal use of many vaccines, this adverse reaction could impact

4,000 persons annually, assuming a birth cohort of 4 million and 100% immunization coverage [5]. Additionally, due to limited follow-up, delayed onset adverse events may be missed. For these reasons, post-licensure surveillance and studies are vital to ensuring continued vaccine safety.

The Vaccine Adverse Events Reporting System (VAERS) is the national *passive* surveillance system that is co-administered by the FDA and the CDC. All healthcare providers of childhood vaccines are required to report certain adverse events to VAERS; the public may also report adverse events. Due to the fact that reports are observations from a variety of sources, not physician confirmed events and there are no standardized case definitions, FDA and CDC medical officers review reports of serious events, deaths, and unusual patterns to identify cases that may represent a safety signal that requires additional safety studies. VAERS has the ability to detect signals of rare events. However, the system suffers from both under- (not all adverse events are reported) and over- (non-vaccine related events are reported) reporting. The reports submitted to VAERS may also be incomplete and insufficient to confirm a diagnosis. Furthermore, the system does not have data on the number of vaccine doses administered (doses distributed are a poor estimate of this number) nor the incidence of the adverse event in unvaccinated populations; therefore, it is not possible to calculate incidence rates in vaccinated versus non-vaccinated persons [6]. Such comparisons are important to assess whether a given adverse event is causally or coincidentally related to vaccination. For example, if the rates were actually the same, then the data would imply that vaccination did not cause the event. On the other hand, if the rate was higher in vaccinees, this would imply vaccine is playing a causal role. Despite the weaknesses of VAERS for assessing causation, VAERS acts as an early warning system of possible vaccine safety problems that may require further investigation

Vaccine safety signals that arise from clinical trials or passive surveillance such as VAERS are often assessed through large-linked databases which include inpatient, outpatient, laboratory and pharmacy records. These large-linked

databases are often referred to as active surveillance as they can be used to rapidly evaluate the safety of newly licensed vaccines or vaccines that are being used in special populations, such as pregnant women.

The Vaccine Safety Datalink (VSD) is the *active* surveillance system which is overseen by the CDC. The VSD is a large-linked database of eight managed care organizations (MCO) that cover 1.8% of the United States population under 18 years of age and 1.5% of those over 18 years [7–9]. VSD sites are closed healthcare systems resulting in all clinical records being readily available. These data include details on vaccines, including vaccination dates, vaccine types and lot numbers. VSD studies often include review of the clinical records, providing far more detail compared to VAERS. Adverse event rates can be calculated using the data, providing the ability to evaluate rare events that could not be detected in clinical trials due to the sample size. VSD data also can be used to assess potential adverse events with delayed onset (as long as the patient is continually enrolled in the site) and among special populations not included in clinical trials for licensure. VSD can rapidly conduct chart reviews to validate outcomes, typically using standardized case definitions developed by the Brighton Collaboration [10]. The VSD facilitates high quality and rapid vaccine safety studies either in an ongoing basis for pre-specified outcomes using Rapid Cycle Analysis or through ad hoc studies. The VSD allows for calculation of the rates of a given illness in vaccinees versus non-vaccinees, which is often critical in determining if vaccine is playing a causal role. Many VSD studies use self-controlled designs in which the risk of an event is compared in a specified time period after vaccination to another time period among vaccinated persons. This study design using individuals as their own controls adjusts for factors such as healthcare seeking behavior. Further, VSD can also look at particular time frames after vaccination and compare the rates of the adverse event in that time frame with what would be expected in an unvaccinated population.

The Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Network was established to supplement VSD for the 2009-10 H1N1 influenza vaccination program [11]. PRISM is now a part of FDA's post-licensure vaccine safety system. PRISM links 8 state immunization registries to capture who received which vaccines with 4 large health insurance plans capturing some vaccine exposures and a broad range of health outcomes for over 100 million persons [12]. PRISM is able to conduct chart review, although not as rapidly as the VSD. PRISM is also used to conduct high quality and rapid vaccine safety studies either in an ongoing basis for pre-specified outcomes using Rapid Cycle Analysis or through ad hoc studies.

Other large-linked databases are used for conducting Rapid Cycle Analysis and ad hoc studies among special population. The Centers for Medicare and Medicaid Services (CMS) focuses primarily on persons aged 65 years and older, including about 14 million vaccinees annually. The Department of Defense (DoD) Medical Surveillance System included military personnel and their families, which is about 2.6 million persons. The Department of Veterans Affairs (VA) includes military veterans not provided care through DoD and Federal Employees, which is about 5 million persons. The Indian Health Services (IHS) includes American Indian and Alaska Native populations, which is about 350,000 persons. CMS, DoD, VA and IHS are able to include chart review and have historically been focused primarily on influenza vaccines.

Coordination of Vaccine Safety Activities

Many government and nongovernmental partners contribute to assessing and monitoring vaccine safety across the United States. The Department of Health and Human Services (HHS)'s National Vaccine Program Office (NVPO) coordinates the efforts of the National Institutes of Health (NIH), the National Vaccine Injury Compensation Program (VICP), FDA, and CDC. The National Vaccine Advisory Committee

(NVAC) advises this office in a capacity similar to the ACIP. Other partners such as state and local health departments, academic institutions, professional medical associations, healthcare providers, insurance companies, philanthropic organizations, and vaccine manufacturers, contribute to the provision of safe vaccines and communicate safety risks to the public [1].

Causality Assessment

Causal relationships between vaccines and adverse events can be established by demonstrating an increased risk of the adverse event in vaccine recipients or through documenting the role of a vaccine component in the pathogenesis of the adverse event [13, 14]. Increased risk is identified from randomized controlled trials or observational epidemiologic studies, such as those performed by the VSD. Prior to licensure, vaccine recipients are compared to placebo or control vaccine recipients in randomized clinical trials to assess differences in adverse events. These randomized studies provide the highest quality of evidence for or against causal associations. However, the sample size in these studies is usually too small to detect small increases in risk and often do not include all the populations who will receive the vaccine after licensure.

After licensure, reports to VAERS of adverse events following immunization (AEFI) are monitored. VAERS reports and case reports in the medical literature of AEFI based on a temporal relationship are commonly misunderstood as causal; a temporal association alone, even with a hypothesis as to how the vaccine might have caused an adverse event, does not establish a causal relationship [13, 14].

If a potential signal for an AEFI is detected, controlled epidemiological studies may be conducted to determine if there is an increased risk in vaccinated persons as compared to people who did not receive the vaccine. Several types of studies have been used including case-control, cohort, and

self-controlled studies. These studies are usually not randomized so they can be subject to several possible biases and confounders. A common concern is healthcare seeking bias. People who chose to be vaccinated may be more likely to seek other healthcare services and consequently be more likely to be diagnosed with other adverse health outcomes. Healthcare seeking bias creates a spurious association between vaccines and adverse events. Usually a single study is insufficient to establish a causal relationship. The evidence is much stronger if consistent associations are found in different studies conducted in different populations by different investigators, sometimes using different methods. Causal relationships have been established between vaccines and adverse events even when the biologic mechanism has not been identified, such as with intussusception following rotavirus vaccines [15–17] and Guillain-Barré syndrome following influenza vaccines [18, 19].

Identifying the biologic mechanism for an adverse event, sometimes referred to as mechanistic evidence, can provide strong evidence for a causal relationship even if epidemiologic studies have not documented an increased risk in the general population [13]. For example, the yellow fever vaccine virus has been found in liver tissue of patients with viscerotropic disease [20] and measles vaccine viruses have been identified in lung tissue in immunocompromised patients with pneumonia [21, 22]. Immediate hypersensitivity reactions, including anaphylaxis, usually occur within minutes after exposure. In the absence of other possible exposures, immediate hypersensitivity reactions that occur shortly after a vaccine are usually assumed to have been caused by the vaccine if there have been no other possible exposures to potential allergens. Skin testing with the vaccine can sometimes provide supportive evidence of allergy to specific vaccines or vaccine components, but false positive reactions do occur [23, 24].

Individual AEFI should be reviewed in a systematic manner for assessment of possible causal associations. In the US, an algorithm approach was developed by the CDC coordinated Clinical Immunization Safety Assessment (CISA) network and has been used in recent years for review of serious adverse

events [14]. The method was modified for use in developing countries by the World Health Organization (WHO) [25, 26]. The method requires persons doing the assessment to collect essential information about the case and to ask key questions in a logical sequence before determining the correct assessment. The validity of the diagnosis should be determined followed by assessment of other possible causes, if a general casual association has been made between the vaccine and the adverse event, and determination if the timing of the event is consistent with existing knowledge. Depending upon the answers to the questions, the algorithm branches to reach a logical conclusion. Use of this approach can prevent the common mistake of assuming causal relationships based upon temporal relationships.

Systematic reviews of causality assessment have historically been conducted in the US, by the Institute of Medicine (IOM), now called the National Academy of Medicine (NAM) [13]. The IOM used stringent criteria for reviews of the evidence. Starting from a neutral position, the committee weighed the available evidence and published conclusions. However, the majority of the assessments conducted have resulted in conclusions of "The evidence is inadequate to accept or reject a causal relationship". These assessments are often not helpful and do not reflect the available evidence for or against a causal relationship. The Institute for Vaccine Safety (IVS) of Johns Hopkins Bloomberg School of Public Health uses similarly rigorous criteria for vaccine causality assessment, focusing on epidemiological evidence and potential biological mechanisms. However, determinations are more frequently conclusive than those of the IOM, as the reviews included in this book and on our website (**http://www.vaccinesafety.edu**) are intended for clinicians, the public and policy makers who are particularly interested in clarity of messages.

Vaccine Injuries and Compensation

The National Childhood Vaccine Injury Act was passed in 1986 spurred by a major increase in litigation against vaccine

manufacturers and healthcare providers who administered vaccines. The primary vaccine of concern at the time was the whole-cell pertussis vaccine. This litigation led to vaccine shortages, some manufacturers dropping out of the market, and other problems. Further, it led to the recognition that when a child is vaccinated, that child is not only protecting him/her self but also is protecting the community by preventing spread of the disease to other persons including persons who cannot be protected by vaccines because of contraindications. Society owed individuals injured by vaccines compensation because of the benefits they were trying to bring to society. Thus, the legislation recognized the broad value of vaccines to the population at the expense of a very small number of people who experienced serious vaccine adverse events, and those persons were owed compensation. As a result, it also fostered the need for improving vaccine safety monitoring to help determine who was eligible for compensation [27]. The act authorized the establishment of the VICP, a no-fault system to provide financial assistance to individuals injured following recommended vaccines incorporated into the program. Compensation is awarded to individuals whose injury is included on the vaccine injury table and occurred within the specified time period, or if the claimant can prove the injury was caused by the vaccine. As this causality assessment is of a much lower standard than is used to establish causality scientifically, there are far more compensations than scientifically accepted vaccine injuries. While compensations through the VICP are essential to the national immunization program, they can be interpreted inaccurately by the public as an admission of wrongdoing by the government or vaccine manufacturers [1, 28].

Conclusion

In summary, the vaccine safety system is extremely rigorous yet complex and often not fully understood by the public or healthcare providers. Vaccines have an excellent safety record and the system has demonstrated its ability to detect, characterize and prevent rare and serious adverse reactions when

they occur. As new vaccines are introduced and populations targeted for vaccines expand, continuous monitoring of vaccine safety is essential for public confidence in immunization programs.

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience, and what I share with my patients, my family, and my friends about the vaccine safety system?
Step 2: Briefly address specific concerns, if any
• What many people don't realize is that there is a ton of work going on behind the scenes to make sure our vaccines are very safe. • Because we give vaccines to healthy people to prevent disease (instead of to sick people to treat disease like most medicines), vaccines are held to a much higher safety standard than other medicines for which common side effects are often tolerated in order to treat the disease.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and dangerous.
Step 4: Convey vaccine effectiveness
• The good news is that there are vaccines that prevent these diseases. • Vaccines have been shown to be very safe and effective.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Department of Health and Human Services (HHS), Department of Veterans Affairs, and Department of Defense, *A Comprehensive Review of Federal Vaccine Safety Programs and Public Health Activities*. 2008.
2. Food and Drug Administration, *Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product*. 1999.
3. Food and Drug Administration. *Vaccine Product Approval Process*. 2015; Available from: https://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/biologicslicenseapplicationsblaprocess/ucm133096.htm.
4. Centers for Disease Control and Prevention. *Advisory Committee on Immunization Practices (ACIP)*. 2017; Available from: https://www.cdc.gov/vaccines/acip/index.html.
5. Ellenberg, S.S., Safety considerations for new vaccine development. Pharmacoepidemiol Drug Saf, 2001. 10(5): p. 411–5.
6. Centers for Disease Control and Prevention (CDC). *Vaccine Adverse Event Reporting System (VAERS)*. 2017; Available from: https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html.
7. Chen, R.T., et al., *The Vaccine Safety Datalink: immunization research in health maintenance organizations in the USA*. Bull World Health Organ, 2000. **78**(2): p. 186–94.
8. Centers for Disease Control and Prevention. *Vaccine Safety Datalink (VSD)*. 2017; Available from: https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html.
9. Baggs, J., et al., *The Vaccine Safety Datalink: a model for monitoring immunization safety*. Pediatrics, 2011. **127 Suppl 1**: p. S45–53.
10. Kohl, K.S., et al., *Advances in Patient Safety The Brighton Collaboration: Creating a Global Standard for Case Definitions (and Guidelines) for Adverse Events Following Immunization*, in *Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology)*, K. Henriksen, et al., Editors. 2005, Agency for Healthcare Research and Quality (US): Rockville (MD).
11. Salmon, D., et al., *Success of program linking data sources to monitor H1N1 vaccine safety points to potential for even*

broader safety surveillance. Health Aff (Millwood), 2012. **31**(11): p. 2518–27.
12. Baker, M.A., et al., *Post-licensure rapid immunization safety monitoring program (PRISM) data characterization*. Vaccine, 2013. **31 Suppl 10**: p. K98–112.
13. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
14. Halsey, N.A., et al., *Algorithm to assess causality after individual adverse events following immunizations*. Vaccine, 2012. **30**(39): p. 5791–8.
15. Aliabadi, N., J.E. Tate, and U.D. Parashar, *Potential safety issues and other factors that may affect the introduction and uptake of rotavirus vaccines*. Clin Microbiol Infect, 2016. **22 Suppl 5**: p. S128–s135.
16. Yih, W.K., et al., *Intussusception risk after rotavirus vaccination in U.S. infants*. N Engl J Med, 2014. **370**(6): p. 503–12.
17. Parashar, U.D., et al., *Value of post-licensure data on benefits and risks of vaccination to inform vaccine policy: The example of rotavirus vaccines*. Vaccine, 2015.
18. Halsey, N.A., et al., *The safety of influenza vaccines in children: An Institute for Vaccine Safety white paper*. Vaccine, 2015. **33**: p. F1–F67.
19. Salmon, D.A., et al., *Association between Guillain-Barre syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis*. Lancet, 2013. **381**(9876): p. 1461–8.
20. Seligman, S.J., *Risk groups for yellow fever vaccine-associated viscerotropic disease (YEL-AVD)*. Vaccine, 2014. **32**(44): p. 5769–75.
21. *Measles pneumonitis following measles-mumps-rubella vaccination of a patient with HIV infection, 1993*. MMWR Morb Mortal Wkly Rep, 1996. **45**(28): p. 603–6.
22. Angel, J.B., et al., *Vaccine-associated measles pneumonitis in an adult with AIDS*. Ann Intern Med, 1998. **129**(2): p. 104–6.
23. Wood, R.A., et al., *An algorithm for treatment of patients with hypersensitivity reactions after vaccines*. Pediatrics, 2008. **122**(3): p. e771–7.
24. Wood, R.A., R. Setse, and N. Halsey, *Irritant skin test reactions to common vaccines*. J Allergy Clin Immunol, 2007. **120**(2): p. 478–81.

25. Tozzi, A.E., et al., *Assessment of causality of individual adverse events following immunization (AEFI): a WHO tool for global use*. Vaccine, 2013. **31**(44): p. 5041–6.
26. World Health Organization, *Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification, 2nd ed*. 2018: World Health Organization.
27. 99th Congress (1985-1986), *National Childhood Vaccine Injury Act*. 1986.
28. Institute of Medicine (US) Committee on Review of Priorities in the National Vaccine Plan, *The Safety of Vaccines and Vaccination Practices, in Priorities for the National Vaccine Plan*. 2010, National Academies Press (US).

Chapter 4
Vaccines and Pregnancy

Below is a table summarizing the recommended use of vaccines during pregnancy in the US. Included in this table is information most relevant to women of child-bearing age for certain vaccines. For more information about these vaccines and their use outside of pregnancy, please see the individual summaries on the following pages, or the websites listed below.

The American College of Obstetricians and Gynecologists (ACOG) provides information on vaccinating during pregnancy at the following website: **http://immunizationforwomen.org/providers/pregnancy/pregnancy.php**. The Centers for Disease Control and Prevention (CDC) lists guidelines for vaccinating during pregnancy at the following website: **https://www.cdc.gov/vaccines/pregnancy/hcp/guidelines.html**.

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_4

Vaccines and Pregnancy

Vaccine	Indication During Pregnancy	Relevant Information
Hepatitis A	Not routinely recommended during pregnancy	The low theoretical risk of vaccination should be weighed against the risk of hepatitis A infection among pregnant women at high risk of exposure.
Hepatitis B	Not routinely recommended during pregnancy	In order to prevent perinatal hepatitis B infection, all pregnant women should be routinely screened for hepatitis B surface antigen (HBsAg), and subsequent postexposure immunoprophylaxis should be administered to infants born to women who are HBsAg-positive or of unknown HBsAg status.
Herpes Zoster	Contraindicated during pregnancy	
Human Papillomavirus (HPV)	Not routinely recommended during pregnancy	If a woman is discovered to be pregnant after receiving HPV vaccine, no intervention is indicated. The remaining doses in the series should be delayed until after the pregnancy.
Inactivated Influenza Vaccine (IIV)	Routinely recommended during pregnancy	Pregnant women and young children are at increased risk of complications and hospitalizations from influenza.
Live Attenuated Influenza Vaccine (LAIV)	Contraindicated during pregnancy	
Measles, Mumps and Rubella (MMR)	Contraindicated during pregnancy	Vaccination against rubella is emphasized for all non-pregnant women of childbearing age, especially those born outside of the US. Those without evidence of immunity should be given MMR vaccine, excluding women who are pregnant or currently attempting to become pregnant. Pregnancy should be avoided for at least 4 weeks following MMR vaccination; however, inadvertent MMR vaccination should not be considered an indication for termination of the pregnancy.
Meningococcal	Not routinely recommended during pregnancy	Pregnancy should not preclude indicated MenACWY vaccination. MenB vaccination should be deferred in pregnant and lactating women unless the woman is at increased risk and the benefits of vaccination outweigh the potential risks.
Pneumococcal	Not routinely recommended during pregnancy	Women who are at high risk of pneumococcal disease should be vaccinated before pregnancy, if possible.
Inactivated Polio Vaccine (IPV)	Not routinely recommended during pregnancy	Vaccination of pregnant women with IPV should generally be avoided. However, if a pregnant woman is at increased risk for polio infection and requires immediate protection, IPV can be administered in accordance with the recommended schedule.
Tetanus, Diphtheria and Pertussis (Tdap)	Routinely recommended vduring pregnancy	Most deaths from pertussis occur in the first few months of life prior to receipt of routine infant vaccines against pertussis. Vaccination with Tdap during pregnancy helps protect infants from pertussis.
Varicella	Contraindicated during pregnancy	Pregnancy should be avoided for at least 4 weeks following varicella vaccination; however, inadvertent varicella vaccination should not be considered an indication for termination of the pregnancy.

Chapter 5
Vaccines and Breastfeeding

Smallpox and yellow fever vaccinations should not be given to women who are currently breastfeeding. Both vaccine viruses have been transmitted to infants from breastfeeding mothers and caused adverse events [1]. However, these vaccines are not routinely recommended to the general population in the US. Other vaccines that are currently routinely recommended for the general population in the US[1] do not affect the safety of breastfeeding for women or their infants.

According to the Advisory Committee on Immunization Practices (ACIP)'s *General Best Practice Guidelines for Immunization* [1]:

"With 2 exceptions, neither inactivated nor live-virus vaccines administered to a lactating woman affect the safety of breastfeeding for women or their infants. Although live viruses in vaccines can replicate in the mother, the majority of live viruses in vaccines have been demonstrated not to be excreted in human milk. Varicella vaccine virus has not been found in human milk. Although rubella vaccine virus has

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_5

been excreted in human milk, the virus usually does not infect the infant. If infection does occur, it is well tolerated because the virus is attenuated. Inactivated, recombinant, subunit, polysaccharide, and conjugate vaccines, as well as toxoids, pose no risk for mothers who are breastfeeding or for their infants. Breastfeeding is a contraindication for smallpox vaccination of the mother because of the theoretical risk for contact transmission from mother to infant. Yellow fever vaccine should be avoided in breastfeeding women, because 2 cases (one confirmed, one probable) of yellow fever vaccine associated acute neurotropic disease (YEL-AND) have been detected in infants whose mothers were vaccinated but were not vaccinated themselves. In both infants, vaccine virus was recovered from the cerebrospinal fluid of the infant, but the exact mode of transmission was not precisely determined because vaccine virus was not recovered from breast milk. However, when nursing mothers cannot avoid or postpone travel to areas endemic for yellow fever in which risk for acquisition is high, these women should be vaccinated.

"Limited data indicate that breastfeeding can enhance the response to certain vaccine antigens. There are no data to suggest that passive transfer of antibodies in human milk can affect the efficacy of live-virus vaccines. Breastfed infants should be vaccinated according to the recommended schedule."

Reference

1. Kroger, A.T., J. Duchin, and M. Vázquez. *General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)*. 2017 [cited 2017 October]; Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.

Part II
Vaccine and Vaccine-Preventable Disease Information Summaries

Chapter 6
Vaccine and Vaccine-Preventable Disease Information Summaries

Information summaries are provided for each vaccine currently routinely recommended for children, adolescents, adults, and pregnant women in the United States, along with the diseases they prevent. Each summary begins with a box summarizing the ***Recommendations from the Advisory Committee on Immunization Practices (ACIP)***, organized by age groups (infants, children, adolescents, and adults).

The next box summarizes the ***Important Information for Obstetric Providers***. This box is color-coded to make it easy to distinguish which vaccines are **routinely recommended during pregnancy (blue)** from those **not routinely recommended during pregnancy (yellow)** and those **contraindicated during pregnancy (red)**.

The summaries then describe the causes, manifestations and burden of disease, followed by pertinent information on the available vaccine(s) and their contraindications and precautions,[1] effectiveness/efficacy, and safety. Our emphasis

[1] Definitions of contraindications and precautions from Chapter 2 of the Pink Book (Epidemiology and Prevention of Vaccine-Preventable Diseases): "Contraindications and precautions to vaccination generally dictate circumstances when vaccines will not be given. Many contraindications and precautions are temporary, and the vaccine can be given at a later time. A contraindication is a condition that increases the likelihood of a serious adverse reaction to a vaccine for a patient with that

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_6

is on vaccine effectiveness rather than efficacy when such data are available, as effectiveness reflects the performance of the vaccine in actual use (rather than a clinical study) and is most relevant to patients. Also provided are talking points that may be used with patients or their family members. These summaries are intended to assist in having discussions with patients or parents about the vaccines they or their children may receive.

These summaries predominantly rely on the published recommendations from the ACIP. Each summary begins with the recommendations from the ACIP, a committee of 15 experts which advises the Centers for Disease Control and Prevention (CDC) and issues comprehensive statements on the 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. The individual ACIP vaccine recommendations can be accessed at the following website: **http://www.cdc.gov/vaccines/hcp/acip-recs/index.html**.

These summaries also benefit from the information provided in the CDC textbook entitled Epidemiology and Prevention of Vaccine-Preventable Diseases, also known as the "Pink Book" [1]. This textbook can be accessed at the following website: **http://www.cdc.gov/vaccines/pubs/pinkbook/index.html**.

The American College of Obstetricians and Gynecologists (ACOG) sets the standards for practice for obstetricians and gynecologists. ACOG provides immunization news,

---

condition… In general, vaccines should not be administered when a contraindication condition is present. A precaution is a condition in a recipient that might increase the chance or severity of a serious adverse reaction, or that might compromise the ability of the vaccine to produce immunity… In general, vaccines are deferred when a precaution condition is present. However, situations may arise when the benefit of protection from the vaccine outweighs the risk of an adverse reaction, and a provider may decide to give the vaccine."

information, resources, and tools for obstetric providers and patients on their website: **http://www.acog.org/About-ACOG/ACOG-Departments/Immunization**. ACOG also runs an external site to provide ob-gyns and their patients with a central, trusted source of up-to-date information on seasonal flu and other vaccine-preventable diseases, including immunization facts and safety, immunization schedules, clinical and practice management guidelines, and links to other reliable immunization resources. This can be found at the following website: **http://www.immunizationforwomen.org/**.

The CDC's Recommended Adult Immunization Schedule includes recommendations for vaccines by age group as well as by underlying condition including pregnancy status. This schedule can be accessed at the following website: **http://www.cdc.gov/vaccines/schedules/hcp/adult.html**. The CDC also lists their guidelines for vaccinating during pregnancy at the following website: **https://www.cdc.gov/vaccines/pregnancy/hcp/guidelines.html**. The recommended adult immunization schedule has been approved by ACIP, ACOG, the American Academy of Family Physicians (AAFP), the American College of Physicians (ACP), and the American College of Nurse-Midwives (ACNM).

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**. These schedules have been approved by ACIP, ACOG, AAFP, and the American Academy of Pediatrics (AAP).

The Community Preventive Services Task Force (CPSTF) has reviewed many evidence-based strategies for increasing vaccination rates. Their findings can be accessed at the following website: **https://www.thecommunityguide.org/topic/vaccination**.

There are some special circumstances for immunization for international travel that are not necessarily covered in this book. The CDC provides information on vaccinating for international travel at the following website: **https://wwwnc.cdc.gov/travel**.

Reference

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, Hamborsky J, Kroger A, Wolfe S, eds. 2015, Centers for Disease Control and Prevention: Washington D.C.

Chapter 7
Haemophilus Influenzae Type B (Hib)

Recommendations from the Advisory Committee on Immunization Practices (ACIP)

Infants

- All infants without contraindications should receive the conjugate Hib vaccine series; either as 3 doses of PRP-OMP (trade name: PedvaxHIB®), or as 4 doses of PRP-T (trade names: ActHIB®, Hiberix®; also included in the DTaP-Hib-IPV combination vaccine Pentacel®).
- 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 and 15 months of age [1–3].

Children, Adolescents and Adults

- Although Hib vaccine is generally not recommended for those over 59 months of age, there are exceptions

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_7

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 [3].

For More Information

- ACIP recommendations: **http://www.cdc.gov/vaccines/hcp/acip-recs/**
- Immunization schedules: **http://www.cdc.gov/vaccines/schedules/index.html**

Important Information for Obstetric Providers

- **Hib vaccines are not routinely recommended during pregnancy**.

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 lead to residual hearing impairment, neurologic sequelae, or even death. Fatality rates range from 3% to 6% for Hib meningitis, 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 [1].

Vaccine(s)

There are two conjugate *Haemophilus influenzae* type b (Hib) vaccines used in the United States: PRP-OMP and PRP-T. 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 is produced by Merck under the name PedvaxHIB®. PRP-T uses tetanus toxoid protein and is manufactured by Sanofi Pasteur under the name ActHIB® (or as part of the DTaP-Hib-IPV combination vaccine Pentacel®) and by GlaxoSmithKline under the name Hiberix®. PedvaxHIB® requires a two-dose primary series followed by a booster. ActHIB® requires a three-dose primary series followed by a booster. The combination vaccines mentioned above should be administered according to the recommendations for the individual vaccines included in them [1].

The Hib-MenCY-TT combination vaccine MenHibrix® was discontinued in the United States in 2016 [4]. The Hib-Hep B combination vaccine Comvax® was discontinued in the United States in 2014 [5].

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 [1].

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% [1].

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[1] are rare [1].

[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=6b68426ec6d55c78a6799d161ba6754c&mc=true&node =se21.5.312_132&rgn=div8**

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about Hib?
Step 2: Briefly address specific concerns, if any
•
Step 3: Pivot to disease risk
• Hib is a bacterium that is spread by droplets in the air – such as through sneezing and coughing. • Hib can cause inflammation of the brain and spinal cord membranes, which can lead to hearing loss, brain damage, and death. • Individuals are most susceptible to Hib from birth to 5 years of age.
Step 4: Convey vaccine effectiveness
• The good news about Hib is that there are effective vaccines. Hib vaccines are over 95% efficacious.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from Hib through vaccination. • I strongly recommend Hib vaccine to my patients, my family, and my friends.

References

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, K.A Hamborsky J., Wolfe S Editor. 2015, Centers for Disease Control and Prevention: Washington D.C.
2. Briere, E.C., *Food and Drug Administration Approval for Use of Hiberix as a 3-Dose Primary Haemophilus influenzae Type b (Hib) Vaccination Series*. MMWR Morb Mortal Wkly Rep, 2016. **65**(16): p. 418–9.
3. Briere, E.C., et al., *Prevention and control of haemophilus influenzae type b disease: recommendations of the advisory committee on immunization practices (ACIP)*. MMWR Recomm Rep, 2014. **63**(Rr-01): p. 1–14.
4. GlaxoSmithKline. *Menhibrix Discontinuation Notice*. 2016; Available from: https://www.gskdirect.com/medias/Menhibrix-Discontinuation-Notice.pdf?context=bWFzdGVyfHJvb3R8NTIyNzQxfGFwcGxpY2F0aW9uL3BkZnxoZTMvaDg1Lzg4NTg3MTMwNjM0NTQucGRmfGYxMjAyMDFmMmU2YjAwYzYyZmUxNWQyNTdjYmUzNjFjMTQ2MDUyODIyMjg4YWIzMTIzNjJhZTZjMWRlNjBlMzg.
5. Immunization Action Coalition. *Merck discontinues production of Comvax vaccine (Hib-HepB)*. IAC Express 2014 [cited 2018 March]; Issue 1136: Available from: http://www.immunize.org/express/issue1136.asp#IACX6.

Chapter 8
Hepatitis A

Recommendations from the Advisory Committee on Immunization Practices (ACIP)

Infants

- All infants without contraindications should receive two doses of hepatitis A vaccine (trade names: Havrix®, Vaqta®) between 12 and 23 months of age. Doses should be given at least 6 months apart.
- Infants between 6 and 11 months of age traveling internationally to countries with high or intermediate endemnicity should also receive hepatitis A vaccine (as recommended by the ACIP at the February 2018 meeting). Such children should still receive hepatitis vaccine between 12 and 23 months of age as normally recommended.

Children, Adolescents and Adults

- 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 endemnicity; men who have sex with

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_8

men; illegal drug users; contacts of recent international adoptees from countries with endemic 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 (as recommended by the ACIP at the February 2018 meeting) [1–3].

For More Information

- ACIP recommendations: **http://www.cdc.gov/vaccines/hcp/acip-recs/**
- Immunization schedules: **http://www.cdc.gov/vaccines/schedules/index.html**

Important Information for Obstetric Providers
- **Hepatitis A vaccine is not routinely recommended during pregnancy**.

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% [1].

Vaccine(s)

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 [1].

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 [1].

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% [1].

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[1] have been shown to be caused by hepatitis A vaccination. Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component is a contraindication to further hepatitis A vaccination [1].

Considerations in Pregnancy

The safety of hepatitis A vaccination during pregnancy has not been determined; however, because hepatitis A is an inactivated vaccine, the theoretic risk to the developing fetus is expected to be low. Therefore, the risk associated with vaccination should be weighed against the risk for hepatitis A in pregnant women who might be at high risk for exposure to HAV [2].

[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=6b68426ec6d55c78a6799d161ba6754c&mc=true&node= se21.5.312_132&rgn=div8**

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about hepatitis A?
Step 2: Briefly address specific concerns, if any
•
Step 3: Pivot to disease risk
• Hepatitis A is a virus that can cause fever, nausea, and yellowing of the skin. In some cases, it can cause death. • You may not even know when someone is infected with hepatitis A, as many people do not have any symptoms. When they do though, the symptoms are often miserable! Adults who get hepatitis A are often out of work for weeks.
Step 4: Convey vaccine effectiveness
• The good news about hepatitis A is that there are effective vaccines. • Hepatitis A vaccines are over 94% efficacious.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from hepatitis A through vaccination. • I strongly recommend hepatitis A vaccine to my patients, my family, and my friends.

References

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, K.A. Hamborsky J, Wolfe S Editor. 2015, Centers for Disease Control and Prevention: Washington D.C.
2. Fiore, A.E., A. Wasley, and B.P. Bell, *Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP)*. MMWR Recomm Rep, 2006. **55**(Rr-7): p. 1–23.
3. Centers for Disease Control and Prevention. *Hepatitis A Vaccines*. in *Meeting of the Advisory Committee on Immunization Practices (ACIP)*. 2018. Atlanta, GA.

Chapter 9
Hepatitis B

Recommendations from the Advisory Committee on Immunization Practices (ACIP)

Infants

- All medically stable infants weighing ≥2,000 grams without contraindications should receive the first dose of hepatitis B vaccine (trade names: Engerix-B®, Recombivax HB®) 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 and 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 and 18 months of age.

Children, Adolescents and Adults

- 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.

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_9

- 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 4–6 months after the second dose. An approved alternative schedule for adolescents 11–15 years of age is two 1.0-mL doses of the Recombivax HB® vaccine separated by 4–6 months.
- Adults at increased risk of hepatitis B-infection (including sex partners or household contacts of hepatitis B infected persons; sexually active persons not in a long-term mutually monogamous relationship; persons seeking evaluation or treatment for a sexually transmitted disease; men who have sex with men; current or recent injection drug users; residents and staff of facilities for developmentally disabled persons; healthcare and public safety workers at risk of exposure to blood or body fluids; persons with end-stage renal disease or diabetes mellitus; HIV-infected individuals; and international travelers to countries with high or intermediate endemnicity) should be vaccinated. If using Recombivax HB® or Engerix-B®, the first two doses should be separated by at least 4 weeks and a third dose administered 4–6 months after the second dose. If using HEPLISAV-B™ vaccine, only two doses (0.5 mL each) are given one month apart, but both doses must be HEPLISAV-B™.
- Persons with chronic liver disease (including, but not limited to, those with hepatitis C virus [HCV] infection, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal) should also be vaccinated [1–5].

For More Information

- ACIP recommendations: **http://www.cdc.gov/vaccines/hcp/acip-recs/**
- Immunization schedules: **http://www.cdc.gov/vaccines/schedules/index.html**

Important Information for Obstetric Providers

- **Hepatitis B vaccine is not routinely recommended during pregnancy**.
- However, pregnancy is not a contraindication to hepatitis B vaccination.
- ACIP recommends testing all pregnant women for hepatitis B surface antigen (HBsAg), testing HBsAg-positive pregnant women for hepatitis B virus deoxyribonucleic acid (HBV DNA),and administration of hepatitis B vaccine and hepatitis B immune globulin (HBIG) for infants born to HBV-infected women within 12 hours of birth, followed by completion of the vaccine series and postvaccination serologic testing [21].

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 [1]. It is highly infectious to susceptible individuals exposed in these manners. Thirty percent of infected individuals in the US have no known exposures [6, 7]. 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; about 5% of acute infections in adults become chronic. Chronic infection is often asymptomatic until complications develop [1].

Vaccine(s)

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 [1, 5].

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 [1].

The Hib-Hep B combination vaccine Comvax® was discontinued in the United States in 2014 [8].

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 [1].

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 >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 [1].

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) [5].

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 [1].

Post-licensure safety studies will be carried out by the manufacturer and CDC independently to monitor the safety of the new vaccine HEPLISAV-B™ [5].

Considerations in Pregnancy

Perinatal transmission from mother to infant at birth is very efficient. If a mother is positive for both hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) and postexposure prophylaxis is not administered, 70–90% of infants will become infected. If the mother is positive only for

HBsAg, the risk of perinatal transmission is about 10%. Up to 90% of infant HBV infections will become chronic and, of these, 25% will die from hepatitis B-related disease [1, 3, 4, 9].

Therefore, prevention of perinatal HBV infection is of the utmost importance. All pregnant women should be screened for hepatitis B surface antigen (HBsAg) and infants born to women who are HBsAg-positive should receive postexposure prophylaxis with hepatitis B immune globulin (HBIG), as well as the hepatitis B vaccine series starting at birth. Not only does hepatitis B vaccine protect against future hepatitis B infection, it is also 70–95% effective as a postexposure prophylaxis in preventing mother-to-infant HBV transmission when the first dose is administered within 24 hours after birth followed by the completion of the three-dose series [1, 3, 4, 9]. The universal birth dose policy for hepatitis B vaccine provides an important safety net for when infected mothers are not identified during pregnancy or when there are communication errors regarding infection status. Vaccination on schedule also prevents potential HBV transmission from infected household contacts to the infant during the particularly vulnerable first months of life [10].

The ACIP now also recommends testing HBsAg-positive pregnant women for hepatitis B virus deoxyribonucleic acid (HBV DNA); postvaccination serologic testing for infants whose mother's HBsAg status remains unknown indefinitely; and single-dose revaccination for infants born to HBsAg-positive women not responding to the initial vaccine series [2]. Please refer to the most recent ACIP recommendations [2] as well as the American Association for the Study of Liver Diseases (AASLD) guidelines for further information on reducing perinatal HBV transmission through maternal antiviral therapy [11, 12].

Pregnancy is not a contraindication to hepatitis B vaccination. This is because the vaccine contains HBsAg, which is not infectious, and because limited data suggest that developing fetuses are not at risk for adverse events when the vaccine is administered during pregnancy [1, 4, 9].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about hepatitis B?
Step 2: Briefly address specific concerns, if any
•
Step 3: Pivot to disease risk
• Hepatitis B is a highly infectious virus that is spread through bodily fluids. • Hepatitis B can cause vomiting, fever, nausea, and yellowing of the skin. In some cases, it can cause liver disease, liver cancer, and death. • You may not even know when someone is infected with hepatitis B, as many people do not have any symptoms. • It is very easy for a pregnant woman to pass hepatitis B on to her baby during delivery.
Step 4: Convey vaccine effectiveness
• The good news about hepatitis B is that there are effective vaccines. • Hepatitis B vaccines are over 95% effective in protecting against hepatitis B disease.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from hepatitis B through vaccination. • I strongly recommend hepatitis B vaccine to my patients, my family, and my friends.

References

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, K.A. Hamborsky J, Wolfe S Editor. 2015, Centers for Disease Control and Prevention: Washington D.C.
2. Schillie, S., C. Vellozzi, and A. Reingold, *Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices.* MMWR Morb Mortal Wkly Rep, 2018. **67**(1): p. 1–31.
3. Mast, E.E., et al., *A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents.* MMWR Recomm Rep, 2005. **54**(Rr-16): p. 1–31.
4. Mast, E.E., et al., *A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults.* MMWR Recomm Rep, 2006. **55**(Rr-16): p. 1–33; quiz CE1-4.
5. Schillie, S., et al., *Recommendations of the Advisory Committee on Immunization Practices for Use of a Hepatitis B Vaccine with a Novel Adjuvant.* MMWR Morb Mortal Wkly Rep, 2018. **67**(15): p. 455–8.
6. Zuckerman, J.N., *Protective efficacy, immunotherapeutic potential, and safety of hepatitis B vaccines.* J Med Virol, 2006. **78**(2): p. 169–77.
7. Ocama, P., C.K. Opio, and W.M. Lee, *Hepatitis B virus infection: current status.* Am J Med, 2005. **118**(12): p. 1413.
8. Immunization Action Coalition. *Merck discontinues production of Comvax vaccine (Hib-HepB)*. IAC Express 2014 [cited 2018 March]; Issue 1136:[Available from: http://www.immunize.org/express/issue1136.asp#IACX6.
9. *Leads from the MMWR. Prevention of perinatal transmission of hepatitis B virus: prenatal screening of all pregnant women for hepatitis B surface antigen.* JAMA, 1988. **260**(2): p. 165, 169–70.
10. *Implementation of newborn hepatitis B vaccination—worldwide, 2006.* MMWR Morb Mortal Wkly Rep, 2008. **57**(46): p. 1249–52.

11. Terrault, N.A., et al., *AASLD guidelines for treatment of chronic hepatitis B.* Hepatology, 2016. **63**(1): p. 261–83.
12. Terrault, N.A., et al., *Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance.* Hepatology, 2018. **67**(4): p. 1560–99.

Chapter 10
Human Papillomavirus (HPV)

Recommendations from the Advisory Committee on Immunization Practices (ACIP)

Adolescents and Adults

- 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 [1,2].

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_10

For More Information

- ACIP recommendations: **http://www.cdc.gov/vaccines/hcp/acip-recs/**
- Immunization schedules: **http://www.cdc.gov/vaccines/schedules/index.html**

Important Information for Obstetric Providers

- **HPV vaccines are not routinely recommended during pregnancy**.
- If a woman is discovered to be pregnant after receiving HPV vaccine, no intervention is indicated. The remaining doses in the series should be delayed until after the pregnancy.

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 US 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 [3].

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 [1]. 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 [3]. 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 [1]. In the US 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 [3].

Vaccine(s)

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 [1].

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 US 9vHPV includes HPV types 16, 18, 6, 11, 31, 33, 45, 52, and 58 [2].

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 [1, 2, 4].

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% to 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 [1, 2, 4].

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 [1]. 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 [5–8].

HPV vaccines are among the most rigorously studied vaccines for safety; except for very rare occurrences of anaphylaxis, no serious adverse events[1] have been associated with

[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,

HPV vaccination. Severe allergic reaction (e.g. anaphylaxis) to a previous dose or vaccine component is a contraindication to further HPV vaccination [1].

Receiving HPV vaccine at the recommended ages does not increase likelihood of sexual activity [9, 10].

Considerations in Pregnancy

HPV vaccines are not routinely recommended during pregnancy due to limited available safety data. However, if a woman is discovered to be pregnant after receiving HPV vaccine, no intervention is indicated. The remaining doses in the series should be delayed until after the pregnancy [4].

Rates of adverse outcomes (e.g. spontaneous abortions, late fetal deaths, and congenital anomalies) among females reporting pregnancy during the 4vHPV clinical trials were consistent between vaccine and placebo groups as well as with those in surveillance registries of women who received one or more doses during pregnancy. In addition, a post-licensure registry enrolled more than 2,800 females who received HPV vaccine within 1 month before their last menstrual period or anytime during pregnancy. The rates of spontaneous abortions and major birth defects among these women were not greater than those of a comparison unexposed population [3]. A large VSD study of women 13–27 years old with a live birth between 2007 and 2013 found that inadvertent administration of HPV4 during pregnancy was not associated with adverse pregnancy or birth outcomes [11].

---

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=6b68426ec6d55c78a6799d161ba6754c&mc=true&node= se21.5.312_132&rgn=div8**

Talking Points

Step 1: Establish empathy and credibility

- As your doctor, I know that you want to make the best choices about vaccines for you and your family.
- I also know there is a lot of information out there, and it is difficult to figure out who to trust.
- Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about HPV?

Step 2: Briefly address specific concerns, if any

- While there have been some myths circulating on the internet, HPV vaccine has been very well studied and is actually known to be extremely safe.
- HPV vaccine is actually most effective when given to adolescents at younger ages than when they get older. We want to give this vaccine well before there is any risk of exposure.
- I don't think of this vaccine as a vaccine to prevent a sexually transmitted infection – I think of it as a vaccine to prevent cancer.

Step 3: Pivot to disease risk

- HPV is a virus that is spread through direct contact with an infected person – it does not require sexual intercourse to be transmitted.
- HPV can cause various cancers, and cervical cancer is the most common type of cancer caused by HPV.
- Oropharygeal (throat) cancers from HPV are on the rise, particularly among men.
- There are about 4,000 deaths in the US every year from cervical cancer – almost all of these are preventable with this vaccine.
- HPV is very common – almost everyone gets this virus.
- You may not even know when someone is infected with HPV, as many people do not have any symptoms.
- Teenagers are most susceptible to HPV.

(continued)

Step 4: Convey vaccine effectiveness
• The good news about HPV is that there are effective vaccines. • HPV vaccines prevent cancer. • Over 97% of people who get two doses of HPV vaccine develop immune protection against all types of HPV included in the vaccine. • The immune response to the vaccine is much better when given at younger ages (9–12) compared to older ages (>15), although it's still important to give it at older ages.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from HPV through vaccination. • I strongly recommend HPV vaccine to my patients, my family, and my friends.

References

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, Hamborsky J, Kroger A, Wolfe S, eds. 2015, Centers for Disease Control and Prevention: Washington D.C.
2. Meites, E., A. Kempe, and L.E. Markowitz, *Use of a 2-Dose Schedule for Human Papillomavirus Vaccination - Updated Recommendations of the Advisory Committee on Immunization Practices.* MMWR Morb Mortal Wkly Rep, 2016. **65**(49): p. 1405–8.
3. Markowitz, L.E., et al., *Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep, 2014. **63**(Rr-05): p. 1–30.
4. Petrosky, E., et al., *Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices.* MMWR Morb Mortal Wkly Rep, 2015. **64**(11): p. 300–4.

5. Kroger, A.T., J. Duchin, and M. Vázquez. *General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)*. 2017 [cited 2017 October]; Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.
6. *Syncope after vaccination--United States, January 2005-July 2007.* MMWR Morb Mortal Wkly Rep, 2008. **57**(17): p. 457–60.
7. Braun, M.M., P.A. Patriarca, and S.S. Ellenberg, *Syncope after immunization.* Arch Pediatr Adolesc Med, 1997. **151**(3): p. 255–9.
8. Bernard, D.M., et al., *The domino effect: adolescent girls' response to human papillomavirus vaccination.* Med J Aust, 2011. **194**(6): p. 297–300.
9. Bednarczyk, R.A., et al., *Sexual Activity–Related Outcomes After Human Papillomavirus Vaccination of 11- to 12-Year-Olds.* Pediatrics, 2012.
10. Naleway, A.L., et al., *Primary Ovarian Insufficiency and Adolescent Vaccination*. Pediatrics, 2018.
11. Lipkind, H.S., et al., *Maternal and Infant Outcomes After Human Papillomavirus Vaccination in the Periconceptional Period or During Pregnancy*. Obstet Gynecol, 2017. **130**(3): p. 599–608.

Chapter 11
Influenza

Recommendations from the Advisory Committee on Immunization Practices (ACIP)

All Age Groups

- All persons without contraindications who are 6 months of age and older should receive annual vaccination with influenza vaccine.
- Inactivated influenza vaccine (abbreviation: IIV; trade names: see the table on the following pages) is recommended for all age groups and during pregnancy [1].
- Live attenuated influenza vaccine (abbreviation: LAIV; trade name: FluMist®) is also an option for non-pregnant persons between 2 and 49 years of age [2].
- Influenza vaccine should be given as soon as it becomes available (usually between August and October in the US) 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 [3].

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_11

Infants and Children

- 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 [1].

For More Information

- ACIP recommendations: **http://www.cdc.gov/vaccines/hcp/acip-recs/**
- Immunization schedules: **http://www.cdc.gov/vaccines/schedules/index.html**

Important Information for Obstetric Providers

- **Inactivated influenza vaccine (IIV) is routinely recommended during pregnancy**.
- **Live attenuated influenza vaccine (LAIV) is contraindicated during pregnancy**.

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.

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.

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 [3].

The incubation period for influenza is generally 2 days. The major clinical symptoms typically last a median of 4 days without treatment and include sore throat, fever, headache, myalgia, and nonproductive cough. Pneumonia is the most common complication of influenza. Other complications include Reye syndrome and myocarditis [3, 4].

Pregnant women, young children, elderly adults, and persons with preexisting medical conditions are at increased risk of complications and hospitalizations from influenza [5–7]. 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 [8].

The CDC estimated an average of 23,607 annual influenza-associated deaths in the United States between 1976 and 2007 among all age groups, although these estimates varied widely from year to year [9]. Studies have also estimated an average of approximately 130,000 annual influenza-associated hospitalizations in the United States [6, 10].

Vaccine(s)

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 [2]. LAIV is administered intranasally using a single dose sprayer containing 0.2 mL, with about half (0.1 mL) sprayed in each nostril [1–3].

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 the three strains mentioned as well as a second B strain [1, 3].

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 [11].

Inactivated influenza vaccine (IIV)

Route of administration

Primarily intramuscular (IM), one intradermal (ID); specified for each vaccine listed below.

Vaccine virus

Inactivated, split or subvirion.

Trade Names	Doses Available	Age Range Of Approval
Standard dose		
Fluzone® Quadrivalent	0.25 mL single-dose prefilled syringe, 0.5 mL single-dose vial or prefilled syringe, or 5.0 mL multi-dose vial (IM)	6–35 months of age (0.25 mL dose); ≥36 months of age (0.5 mL dose)
Fluarix® Quadrivalent	0.5 mL single-dose prefilled syringe (IM)	≥6 months of age
FluLaval® Quadrivalent	0.5 mL single-dose prefilled syringe or 5.0 mL multi-dose vial (IM)	≥6 months of age

(continued)

Inactivated influenza vaccine (IIV)		
Flucelvax® Quadrivalent	0.5 mL single-dose prefilled syringe or 5.0 mL multi-dose vial (IM), cell culture-based	≥4 years of age
Afluria®	0.5 mL single-dose prefilled syringe or 5.0 mL multi-dose vial (IM)	≥5 years of age
Afluria® Quadrivalent	0.5 mL prefilled syringe or 5.0 mL multi-dose vial (IM)	≥5 years of age (by needle/syringe); 18–64 years of age (by jet injector)
Fluvirin®	0.5 mL single-dose prefilled syringe or 5.0 mL multi-dose vial (IM)	≥4 years of age
Fluad®	0.5 mL single-dose prefilled syringe (IM)	≥65 years of age
High dose		
Fluzone® High-Dose	0.5 mL single-dose prefilled syringe (IM) (higher antigen content)	≥65 years of age
Recombinant		
Flublok®	0.5 mL single-dose vial (IM)	≥18 years of age
Flublok® Quadrivalent	0.5 mL single-dose prefilled syringe (IM)	≥18 years of age
Intradermal		
Fluzone® Intradermal Quadrivalent	0.1 mL single-dose prefilled microinjection (ID) (lower antigen content)	18–64 years of age

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®) [1]. The vaccines marketed in the United States have been found to contain extremely small or undetectable amounts of egg protein and recent studies have indicated that egg allergic patients can safely receive influenza vaccines [12, 13]. 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 [1]. 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 [14, 15].

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 [1].

The complete current recommendations of the ACIP regarding influenza vaccine delivery can be found at the following website: **https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html**.

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 [3]. Effectiveness has been shown to decline significantly over the first six months post-vaccination, albeit at different rates depending on the vaccine [16–18]. 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 [19].

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 only a few hours. Such symptoms are usually mild but have been reported in 4–<30% of children receiving IIV [20–26]. 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 [27], with even higher rates among recipients of the 2009 pandemic H1N1 vaccine [28].

Rarely, allergic reactions such as hives, angioedema, allergic asthma, or systemic anaphylaxis occur after vaccination, probably due to hypersensitivity to a vaccine component. See the *Do Vaccines Cause Hypersensitivity Reactions?* summary for more details.

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 [29, 30]. See the *Do Vaccines Cause Guillain-Barré Syndrome? (GBS)* summary for more details.

IIV cannot cause influenza, as all viruses contained in the vaccine are inactivated and noninfectious [31]. LAIV also cannot cause influenza as it is made from weakened flu virus [32].

Considerations in Pregnancy

Pregnant women may receive any licensed, recommended, age-appropriate IIV. LAIV is contraindicated during pregnancy [1–3].

Pregnant women and young children are at increased risk of complications and hospitalizations from influenza. 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 [5]. A recent Centers for Disease Control and Prevention (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 [33].

IIV was shown to reduce non-specific febrile respiratory illness in pregnant women by over one third. Vaccine effectiveness was most pronounced during influenza season. Vaccination in pregnancy is beneficial not just for the mother, but for her unborn child as well. Maternal influenza vaccination was shown in one study to reduce proven influenza illness in infants under 6 months of age by up to 63% [34]. In several other studies, IIV was shown to reduce the risk of low birthweight and premature birth [35, 36]. Some studies have found that pregnant women who received influenza vaccine had a lower likelihood of stillbirth than those who did not [37–39], although the evidence for this is inconsistent and has methodological limitations [39–41].

A large body of evidence demonstrates the safety of IIV for both pregnant women and their unborn children [42–50]. Concomitant administration of Tdap and influenza vaccines during pregnancy is not associated with a higher risk of adverse outcomes compared to sequential vaccination [51].

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 [52]. 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 [52]. 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 [53]. One recent randomized trial recruiting women at 17–34 weeks gestation [54], thirteen other observational studies [55–67], two systematic reviews [46, 68], and one meta-analysis [37] 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. See the *Do Vaccines Cause Spontaneous Abortion?* summary for more details.

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about influenza, or the flu for short?
Step 2: Briefly address specific concerns, if any
• Flu vaccine actually doesn't cause the flu. Although some people get some soreness or are a little achy after a flu vaccine, that's just a sign that your immune system is responding to the vaccine. • Even though the flu vaccine doesn't work 100% of the time at preventing the flu, that doesn't mean it doesn't help – it's still the best way to protect yourself from getting the flu.

(continued)

(continued)

Step 3: Pivot to disease risk
• Most people don't realize what a severe illness influenza can be – getting the flu is pretty miserable. • Influenza is a virus that is spread by droplets in the air – such as through sneezing and coughing. • The flu can cause a sore throat, fever, headache, and cough. It can also cause more severe illness, such as pneumonia and sinus infections. • More than 20,000 people die from the flu in the US every year. • Pregnant women and infants are at high risk of developing serious complications from the flu and dying from the flu.
Step 4: Convey vaccine effectiveness
• The good news about the flu is that there are vaccines. • Flu vaccines are updated every year to match the seasonal strain. You should receive a flu vaccine every year as soon as it is available to protect yourself. • 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. • Getting the flu vaccine also helps to protect those around you who are most vulnerable to serious influenza illness, such as young children, pregnant women, and the elderly.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from the flu through vaccination. • I strongly recommend flu vaccine to my patients, my family, and my friends.

References

1. Grohskopf, L.A., et al., *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices-United States, 2018–19 Influenza Season*. MMWR Recomm Rep, 2018. **67**(3): p. 1–20.

2. Grohskopf, L.A., et al., *Update: ACIP Recommendations for the Use of Quadrivalent Live Attenuated Influenza Vaccine (LAIV4) - United States, 2018–19 Influenza Season*. MMWR Morb Mortal Wkly Rep, 2018. **67**(22): p. 643–5.
3. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, Hamborsky J, Kroger A, Wolfe S, eds. 2015, Centers for Disease Control and Prevention: Washington D.C.
4. Fry, A.M., et al., *Efficacy of oseltamivir treatment started within 5 days of symptom onset to reduce influenza illness duration and virus shedding in an urban setting in Bangladesh: a randomised placebo-controlled trial.* Lancet Infect Dis, 2014. **14**(2): p. 109–18.
5. Tamma, P.D., M.C. Steinhoff, and S.B. Omer, *Influenza infection and vaccination in pregnant women.* Expert Rev Respir Med, 2010. **4**(3): p. 321–8.
6. Kostova, D., et al., *Influenza Illness and Hospitalizations Averted by Influenza Vaccination in the United States, 2005–2011.* PLoS One, 2013. **8**(6): p. e66312.
7. Centers for Disease Control and Prevention. *People at High Risk of Developing Flu–Related Complications*. 2018 [cited 2018 March]; Available from: https://www.cdc.gov/flu/about/disease/high_risk.htm.
8. Shang, M., et al., *Influenza-Associated Pediatric Deaths in the United States, 2010–2016.* Pediatrics, 2018.
9. *Estimates of deaths associated with seasonal influenza --- United States, 1976–2007.* MMWR Morb Mortal Wkly Rep, 2010. **59**(33): p. 1057–62.
10. Thompson, W.W., et al., *Influenza-associated hospitalizations in the United States.* JAMA, 2004. **292**(11): p. 1333–40.
11. Garten, R., et al., *Update: Influenza Activity in the United States During the 2017–18 Season and Composition of the 2018–19 Influenza Vaccine.* MMWR Morb Mortal Wkly Rep, 2018. **67**(22): p. 634–42.
12. Greenhawt, M.J., et al., *Safe administration of the seasonal trivalent influenza vaccine to children with severe egg allergy.* Ann Allergy Asthma Immunol, 2012. **109**(6): p. 426–30.
13. Greenhawt, M., P.J. Turner, and J.M. Kelso, *Administration of influenza vaccines to egg allergic recipients: A practice parameter update 2017.* Annals of Allergy, Asthma & Immunology. **120**(1): p. 49–52.
14. American Academy of Allergy Asthma and Immunology. *Egg Allergy and the Flu Vaccine*. [cited 2018 March]; Available from: https://www.aaaai.org/conditions-and-treatments/library/allergy-library/egg-allergy-and-the-flu-vaccine.

15. Dreskin, S.C., et al., *International Consensus (ICON): allergic reactions to vaccines.* World Allergy Organ J, 2016. **9**(1): p. 32.
16. Young, B., et al., *Duration of Influenza Vaccine Effectiveness: A Systematic Review, Meta-analysis, and Meta-regression of Test-Negative Design Case-Control Studies.* J Infect Dis, 2018. **217**(5): p. 731–41.
17. Clements, M.L., et al., *Resistance of adults to challenge with influenza A wild-type virus after receiving live or inactivated virus vaccine.* J Clin Microbiol, 1986. **23**(1): p. 73–6.
18. Belshe, R.B., et al., *Live attenuated versus inactivated influenza vaccine in infants and young children.* N Engl J Med, 2007. **356**(7): p. 685–96.
19. Centers for Disease Control and Prevention. *Vaccine Effectiveness - How Well Does the Flu Vaccine Work?* 2017 [cited 2018 March]; Available from: https://www.cdc.gov/flu/about/qa/vaccineeffect.htm.
20. Brady, R.C., et al., *Randomized trial to compare the safety and immunogenicity of CSL Limited's 2009 trivalent inactivated influenza vaccine to an established vaccine in United States children.* Vaccine, 2014. **32**(52): p. 7141–7.
21. Greenberg, D.P., et al., *Safety and immunogenicity of an inactivated quadrivalent influenza vaccine in children 6 months through 8 years of age.* Pediatr Infect Dis J, 2014. **33**(6): p. 630–6.
22. Baxter, R., et al., *A Phase III evaluation of immunogenicity and safety of two trivalent inactivated seasonal influenza vaccines in US children.* Pediatr Infect Dis J, 2010. **29**(10): p. 924–30.
23. Nolan, T., et al., *Safety and immunogenicity of an inactivated thimerosal-free influenza vaccine in infants and children.* Influenza Other Respir Viruses, 2009. **3**(6): p. 315–25.
24. Domachowske, J.B., et al., *A randomized trial of candidate inactivated quadrivalent influenza vaccine versus trivalent influenza vaccines in children aged 3–17 years.* J Infect Dis, 2013. **207**(12): p. 1878–87.
25. Langley, J.M., et al., *Immunogenicity and safety of an inactivated quadrivalent influenza vaccine candidate: a phase III randomized controlled trial in children.* J Infect Dis, 2013. **208**(4): p. 544–53.
26. Tregnaghi, M.W., et al., *Immunogenicity, safety, and tolerability of two trivalent subunit inactivated influenza vaccines: a phase III, observer-blind, randomized, controlled multicenter study.* Viral Immunol, 2012. **25**(3): p. 216–25.
27. Beran, J., et al., *Immunogenicity and safety of quadrivalent versus trivalent inactivated influenza vaccine: a randomized, controlled trial in adults.* BMC Infect Dis, 2013. **13**: p. 224.

28. Nicholson, K.G., et al., *Immunogenicity and safety of a two-dose schedule of whole-virion and AS03A-adjuvanted 2009 influenza A (H1N1) vaccines: a randomised, multicentre, age-stratified, head-to-head trial.* Lancet Infect Dis, 2011. **11**(2): p. 91–101.
29. Salmon, D.A., et al., *Association between Guillain-Barre syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis.* Lancet, 2013. **381**(9876): p. 1461–8.
30. Vellozzi, C., S. Iqbal, and K. Broder, *Guillain-Barre syndrome, influenza, and influenza vaccination: the epidemiologic evidence.* Clin Infect Dis, 2014. **58**(8): p. 1149–55.
31. Centers for Disease Control and Prevention. *Misconceptions about Seasonal Flu and Flu Vaccines*. 2017 [cited 2018 March]; Available from: https://www.cdc.gov/flu/about/qa/misconceptions.htm.
32. Centers for Disease Control and Prevention, *Vaccine Information Statement - Live Attenuated Influenza Vaccine*. 2015.
33. Callaghan, W.M., A.A. Creanga, and D.J. Jamieson, *Pregnancy-Related Mortality Resulting From Influenza in the United States During the 2009–2010 Pandemic.* Obstet Gynecol, 2015. **126**(3): p. 486–90.
34. Zaman, K., et al., *Effectiveness of maternal influenza immunization in mothers and infants.* N Engl J Med, 2008. **359**(15): p. 1555–64.
35. Rasmussen, S.A., D.J. Jamieson, and T.M. Uyeki, *Effects of influenza on pregnant women and infants.* Am J Obstet Gynecol, 2012. **207**(3 Suppl): p. S3–8.
36. Phadke, V.K. and S.B. Omer, *Maternal vaccination for the prevention of influenza: current status and hopes for the future.* Expert Rev Vaccines, 2016. **15**(10): p. 1255–80.
37. Bratton, K.N., et al., *Maternal influenza immunization and birth outcomes of stillbirth and spontaneous abortion: a systematic review and meta-analysis.* Clin Infect Dis, 2015. **60**(5): p. e11–9.
38. Regan, A.K., et al., *Seasonal Trivalent Influenza Vaccination During Pregnancy and the Incidence of Stillbirth: Population-Based Retrospective Cohort Study.* Clin Infect Dis, 2016. **62**(10): p. 1221–7.
39. Fell, D.B., et al., *Fetal death and preterm birth associated with maternal influenza vaccination: systematic review.* BJOG: An International Journal of Obstetrics & Gynaecology, 2015. **122**(1): p. 17–26.
40. Fell, D.B., et al., *Report of the WHO technical consultation on the effect of maternal influenza and influenza vaccination on the*

developing fetus: Montreal, Canada, September 30-October 1, 2015. Vaccine, 2017. **35**(18): p. 2279–87.
41. Savitz, D.A., et al., *Does influenza vaccination improve pregnancy outcome? Methodological issues and research needs.* Vaccine, 2015. **33**(47): p. 6430–5.
42. Tamma, P.D., et al., *Safety of influenza vaccination during pregnancy.* Am J Obstet Gynecol, 2009. **201**(6): p. 547–52.
43. Bednarczyk, R.A., D. Adjaye-Gbewonyo, and S.B. Omer, *Safety of influenza immunization during pregnancy for the fetus and the neonate.* Am J Obstet Gynecol, 2012. **207**(3 Suppl): p. S38–46.
44. Keller-Stanislawski, B., et al., *Safety of immunization during pregnancy: a review of the evidence of selected inactivated and live attenuated vaccines.* Vaccine, 2014. **32**(52): p. 7057–64.
45. *Vaccines against influenza WHO position paper - November 2012.* Wkly Epidemiol Rec, 2012. **87**(47): p. 461–76.
46. McMillan, M., et al., *Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes.* Vaccine, 2015. **33**(18): p. 2108–17.
47. Polyzos, K.A., et al., *Maternal Influenza Vaccination and Risk for Congenital Malformations: A Systematic Review and Meta-analysis.* Obstet Gynecol, 2015. **126**(5): p. 1075–84.
48. Kharbanda, E.O., et al., *Inactivated influenza vaccine during pregnancy and risks for adverse obstetric events.* Obstet Gynecol, 2013. **122**(3): p. 659–67.
49. Fabiani, M., et al., *A/H1N1 pandemic influenza vaccination: A retrospective evaluation of adverse maternal, fetal and neonatal outcomes in a cohort of pregnant women in Italy.* Vaccine, 2015. **33**(19): p. 2240–7.
50. Ludvigsson, J.F., et al., *Risk for Congenital Malformation With H1N1 Influenza Vaccine: A Cohort Study With Sibling Analysis.* Ann. Intern. Med, 2016. **165**(12): p. 848–55.
51. Sukumaran, L., et al., *Safety of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis and Influenza Vaccinations in Pregnancy.* Obstet Gynecol, 2015. **126**(5): p. 1069–74.
52. Donahue, J.G., et al., *Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010–11 and 2011–12.* Vaccine, 2017. **35**(40): p. 5314–22.
53. Chambers, C.D., R. Xu, and A.A. Mitchell, *Commentary on: "Association of spontaneous abortion with receipt of inactivated*

influenza vaccine containing H1N1pdm09 in 2010–11 and 2011–12". Vaccine, 2017. **35**(40): p. 5323–24.
54. Steinhoff, M.C., et al., *Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial.* Lancet Infect Dis, 2017. **17**(9): p. 981–89.
55. Chambers, C.D., et al., *Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants.* Vaccine, 2013. **31**(44): p. 5026–32.
56. Chambers, C.D., et al., *Safety of the 2010–11, 2011–12, 2012–13, and 2013–14 seasonal influenza vaccines in pregnancy: Birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants, a study from the cohort arm of VAMPSS.* Vaccine, 2016. **34**(37): p. 4443–49.
57. Chavant, F., et al., *The PREGVAXGRIP Study: a Cohort Study to Assess Foetal and Neonatal Consequences of In Utero Exposure to Vaccination Against A(H1N1)v2009 Influenza.* Drug Safety, 2013. **36**(6): p. 455–65.
58. Huang, W.T., et al., *Safety of inactivated monovalent pandemic (H1N1) 2009 vaccination during pregnancy: a population-based study in Taiwan.* Vaccine, 2014. **32**(48): p. 6463–8.
59. Ludvigsson, J.F., et al., *Maternal vaccination against H1N1 influenza and offspring mortality: population based cohort study and sibling design.* Bmj, 2015. **351**: p. h5585.
60. Ma, F., et al., *Prospective cohort study of the safety of an influenza A(H1N1) vaccine in pregnant Chinese women.* Clin Vaccine Immunol, 2014. **21**(9): p. 1282–7.
61. Oppermann, M., et al., *A(H1N1)v2009: A controlled observational prospective cohort study on vaccine safety in pregnancy.* Vaccine, 2012. **30**(30): p. 4445–52.
62. Pasternak, B., et al., *Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study in Denmark.* BMJ : British Medical Journal, 2012. **344**.
63. Tavares, F., et al., *Pregnancy and safety outcomes in women vaccinated with an AS03-adjuvanted split virion H1N1 (2009) pandemic influenza vaccine during pregnancy: A prospective cohort study.* Vaccine, 2011. **29**(37): p. 6358–65.
64. Irving, S.A., et al., *Trivalent Inactivated Influenza Vaccine and Spontaneous Abortion.* Obstetrics & Gynecology, 2013. **121**(1): p. 159–65.

65. Sammon, C.J., et al., *Evaluating the hazard of foetal death following H1N1 influenza vaccination; a population based cohort study in the UK GPRD.* PLoS One, 2012. **7**(12): p. e51734.
66. Heikkinen, T., et al., *Safety of MF59-adjuvanted A/H1N1 influenza vaccine in pregnancy: a comparative cohort study.* Am J Obstet Gynecol, 2012. **207**(3): p. 177.e1–8.
67. de Vries, L., et al., *Adjuvanted A/H1N1 (2009) influenza vaccination during pregnancy: description of a prospective cohort and spontaneously reported pregnancy-related adverse reactions in the Netherlands.* Birth Defects Res A Clin Mol Teratol, 2014. **100**(10): p. 731–8.
68. Bednarczyk, R.A., D. Adjaye-Gbewonyo, and S.B. Omer, *Safety of influenza immunization during pregnancy for the fetus and the neonate.* American Journal of Obstetrics & Gynecology, 2012. **207**(3): p. S38–S46.

Chapter 12
Measles, Mumps and Rubell (MMR)

Recommendations from the Advisory Committee on Immunization Practices (ACIP)

Infants and Children

- All children without contraindications should receive two doses of measles-mumps-rubella combination vaccine (trade name: M-M-R II®) 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 (trade name: Varivax®) 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 (abbreviation: MMRV; trade name: ProQuad®) compared to the separate but simultaneous administration of MMR and varicella vaccines. MMRV is generally preferred for the second dose.

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_12

Adults

- One dose of MMR should be administered to all adults 18 years of age and older without evidence of immunity to these diseases (acceptable evidence of immunity includes documentation of previous receipt of MMR or MMRV vaccine, laboratory confirmation of immunity or disease, or having been born before 1957). Two doses separated by at least 4 weeks are recommended for adults at high risk for exposure and transmission (such as international travelers; college students; and healthcare personnel) [1, 2].

All Age Groups

- Persons previously vaccinated with two doses of a mumps-containing vaccine who are identified by public health as at increased risk for mumps because of an outbreak should receive a third dose of a mumps-containing vaccine to improve protection against mumps disease and related complications [3].

For More Information

- ACIP recommendations: **http://www.cdc.gov/vaccines/hcp/acip-recs/**
- Immunization schedules: **http://www.cdc.gov/vaccines/schedules/index.html**

Important Information for Obstetric Providers

- **Measles, Mumps and Rubella are all live attenuated vaccines and are contraindicated during pregnancy.**
- However, rubella vaccination is emphasized for all non-pregnant women of childbearing age, especially those born outside of the United States. Rubella immunity should be verified either by documentation of at least one dose of rubella-containing vaccine given after the first year of life or by serology. Those without such evidence of immunity should be given MMR vaccine, excluding women who are pregnant or likely to become pregnant within the next 4 weeks.
- If a pregnant woman is inadvertently vaccinated or becomes pregnant within 4 weeks after MMR vaccination, she should be counseled again as to the theoretical risks, but this should not be considered an indication for termination of the pregnancy.

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 the air or on surfaces. The average incubation period is 10–12 days. Common symptoms include 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.

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.

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 14–17 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 [1]. Among pregnant women who are infected with wild-type rubella virus, transplacental infection of the fetus can occur, causing congenital defects or stillbirth [1, 2].

Vaccine(s)

Measles, mumps and rubella vaccines are all live attenuated viral vaccines that are only available in combination as MMR in the United States. The MMRV vaccine also includes varicella vaccine [1].

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 [1, 4].

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 [1, 2, 5].

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 [6].

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 7–12 days after the first dose. A transient rash may also appear during this time frame, occurring in approximately 5% of those vaccinated [1].

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 [1, 7–13]. 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 [14]. There is no increased risk of fever or febrile seizures in children receiving their second dose of measles-containing vaccine at 4–6 years of age, whether given MMR or MMRV [1, 15]. See the *Do Vaccines Cause Seizures?* summary for more details.

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. See the *Do Vaccines Cause Arthralgia or Arthritis?* summary for more details.

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. See the *Do Vaccines Cause Immune Thrombocytopenic Purpura?*, the *Do Vaccines Cause Meningitis or Encephalitis?*, and the *Do Vaccines Cause Hypersensitivity Reactions?* summaries for more details.

There is convincing evidence that MMR does not cause autism [1]. See the *Do Vaccines Cause Autism?* summary for more details.

Considerations in Pregnancy

Transplacental infection of the fetus with wild-type rubella virus can occur causing congenital defects or stillbirth. Congenital Rubella Syndrome (CRS) can include deafness, cataracts, heart defects, neurologic abnormalities including severe retardation, autism, bone alterations, and liver and spleen enlargement. Infants with CRS may shed rubella virus for longer than a year. The greatest risk for congenital malformations from rubella is associated with infection in the first trimester, with as many as 85% of such infants affected. In contrast, congenital malformations are rare when the infection occurs after the 20th week of gestation. The 1964–65 rubella epidemic was associated with an estimated 20,000 cases of congenital malformations, with deafness and heart disease the most common [1, 2].

Vaccination against rubella is emphasized for all nonpregnant women of childbearing age, especially those born outside of the United States. Rubella immunity should be verified by their healthcare providers either by documentation of at least one dose of rubella-containing vaccine given after the first year of life or by serology. Those without such evidence of immunity should be given MMR vaccine, excluding women who are pregnant or currently attempting to become pregnant (pregnancy should be avoided for at least 4 weeks following MMR vaccination). ACIP recommends that providers of MMR vaccine counsel women on the importance of not becoming pregnant during the 4 weeks following vaccination. Routine pregnancy screening before vaccination is not recommended [1, 2].

If a pregnant woman is inadvertently vaccinated or becomes pregnant within 4 weeks after MMR vaccination, she should be counseled again as to the theoretical risks, but this should not be considered an indication for termination of the pregnancy. The theoretical concerns regarding MMR vaccination during pregnancy stem from the fact that MMR is a live attenuated viral vaccine and wild-type rubella virus is known to be teratogenic as described above. The CDC followed women who were vaccinated against rubella during pregnancy from 1971 to 1989 through the Vaccine in Pregnancy

(VIP) Registry. Although subclinical fetal infection was detected serologically in about 1–2% of their infants, the VIP Registry showed no evidence of the occurrence of CRS [1, 2]. More recent studies have also found no evidence of CRS in women who were vaccinated while unknowingly pregnant [16–19]. However, because a small risk cannot be entirely ruled out, women should not be given MMR vaccine during pregnancy [1, 2].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about measles, mumps and rubella?
Step 2: Briefly address specific concerns, if any
• The MMR vaccine does not cause autism. Period. The original study that suggested it did was fraudulent and the doctor who published it lost his medical license because of that. Many scientific studies have shown that the MMR vaccine is very safe.
Step 3: Pivot to disease risk
• Measles is one of the most contagious diseases. It is easily spread through droplets in the air – such as sneezing and coughing. Mumps and rubella are also caused by viruses spread through droplets in the air. • Measles can cause a high fever, rash, and in some cases inflammation of the brain, seizures, and death. Mumps can cause a fever, and in some cases deafness and inflammation of the brain and spinal cord membranes. Rubella can cause a fever and rash.

(continued)

(continued)

Step 4: Convey vaccine effectiveness
• The good news is that there is an effective vaccine that protects you from measles, mumps, and rubella. It is called the MMR vaccine. • Over 99% of children who receive two doses of MMR develop immune protection against measles. The MMR vaccine is also over 90% effective against rubella, and over 66% effective against mumps.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from measles, mumps, and rubella through vaccination. • I strongly recommend MMR vaccine to my patients, my family, and my friends.

References

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, K.A. Hamborsky J, Wolfe S Editor. 2015, Centers for Disease Control and Prevention: Washington D.C.
2. McLean, H.Q., et al., *Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep, 2013. **62**(RR-04): p. 1–34.
3. Marin, M., et al., *Recommendation of the Advisory Committee on Immunization Practices for Use of a Third Dose of Mumps Virus-Containing Vaccine in Persons at Increased Risk for Mumps During an Outbreak.* MMWR Morb Mortal Wkly Rep, 2018. **67**(1): p. 3–38.
4. Kroger, A.T., J. Duchin, and M. Vázquez. *General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)*. 2017 [cited 2017 October]; Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.
5. Demicheli, V., et al., *Vaccines for measles, mumps and rubella in children.* Cochrane Database Syst Rev, 2012. **2**: p. Cd004407.

6. Cardemil, C.V., et al., *Effectiveness of a Third Dose of MMR Vaccine for Mumps Outbreak Control.* N Engl J Med, 2017. **377**(10): p. 947–56.
7. Cortese, M.M. and U.D. Parashar, *Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep, 2009. **58**(Rr-2): p. 1–25.
8. Briere, E.C., *Food and Drug Administration Approval for Use of Hiberix as a 3-Dose Primary Haemophilus influenzae Type b (Hib) Vaccination Series.* MMWR Morb Mortal Wkly Rep, 2016. **65**(16): p. 418–9.
9. Briere, E.C., et al., *Prevention and control of haemophilus influenzae type b disease: recommendations of the advisory committee on immunization practices (ACIP).* MMWR Recomm Rep, 2014. **63**(Rr-01): p. 1–14.
10. (AAP), A.A.o.P., *Neurodiagnostic evaluation of the child with a simple febrile seizure.* Pediatrics, 2011. **127**(2): p. 389–94.
11. (AAP), A.A.o.P., *Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures.* Pediatrics, 2008. **121**(6): p. 1281–6.
12. Bonhoeffer, J., et al., *Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation.* Vaccine, 2004. **22**(5–6): p. 557–62.
13. Tse, A., et al., *Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011.* Vaccine, 2012. **30**(11): p. 2024–31.
14. Klein, N.P., et al., *Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures.* Pediatrics, 2010. **126**(1): p. e1–8.
15. Centers for Disease Control and Prevention. *Vaccine Information Statements (VIS)*. August 7, 2015 [cited 2015; Available from: http://www.cdc.gov/vaccines/hcp/vis/current-vis.html.
16. Badilla, X., et al., *Fetal risk associated with rubella vaccination during pregnancy.* Pediatr Infect Dis J, 2007. **26**(9): p. 830–5.
17. Castillo-Solorzano, C., et al., *Rubella vaccination of unknowingly pregnant women during mass campaigns for rubella and congenital rubella syndrome elimination, the Americas 2001–2008.* J Infect Dis, 2011. **204 Suppl 2**: p. S713–7.

18. Soares, R.C., et al., *Follow-up study of unknowingly pregnant women vaccinated against rubella in Brazil, 2001–2002.* J Infect Dis, 2011. **204 Suppl 2**: p. S729–36.
19. da Silva e Sa, G.R., et al., *Pregnancy outcomes following rubella vaccination: a prospective study in the state of Rio de Janeiro, Brazil, 2001–2002.* J Infect Dis, 2011. **204 Suppl 2**: p. S722–8.

Chapter 13
Meningococcal

Recommendations from the Advisory Committee on Immunization Practices (ACIP)

Adolescents

- All adolescents 11–18 years of age without contraindications should receive two doses of meningococcal conjugate vaccine (abbreviations: MCV4, MenACWY; trade names: Menactra®, Menveo®), 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.

All Age Groups

- 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 (trade names: Trumenba®, Bexsero®) is recommended for all persons starting at 10 years of age who are at increased risk for serogroup B meningococcal disease (such as

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_13

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 [1, 2].

For More Information

- ACIP recommendations: **http://www.cdc.gov/vaccines/hcp/acip-recs/**
- Immunization schedules: **http://www.cdc.gov/vaccines/schedules/index.html**

Important Information for Obstetric Providers

- **Meningococcal vaccines are not routinely recommended during pregnancy**.
- However, pregnancy should not preclude indicated MenACWY vaccination.
- MenB vaccination should be deferred in pregnant and lactating women unless the woman is at increased risk.

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% to 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%) [3].

Vaccine(s)

There are several MCVs licensed in the United States. The MCV4 vaccines MenACWY-D (Menactra®) and MenACWY-CRM (Menveo®) protect against serogroups A, C, W and Y [3], and the single-component vaccines MenB-FHbp (Trumenba®) and MenB-4C (Bexsero®) protect against serogroup B [1].

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 [3]. MenB-FHbp and MenB-4C are approved for use in persons 10–25 years of age [1]. 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 MPSV4 (Menomune®), which was a plain polysaccharide vaccine not conjugated to protein, is no longer recommended for routine use [3].

The Hib-MenCY-TT combination vaccine, MenHibrix®, was discontinued in the United States in 2016 [4].

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 [3].

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 [3].

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%) [3]. 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 [5–8]. Serious adverse events[1] are rare. Hib-MenCY-TT had rates of adverse events comparable to Hib-TT vaccine [3].

[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=6b68426ec6d55c78a6799d161ba6754c&mc=true&node=se21.5.312_132&rgn=div8**

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%) [1].

Considerations in Pregnancy

No randomized, controlled clinical trials have been conducted to evaluate use of MenACWY or MenB vaccines in pregnant or lactating women. However, pregnancy should not preclude indicated MenACWY vaccination. MenB vaccination should be deferred in pregnant and lactating women unless the woman is at increased risk and, after consultation with her healthcare provider, the benefits of vaccination are considered to outweigh the potential risks [1, 9].

Between January 1, 2005 and June 30, 2010, a total of 80 reports were submitted to the Vaccine Adverse Events Reporting System (VAERS) regarding pregnant women or infants born to women who received MenACWY-D during pregnancy. No concerning patterns of adverse events after MenACWY-D in pregnancy were identified [10].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about meningococcus?
Step 2: Briefly address specific concerns, if any
•

(continued)

(continued)

Step 3: Pivot to disease risk
• Meningococcal disease is rare, but it is a devastating disease for those who get it. • Meningococcus is a bacterium that is spread by droplets in the air – such as through sneezing and coughing. • Meningococcus can cause inflammation of the brain and spinal cord membranes as well as pneumonia and joint pain. About 10–15% of people who experience inflammation of the brain and spinal cord membranes from meningococcus end up dying from it.
Step 4: Convey vaccine effectiveness
• The good news about meningococcus is that there are effective vaccines. • Meningococcus ACWY vaccines are over 80% effective in protecting against meningococcal disease.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from meningococcal disease through vaccination. • I strongly recommend meningococcal vaccine to my patients, my family, and my friends.

References

1. MacNeil, J.R., et al., *Use of Serogroup B Meningococcal Vaccines in Adolescents and Young Adults: Recommendations of the Advisory Committee on Immunization Practices, 2015.* MMWR Morb Mortal Wkly Rep, 2015. **64**(41): p. 1171–6.
2. Patton, M.E., et al., *Updated Recommendations for Use of MenB-FHbp Serogroup B Meningococcal Vaccine - Advisory Committee on Immunization Practices, 2016.* MMWR Morb Mortal Wkly Rep, 2017. **66**(19): p. 509–513.
3. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, Hamborsky J, Kroger A, Wolfe S, eds. 2015, Centers for Disease Control and Prevention: Washington D.C.

4. GlaxoSmithKline. *Menhibrix Discontinuation Notice*. 2016; Available from: https://www.gskdirect.com/medias/Menhibrix-Discontinuation-Notice.pdf?context=bWFzdGVyfHJvb3R8NTIyNzQxfGFwcGxpY2F0aW9uL3BkZnxoZTMvaDg1Lzg4NTg3MTMwNjM0NTQucGRmfGYxMjAyMDFmMmU2YjAwYzYyZmUxNWQyNTdjYmUzNjFjMTQ2MDUyODIyMjg4YWIzMTIzNjJhZTZjMWRlNjBlMzg.
5. Kroger, A.T., J. Duchin, and M. Vázquez. *General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)*. 2017 [cited 2017 October]; Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.
6. *Syncope after vaccination--United States, January 2005–July 2007.* MMWR Morb Mortal Wkly Rep, 2008. **57**(17): p. 457–60.
7. Braun, M.M., P.A. Patriarca, and S.S. Ellenberg, *Syncope after immunization.* Arch Pediatr Adolesc Med, 1997. **151**(3): p. 255–9.
8. Bernard, D.M., et al., *The domino effect: adolescent girls' response to human papillomavirus vaccination.* Med J Aust, 2011. **194**(6): p. 297–300.
9. MacNeil, J.R., et al., *Recommendations for Use of Meningococcal Conjugate Vaccines in HIV-Infected Persons - Advisory Committee on Immunization Practices, 2016.* MMWR Morb Mortal Wkly Rep, 2016. **65**(43): p. 1189–94.
10. Cohn, A.C., et al., *Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep, 2013. **62**(Rr-2): p. 1–28.

Chapter 14
Pneumococcal

Recommendations from the Advisory Committee on Immunization Practices (ACIP)

Infants

- All infants without contraindications should receive four doses of pneumococcal conjugate vaccine (abbreviation: PCV13; trade name: Prevnar13®), 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 and 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, Adolescents, and Adults

- 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.

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_14

- Adults over 18 years of age with any of the aforementioned risk factors should also receive a dose of PCV13 followed by a dose of pneumococcal polysaccharide vaccine (abbreviation: PPSV23; trade name: Pneumovax 23®) at least 8 weeks later if they have not previously received it.
- 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 65th birthday at least 5 years after 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 [1, 2].

For More Information

- ACIP recommendations: **http://www.cdc.gov/vaccines/hcp/acip-recs/**
- Immunization schedules: **http://www.cdc.gov/vaccines/schedules/index.html**

Important Information for Obstetric Providers

- **Pneumococcal vaccines are not routinely recommended during pregnancy**.

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 [1]. The World Health Organization (WHO) estimates that over 1.6 million people, including 700,000–1 million children under 2 years of age, die every year from pneumococcal infections worldwide [3].

Vaccine(s)

The pneumococcal conjugate vaccine licensed for use in the United States is the aluminum phosphate-adjuvanted 13-valent PCV13, 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* [1].

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 [1].

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 [1].

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% [1]. Cellulitis-like reactions after Pneumovax 23® vaccination have also been reported in the literature [4, 5].

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 [6–9]. 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 [9]. See the *Do Vaccines Cause Seizures?* summary for more details.

Considerations in Pregnancy

The safety of PPSV23 vaccine in pregnancy has not been studied. However, no adverse outcomes have been reported among newborns whose mothers were inadvertently vaccinated with PPSV23 during pregnancy. Women who are at high risk of pneumococcal disease should be vaccinated before pregnancy, if possible [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about pneumococcus?
Step 2: Briefly address specific concerns, if any
•
Step 3: Pivot to disease risk
• This particular bacteria can be devastating – sometimes it just causes things like ear infections or sinus infections, but it can cause severe pneumonia and meningitis • Pneumococcus is a bacterium that is spread by droplets in the air – such as through sneezing and coughing. • Pneumococcus can cause pneumonia, inflammation of the brain and spinal cord membranes, sepsis, and death. • Individuals under the age of 2 are most susceptible to pneumococcus.
Step 4: Convey vaccine effectiveness
• The good news about pneumococcus is that there is an effective vaccine, called PCV13. • PCV13 is over 90% effective in protecting against pneumococcal disease.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from pneumococcal disease through vaccination. • I strongly recommend pneumococcal vaccine to my patients, my family, and my friends.

References

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, Hamborsky J, Kroger A, Wolfe S, eds. 2015, Centers for Disease Control and Prevention: Washington D.C.
2. Kobayashi, M., et al., *Intervals Between PCV13 and PPSV23 Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Morb Mortal Wkly Rep, 2015. **64**(34): p. 944–7.
3. Organization, W.H., *Pneumococcal vaccines WHO position paper--2012.* Wkly Epidemiol Rec, 2012. **87**(14): p. 129–44.
4. von Elten, K.A., et al., *Systemic inflammatory reaction after pneumococcal vaccine: a case series.* Hum Vaccin Immunother, 2014. **10**(6): p. 1767–70.
5. Huang, D.T., et al., *Protracted fever with cellulitis-like reaction in pneumococcal polysaccharide-vaccinated children.* Pediatr Infect Dis J, 2008. **27**(10): p. 937–9.
6. (AAP), A.A.o.P., *Neurodiagnostic evaluation of the child with a simple febrile seizure.* Pediatrics, 2011. **127**(2): p. 389–94.
7. (AAP), A.A.o.P., *Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures.* Pediatrics, 2008. **121**(6): p. 1281–6.
8. Bonhoeffer, J., et al., *Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation.* Vaccine, 2004. **22**(5–6): p. 557–62.
9. Tse, A., et al., *Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011.* Vaccine, 2012. **30**(11): p. 2024–31.

Chapter 15
Polio

Recommendations from the Advisory Committee on Immunization Practices (ACIP)

Infants

- All infants without contraindications should receive 3 doses of inactivated polio vaccine (abbreviation: IPV; trade name: Ipol®), 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.

Children

- 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.

Adults

- A full primary vaccination series with IPV is also recommended for adults at increased risk of infection (such as international travelers to epidemic or endemic countries, members of communities or groups with disease caused by wild polioviruses, laboratory workers who handle specimens that may

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_15

contain polioviruses, healthcare workers who have close contact with patients who may be excreting wild polioviruses, and unvaccinated adults whose children will be receiving oral poliovirus vaccine, although there is no oral poliovirus available in the United States at this time).
- For adults at high risk of exposure, who have previously been fully vaccinated as children, a one-time additional dose of IPV is recommended [1, 2].

For More Information

- ACIP recommendations: **http://www.cdc.gov/vaccines/hcp/acip-recs/**
- Immunization schedules: **http://www.cdc.gov/vaccines/schedules/index.html**

Important Information for Obstetric Providers

- **Polio vaccine is not routinely recommended during pregnancy**.

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 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% and 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 [1].

Vaccine(s)

IPV 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®) [1]. The following is 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." [2]

Oral poliovirus vaccine (OPV) is a live attenuated vaccine that is no longer used in the United States [1].

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.

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 [1].

Vaccine Safety

Minor local reactions such as pain and redness occur occasionally occur after receiving IPV [1].

Considerations in Pregnancy

Although no adverse effects of IPV have been documented among pregnant women or their unborn infants, vaccination of pregnant women with IPV should generally be avoided. However, if a pregnant woman is at increased risk for polio infection and requires immediate protection, IPV can be administered in accordance with the recommended schedule [3].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about polio?
Step 2: Briefly address specific concerns, if any
•

(continued)

Step 3: Pivot to disease risk
• Polio can cause inflammation of the brain and spinal cord membranes and paralysis. • Although we haven't seen polio in the US in many years, that's because almost everyone gets the vaccine, but, in this global society, it's only a plane ride away.
Step 4: Convey vaccine effectiveness
• The good news about polio is that there is an effective vaccine called IPV. • Over 99% of people who get three doses of IPV develop immune protection.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from polio through vaccination. • I strongly recommend IPV to my patients, my family, and my friends.

References

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, Hamborsky J, Kroger A, Wolfe S, eds. 2015, Centers for Disease Control and Prevention: Washington D.C.
2. *Updated recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding routine poliovirus vaccination.* MMWR Morb Mortal Wkly Rep, 2009. **58**(30): p. 829–30.
3. Prevots, D.R., et al., *Poliomyelitis prevention in the United States. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep, 2000. **49**(Rr-5): p. 1–22; quiz CE1-7.

Chapter 16
Rotavirus

Recommendations from the Advisory Committee on Immunization Practices (ACIP)

Infants

- All infants without contraindications should receive the rotavirus vaccine (RV) series; consisting of either two oral doses of RV1 (trade name: Rotarix®) or three oral doses of RV5 (trade name: RotaTeq®) 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 [1, 2].

For More Information

- ACIP recommendations: **http://www.cdc.gov/vaccines/hcp/acip-recs/**
- Immunization schedules: **http://www.cdc.gov/vaccines/schedules/index.html**

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_16

Important Information for Obstetric Providers

- **Rotavirus vaccines are live attenuated vaccines that are only given to infants under 8 months of age, and are thus contraindicated during pregnancy**.

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 [1, 2].

Vaccine(s)

RVs 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 [1]. Both vaccines provide protection against the majority, but not all strains of rotavirus circulating in the United States.

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 [1].

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 [1].

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 [1]. 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 1–6 excess cases per 100,000 vaccinated infants [3, 4]. However, this small risk is outweighed greatly by the large health benefit of RV [1, 5, 6].

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 [7, 8]. Rarely, RV5 has been shown to cause moderate to severe diarrhea associated with internal recombination of the vaccine strains [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about rotavirus?
Step 2: Briefly address specific concerns, if any
•
Step 3: Pivot to disease risk
• Rotavirus causes particularly severe diarrhea – lots of children are hospitalized with it every year although that has gone down a lot since we started using the vaccine. • Rotavirus can cause dehydrating diarrhea, vomiting, and fever. • Children under the age of 2 are most susceptible to rotavirus. • Although most children who get rotavirus in the US survive, it's still a miserable illness!

(continued)

Step 4: Convey vaccine effectiveness
• The good news about rotavirus is that there are effective vaccines. • Hospitalizations for rotavirus have gone way done since we started using the vaccine.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from rotavirus through vaccination. • I strongly recommend rotavirus vaccine to my patients, my family, and my friends.

References

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, Hamborsky J, Kroger A, Wolfe S, eds. 2015, Centers for Disease Control and Prevention: Washington D.C.
2. Cortese, M.M. and U.D. Parashar, *Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP)*. MMWR Recomm Rep, 2009. **58**(Rr-2): p. 1–25.
3. Aliabadi, N., J.E. Tate, and U.D. Parashar, *Potential safety issues and other factors that may affect the introduction and uptake of rotavirus vaccines.* Clin Microbiol Infect, 2016. **22 Suppl 5**: p. S128–s135.
4. Yih, W.K., et al., *Intussusception risk after rotavirus vaccination in U.S. infants.* N Engl J Med, 2014. **370**(6): p. 503–12.
5. Parashar, U.D., et al., *Value of post-licensure data on benefits and risks of vaccination to inform vaccine policy: The example of rotavirus vaccines.* Vaccine, 2015.
6. Centers for Disease Control and Prevention. *Vaccine Information Statements (VIS)*. August 7, 2015 [cited 2015; Available from: http://www.cdc.gov/vaccines/hcp/vis/current-vis.html.
7. Bogaert, D., et al., *Persistent rotavirus diarrhea post-transplant in a novel JAK3-SCID patient after vaccination.* Pediatr Allergy Immunol, 2016. **27**(1): p. 93–6.

8. Bakare, N., et al., *Severe combined immunodeficiency (SCID) and rotavirus vaccination: reports to the Vaccine Adverse Events Reporting System (VAERS)*. Vaccine, 2010. **28**(40): p. 6609–12.

Chapter 17
Tetanus, Diphtheria and Pertussis

Recommendations from the Advisory Committee on Immunization Practices (ACIP)

Infants and Children

- All infants without contraindications should receive three doses of the child formulation of tetanus-diphtheria-pertussis combination vaccine (abbreviation: DTaP; trade names: Daptacel®, Infanrix®), given at 2, 4, and 6 months of age.
- A fourth dose should be given 6–12 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.

Adolescents and Adults

- One dose of the tetanus-diphtheria-pertussis booster vaccine (abbreviation: Tdap; trade names: Boostrix®, Adacel®) should be given to all adolescents between the ages of 11 and 18 years.
- Tdap vaccine should also be given to all adolescents and adults who have never previously received it, particularly if they will be in contact with newborn infants in the near future [1–3].

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_17

For More Information

- ACIP recommendations: **http://www.cdc.gov/vaccines/hcp/acip-recs/**
- Immunization schedules: **http://www.cdc.gov/vaccines/schedules/index.html**

Important Information for Obstetric Providers

- **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 [1-3].

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.

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 to 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 US, 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").

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 US but since introduction of the vaccine, incidence of pertussis has decreased by more than 80%. However, incidence of pertussis has been gradually increasing again over the past several decades [1].

Vaccine(s)

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 6 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 10–64 years (Boostrix®) or 11–64 years (Adacel®) of age [1].

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.

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 [4], 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.

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 [1].

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 US 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 [1, 5, 6]. Infants born to mothers immunized during pregnancy have 50–100% of the pertussis antibody titers of their mothers at birth, although this passive immunity wanes rapidly [7].

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 [1].

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 [1].

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[1] 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 [1].

[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=6b68426ec6d55c78a6799d161ba6754c&mc=true&node =se21.5.312_132&rgn=div8**

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 [8–11]. See the *Do Vaccines Cause Seizures?* summary for more details.

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 [12–15].

Considerations in Pregnancy

Vaccination with Tdap during pregnancy helps protect infants from pertussis. Newborns and infants in the first few months of life are dependent on transplacentally acquired maternal pertussis antibodies and prevention of exposure from close contacts for protection against pertussis disease, since active immunization of the infant does not begin until 2 months of age and several doses are needed to induce protection against pertussis in most infants. Almost all deaths from pertussis occur in the first few months of life, most prior to receipt of routine infant vaccines against pertussis [16–18].

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 [19].

A large body of evidence demonstrates the safety of the Tdap vaccine for both pregnant women and their unborn children [16–18, 20–24]. 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 [25]. Having recently received a tetanus-containing

vaccination does not increase the risk of adverse outcomes after Tdap vaccination in pregnancy [26]. Concomitant administration of Tdap and influenza vaccines during pregnancy is not associated with a higher risk of adverse outcomes compared to sequential vaccination [27].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about tetanus, diphtheria and pertussis?
Step 2: Briefly address specific concerns, if any
•
Step 3: Pivot to disease risk
• Pertussis is a potentially deadly disease, particularly for young infants. Even for healthy people though, it's pretty miserable – it's also known as the "100 day cough" because it can last so long. • Tetanus is a bacterium that enters the body through a cut in the skin. Diphtheria is a bacterium that is spread by droplets in the air – such as through sneezing and coughing. Pertussis, also called whooping cough, is a bacterium that is also spread through droplets in the air. • Tetanus can cause lockjaw and death. Diphtheria can cause respiratory problems, coma, and death. Pertussis, or whooping cough, can cause pneumonia and death. • Since tetanus comes from the environment instead of being transmitted person to person like other diseases, "herd immunity" or "community protection" from high vaccine coverage in the US does not apply. Everyone must be vaccinated themselves to be protected from tetanus.

(continued)

(continued)

- Pertussis is known as whooping cough because of the characteristic sound of the violent and intense cough that it causes. It is also known as the "100-day cough" because of how long it can persist. Pertussis has been making a resurgence in the US in recent years.
- Infants under the age of 2 and unborn babies are particularly at risk for contracting pertussis. Pregnant women can protect their unborn babies by getting vaccinated while pregnant.

Step 4: Convey vaccine effectiveness

- The good news about tetanus, diphtheria, and whooping cough is that there are effective vaccines that provide protection against all three diseases – called Tdap for adolescents and adults, and DTaP for infants and children.
- The primary three-dose series of DTaP is over 95% efficacious against tetanus and almost 100% efficacious against diphtheria. It is also 84% efficacious against pertussis during the three years after series completion. Adults receiving one dose of Tdap vaccine develop similar immune protection to infants receiving three doses of DTaP.

Step 5: Give a strong and personalized recommendation

- You and I have the same goal: to keep you and your family healthy.
- You have the power to protect yourself and your family from tetanus, diphtheria, and whooping cough through vaccination.
- I strongly recommend the appropriate vaccines to my patients, my family, and my friends.

References

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, Hamborsky J, Kroger A, Wolfe S, eds. 2015, Centers for Disease Control and Prevention: Washington D.C.
2. *Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunization Practices, 2010.* MMWR Morb Mortal Wkly Rep, 2011. **60**(1): p. 13–5.

3. Liang, J.L., et al., *Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep, 2018. **67**(2): p. 1–44.
4. Gold, M.S., *Hypotonic-hyporesponsive episodes following pertussis vaccination: a cause for concern?* Drug Saf, 2002. **25**(2): p. 85–90.
5. Fulton, T.R., et al., *Protective Effect of Contemporary Pertussis Vaccines: A Systematic Review and Meta-analysis.* Clin Infect Dis, 2016. **62**(9): p. 1100–10.
6. Zhang, L., et al., *Acellular vaccines for preventing whooping cough in children.* Cochrane Database Syst Rev, 2014(9): p. Cd001478.
7. Van Rie, A., A.M. Wendelboe, and J.A. Englund, *Role of maternal pertussis antibodies in infants.* Pediatr Infect Dis J, 2005. **24**(5 Suppl): p. S62–5.
8. (AAP), A.A.o.P., *Neurodiagnostic evaluation of the child with a simple febrile seizure.* Pediatrics, 2011. **127**(2): p. 389–94.
9. (AAP), A.A.o.P., *Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures.* Pediatrics, 2008. **121**(6): p. 1281–6.
10. Bonhoeffer, J., et al., *Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation.* Vaccine, 2004. **22**(5–6): p. 557–62.
11. Tse, A., et al., *Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011.* Vaccine, 2012. **30**(11): p. 2024–31.
12. Kroger, A.T., J. Duchin, and M. Vázquez. *General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)*. 2017 [cited 2017 October]; Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.
13. *Syncope after vaccination--United States, January 2005–July 2007.* MMWR Morb Mortal Wkly Rep, 2008. **57**(17): p. 457–60.
14. Braun, M.M., P.A. Patriarca, and S.S. Ellenberg, *Syncope after immunization.* Arch Pediatr Adolesc Med, 1997. **151**(3): p. 255–9.
15. Bernard, D.M., et al., *The domino effect: adolescent girls' response to human papillomavirus vaccination.* Med J Aust, 2011. **194**(6): p. 297–300.

16. *ACOG Committee Opinion No. 566: Update on immunization and pregnancy: tetanus, diphtheria, and pertussis vaccination.* Obstet Gynecol, 2013. **121**(6): p. 1411–4.
17. *Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women--Advisory Committee on Immunization Practices (ACIP), 2012.* MMWR Morb Mortal Wkly Rep, 2013. **62**(7): p. 131–5.
18. *Committee Opinion No. 718: Update on Immunization and Pregnancy: Tetanus, Diphtheria, and Pertussis Vaccination.* Obstet Gynecol, 2017. **130**(3): p. e153–e157.
19. Amirthalingam, G., et al., *Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction.* Clin Infect Dis, 2016. **63**(suppl 4): p. S236–s243.
20. McMillan, M., et al., *Safety of Tetanus, Diphtheria, and Pertussis Vaccination During Pregnancy: A Systematic Review.* Obstet Gynecol, 2017. **129**(3): p. 560–73.
21. Kharbanda, E.O., et al., *Maternal Tdap vaccination: Coverage and acute safety outcomes in the vaccine safety datalink, 2007–2013.* Vaccine, 2016. **34**(7): p. 968–73.
22. Petousis-Harris, H., et al., *Safety of Tdap vaccine in pregnant women: an observational study.* BMJ Open, 2016. **6**(4): p. e010911.
23. Layton, J.B., et al., *Prenatal Tdap immunization and risk of maternal and newborn adverse events.* Vaccine, 2017. **35**(33): p. 4072–8.
24. DeSilva, M., et al., *Maternal Tdap vaccination and risk of infant morbidity.* Vaccine, 2017. **35**(29): p. 3655–60.
25. Kharbanda, E.O., et al., *Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes.* JAMA, 2014. **312**(18): p. 1897–904.
26. Sukumaran, L., et al., *Association of Tdap Vaccination With Acute Events and Adverse Birth Outcomes Among Pregnant Women With Prior Tetanus-Containing Immunizations.* JAMA, 2015. **314**(15): p. 1581–7.
27. Sukumaran, L., et al., *Safety of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis and Influenza Vaccinations in Pregnancy.* Obstet Gynecol, 2015. **126**(5): p. 1069–74.

Chapter 18
Varicella and Herpes Zoster

Recommendations from the Advisory Committee on Immunization Practices (ACIP)

Infants and Children

- All children without contraindications should receive two doses of varicella vaccine (trade name: Varivax®) 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 (abbreviation: MMR; trade name: M-M-R II®).
- 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 the measles-mumps-rubella-varicella combination vaccine (abbreviation: MMRV; trade name: ProQuad®) can be administered for the second dose.

Adolescents and Adults

- The ACIP recommends all persons over 13 years of age without evidence of varicella immunity receive 2 doses of varicella vaccine separated by a minimum of

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_18

4 weeks. Immunity to varicella is especially important for healthcare personnel [1, 2].
- Two doses of recombinant zoster vaccine (abbreviation: RZV; trade name: Shingrix®) are recommended for all persons without contraindications over 50 years of age, including among those who have previously been vaccinated with live attenuated zoster vaccine (abbreviation: ZVL; trade name: Zostavax®).
- One dose of ZVL is still recommended for all persons without contraindications over 60 years of age in the absence of RZV. However, there is now a preferential recommendation for RZV over ZVL [3].

For More Information

- ACIP recommendations: **http://www.cdc.gov/vaccines/hcp/acip-recs/**
- Immunization schedules: **http://www.cdc.gov/vaccines/schedules/index.html**

Important Information for Obstetric Providers

- **Varicella and ZVL are live attenuated vaccines and are thus contraindicated during pregnancy**.
- Having a pregnant household member is not a contraindication to varicella or zoster vaccination.
- Women who are vaccinated for varicella should avoid becoming pregnant for a month after each injection. If a pregnant woman is inadvertently vaccinated or becomes pregnant within 4 weeks after varicella vaccination, she should be counseled as to the potential effects on the fetus, but this should not be considered an indication for termination of the pregnancy.

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 birthweight, 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 500,000 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 [1].

Vaccine(s)

Varicella vaccine is a live attenuated viral vaccine. MMRV is a combination vaccine that includes measles, mumps, rubella and varicella vaccines [1].

There are two herpes zoster vaccines licensed in the United States: live attenuated zoster vaccine (abbreviation: ZVL; trade name: Zostavax®), and inactivated, recombinant, adjuvanted, subunit zoster vaccine (abbreviation: RZV; trade name: Shingrix®). ACIP has given a preferential recommendation for RZV over ZVL [3]. The ZVL vaccine has the same antigen as the aforementioned varicella vaccine but at a much higher titer [1].

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, including herpes

zoster vaccine. Other contraindications to vaccination with varicella-containing vaccines or ZVL include pregnancy, altered immunity, and family history of altered immunocompetence [1, 2, 4]. The following is 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." [2]

The following is from the 2008 ACIP recommendations regarding the contraindication of ZVL in immunocompromised persons. New guidelines are in preparation.

"Zoster vaccine should not be administered to persons with primary or acquired immunodeficiency including:

"Persons with leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic system. However, patients whose leukemia is in remission and who have not received chemotherapy (e.g., alkylating drugs or antimetabolites) or radiation for at least 3 months can receive zoster vaccine.

"Persons with AIDS or other clinical manifestations of HIV, including persons with CD4+ T-lymphocyte values <200 per mm^3 or <15% of total lymphocytes.

"Persons on immunosuppressive therapy, including high-dose corticosteroids (>20 mg/day of prednisone or equivalent) lasting two or more weeks. Zoster vaccination should be deferred for at least 1 month after discontinuation of such therapy. Short-term corticosteroid therapy (<14 days); low-to-moderate dose (<20 mg/day of prednisone or equivalent); topical (e.g., nasal, skin, inhaled); intra-articular, bursal, or tendon injections; or long-term alternate-day treatment with low to moderate doses of short-acting systemic corticosteroids are not considered to be sufficiently immunosuppressive to cause concerns for vaccine safety. Persons receiving this dose or schedule can receive zoster vaccine. Therapy with low-doses of methotrexate (<0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day), or 6-mercaptopurine (<1.5 mg/kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease, and other conditions are also not considered sufficiently immunosuppressive to create vaccine safety concerns and are not contraindications for administration of zoster vaccine.

"Persons with clinical or laboratory evidence of other unspecified cellular immunodeficiency. However, persons with impaired humoral immunity (e.g. hypogammaglobulinemia or dysgammaglobulinemia) can receive zoster vaccine.

"Persons undergoing hematopoietic stem cell transplantation (HSCT). The experience of HSCT recipients with VZV-containing vaccines (e.g., zoster vaccine) is limited. Physicians should assess the immune status of the recipient on a case-by-case basis to determine the relevant risks. If a decision is made to vaccinate with zoster vaccine, the vaccine should be administered at least 24 months after transplantation.

"Persons receiving recombinant human immune mediators and immune modulators, especially the antitumor necrosis factor agents adalimumab, infliximab, and etanercept. The safety and efficacy of zoster vaccine administered concurrently with these agents is unknown. If it is not possible to administer zoster vaccine to patients before initiation of therapy, physicians should assess the immune status of the recipient on a case-by-case basis to determine the relevant risks and benefits. Otherwise, vaccination with zoster vaccine should be deferred for at least 1 month after discontinuation of such therapy." [5]

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 [1, 2]. "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 Centers for Disease Control and Prevention (CDC)'s *General Best Practice Guidelines for Immunization* report [4].

Precautions to vaccination with RZV include current herpes zoster infection, pregnancy and breastfeeding [3].

For more details, please see the most recent ACIP recommendations (**http://www.cdc.gov/vaccines/hcp/acip-recs/**).

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 [6–8]. Effectiveness decreases with time since vaccination [2]. Effectiveness after two doses is estimated to be 94% against any varicella and 98% against moderate or severe varicella [8].

Efficacy of RZV (Shingrix®) against herpes zoster was estimated to be 96.6% for those aged 50–59, 97.4% for those aged 60–69, 91.3% for those aged 70–79, and 91.4% for those age 80 or above. RZV was shown to have a good duration of protection, maintaining efficacy of at least 85% among those over 70 years of age even after 4 years post-vaccination [3, 9–11]. In comparison, efficacy of ZVL (Zostavax®) against herpes zoster was estimated to be 70% for those aged 50–59, 64% for those aged 60–69, 41% for those aged 70–79, and 18% for those age 80 or above. Efficacy of ZVL was shown to decline each year after vaccination, estimated at less than 35% after 6 years post-vaccination [3, 12–15]. ZVL recipients 60–80 years of age had 51% fewer zoster episodes than a comparison control group [1]. In a community based retrospective cohort study of Medicare participants over 65 years of age, the effectiveness of ZVL was 33% for the first 3 years after vaccination, and 19% after 4 years post-vaccination. Effectiveness against post-herpetic neuralgia was higher; 57% for the first 3 years and 45% after 4 years post-vaccination [13].

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 [2].

Injection site reactions are also the most common adverse reactions following herpes zoster vaccination. Such reactions were reported in 48.3% of ZVL (Zostavax®) recipients versus 16.6% of placebo recipients in the Shingles Prevention Study [5], and in 81.5% of RZV (Shingrix®) recipients versus 11.9%

of placebo recipients in the Zoster Efficacy Study in Adults 50 Years of Age or Older (ZOE-50) [9]. Minor systemic adverse events such as headaches were reported slightly more commonly in ZVL vaccine recipients (6.3%) than placebo recipients (4.9%), but no difference in risk of fever after vaccination was shown. In comparison, systemic adverse events were reported much more commonly in RZV vaccine recipients (66.1%) than placebo recipients (29.5%). Most reactions to ZVL were mild and resolved within 4 days. Most reactions to RZV were of mild or moderate intensity, with a median duration of 1–3 days. However, grade 3 reactions (symptoms prevented normal everyday activities) were reported in 17% of RZV vaccinees compared to only 3% of controls. No difference in serious adverse events between vaccinated and control groups was shown for either RZV or ZVL [3, 5, 9, 11].

Mild zoster illness resulting from a latent infection with varicella vaccine virus has been reported [16]. 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 [1]. See the *Do Vaccines Cause Hepatitis?,* the *Do Vaccines Cause Meningitis or Encephalitis?*, the *Do Vaccines Cause Disseminated Varicella Infection?*, and the *Do Vaccines Cause Herpes Zoster?* summaries for more details.

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 [17–20]. The rate of febrile seizures in the 7–10 days after vaccination was approximately 2–3 times higher for children who received MMRV as com-

pared to MMR and varicella vaccines administered separately on the same day, and 4 times higher as compared to MMR alone [21]. There is no increased risk of fever or febrile seizures in children receiving their second dose of measles-containing vaccine at 4–6 years of age, whether given MMR or MMRV [1, 22]. See the *Do Vaccines Cause Seizures?* summary for more details.

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 [1]. There is no risk of transmission following the inactivated zoster vaccine (RZV).

Post-licensure safety studies will be carried out by the manufacturer and CDC independently to monitor the safety of RZV (Shingrix®) [11].

Considerations in Pregnancy

Women who are vaccinated for varicella should avoid becoming pregnant for a month after each injection. If a pregnant woman is inadvertently vaccinated or becomes pregnant within 4 weeks after varicella vaccination, she should be counseled as to the potential effects on the fetus, but this should not be considered an indication for termination of the pregnancy.

The theoretical concerns stem from the fact that wild-type varicella poses a low risk of development of congenital varicella syndrome and its associated birth defects; however, since the virulence of the attenuated vaccine virus is substantially less than the wild-type virus, the risk to the fetus from the vaccine, if any, should be even lower. Beginning in 1995, the Merck/CDC Pregnancy Registry for VZV-Containing Vaccines monitored the maternal and fetal outcomes of pregnant women who were inadvertently administered any varicella-containing vaccine up to 3 months before or at any time during pregnancy, and no birth defects consistent with

congenital varicella syndrome were documented. Although this does not exclude the possibility of such events, the potential risk, if any, is low. Due to the low rate of exposure of pregnant women to this vaccine and the rarity of congenital varicella syndrome, new patient enrollment in the VARIVAX® Pregnancy Registry was discontinued in 2013 [2, 23].

There is not yet any data to establish whether RZV is safe during pregnancy or breastfeeding, thus there is currently no ACIP recommendation for RZV in pregnant or breastfeeding women. For now, the CDC says to consider delaying vaccination with RZV under such circumstances [3].

Talking Points

Varicella Vaccine
Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about varicella?
Step 2: Briefly address specific concerns, if any
•
Step 3: Pivot to disease risk
• A lot of people think of chicken pox as a pretty mild disease, but it can actually be pretty severe in some cases, and that's why we give the vaccine – to prevent the severe cases. • Varicella, also known as chicken pox, is a disease caused by a virus and is spread by droplets in the air – such as through sneezing and coughing. • Varicella can cause skin lesions, pneumonia, and inflammation of the brain and spinal cord membranes. • Individuals under the age of 1 year are particularly at risk.

(continued)

Step 4: Convey vaccine effectiveness

- The good news about varicella is that there is an effective vaccine.
- The two-dose series of varicella vaccine is 94% effective against varicella disease.

Step 5: Give a strong and personalized recommendation

- You and I have the same goal: to keep you and your family healthy.
- You have the power to protect yourself and your family from varicella through vaccination.
- I strongly recommend varicella vaccine to my patients, my family, and my friends.

Herpes Zoster Vaccine

Step 1: Establish empathy and credibility

- As your doctor, I know that you want to make the best choices about vaccines for you and your family.
- I also know there is a lot of information out there, and it is difficult to figure out who to trust.
- Would it be okay if I share with you what I have learned from my experience, and what I share with my patients, my family and my friends about herpes zoster, commonly known as shingles?

Step 2: Briefly address specific concerns, if any

-

Step 3: Pivot to disease risk

- Shingles is a disease caused by a virus and can cause painful skin lesions, rash, and blisters.
- Shingles is spread by skin-to-skin contact with a person that has shingles blisters.
- Individuals over the age of 60 are particularly at risk.

(continued)

(continued)

Step 4: Convey vaccine effectiveness
• The good news about shingles is that there are effective vaccines. • The newest shingles vaccine can reduce the chances of getting shingles by more than 85%.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from shingles through vaccination. • I strongly recommend shingles vaccine to my patients, my family, and my friends.

References

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, Hamborsky J, Kroger A, Wolfe S, eds. 2015, Centers for Disease Control and Prevention: Washington D.C.
2. Marin, M., et al., *Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep, 2007. **56**(Rr-4): p. 1–40.
3. Dooling, K.L., et al., *Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines.* MMWR Morb Mortal Wkly Rep, 2018. **67**(3): p. 103–8.
4. Kroger, A.T., J. Duchin, and M. Vázquez. *General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)*. 2017 [cited 2017 October]; Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.
5. Harpaz, R., I.R. Ortega-Sanchez, and J.F. Seward, *Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep, 2008. **57**(Rr-5): p. 1–30; quiz CE2-4.
6. Seward, J.F., M. Marin, and M. Vazquez, *Varicella vaccine effectiveness in the US vaccination program: a review.* J Infect Dis, 2008. **197 Suppl 2**: p. S82–9.

7. Shapiro, E.D., et al., *Effectiveness of 2 doses of varicella vaccine in children.* J Infect Dis, 2011. **203**(3): p. 312–5.
8. Perella, D., et al., *Varicella Vaccine Effectiveness in Preventing Community Transmission in the 2-Dose Era.* Pediatrics, 2016. **137**(4).
9. Lal, H., et al., *Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults.* N Engl J Med, 2015. **372**(22): p. 2087–96.
10. Cunningham, A.L., et al., *Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older.* New England Journal of Medicine, 2016. **375**(11): p. 1019–32.
11. Centers for Disease Control and Prevention. *Herpes Zoster Vaccine*. in *Meeting of the Advisory Committee on Immunization Practices (ACIP)*. 2017. Atlanta, GA.
12. Schmader, K.E., et al., *Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy.* Clin Infect Dis, 2012. **55**(10): p. 1320–8.
13. Izurieta, H.S., et al., *Effectiveness and Duration of Protection Provided by the Live-attenuated Herpes Zoster Vaccine in the Medicare Population Ages 65 Years and Older.* Clin Infect Dis, 2017. **64**(6): p. 785–93.
14. Baxter, R., et al., *Long-Term Effectiveness of the Live Zoster Vaccine in Preventing Shingles: A Cohort Study.* Am J Epidemiol, 2018. **187**(1): p. 161–9.
15. Tseng, H.F., et al., *Declining Effectiveness of Herpes Zoster Vaccine in Adults Aged >/=60 Years.* J Infect Dis, 2016. **213**(12): p. 1872–5.
16. Dreyer, S., et al., *Pediatric vaccine-strain herpes zoster: a case series.* Pediatr Dermatol, 2017.
17. (AAP), A.A.o.P., *Neurodiagnostic evaluation of the child with a simple febrile seizure.* Pediatrics, 2011. **127**(2): p. 389–94.
18. (AAP), A.A.o.P., *Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures.* Pediatrics, 2008. **121**(6): p. 1281–6.
19. Bonhoeffer, J., et al., *Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation.* Vaccine, 2004. **22**(5–6): p. 557–62.
20. Tse, A., et al., *Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011.* Vaccine, 2012. **30**(11): p. 2024–31.

21. Klein, N.P., et al., *Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures.* Pediatrics, 2010. **126**(1): p. e1–8.
22. Centers for Disease Control and Prevention. *Vaccine Information Statements (VIS)*. August 7, 2015 [cited 2015; Available from: http://www.cdc.gov/vaccines/hcp/vis/current-vis.html
23. Marin, M., et al., *Closure of varicella-zoster virus-containing vaccines pregnancy registry - United States, 2013.* MMWR Morb Mortal Wkly Rep, 2014. **63**(33): p. 732–3.

Part III
Potential Adverse Events Following Immunization

Chapter 19
Potential Adverse Events Following Immunization

Summaries of the Evidence

This section addresses the numerous potential adverse events that have been studied to determine if an association exists with routine immunization in the United States and supplements the vaccine information summaries for those seeking more information about a specific adverse event.

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* [1] was relied upon heavily to compile both the list of adverse events and the sources providing the best evidence for each adverse event. 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* [2] was used to update and supplement the IOM report, as well as our own systematic literature searches and general knowledge. The AHRQ report was summarized in a review article in the journal Pediatrics [3].

In order to consistently and succinctly characterize the frequency of adverse events in this section, definitions used by the World Health Organization are used here, as outlined in the table below.

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_19

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%)

In order to summarize the evidence regarding potential adverse events in an accurate, concise, practical and standardized manner, we established the categories of causality conclusions outlined the table below.

Categories of Causality Conclusions[1]

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 US.
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 US, 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.

[1] 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).

Regarding the category, 'Vaccines **have not been shown to cause** the event,' some may misrepresent conclusions such as this to suggest that the adverse event in question has not been examined and therefore is likely, offering personal anecdotes in support of their argument. We caution against such interpretations. In most of these instances, the specific condition in question is quite rare in the general population (for example, affecting fewer than 1 in 10,000 individuals in a given year). Simply because of their rarity, it is very difficult to quantify risk estimates for such conditions. In almost all cases where we conclude, "Vaccines have not been shown to cause the event," 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. For rare conditions, it is inherently difficult to quantify very rare risks.

We summarize several special topics of interest related to vaccine safety, as shown in the table below.

Special Topics of Interest Related To Vaccines

Currently Routinely Recommended for The General Population in The United States1

Topic	Conclusion
Combination Vaccines or Simultaneous Vaccination	MMRV can rarely cause febrile seizures in infants and young children, at slightly higher rates than individual administration of MMR and varicella vaccines. Simultaneous administration of influenza and pneumococcal conjugate vaccines can rarely cause febrile seizures in infants and young children, at slightly higher rates than separate administration of these vaccines. No other adverse events have been shown to be caused by combination vaccines or simultaneous vaccination as compared to separate administration of available individual vaccine components.
Vaccine Ingredients	Certain ingredients found in some vaccines, such as gelatin or neomycin, can very rarely cause severe hypersensitivity reactions (e.g. anaphylaxis) in those who are allergic to these specific ingredients.

The summaries are arranged in alphabetical order by potential adverse events. They have also been organized by the conclusions drawn in the tables below for convenience purposes. For the majority of these potential adverse events, there are no studies of quality that show an association with routine immunization in the United States.

Causal Relationship Established With Vaccines Currently Routinely Recommended for The General Population in The United States[1]

Adverse Event	Conclusion
Anaphylaxis	Vaccine components can very rarely cause anaphylaxis.
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 US 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.
Deltoid Bursitis	Incorrect administration of vaccines can cause deltoid bursitis.
Disseminated Varicella Infection	Varicella vaccine can rarely cause disseminated varicella infection in immune deficient individuals for whom the vaccine is contraindicated.
Encephalitis	Measles vaccine can very rarely cause encephalitis. Mumps vaccine used in other countries did cause encephalitis (but not the vaccine licensed in the US).
Febrile Seizures	Vaccines that induce fever in infants and young children, such as MMRV, influenza, and PCV vaccines, can rarely cause febrile seizures.
Guillain-Barré Syndrome (GBS)	Influenza vaccine can cause GBS very rarely in adults. An old formulation of rabies vaccine (no longer available) did cause GBS. Other vaccines, including current rabies vaccine, have not been shown to cause GBS.

(continued)

Causal Relationship Established With Vaccines Currently Routinely Recommended for The General Population in The United States[1]

Adverse Event	Conclusion
Hepatitis	Varicella vaccine can rarely cause hepatitis in persons with certain immune deficiencies. Vaccines given to immunocompetent persons do not cause hepatitis.
Herpes Zoster	Varicella vaccine can rarely cause herpes zoster due to vaccine-strain viral reactivation.
Immune Thrombocytopenic Purpura (ITP)	MMR vaccine can very rarely cause ITP in children.
Meningitis	Reactivation of varicella vaccine can very rarely cause meningitis. Mumps vaccine used in other countries (but not the vaccine licensed in the US) did cause meningitis.
Syncope	Vaccines (and other injections) can rarely cause syncope.

No Causal Relationship Established With Vaccines Currently Routinely Recommended for the General Population in The United States[1]

Adverse Event	Conclusion
Acute Disseminated Encephalomyelitis (ADEM)	An old formulation of rabies vaccine (no longer available) did cause ADEM. Other vaccines, including current rabies vaccine, have not been shown to cause ADEM.
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.
Ataxia	Vaccines have not been shown to cause ataxia.

(continued)

(continued)

No Causal Relationship Established With Vaccines Currently Routinely Recommended for the General Population in The United States[1]

Adverse Event	Conclusion
Autism	Childhood vaccines do not cause autism. Maternal vaccines have not been shown to cause autism.
Bell's Palsy	One influenza vaccine used in other countries (no longer available) did cause Bell's Palsy. US vaccines have not been shown to cause Bell's Palsy.
Brachial Neuritis	Vaccines have not been shown to cause brachial neuritis.
Chronic Fatigue Syndrome	Vaccines have not been shown to cause chronic fatigue syndrome.
Chronic Inflammatory Disseminated Polyneuropathy (CIDP)	Vaccines have not been shown to cause CIDP.
Chronic Urticaria	Vaccines have not been shown to cause chronic urticaria.
Complex Regional Pain Syndrome (CRPS)	Vaccines have not been shown to cause CRPS.
Diabetes	Vaccines do not cause diabetes.
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.

(continued)

No Causal Relationship Established With Vaccines Currently Routinely Recommended for the General Population in The United States[1]

Adverse Event	Conclusion
Infantile Spasms	Vaccines have not been shown to cause infantile spasms.
Multiple Sclerosis (MS)	Influenza vaccine does not cause MS in adults. Influenza vaccine has not been shown to cause MS in children. Other vaccines have not been shown to cause MS.
Myocardial Infarction (MI)	Vaccines have not been shown to cause MI.
Myocarditis	Smallpox vaccine can very rarely cause myocarditis, but is not routinely recommended to the general population in the US. Other vaccines have not been shown to cause myocarditis.
Narcolepsy	Current vaccines have not been shown to cause narcolepsy. AS03-adjuvanted 2009 pandemic H1N1 influenza vaccine used in Europe (not used in the US) did very rarely cause narcolepsy.
Neuromyelitis Optica	Vaccines have not been shown to cause neuromyelitis optica.
Oculorespiratory syndrome (ORS)	Two influenza vaccines used in Canada (but not used in the US) 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.
Polyarteritis Nodosa	Vaccines have not been shown to cause polyarteritis nodosa.

(continued)

(continued)

No Causal Relationship Established With Vaccines

Currently Routinely Recommended for the General Population in The United States[1]

Adverse Event	Conclusion
Primary Ovarian Insufficiency (POI)	Vaccines have not been shown to cause POI.
Transverse Myelitis	Vaccines have not been shown to cause transverse myelitis.
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	Maternal vaccines have not been shown to cause spontaneous abortion.
Stroke	Vaccines have not been shown to cause stroke.
Sudden Infant Death Syndrome (SIDS)	DTP and hepatitis B vaccines do not cause SIDS. Other vaccines have not been shown to cause SIDS.
Systemic Lupus Erythematosus (SLE)	Vaccines have not been shown to cause SLE.
Vasculitis	Vaccines have not been shown to cause vasculitis.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Maglione MA, G.C., Das L, Raaen L, Smith A, Chari R, Newberry S, Hempel S, Shanman R, Perry T, Goetz MB, *Safety of Vaccines Used for Routine Immunization in the United States. Evidence Report/Technology Assessment No. 215*. 2014, Agency for Healthcare Research and Quality: Rockville, MD.
3. Maglione, M.A., et al., *Safety of vaccines used for routine immunization of U.S. children: a systematic review.* Pediatrics, 2014. **134**(2): p. 325–37.

Chapter 20
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; 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 US[1]

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_20

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 were recommended for children under two years of age. As new vaccines have been developed, the 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 US as part of the rigorous Food and Drug Administration (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 (AAP) and the American Academy of Family Physicians (AAFP) 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 [1–12].

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 [13–16]. See the *Do Vaccines Cause Seizures?* summary for more details.

Febrile seizures occurred at a rate of 26.4 per 1,000 person-years after MMR and 84.6 per 1,000 person-years after MMRV (ProQuad®) in the 7–10 days after vaccination [17]. 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®) [17–22]. There is no increased risk of fever or febrile seizures in children receiving their second dose of measles-containing vaccine at 4–6 years of age, whether given MMR or MMRV [23, 24]. Delaying MMR or MMRV vaccines past 15 months of age results in a higher risk of seizures than vaccinating according to the recommended schedule [25, 26].

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 [16].

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 [27]. A large Vaccine Safety Datalink (VSD) study found no association between seizures and the DTaP-IPV combination vaccine (Kinrix®) among children 4–6 years of age [28].

Two methodologically sound, controlled epidemiological studies and a meta-analysis found no association between autism spectrum disorder (ASD) and simultaneous vaccination with multiple vaccines [29–31]. 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 [32].

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 recommended childhood immunization schedule [33].

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 [34].

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 [35]

A phase II randomized study found that co-administration of bivalent meningococcal B vaccine and DTaP/IPV was safe and well tolerated [36].

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 [37], 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 [38]. 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 [39].

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 2–4 years with infections not targeted by the vaccines versus children without such infections [40].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family, and vaccinate your child using the safest schedule possible. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about receiving multiple vaccines in the same visit?
Step 2: Briefly address specific concerns, if any
• Our practice follows the recommended childhood schedule which is carefully constructed by experts to provide the greatest possible safety and protection against disease. Alternative schedules have not been studied nearly as well. • Delaying vaccines or spreading out the schedule leaves babies at risk of getting diseases, particularly when they are at highest risk of getting very ill. • 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 before approval for use in the US by the FDA.

(continued)

(continued)

Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time. • For many of the diseases we're talking about, the risk is greatest for the younger infants, which is why it's important to get infants vaccinated as soon as they are eligible.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Phadke, V.K., et al., *Association Between Vaccine Refusal and Vaccine-Preventable Diseases in the United States: A Review of Measles and Pertussis.* JAMA, 2016. **315**(11): p. 1149–58.
2. Feikin, D.R., et al., *Individual and community risks of measles and pertussis associated with personal exemptions to immunization.* JAMA, 2000. **284**(24): p. 3145–50.
3. Omer, S.B., et al., *Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases.* N Engl J Med, 2009. **360**(19): p. 1981–8.
4. Salmon, D.A., et al., *Health consequences of religious and philosophical exemptions from immunization laws: individual and societal risk of measles.* JAMA, 1999. **282**(1): p. 47–53.
5. Smith, P.J., et al., *The association between intentional delay of vaccine administration and timely childhood vaccination coverage.* Public Health Rep, 2010. **125**(4): p. 534–41.

6. Luman, E.T., et al., *Timeliness of childhood vaccinations in the United States: days undervaccinated and number of vaccines delayed.* JAMA, 2005. **293**(10): p. 1204–11.
7. *Invasive Haemophilus influenzae Type B disease in five young children--Minnesota, 2008.* MMWR Morb Mortal Wkly Rep, 2009. **58**(3): p. 58–60.
8. Glanz, J.M., et al., *Parental refusal of varicella vaccination and the associated risk of varicella infection in children.* Arch Pediatr Adolesc Med, 2010. **164**(1): p. 66–70.
9. Glanz, J.M., et al., *Parental decline of pneumococcal vaccination and risk of pneumococcal related disease in children.* Vaccine, 2011. **29**(5): p. 994–9.
10. Omer, S.B., et al., *Nonmedical exemptions to school immunization requirements: secular trends and association of state policies with pertussis incidence.* JAMA, 2006. **296**(14): p. 1757–63.
11. Zipprich, J., et al., *Measles outbreak--California, December 2014-February 2015.* MMWR Morb Mortal Wkly Rep, 2015. **64**(6): p. 153–4.
12. Clemmons, N.S., et al., *Measles - United States, January 4-April 2, 2015.* MMWR Morb Mortal Wkly Rep, 2015. **64**(14): p. 373–6.
13. (AAP), A.A.o.P., *Neurodiagnostic evaluation of the child with a simple febrile seizure.* Pediatrics, 2011. **127**(2): p. 389–94.
14. (AAP), A.A.o.P., *Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures.* Pediatrics, 2008. **121**(6): p. 1281–6.
15. Bonhoeffer, J., et al., *Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation.* Vaccine, 2004. **22**(5–6): p. 557–62.
16. Tse, A., et al., *Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011.* Vaccine, 2012. **30**(11): p. 2024–31.
17. Klein, N.P., et al., *Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures.* Pediatrics, 2010. **126**(1): p. e1–8.
18. Jacobsen, S.J., et al., *Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting.* Vaccine, 2009. **27**(34): p. 4656–61.
19. Klopfer, S.O., et al., *Analysis of safety data in children after receiving two doses of ProQuad(R) (MMRV).* Vaccine, 2014. **32**(52): p. 7154–60.

20. Macartney, K.K., et al., *Febrile seizures following measles and varicella vaccines in young children in Australia.* Vaccine, 2015. **33**(11): p. 1412–7.
21. MacDonald, S.E., et al., *Risk of febrile seizures after first dose of measles-mumps-rubella-varicella vaccine: a population-based cohort study.* Cmaj, 2014. **186**(11): p. 824–9.
22. Schink, T., et al., *Risk of febrile convulsions after MMRV vaccination in comparison to MMR or MMR+V vaccination.* Vaccine, 2014. **32**(6): p. 645–50.
23. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, Hamborsky J, Kroger A, Wolfe S, eds. 2015, Centers for Disease Control and Prevention: Washington D.C.
24. Centers for Disease Control and Prevention. *Vaccine Information Statements (VIS)*. August 7, 2015 [cited 2015; Available from: http://www.cdc.gov/vaccines/hcp/vis/current-vis.html
25. Hambidge, S.J., et al., *Timely versus delayed early childhood vaccination and seizures.* Pediatrics, 2014. **133**(6): p. e1492–9.
26. Rowhani-Rahbar, A., et al., *Effect of age on the risk of Fever and seizures following immunization with measles-containing vaccines in children.* JAMA Pediatr, 2013. **167**(12): p. 1111–7.
27. Sun, Y., et al., *Risk of febrile seizures and epilepsy after vaccination with diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenzae type B.* JAMA, 2012. **307**(8): p. 823–31.
28. Daley, M.F., et al., *Safety of diphtheria, tetanus, acellular pertussis and inactivated poliovirus (DTaP-IPV) vaccine.* Vaccine, 2014. **32**(25): p. 3019–24.
29. Uno, Y., et al., *The combined measles, mumps, and rubella vaccines and the total number of vaccines are not associated with development of autism spectrum disorder: the first case-control study in Asia.* Vaccine, 2012. **30**(28): p. 4292–8.
30. DeStefano, F., C.S. Price, and E.S. Weintraub, *Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism.* J Pediatr, 2013. **163**(2): p. 561–7.
31. Taylor, L.E., A.L. Swerdfeger, and G.D. Eslick, *Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies.* Vaccine, 2014. **32**(29): p. 3623–9.
32. Institute of Medicine Immunization Safety Review, C., in *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction*, K. Stratton, C.B. Wilson, and M.C. McCormick, Editors. 2002, National Academies Press (US): Washington (DC).

33. Institute of Medicine, in *The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies*. 2013, National Academies Press (US): Washington (DC).
34. Ofori-Anyinam, O., et al., Immunogenicity and safety of an inactivated quadrivalent influenza vaccine co-administered with a 23-valent pneumococcal polysaccharide vaccine versus separate administration, in adults >/=50years of age: Results from a phase III, randomized, non-inferiority trial. Vaccine, 2017. **35**(46): p. 6321–28.
35. Gasparini, R., et al., Safety and Immunogenicity of a Quadrivalent Meningococcal Conjugate Vaccine and Commonly Administered Vaccines After Coadministration. Pediatr Infect Dis J, 2016. **35**(1): p. 81–93.
36. Vesikari, T., et al., Immunogenicity, Safety, and Tolerability of Bivalent rLP2086 Meningococcal Group B Vaccine Administered Concomitantly With Diphtheria, Tetanus, and Acellular Pertussis and Inactivated Poliomyelitis Vaccines to Healthy Adolescents. J Pediatric Infect Dis Soc, 2016. **5**(2): p. 180–7.
37. Sukumaran, L., et al., *Infant Hospitalizations and Mortality After Maternal Vaccination.* Pediatrics, 2018.
38. Sukumaran, L., et al., *Association of Tdap Vaccination With Acute Events and Adverse Birth Outcomes Among Pregnant Women With Prior Tetanus-Containing Immunizations.* JAMA, 2015. **314**(15): p. 1581–7.
39. Sukumaran, L., et al., *Safety of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis and Influenza Vaccinations in Pregnancy.* Obstet Gynecol, 2015. **126**(5): p. 1069–74.
40. Glanz, J.M., et al., *Association between estimated cumulative vaccine antigen exposure through the first 23 months of life and non–vaccine-targeted infections from 24 through 47 months of age.* JAMA, 2018. **319**(9): p. 906–13.

Chapter 21
Do Vaccine Ingredients Cause Adverse Events?

Conclusion: Certain ingredients (other than disease-specific antigens), such as gelatin or neomycin, present in some vaccines **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 US[1] **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 [1].

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_21

However, the exposure exceeded the United States Environmental Protection Agency (EPA) guidelines for methylmercury exposure; there were no available guidelines for ethyl-mercury, 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 ethyl-mercury 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).

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 [2]. 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 [3]. 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 contained in vaccines (which is typically much less than is found naturally in the body, common food or the envi-

ronment), and serve only to stabilize the vaccine or enhance the immune response [4]. 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 Bloomber School of Public Health 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 ASD and thimerosal in vaccines [5–10], as well as the relevant systematic reviews [11, 12] and a meta-analysis [13]. 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 [14]. 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% [15–18]. 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 [19, 20]. A 2017 review found that current data do not support a causal relationship between aluminum containing vaccines and a variety of autoimmune disorders [21]. 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 [22].

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 [4]. See the *Do Vaccines Cause Hypersensitivity Reactions?* summary for more details.

Talking Points

Step 1: Establish empathy and credibility

- As your doctor, I know that you want to make the best choices about vaccines for you and your family, and I understand why you want to be careful with what goes into your (your child's) body.
- I also know there is a lot of information out there, and it is difficult to figure out who to trust.
- Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about vaccine ingredients?

Step 2: Briefly address specific concerns, if any

- Based on the best available science, it does not appear that ingredients contained in vaccines cause any serious adverse events other than specific allergic reactions.
- Ingredients in vaccines have important purposes, such as preventing contamination, stabilizing the vaccine, or enhancing the immune response to the vaccine.
- Thimerosal, a preservative that used to be in some vaccines, contains ethyl-mercury. Thimerosal is no longer used as a preservative in childhood vaccines except influenza - small amounts are still present in multi-dose vials of influenza vaccine to prevent contamination. Other vaccines may contain tiny, trace amounts of thimerosal that are too small to have an impact.
- Some vaccine ingredients can sound scary just based on their scientific names. Remember that dihydrogen monoxide is just another way to say water.
- Some ingredients, such as aluminum and formaldehyde, are toxic when consumed in large quantities. However, in the tiny amounts present in vaccines, they present no danger. These ingredients are often found in food or naturally occurring in the body in much larger quantities than is in any vaccine. For example, formaldehyde is found in many foods, including pears, as well as naturally in the body, in much larger quantities than is in vaccines.

Step 3: Pivot to disease risk

- Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.

(continued)

Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Ball, L.K., R. Ball, and R.D. Pratt, *An assessment of thimerosal use in childhood vaccines.* Pediatrics, 2001. **107**(5): p. 1147–54.
2. Bernard, S., et al., *Autism: a novel form of mercury poisoning.* Med Hypotheses, 2001. **56**(4): p. 462–71.
3. Nelson, K.B. and M.L. Bauman, *Thimerosal and autism?* Pediatrics, 2003. **111**(3): p. 674–9.
4. Offit, P.A. and R.K. Jew, *Addressing parents' concerns: do vaccines contain harmful preservatives, adjuvants, additives, or residuals?* Pediatrics, 2003. **112**(6 Pt 1): p. 1394–7.
5. Hviid, A., et al., *Association between thimerosal-containing vaccine and autism.* JAMA, 2003. **290**(13): p. 1763–6.
6. Verstraeten, T., et al., *Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases.* Pediatrics, 2003. **112**(5): p. 1039–48.
7. Andrews, N., et al., *Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United kingdom does not support a causal association.* Pediatrics, 2004. **114**(3): p. 584–91.
8. Croen, L.A., et al., *Maternal Rh D status, anti-D immune globulin exposure during pregnancy, and risk of autism spectrum disorders.* Am J Obstet Gynecol, 2008. **199**(3): p. 234.e1–6.
9. Price, C.S., et al., *Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism.* Pediatrics, 2010. **126**(4): p. 656–64.
10. Uno, Y., et al., *Early exposure to the combined measles-mumps-rubella vaccine and thimerosal-containing vaccines and risk of autism spectrum disorder. Vaccine*, 2015. **33**(21): p. 2511–6.

11. Parker, S.K., et al., *Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data.* Pediatrics, 2004. **114**(3): p. 793–804.
12. Schultz, S.T., *Does thimerosal or other mercury exposure increase the risk for autism? A review of current literature.* Acta Neurobiol Exp (Wars), 2010. **70**(2): p. 187–95.
13. Taylor, L.E., A.L. Swerdfeger, and G.D. Eslick, *Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies.* Vaccine, 2014. **32**(29): p. 3623–9.
14. Institute of Medicine Immunization Safety Review, C., *The National Academies Collection: Reports funded by National Institutes of Health*, in *Immunization Safety Review: Vaccines and Autism*. 2004, National Academies Press (US): Washington (DC).
15. Baylor, N.W., W. Egan, and P. Richman, *Aluminum salts in vaccines--US perspective.* Vaccine, 2002. **20 Suppl 3**: p. S18–23.
16. Bergfors, E., et al., *How common are long-lasting, intensely itching vaccination granulomas and contact allergy to aluminium induced by currently used pediatric vaccines? A prospective cohort study.* Eur J Pediatr, 2014. **173**(10): p. 1297–307.
17. Bergfors, E., B. Trollfors, and A. Inerot, *Unexpectedly high incidence of persistent itching nodules and delayed hypersensitivity to aluminium in children after the use of adsorbed vaccines from a single manufacturer.* Vaccine, 2003. **22**(1): p. 64–9.
18. Netterlid, E., et al., *Persistent itching nodules after the fourth dose of diphtheria-tetanus toxoid vaccines without evidence of delayed hypersensitivity to aluminium.* Vaccine, 2004. **22**(27–28): p. 3698–706.
19. Keith, L.S., D.E. Jones, and C.H. Chou, *Aluminum toxicokinetics regarding infant diet and vaccinations.* Vaccine, 2002. **20 Suppl 3**: p. S13–7.
20. Mitkus, R.J., et al., *Updated aluminum pharmacokinetics following infant exposures through diet and vaccination.* Vaccine, 2011. **29**(51): p. 9538–43.
21. Ameratunga, R., et al., *Evidence Refuting the Existence of Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants (ASIA)*. J Allergy Clin Immunol Pract, 2017. **5**(6): p. 1551–1555.e1.
22. Stassijns, J., et al., *A systematic review and meta-analysis on the safety of newly adjuvanted vaccines among children*. Vaccine, 2016. **34**(6): p. 714–22.

Chapter 22
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 US[1] **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 [1]. Studies published since the 2012 IOM report have found no association between ADEM and the pandemic H1N1 influenza vaccine Pandemrix™ [2], quadrivalent HPV vaccine (Gardasil®) [3–5] or hepatitis B vaccine [4]. However, one recent Vaccine Safety Datalink study did find a possible

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_22

association between ADEM and Tdap vaccine estimated at no more than 1.16 excess cases per million vaccines administered [6].

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 [1]. However, the pathophysiology of ADEM is not fully understood. Also, ADEM has been reported 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 [7] and molecular mimicry [8, 9], 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 [10]. Although a temporal association with ADEM has been described for vaccines such as Japanese encephalitis, yellow fever, measles, influenza, varicella, and hepatitis [11–13], the only clear pathological association ever demonstrated was with the Semple rabies vaccine [14].

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 [15, 16]; however, these were insufficient to conclude a causal association [1]. The report also described one case of ADEM after tetanus toxoid vaccination [17]; 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 vac-

cines, as the publications reviewed provided no evidence beyond a temporal association [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about ADEM?
Step 2: Briefly address specific concerns, if any
• An older rabies vaccine was associated with ADEM. However, other vaccines including the current rabies vaccine have not been shown to cause ADEM, and rabies vaccine is not recommended for most people.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Persson, I., et al., *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): p. 172–90.
3. Chao, C., et al., *Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine.* J Intern Med, 2012. **271**(2): p. 193–203.
4. Langer-Gould, A., et al., *Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases.* JAMA Neurol, 2014. **71**(12): p. 1506–13.
5. Scheller, N.M., et al., *Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system.* JAMA, 2015. **313**(1): p. 54–61.
6. Baxter, R., et al., *Acute Demyelinating Events Following Vaccines: A Case-Centered Analysis.* Clin Infect Dis, 2016.
7. Harter, D.H. and P.W. Choppin, *Possible mechanisms in the pathogenesis of "postinfectious" encephalomyelitis.* Res Publ Assoc Res Nerv Ment Dis, 1971. **49**: p. 342–55.
8. Miller, S.D., et al., *Evolution of the T-cell repertoire during the course of experimental immune-mediated demyelinating diseases.* Immunol Rev, 1995. **144**: p. 225–44.
9. Evans, C.F., et al., *Viral infection of transgenic mice expressing a viral protein in oligodendrocytes leads to chronic central nervous system autoimmune disease.* J Exp Med, 1996. **184**(6): p. 2371–84.
10. Paterson, P.Y., *Joseph E. Smadel Memorial Lecture: neuroimmunologic diseases of animals and humans.* Rev Infect Dis, 1979. **1**(3): p. 469–82.
11. Ohtaki, E., et al., *Acute disseminated encephalomyelitis after Japanese B encephalitis vaccination.* Pediatr Neurol, 1992. **8**(2): p. 137–9.
12. Sejvar, J.J., et al., *Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data.* Vaccine, 2007. **25**(31): p. 5771–92.

13. Karussis, D. and P. Petrou, *The spectrum of post-vaccination inflammatory CNS demyelinating syndromes.* Autoimmun Rev, 2014. **13**(3): p. 215–24.
14. Hemachudha, T., et al., *Myelin basic protein as an encephalitogen in encephalomyelitis and polyneuritis following rabies vaccination.* N Engl J Med, 1987. **316**(7): p. 369–74.
15. Konstantinou, D., et al., *Two episodes of leukoencephalitis associated with recombinant hepatitis B vaccination in a single patient.* Clin Infect Dis, 2001. **33**(10): p. 1772–3.
16. Tourbah, A., et al., *Encephalitis after hepatitis B vaccination: recurrent disseminated encephalitis or MS?* Neurology, 1999. **53**(2): p. 396–401.
17. Lopez Pison, J., et al., *[Episodic disseminated inflammation of the central nervous system. Case mix review over a 13 year period].* Rev Neurol, 2004. **38**(5): p. 405–10.

Chapter 23
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 (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 US[1] **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 [1].

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_23

The 2012 report by the Institute of Medicine (IOM) [2], now called the National Academy of Medicine (NAM), described four studies in women [3–6] and seven studies in children [7–13] 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 [5, 6] and two studies assessing arthropathy in men [14, 15] after rubella or MMR vaccination; one study assessing the association between HPV vaccine and transient arthralgia [16]; one study assessing the association between hepatitis B vaccination and exacerbation of rheumatoid arthritis [17]; and two studies assessing the association between diphtheria or tetanus toxoid vaccination and chronic arthritis [15, 18]; 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 [2].

Most studies published since the 2012 IOM report did not show a statistically significant association between influenza and HPV vaccines and arthralgia [19–22]. 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 [23], 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 [24]. No association has been found between vaccination and arthritis [25–29]. Studies in patients with autoimmune inflammatory arthritis showed no change in disease severity or relapse rates after influenza vaccination [30–36].

Proposed biological mechanism: Environmental factors such as infections may trigger or contribute to the pathogenesis of arthritis; however, the exact mechanisms are still unclear [37–40].

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 [3, 41–43];

however, there was less evidence for a relationship between rubella vaccine in women and chronic arthralgia [43–45] or arthritis [42, 45]. There was little evidence for a relationship between rubella vaccine and arthropathy in men, transient arthralgia in children or chronic arthropathy in children [46, 47], for influenza vaccine and onset or exacerbation of arthropathy [48], or for hepatitis B vaccine and onset or exacerbation of arthritis [49, 50]. The IOM also concluded that there was no mechanistic evidence for an association between all other vaccines and arthralgia, arthritis or arthropathy.

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience, and what I share with my patients, my family and my friends about arthritis and arthralgia (joint pain)?
Step 2: Briefly address specific concerns, if any
• The MMR vaccine, which provides protection against measles, mumps, and rubella, can cause mild arthralgia and arthritis very commonly in adult women lasting up to 3 weeks, but only rarely in children. • Based on the best available science, it does not appear that other vaccines cause arthralgia or arthritis.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time. • Measles is one of the most contagious diseases and can cause a high fever, rash, and in some cases inflammation of the brain, seizures, and death.

(continued)

(continued)

Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases. • Over 99% of children who receive two doses of MMR develop immune protection against measles. The MMR vaccine is also over 90% effective against rubella, and over 66% effective against mumps.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, Hamborsky J, Kroger A, Wolfe S, eds. 2015, Centers for Disease Control and Prevention: Washington D.C.
2. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
3. Mitchell, L.A., et al., *HLA-DR class II associations with rubella vaccine-induced joint manifestations.* J Infect Dis, 1998. **177**(1): p. 5–12.
4. Slater, P.E., et al., *Absence of an association between rubella vaccination and arthritis in underimmune postpartum women.* Vaccine, 1995. **13**(16): p. 1529–32.
5. Ray, P., et al., *Risk of chronic arthropathy among women after rubella vaccination. Vaccine Safety Datalink Team.* JAMA, 1997. **278**(7): p. 551–6.
6. Tingle, A.J., et al., *Randomised double-blind placebo-controlled study on adverse effects of rubella immunisation in seronegative women.* Lancet, 1997. **349**(9061): p. 1277–81.
7. Benjamin, C.M., G.C. Chew, and A.J. Silman, *Joint and limb symptoms in children after immunisation with measles, mumps, and rubella vaccine.* BMJ, 1992. **304**(6834): p. 1075–8.

8. Davis, R.L., et al., *MMR2 immunization at 4 to 5 years and 10 to 12 years of age: a comparison of adverse clinical events after immunization in the Vaccine Safety Datalink project. The Vaccine Safety Datalink Team.* Pediatrics, 1997. **100**(5): p. 767–71.
9. Dos Santos, B.A., et al., *An evaluation of the adverse reaction potential of three measles-mumps-rubella combination vaccines.* Rev Panam Salud Publica, 2002. **12**(4): p. 240–6.
10. Heijstek, M.W., et al., *Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis.* Ann Rheum Dis, 2007. **66**(10): p. 1384–7.
11. LeBaron, C.W., et al., *Evaluation of potentially common adverse events associated with the first and second doses of measles-mumps-rubella vaccine.* Pediatrics, 2006. **118**(4): p. 1422–30.
12. Peltola, H. and O.P. Heinonen, *Frequency of true adverse reactions to measles-mumps-rubella vaccine. A double-blind placebo-controlled trial in twins.* Lancet, 1986. **1**(8487): p. 939–42.
13. Virtanen, M., et al., *Day-to-day reactogenicity and the healthy vaccinee effect of measles-mumps-rubella vaccination.* Pediatrics, 2000. **106**(5): p. E62.
14. Chen, R.T., et al., *Adverse events following measles-mumps-rubella and measles vaccinations in college students.* Vaccine, 1991. **9**(5): p. 297–9.
15. Pattison, E., et al., *Environmental risk factors for the development of psoriatic arthritis: results from a case-control study.* Ann Rheum Dis, 2008. **67**(5): p. 672–6.
16. Bhatla, N., et al., *Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women.* J Obstet Gynaecol Res, 2010. **36**(1): p. 123–32.
17. Elkayam, O., M. Yaron, and D. Caspi, *Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis.* Ann Rheum Dis, 2002. **61**(7): p. 623–5.
18. Bengtsson, C., et al., *Common vaccinations among adults do not increase the risk of developing rheumatoid arthritis: results from the Swedish EIRA study.* Ann Rheum Dis, 2010. **69**(10): p. 1831–3.
19. Frey, S., et al., *Clinical efficacy of cell culture-derived and egg-derived inactivated subunit influenza vaccines in healthy adults.* Clin Infect Dis, 2010. **51**(9): p. 997–1004.
20. Jackson, L.A., et al., *Safety, efficacy, and immunogenicity of an inactivated influenza vaccine in healthy adults: a randomized, placebo-controlled trial over two influenza seasons.* BMC Infect Dis, 2010. **10**: p. 71.

21. Madhi, S.A., et al., *Trivalent inactivated influenza vaccine in African adults infected with human immunodeficient virus: double blind, randomized clinical trial of efficacy, immunogenicity, and safety.* Clin Infect Dis, 2011. **52**(1): p. 128–37.
22. Ngan, H.Y., et al., *Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in healthy Chinese women from Hong Kong.* Hong Kong Med J, 2010. **16**(3): p. 171–9.
23. Barrett, P.N., et al., *Efficacy, safety, and immunogenicity of a Vero-cell-culture-derived trivalent influenza vaccine: a multicentre, double-blind, randomised, placebo-controlled trial.* Lancet, 2011. **377**(9767): p. 751–9.
24. Kim, S.C., et al., *Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in 15–25 years old healthy Korean women.* J Gynecol Oncol, 2011. **22**(2): p. 67–75.
25. Chao, C., et al., *Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine.* J Intern Med, 2012. **271**(2): p. 193–203.
26. Eder, L., et al., *Association between environmental factors and onset of psoriatic arthritis in patients with psoriasis.* Arthritis Care Res (Hoboken), 2011. **63**(8): p. 1091–7.
27. Bardage, C., et al., *Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden* BMJ, 2011. **343**: p. d5956.
28. Baxter, R., et al., *A postmarketing evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in children 5 through 17 years of age.* Vaccine, 2012. **30**(19): p. 2989–98.
29. Ray, P., et al., *Risk of rheumatoid arthritis following vaccination with tetanus, influenza and hepatitis B vaccines among persons 15–59 years of age.* Vaccine, 2011. **29**(38): p. 6592–7.
30. Aikawa, N.E., et al., *Glucocorticoid: major factor for reduced immunogenicity of 2009 influenza A (H1N1) vaccine in patients with juvenile autoimmune rheumatic disease.* J Rheumatol, 2012. **39**(1): p. 167–73.
31. Gabay, C., et al., *Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study.* Arthritis Rheum, 2011. **63**(6): p. 1486–96.

32. Muller, R.B., et al., *Efficient boosting of the antiviral T cell response in B cell-depleted patients with autoimmune rheumatic diseases following influenza vaccination.* Clin Exp Rheumatol, 2013. **31**(5): p. 723–30.
33. Oren, S., et al., *Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response.* Ann Rheum Dis, 2008. **67**(7): p. 937–41.
34. Saad, C.G., et al., *Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases.* Ann Rheum Dis, 2011. **70**(6): p. 1068–73.
35. Shinoki, T., et al., *Safety and response to influenza vaccine in patients with systemic-onset juvenile idiopathic arthritis receiving tocilizumab.* Mod Rheumatol, 2012. **22**(6): p. 871–6.
36. Toplak, N., et al., *Safety and efficacy of influenza vaccination in a prospective longitudinal study of 31 children with juvenile idiopathic arthritis.* Clin Exp Rheumatol, 2012. **30**(3): p. 436–44.
37. Angeles-Han, S. and S. Prahalad, *The genetics of juvenile idiopathic arthritis: what is new in 2010?* Curr Rheumatol Rep, 2010. **12**(2): p. 87–93.
38. Berkun, Y. and S. Padeh, *Environmental factors and the geoepidemiology of juvenile idiopathic arthritis.* Autoimmun Rev, 2010. **9**(5): p. A319–24.
39. Aslan, M., et al., *Do infections trigger juvenile idiopathic arthritis?* Rheumatol Int, 2011. **31**(2): p. 215–20.
40. Frenkel, L.M., et al., *A search for persistent rubella virus infection in persons with chronic symptoms after rubella and rubella immunization and in patients with juvenile rheumatoid arthritis.* Clin Infect Dis, 1996. **22**(2): p. 287–94.
41. Best, J.M., J.E. Banatvala, and J.M. Bowen, *New Japanese rubella vaccine: comparative trials.* Br Med J, 1974. **3**(5925): p. 221–4.
42. Tingle, A.J., et al., *Prospective immunological assessment of arthritis induced by rubella vaccine.* Infect Immun, 1983. **40**(1): p. 22–8.
43. Mitchell, L.A., et al., *Rubella virus vaccine associated arthropathy in postpartum immunized women: influence of preimmunization serologic status on development of joint manifestations.* J Rheumatol, 2000. **27**(2): p. 418–23.
44. Mitchell, L.A., et al., *Chronic rubella vaccine-associated arthropathy.* Arch Intern Med, 1993. **153**(19): p. 2268–74.

45. Tingle, A.J., et al., *Postpartum rubella immunization: association with development of prolonged arthritis, neurological sequelae, and chronic rubella viremia.* J Infect Dis, 1985. **152**(3): p. 606–12.
46. Geiger, R., et al., *Persistent rubella infection after erroneous vaccination in an immunocompromised patient with acute lymphoblastic leukemia in remission.* J Med Virol, 1995. **47**(4): p. 442–4.
47. Peters, M.E. and S. Horowitz, *Bone changes after rubella vaccination.* AJR Am J Roentgenol, 1984. **143**(1): p. 27–8.
48. Thurairajan, G., et al., *Polyarthropathy, orbital myositis and posterior scleritis: an unusual adverse reaction to influenza vaccine.* Br J Rheumatol, 1997. **36**(1): p. 120–3.
49. Biasi, D., et al., *A new case of reactive arthritis after hepatitis B vaccination.* Clin Exp Rheumatol, 1993. **11**(2): p. 215.
50. Maillefert, J.F., et al., *Rheumatic disorders developed after hepatitis B vaccination.* Rheumatology (Oxford), 1999. **38**(10): p. 978–83.

Chapter 24
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 US[1] **have not been shown to cause** asthma or asthma exacerbation.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM) [1], 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 [2–10]. 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 [11–17]. However, a 2015 white paper on the safety of influenza vaccines concluded that LAIV was associated with an increase in wheezing in children ages 18–35 months who had a history of wheezing [18]. Two studies of the 2013–2014 and 2014–2015

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_24

flu seasons in the United Kingdom study found that LAIV seemed to be well tolerated among those with well-controlled asthma or recurrent wheezing [19, 20]. 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 season [21]. One study published in 2015 suggests a possible protective effect of MMR vaccination against asthma [22].

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 [23].

The 2012 IOM report described cases of asthma exacerbation after both inactivated and live attenuated influenza vaccination [24]; however, even after considering knowledge about the aforementioned natural infection, the IOM concluded that this mechanistic evidence was weak [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about asthma?
Step 2: Briefly address specific concerns, if any
• Studies have concluded that flu vaccines do not cause asthma.

(continued)

Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time. • The flu can cause a sore throat, fever, headache, and cough. It can also cause more severe illness, such as pneumonia and sinus infections. More than 20,000 people die from the flu in the US every year. • Pregnant women and infants are at high risk of developing serious complications from the flu and dying from the flu.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. *The safety of inactivated influenza vaccine in adults and children with asthma.* N Engl J Med, 2001. **345**(21): p. 1529–36.
3. Bueving, H.J., et al., *Does influenza vaccination exacerbate asthma in children?* Vaccine, 2004. **23**(1): p. 91–6.
4. France, E.K., et al., *Safety of the trivalent inactivated influenza vaccine among children: a population-based study.* Arch Pediatr Adolesc Med, 2004. **158**(11): p. 1031–6.

5. Hambidge, S.J., et al., *Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old.* JAMA, 2006. **296**(16): p. 1990–7.
6. Kmiecik, T., et al., *Influenza vaccination in adults with asthma: safety of an inactivated trivalent influenza vaccine.* J Asthma, 2007. **44**(10): p. 817–22.
7. Nicholson, K.G., et al., *Randomised placebo-controlled crossover trial on effect of inactivated influenza vaccine on pulmonary function in asthma.* Lancet, 1998. **351**(9099): p. 326–31.
8. Pedroza, A., et al., *The safety and immunogenicity of influenza vaccine in children with asthma in Mexico.* Int J Infect Dis, 2009. **13**(4): p. 469–75.
9. Stenius-Aarniala, B., et al., *Lack of clinical exacerbations in adults with chronic asthma after immunization with killed influenza virus.* Chest, 1986. **89**(6): p. 786–9.
10. Tata, L.J., et al., *Does influenza vaccination increase consultations, corticosteroid prescriptions, or exacerbations in subjects with asthma or chronic obstructive pulmonary disease?* Thorax, 2003. **58**(10): p. 835–9.
11. Belshe, R.B., et al., *Live attenuated versus inactivated influenza vaccine in infants and young children.* N Engl J Med, 2007. **356**(7): p. 685–96.
12. Ashkenazi, S., et al., *Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections.* Pediatr Infect Dis J, 2006. **25**(10): p. 870–9.
13. Belshe, R.B., et al., *Safety, efficacy, and effectiveness of live, attenuated, cold-adapted influenza vaccine in an indicated population aged 5–49 years.* Clin Infect Dis, 2004. **39**(7): p. 920–7.
14. Bergen, R., et al., *Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents.* Pediatr Infect Dis J, 2004. **23**(2): p. 138–44.
15. Gaglani, M.J., et al., *Safety of the intranasal, trivalent, live attenuated influenza vaccine (LAIV) in children with intermittent wheezing in an open-label field trial.* Pediatr Infect Dis J, 2008. **27**(5): p. 444–52.
16. Piedra, P.A., et al., *Live attenuated influenza vaccine, trivalent, is safe in healthy children 18 months to 4 years, 5 to 9 years, and 10 to 18 years of age in a community-based, nonrandomized, open-label trial.* Pediatrics, 2005. **116**(3): p. e397–407.
17. Fleming, D.M., et al., *Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent*

inactivated influenza virus vaccine in children and adolescents with asthma. Pediatr Infect Dis J, 2006. **25**(10): p. 860–9.
18. Halsey, N.A., et al., *The safety of influenza vaccines in children: An Institute for Vaccine Safety white paper.* Vaccine, 2015. **33**: p. F1–F67.
19. Turner, P.J., et al., *Safety of live attenuated influenza vaccine in young people with egg allergy: multicentre prospective cohort study.* Bmj, 2015. **351**: p. h6291.
20. Turner, P.J., et al., *Safety of live attenuated influenza vaccine in atopic children with egg allergy.* J Allergy Clin Immunol, 2015. **136**(2): p. 376–81.
21. Baxter, R., et al., *Safety of quadrivalent live attenuated influenza vaccine in subjects aged 2–49years.* Vaccine, 2017. **35**(9): p. 1254–8.
22. Timmermann, C.A., et al., *Asthma and allergy in children with and without prior measles, mumps, and rubella vaccination.* Pediatr Allergy Immunol, 2015. **26**(8): p. 742–9.
23. Jackson, D.J. and S.L. Johnston, *The role of viruses in acute exacerbations of asthma.* J Allergy Clin Immunol, 2010. **125**(6): p. 1178–87; quiz 1188–9.
24. de Jongste, J.C., et al., *Bronchial responsiveness and leucocyte reactivity after influenza vaccine in asthmatic patients.* Eur J Respir Dis, 1984. **65**(3): p. 196–200.

Chapter 25
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 US[1] **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 [1].

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 57–180 days after vaccination [2]. Per the 2007 ACIP recommendations, acute cerebellar

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_25

ataxia has been previously described as potentially associated with single-antigen varicella vaccine (Varivax®); however, available data are insufficient to determine a causal association [3].

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 [1]. 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 [4]; 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 [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about ataxia (loss of full control of bodily movements)?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause ataxia.

(continued)

Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Klein, N.P., et al., *Safety of measles-containing vaccines in 1-year-old children.* Pediatrics, 2015. **135**(2): p. e321–9.
3. Marin, M., et al., *Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep, 2007. **56**(Rr-4): p. 1–40.
4. Landrigan, P.J. and J.J. Witte, *Neurologic disorders following live measles-virus vaccination.* JAMA, 1973. **223**(13): p. 1459–62.

Chapter 26
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 [1, 2]. 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 [3]. 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 [4, 5]. 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,

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_26

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 [6–11]. 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 [12–19], thimerosal in vaccines [20–24], and simultaneous vaccination with multiple vaccines [25, 26], in addition to the relevant systematic reviews [2, 27–30] and one meta-analysis [31]. Together, these studies included more than 1.8 million children. Notwithstanding 11 studies from another pair of authors [32–42], all of which had substantial methodological flaws [2, 28, 29, 43], 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 [44]. Another recent study showed that receiving Tdap vaccine during pregnancy is not associated with increased risk of ASD in the child [45].

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 [46]. 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 [3]. However, his referenced study was found to be fraudulent, and no evidence of persistent infection has been shown in studies that used appropriate methods [47–49]. Another proposed trigger for ASD was thimerosal, an ethyl-mercury 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 [50]; however, the degree of these similarities and the plausibility of this suspected association was refuted by neurologists [51]. The IOM found no valid mechanistic evidence connecting MMR or thimerosal-containing vaccines and ASD [1, 2].

Talking Points

Step 1: Establish empathy and credibility

- As your doctor, I know that you want to make the best choices about vaccines for you and your family.
- I also know there is a lot of information out there, and it is difficult to figure out who to trust.
- Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about autism?

(continued)

(continued)

Step 2: Briefly address specific concerns, if any
• The idea that childhood vaccines cause autism is a myth. Childhood vaccines do not cause autism. • There have been 15 well conducted studies to see if childhood vaccines cause autism. All of them have concluded that childhood vaccines do not cause autism. • MMR vaccine actually prevents congenital rubella syndrome and its associated cases of autism.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time. • Measles in particular is making a comeback in the United States and can cause inflammation of the brain, seizures, and death.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases. • Over 99% of children who receive two doses of MMR develop immune protection against measles. The MMR vaccine is also over 90% effective against rubella, and over 66% effective against mumps.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).

2. Institute of Medicine Immunization Safety Review, C., *The National Academies Collection: Reports funded by National Institutes of Health*, in *Immunization Safety Review: Vaccines and Autism*. 2004, National Academies Press (US): Washington (DC).
3. Wakefield, A.J., et al., *Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children.* Lancet, 1998. **351**(9103): p. 637–41.
4. Horton, R., *A statement by the editors of The Lancet.* Lancet, 2004. **363**(9411): p. 820–1.
5. Murch, S.H., et al., *Retraction of an interpretation.* Lancet, 2004. **363**(9411): p. 750.
6. Eggertson, L., *Lancet retracts 12-year-old article linking autism to MMR vaccines.* Cmaj, 2010. **182**(4): p. E199–200.
7. *Retraction--Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children.* Lancet, 2010. **375**(9713): p. 445.
8. Deer, B., *Wakefield's "autistic enterocolitis" under the microscope.* BMJ, 2010. **340**: p. c1127.
9. Deer, B., *How the case against the MMR vaccine was fixed.* BMJ, 2011. **342**: p. c5347.
10. Deer, B., *Secrets of the MMR scare. How the vaccine crisis was meant to make money.* BMJ, 2011. **342**: p. c5258.
11. Deer, B., *Secrets of the MMR scare. The Lancet's two days to bury bad news.* BMJ, 2011. **342**: p. c7001.
12. Taylor, B., et al., *Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association.* Lancet, 1999. **353**(9169): p. 2026–9.
13. Taylor, B., et al., *Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study.* BMJ, 2002. **324**(7334): p. 393–6.
14. Farrington, C.P., E. Miller, and B. Taylor, *MMR and autism: further evidence against a causal association.* Vaccine, 2001. **19**(27): p. 3632–5.
15. Madsen, K.M., et al., *A population-based study of measles, mumps, and rubella vaccination and autism.* N Engl J Med, 2002. **347**(19): p. 1477–82.
16. Smeeth, L., et al., *MMR vaccination and pervasive developmental disorders: a case-control study.* Lancet, 2004. **364**(9438): p. 963–9.
17. Makela, A., J.P. Nuorti, and H. Peltola, *Neurologic disorders after measles-mumps-rubella vaccination.* Pediatrics, 2002. **110**(5): p. 957–63.

18. Uno, Y., et al., *Early exposure to the combined measles-mumps-rubella vaccine and thimerosal-containing vaccines and risk of autism spectrum disorder.* Vaccine, 2015. **33**(21): p. 2511–6.
19. Jain, A., et al., *Autism occurrence by MMR vaccine status among US children with older siblings with and without autism.* JAMA, 2015. **313**(15): p. 1534–40.
20. Hviid, A., et al., *Association between thimerosal-containing vaccine and autism.* JAMA, 2003. **290**(13): p. 1763–6.
21. Verstraeten, T., et al., *Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases.* Pediatrics, 2003. **112**(5): p. 1039–48.
22. Andrews, N., et al., *Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United kingdom does not support a causal association.* Pediatrics, 2004. **114**(3): p. 584–91.
23. Croen, L.A., et al., *Maternal Rh D status, anti-D immune globulin exposure during pregnancy, and risk of autism spectrum disorders.* Am J Obstet Gynecol, 2008. **199**(3): p.234.e1–6.
24. Price, C.S., et al., *Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism.* Pediatrics, 2010. **126**(4): p. 656–64.
25. Uno, Y., et al., *The combined measles, mumps, and rubella vaccines and the total number of vaccines are not associated with development of autism spectrum disorder: the first case-control study in Asia.* Vaccine, 2012. **30**(28): p. 4292–8.
26. DeStefano, F., C.S. Price, and E.S. Weintraub, *Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism.* J Pediatr, 2013. **163**(2): p. 561–7.
27. Maglione, M.A., et al., *Safety of vaccines used for routine immunization of U.S. children: a systematic review.* Pediatrics, 2014. **134**(2): p. 325–37.
28. Parker, S.K., et al., *Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data.* Pediatrics, 2004. **114**(3): p. 793–804.
29. Schultz, S.T., *Does thimerosal or other mercury exposure increase the risk for autism? A review of current literature.* Acta Neurobiol Exp (Wars), 2010. **70**(2): p. 187–95.
30. Institute of Medicine Immunization Safety Review, C., in *Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism*, K. Stratton, et al., Editors. 2001, National Academies Press (US): Washington (DC).

31. Taylor, L.E., A.L. Swerdfeger, and G.D. Eslick, *Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies.* Vaccine, 2014. **32**(29): p. 3623–9.
32. Geier, M.R. and D.A. Geier, *Neurodevelopmental disorders after thimerosal-containing vaccines: a brief communication.* Exp Biol Med (Maywood), 2003. **228**(6): p. 660–4.
33. Geier, D.A. and M.R. Geier, *An assessment of the impact of thimerosal on childhood neurodevelopmental disorders.* Pediatr Rehabil, 2003. **6**(2): p. 97–102.
34. Geier, D. and M.R. Geier, *Neurodevelopmental disorders following thimerosal-containing childhood immunizations: a follow-up analysis.* Int J Toxicol, 2004. **23**(6): p. 369–76.
35. Geier, D.A. and M.R. Geier, *An evaluation of serious neurological disorders following immunization: a comparison of whole-cell pertussis and acellular pertussis vaccines.* Brain Dev, 2004. **26**(5): p. 296–300.
36. Geier, D.A. and M.R. Geier, *A comparative evaluation of the effects of MMR immunization and mercury doses from thimerosal-containing childhood vaccines on the population prevalence of autism.* Med Sci Monit, 2004. **10**(3): p. Pi33–9.
37. Geier, D.A. and M.R. Geier, *A two-phased population epidemiological study of the safety of thimerosal-containing vaccines: a follow-up analysis.* Med Sci Monit, 2005. **11**(4): p. Cr160–70.
38. Geier, D.A. and M.R. Geier, *An evaluation of the effects of thimerosal on neurodevelopmental disorders reported following DTP and Hib vaccines in comparison to DTPH vaccine in the United States.* J Toxicol Environ Health A, 2006. **69**(15): p. 1481–95.
39. Geier, D.A. and M.R. Geier, *A meta-analysis epidemiological assessment of neurodevelopmental disorders following vaccines administered from 1994 through 2000 in the United States.* Neuro Endocrinol Lett, 2006. **27**(4): p. 401–13.
40. Geier, D.A. and M.R. Geier, *An assessment of downward trends in neurodevelopmental disorders in the United States following removal of Thimerosal from childhood vaccines.* Med Sci Monit, 2006. **12**(6): p. Cr231–9.
41. Young, H.A., D.A. Geier, and M.R. Geier, *Thimerosal exposure in infants and neurodevelopmental disorders: an assessment of computerized medical records in the Vaccine Safety Datalink.* J Neurol Sci, 2008. **271**(1–2): p. 110–8.

42. Kern, J.K., et al., *Thimerosal exposure and the role of sulfation chemistry and thiol availability in autism.* Int J Environ Res Public Health, 2013. **10**(8): p. 3771–800.
43. Deer, B., *Autism research: What makes an expert?* BMJ, 2007. **334**(7595): p. 666–7.
44. Zerbo, O., et al., *Association Between Influenza Infection and Vaccination During Pregnancy and Risk of Autism Spectrum Disorder.* JAMA Pediatr, 2017. **171**(1): p. e163609.
45. Becerra-Culqui, T.A., et al., *Prenatal Tetanus, Diphtheria, Acellular Pertussis Vaccination and Autism Spectrum Disorder.* Pediatrics, 2018.
46. Halsey, N.A. and S.L. Hyman, *Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the New Challenges in Childhood Immunizations Conference convened in Oak Brook, Illinois, June 12–13, 2000.* Pediatrics, 2001. **107**(5): p. E84.
47. Hornig, M., et al., *Lack of association between measles virus vaccine and autism with enteropathy: a case-control study.* PLoS One, 2008. **3**(9): p. e3140.
48. Libbey, J.E., et al., *Are there altered antibody responses to measles, mumps, or rubella viruses in autism?* J Neurovirol, 2007. **13**(3): p. 252–9.
49. D'Souza, Y., E. Fombonne, and B.J. Ward, *No evidence of persisting measles virus in peripheral blood mononuclear cells from children with autism spectrum disorder.* Pediatrics, 2006. **118**(4): p. 1664–75.
50. Bernard, S., et al., *Autism: a novel form of mercury poisoning.* Med Hypotheses, 2001. **56**(4): p. 462–71.
51. Nelson, K.B. and M.L. Bauman, *Thimerosal and autism?* Pediatrics, 2003. **111**(3): p. 674–9.

Chapter 27
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 US[1] **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 [1]. It was never used in the United States.

The 2012 report by the Institute of Medicine (IOM) [2], now called the National Academy of Medicine (NAM), described two studies with sufficient validity and precision that both reported no association between inactivated

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_27

influenza vaccine and Bell's Palsy [3, 4]. The report also described one study assessing an association between acellular pertussis vaccination and Bell's Palsy [5]; however, this study did not provide convincing evidence due to a lack of validity and precision [2]. Most studies published since the 2012 IOM report have also reported no association between vaccination and Bell's Palsy [6–8]; however, one study did find a temporal association between receipt of meningococcal conjugate vaccine concomitantly with other vaccines and Bell's Palsy [9].

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 [2]. Although other viral infections such as herpes simplex virus (HSV) and varicella zoster virus (VZV) have also been associated with Bell's Palsy [10–13], the pathogenesis of Bell's Palsy remains poorly understood. Hypotheses include reactivation of latent viral infections in facial nerve ganglia [14] or an autoimmune mechanism possibly with segmental demyelination [15]. 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 [16, 17].

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 [2].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about Bell's Palsy?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause Bell's Palsy. • The chicken pox and Tdap vaccines actually prevent Bell's Palsy.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Mutsch, M., et al., *Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland.* N Engl J Med, 2004. **350**(9): p. 896–903.

2. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
3. Greene, S.K., et al., *Near real-time surveillance for influenza vaccine safety: Proof-of-concept in the vaccine safety datalink project.* American Journal of Epidemiology, 2010. **171**(2): p. 177–88.
4. Stowe, J., et al., *Bell's palsy and parenteral inactivated influenza vaccine.* Hum Vaccin, 2006. **2**(3): p. 110–2.
5. Yih, W.K., et al., *An assessment of the safety of adolescent and adult tetanus-diphtheria-acellular pertussis (Tdap) vaccine, using active surveillance for adverse events in the Vaccine Safety Datalink.* Vaccine, 2009. **27**(32): p. 4257–62.
6. Lee, G.M., et al., *H1N1 and seasonal influenza vaccine safety in the vaccine safety datalink project.* Am J Prev Med, 2011. **41**(2): p. 121–8.
7. Rowhani-Rahbar, A., et al., *Immunization and Bell's palsy in children: a case-centered analysis.* Am J Epidemiol, 2012. **175**(9): p. 878–85.
8. Wijnans, L., et al., *Bell's palsy and influenza(H1N1)pdm09 containing vaccines: A self-controlled case series*. PLoS One, 2017. **12**(5): p. e0175539.
9. Tseng, H.F., et al., *Safety of Quadrivalent Meningococcal Conjugate Vaccine in 11- to 21-Year-Olds.* Pediatrics, 2017. **139**(1).
10. Ravin, L.C., *Facial paralysis as a complication of chickenpox.* Am J Ophthalmol, 1961. **52**: p. 723–4.
11. Peitersen, E. and A.E. Caunt, *The incidence of herpes zoster antibodies in patients with peripheral facial palsy.* J Laryngol Otol, 1970. **84**(1): p. 65–70.
12. Tomita, H. and W. Hayakawa, *Varicella-Zoster virus in idiopathic facial palsy.* Arch Otolaryngol, 1972. **95**(4): p. 364–8.
13. McCormick, D.P., *Herpes-simplex virus as a cause of Bell's palsy.* Lancet, 1972. **1**(7757): p. 937–9.
14. Murakami, S., et al., *Bell palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle.* Ann Intern Med, 1996. **124**(1 Pt 1): p. 27–30.
15. Manos-Pujol, M., et al., *Etiopathogenesis of Bell's palsy: an immune-mediated theory.* Eur Arch Otorhinolaryngol, 1994: p. S445–6.
16. Halsey, N.A., et al., *The safety of influenza vaccines in children: An Institute for Vaccine Safety white paper.* Vaccine, 2015. **33**: p. F1–F67.
17. Lewis, D.J., et al., *Transient facial nerve paralysis (Bell's palsy) following intranasal delivery of a genetically detoxified mutant of Escherichia coli heat labile toxin.* PLoS One, 2009. **4**(9): p. e6999.

Chapter 28
Do Vaccines Cause Brachial Neuritis?

Conclusion: Vaccines currently routinely recommended to the general population in the US[1] **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 [1]. No relevant studies of quality have been published since the 2012 IOM 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 function 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 [2].

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_28

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 [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience, and what I share with my patients, my family and my friends about brachial neuritis.
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause brachial neuritis.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Shaikh, M.F., T.J. Baqai, and H. Tahir, *Acute brachial neuritis following influenza vaccination.* BMJ Case Rep, 2012. **2012**.

Chapter 29
Do Vaccines Cause Chronic Inflammatory Disseminated Polyneuropathy (CIDP)?

Conclusion: Vaccines currently routinely recommended to the general population in the US[1] **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 [1]. No relevant studies of quality have been published since the 2012 IOM report.

Proposed biological mechanism: One potential mechanism that could contribute to CIDP is molecular mimicry [1], 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.

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_29

The 2012 IOM report described three reports of CIDP after influenza vaccine, in two reports, development of CIDP occurred in the patients after vaccine administration in two separate years [2]. 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, hepatitis A, hepatitis B, HPV or meningococcal conjugate vaccines, as the publications reviewed provided no evidence beyond a temporal association [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about CIDP?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause CIDP.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.

(continued)

Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Vellozzi, C., et al., *Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring.* Vaccine, 2009. **27**(15): p. 2114–20.

Chapter 30
Do Vaccines Cause Complex Regional Pain Syndrome (CRPS)?

Conclusion: Vaccines currently routinely recommended to the general population in the US[1] **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 [1]. A combined analysis of seven Phase III clinical trials of 9-valent HPV vaccine published since the 2012 IOM report found no association between the vaccine and CRPS [2].

Proposed biological mechanism: Previous controlled studies have shown an association between pain and injection of norepinephrine and phenylephrine [3, 4]. About half of patients with CRPS have documented trauma to the affected area prior to injection [1].

The 2012 IOM report described one case of CRPS after hepatitis B vaccination showing a reoccurrence of symptoms

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_30

after vaccine re-challenge [5]. However, the rest of the publications reviewed provided little evidence beyond a temporal association [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about CRPS?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause CRPS.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Moreira, E.D., Jr., et al., *Safety Profile of the 9-Valent HPV Vaccine: A Combined Analysis of 7 Phase III Clinical Trials.* Pediatrics, 2016. **138**(2).
3. Ali, Z., et al., *Intradermal injection of norepinephrine evokes pain in patients with sympathetically maintained pain.* Pain, 2000. **88**(2): p. 161–8.
4. Mailis-Gagnon, A. and G.J. Bennett, *Abnormal contralateral pain responses from an intradermal injection of phenylephrine in a subset of patients with complex regional pain syndrome (CRPS).* Pain, 2004. **111**(3): p. 378–84.
5. Jastaniah, W.A., et al., *Complex regional pain syndrome after hepatitis B vaccine.* J Pediatr, 2003. **143**(6): p. 802–4.

Chapter 31
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 [1]; however, this study did not provide convincing evidence due to a lack of validity and precision [2].

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 [3–5]. 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 [6–10]. 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 [11, 12].

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_31

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about deltoid bursitis?
Step 2: Briefly address specific concerns, if any
• Vaccines can cause deltoid bursitis, but only if administered incorrectly, such as too high in the deltoid (shoulder) muscle or with a needle that is of an inappropriate length.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Black, S., et al., *A post-licensure evaluation of the safety of inactivated hepatitis A vaccine (VAQTA, Merck) in children and adults.* Vaccine, 2004. **22**(5–6): p. 766–72.

2. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
3. Cooke, T.D., et al., *The pathogenesis of chronic inflammation in experimental antigen-induced arthritis. II. Preferential localization of antigen-antibody complexes to collagenous tissues.* J Exp Med, 1972. **135**(2): p. 323–38.
4. Cooke, T.D. and H.E. Jasin, *The pathogenesis of chronic inflammation in experimental antigen-induced arthritis. I. The role of antigen on the local immune response.* Arthritis Rheum, 1972. **15**(4): p. 327–37.
5. Dumonde, D.C. and L.E. Glynn, *The production of arthritis in rabbits by an immunological reaction to fibrin.* Br J Exp Pathol, 1962. **43**: p. 373–83.
6. Bodor, M. and E. Montalvo, *Vaccination-related shoulder dysfunction.* Vaccine, 2007. **25**(4): p. 585–7.
7. Cook, I.F., M. Williamson, and D. Pond, *Definition of needle length required for intramuscular deltoid injection in elderly adults: an ultrasonographic study.* Vaccine, 2006. **24**(7): p. 937–40.
8. Koster, M.P., et al., *Needle length for immunization of early adolescents as determined by ultrasound.* Pediatrics, 2009. **124**(2): p. 667–72.
9. Lippert, W.C. and E.J. Wall, *Optimal intramuscular needle-penetration depth.* Pediatrics, 2008. **122**(3): p. e556–63.
10. Poland, G.A., et al., *Determination of deltoid fat pad thickness. Implications for needle length in adult immunization.* JAMA, 1997. **277**(21): p. 1709–11.
11. Vellozzi, C., et al., *Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring.* Vaccine, 2009. **27**(15): p. 2114–20.
12. Atanasoff, S., et al., *Shoulder injury related to vaccine administration (SIRVA).* Vaccine, 2010. **28**(51): p. 8049–52

Chapter 32
Do Vaccines Cause Diabetes?

Conclusion: Vaccines currently routinely recommended to the general population in the US[1] **do not cause** diabetes.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM) [1], 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 [2–7]. Studies published since the 2012 IOM report also reported a null, or in some cases even protective, association between vaccination and type 1 diabetes [8–14]. This includes a meta-analysis of 23 observational studies investigating 16 different vaccines [15]. Studies examining inactivated seasonal influenza and Tdap vaccinations in pregnancy reported either no association with, or even a possible protective effect against, gestational diabetes [16–19]. National Health and Nutrition Examination Survey (NHANES) data from 2005–2010 suggested a possible protective effect of hepatitis B vaccination against diabetes as well [20]. 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 [21].

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_32

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 recommended for all persons with diabetes by the American Diabetes Association [22, 23]. In addition, the ACIP recommends the administration of hepatitis b vaccine to all unvaccinated adults with diabetes mellitus aged 19–59 [24].

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 function 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 [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about diabetes?
Step 2: Briefly address specific concerns, if any
• Studies have concluded that vaccines do not cause diabetes.

(continued)

Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. DeStefano, F., et al., *Childhood vaccinations, vaccination timing, and risk of type 1 diabetes mellitus.* Pediatrics, 2001. **108**(6): p. E112.
3. Klein, N.P., et al., *Post-marketing safety evaluation of a tetanus toxoid, reduced diphtheria toxoid and 3-component acellular pertussis vaccine administered to a cohort of adolescents in a United States health maintenance organization.* Pediatr Infect Dis J, 2010. **29**(7): p. 613–7.
4. Altobelli, E., et al., *Infections and risk of type I diabetes in childhood: a population-based case-control study.* Eur J Epidemiol, 2003. **18**(5): p. 425–30.
5. Blom, L., L. Nystrom, and G. Dahlquist, *The Swedish childhood diabetes study. Vaccinations and infections as risk determinants for diabetes in childhood.* Diabetologia, 1991. **34**(3): p. 176–81.

6. Hviid, A., et al., *Childhood vaccination and type 1 diabetes.* N Engl J Med, 2004. **350**(14): p. 1398–404.
7. Patterson, C.C., *Infections and vaccinations as risk factors for childhood type I (insulin-dependent) diabetes mellitus: a multicentre case-control investigation. EURODIAB Substudy 2 Study Group.* Diabetologia, 2000. **43**(1): p. 47–53.
8. Elding Larsson, H., et al., *Pandemrix(R) vaccination is not associated with increased risk of islet autoimmunity or type 1 diabetes in the TEDDY study children.* Diabetologia, 2018. **61**(1): p. 193–202.
9. Vaarala, O., et al., *Rotavirus Vaccination and the Risk of Celiac Disease or Type 1 Diabetes in Finnish Children at Early Life.* Pediatr Infect Dis J, 2017. **36**(7): p. 674–5.
10. Chao, C., et al., *Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine.* J Intern Med, 2012. **271**(2): p. 193–203.
11. Duderstadt, S.K., et al., *Vaccination and risk of type 1 diabetes mellitus in active component U.S. Military, 2002–2008.* Vaccine, 2012. **30**(4): p. 813–9.
12. Hummel, M., et al., *No major association of breast-feeding, vaccinations, and childhood viral diseases with early islet autoimmunity in the German BABYDIAB Study.* Diabetes Care, 2000. **23**(7): p. 969–74.
13. Black, S.B., et al., *Lack of association between receipt of conjugate haemophilus influenzae type B vaccine (HbOC) in infancy and risk of type 1 (juvenile onset) diabetes: long term follow-up of the HbOC efficacy trial cohort.* Pediatr Infect Dis J, 2002. **21**(6): p. 568–9.
14. Karvonen, M., Z. Cepaitis, and J. Tuomilehto, *Association between type 1 diabetes and Haemophilus influenzae type b vaccination: birth cohort study.* BMJ, 1999. **318**(7192): p. 1169–72.
15. Morgan, E., et al., *Vaccinations and childhood type 1 diabetes mellitus: a meta-analysis of observational studies.* Diabetologia, 2016. **59**(2): p. 237–43.
16. Fabiani, M., et al., *A/H1N1 pandemic influenza vaccination: A retrospective evaluation of adverse maternal, fetal and neonatal outcomes in a cohort of pregnant women in Italy.* Vaccine, 2015. **33**(19): p. 2240–7.
17. Kharbanda, E.O., et al., *Maternal Tdap vaccination: Coverage and acute safety outcomes in the vaccine safety datalink, 2007–2013.* Vaccine, 2016. **34**(7): p. 968–73.

18. Kharbanda, E.O., et al., *Inactivated influenza vaccine during pregnancy and risks for adverse obstetric events.* Obstet Gynecol, 2013. **122**(3): p. 659–67.
19. Naleway, A.L., et al., *Safety of influenza vaccination during pregnancy: a review of subsequent maternal obstetric events and findings from two recent cohort studies.* Vaccine, 2014. **32**(26): p. 3122–7.
20. Karnchanasorn, R., et al., *Viral Hepatitis and Diabetes: Clinical Implications of Diabetes Prevention Through Hepatitis Vaccination.* Curr Diab Rep, 2016. **16**(10): p. 101.
21. Hansen, J., et al., *Safety of DTaP-IPV/Hib vaccine administered routinely to infants and toddlers.* Vaccine, 2016. **34**(35): p. 4172–9.
22. *Vaccination Practices for Hepatitis B, Influenza, and Pneumococcal Disease for People With Diabetes.* The Diabetes Educator, 2014. **40**(1): p. 122–124.
23. *Standards of Medical Care in Diabetes-2016 Abridged for Primary Care Providers.* Clin Diabetes, 2016. **34**(1): p. 3–21.
24. *Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Morb Mortal Wkly Rep, 2011. **60**(50): p. 1709–11.

Chapter 33
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 US[1] **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 [1]; however, it did not provide convincing evidence due to a lack of validity and precision [2].

Proposed biological mechanism: Varicella vaccines are live attenuated viral vaccines and are therefore able to replicate

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_33

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.

The 2012 IOM report described cases of disseminated varicella infection after varicella vaccination [3–22], and concluded that these cases together presented strong mechanistic evidence supporting an association [2]. In immunodeficient persons, disseminated varicella infection can also result in pneumonia [3–5, 14–16], meningitis [7], or hepatitis [3–5, 9, 11].

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 [23–26].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about disseminated varicella infection?
Step 2: Briefly address specific concerns, if any
• The varicella vaccine, the vaccine that protects against chicken pox, can cause disseminated varicella infection among those with severe immune deficiency, but this is rare.

(continued)

Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time. • Varicella can cause skin lesions, pneumonia, and inflammation of the brain and spinal cord membranes. Individuals under the age of 1 year are particularly at risk.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases. • The two-dose series of varicella vaccine is 94% effective against varicella disease.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Black, S., et al., *Postmarketing evaluation of the safety and effectiveness of varicella vaccine.* Pediatr Infect Dis J, 1999. **18**(12): p. 1041–6.
2. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
3. Galea, S.A., et al., *The safety profile of varicella vaccine: a 10-year review.* J Infect Dis, 2008. **197 Suppl 2**: p. S165–9.
4. Sharrar, R.G., et al., *The postmarketing safety profile of varicella vaccine.* Vaccine, 2000. **19**(7–8): p. 916–23.
5. Wise, R.P., et al., *Postlicensure safety surveillance for varicella vaccine.* JAMA, 2000. **284**(10): p. 1271–9.

6. Angelini, P., et al., *Aplastic anemia following varicella vaccine.* Pediatr Infect Dis J, 2009. **28**(8): p. 746–8.
7. Bryan, C.J., et al., *Acyclovir-resistant chronic verrucous vaccine strain varicella in a patient with neuroblastoma.* Pediatr Infect Dis J, 2008. **27**(10): p. 946–8.
8. Chaves, S.S., et al., *Safety of varicella vaccine after licensure in the United States: experience from reports to the vaccine adverse event reporting system, 1995–2005.* J Infect Dis, 2008. **197 Suppl 2**: p. S170–7.
9. Ghaffar, F., et al., *Disseminated infection with varicella-zoster virus vaccine strain presenting as hepatitis in a child with adenosine deaminase deficiency.* Pediatr Infect Dis J, 2000. **19**(8): p. 764–6.
10. Goulleret, N., et al., *Safety profile of live varicella virus vaccine (Oka/Merck): five-year results of the European Varicella Zoster Virus Identification Program (EU VZVIP).* Vaccine, 2010. **28**(36): p. 5878–82.
11. Ihara, T., et al., *Viremic phase in a leukemic child after live varicella vaccination.* Pediatrics, 1992. **89**(1): p. 147–9.
12. Jean-Philippe, P., et al., *Severe varicella caused by varicella-vaccine strain in a child with significant T-cell dysfunction.* Pediatrics, 2007. **120**(5): p. e1345–9.
13. Kraft, J.N. and J.C. Shaw, *Varicella infection caused by Oka strain vaccine in a heart transplant recipient.* Arch Dermatol, 2006. **142**(7): p. 943–5.
14. Kramer, J.M., et al., *Disseminated vaccine strain varicella as the acquired immunodeficiency syndrome-defining illness in a previously undiagnosed child.* Pediatrics, 2001. **108**(2): p. E39.
15. Levy, O., et al., *Disseminated varicella infection due to the vaccine strain of varicella-zoster virus, in a patient with a novel deficiency in natural killer T cells.* J Infect Dis, 2003. **188**(7): p. 948–53.
16. Waters, V., K.S. Peterson, and P. LaRussa, *Live viral vaccines in a DiGeorge syndrome patient.* Arch Dis Child, 2007. **92**(6): p. 519–20.
17. Chan, Y., et al., *Herpes zoster due to Oka vaccine strain of varicella zoster virus in an immunosuppressed child post cord blood transplant.* J Paediatr Child Health, 2007. **43**(10): p. 713–5.
18. Ota, K., et al., *Vaccine-strain varicella zoster virus causing recurrent herpes zoster in an immunocompetent 2-year-old.* Pediatr Infect Dis J, 2008. **27**(9): p. 847–8.

19. Chouliaras, G., et al., *Vaccine-associated herpes zoster ophthalmicus [correction of opthalmicus] and encephalitis in an immunocompetent child.* Pediatrics, 2010. **125**(4): p. e969–72.
20. Iyer, S., M.K. Mittal, and R.L. Hodinka, *Herpes zoster and meningitis resulting from reactivation of varicella vaccine virus in an immunocompetent child.* Ann Emerg Med, 2009. **53**(6): p. 792–5.
21. Levin, M.J., et al., *Development of resistance to acyclovir during chronic infection with the Oka vaccine strain of varicella-zoster virus, in an immunosuppressed child.* J Infect Dis, 2003. **188**(7): p. 954–9.
22. Levin, M.J., et al., *Herpes zoster with skin lesions and meningitis caused by 2 different genotypes of the Oka varicella-zoster virus vaccine.* J Infect Dis, 2008. **198**(10): p. 1444–7.
23. Leung, J., et al., *Fatal varicella due to the vaccine-strain varicella-zoster virus.* Hum Vaccin Immunother, 2014. **10**(1): p. 146–9.
24. Schrauder, A., et al., *Varicella vaccination in a child with acute lymphoblastic leukaemia.* Lancet, 2007. **369**(9568): p. 1232.
25. Woo, E.J., *Letter to the editor: Fatal varicella due to the vaccine-strain varicella-zoster virus.* Hum Vaccin Immunother, 2015. **11**(3): p. 679.
26. Dutmer, C.M., et al., *Late Onset Hypomorphic RAG2 Deficiency Presentation with Fatal Vaccine-Strain VZV Infection.* J Clin Immunol, 2015. **35**(8): p. 754–60.

Chapter 34
Do Vaccines Cause Erythema Nodosum (EN)?

Conclusion: Vaccines currently routinely recommended to the general population in the US[1] **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 [1]. No relevant studies of quality have been published since the 2012 IOM report.

Proposed biological mechanism: The most common cause of EN is infection [2]. 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 [3]. Another possible mechanism is activation of the complement system, in which a cascade of proteolysis and successive release of cytokines function 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 [1].

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_34

The 2012 IOM report described one case of EN after hepatitis B vaccination [4]; however, the IOM concluded that this mechanistic evidence was weak.

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about EN?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause EN.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Chowaniec, M., A. Starba, and P. Wiland, *Erythema nodosum - review of the literature.* Reumatologia, 2016. **54**(2): p. 79–82.
3. Blake, T., M. Manahan, and K. Rodins, *Erythema nodosum - a review of an uncommon panniculitis.* Dermatol Online J, 2014. **20**(4): p. 22376.
4. Goolsby, P.L., *Erythema nodosum after Recombivax HB hepatitis B vaccine.* N Engl J Med, 1989. **321**(17): p. 1198–9.

Chapter 35
Do Vaccines Cause Fibromyalgia or Chronic Fatigue Syndrome (CFS)?

Conclusion: Vaccines currently routinely recommended to the general population in the US[1] **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 [1]. One self-controlled case series published since the 2012 IOM report found no association between CFS and bivalent HPV vaccine (Cervarix®) [2]. Two Norwegian register-based studies found no increased risk of CFS following pH1N1 vaccination [3] or HPV vaccination [4], respectively.

Proposed biological mechanism: The etiological causes and underlying pathogenic mechanisms of fibromyalgia and CFS are still unclear and the subject of much debate [5–7]. Theories that attempt to explain the mechanisms behind the development of these two disorders generally focus on sympathetic nervous

[1]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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_35

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 causes or just byproducts of these syndromes [8, 9]. Environmental stimuli such as stress or viral infection are thought to be able to trigger the pathogenesis of these disorders in genetically predisposed individuals [6, 10].

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 [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about fibromyalgia and CFS?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause fibromyalgia or CFS.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.

(continued)

Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Donegan, K., et al., *Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK.* Vaccine, 2013. **31**(43): p. 4961–7.
3. Magnus, P., et al., *Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated with pandemic influenza infection, but not with an adjuvanted pandemic influenza vaccine.* Vaccine, 2015. **33**(46): p. 6173–7.
4. Feiring, B., et al., *HPV vaccination and risk of chronic fatigue syndrome/myalgic encephalomyelitis: A nationwide register-based study from Norway.* Vaccine, 2017. **35**(33): p. 4203–12.
5. Bazzichi, L., et al., *Fibromyalgia: a critical digest of the recent literature.* Clin Exp Rheumatol, 2011. **29**(6 Suppl 69): p. S1–11.
6. Moss-Morris, R., V. Deary, and B. Castell, *Chronic fatigue syndrome.* Handb Clin Neurol, 2013. **110**: p. 303–14.
7. Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue, S., P. Board on the Health of Select, and M. Institute of, *The National Academies Collection: Reports funded by National Institutes of Health*, in *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness*. 2015, National Academies Press (US) Copyright 2015 by the National Academy of Sciences. All rights reserved.: Washington (DC).
8. Romano, G.F., et al., *Fibromyalgia and chronic fatigue: the underlying biology and related theoretical issues.* Adv Psychosom Med, 2015. **34**: p. 61–77.

9. Martinez-Martinez, L.A., et al., *Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies.* J Clin Rheumatol, 2014. **20**(3): p. 146–50.
10. Buskila, D., F. Atzeni, and P. Sarzi-Puttini, *Etiology of fibromyalgia: the possible role of infection and vaccination.* Autoimmun Rev, 2008. **8**(1): p. 41–3.

Chapter 36
Do Vaccines Cause Guillain-Barré Syndrome (GBS)?

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 US[1] **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 [1, 2]. **Therefore, the very small risk of GBS from influenza vaccines pales in comparison to the benefits of the vaccine.**

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_36

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 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 then [2, 3].

Epidemiological evidence: The incidence of GBS due to all causes has been estimated as 0.4–4.0 cases per 100,000 person-years [2]. Clinical trials do not approach the size necessary to examine a potential causal association between vaccines and a rare adverse event like GBS [4]. A systematic literature review identified 24 relevant controlled studies with unduplicated data, including 9 cohort [5, 3, 6–12], 3 case-control [13–15] and 12 self-controlled studies [16–27].

Adults who received the 1976–77 swine flu vaccine were 9.5 (95%CI 8.2–10.3) times more likely to develop GBS compared to those who did not receive the vaccine [3]. 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 US 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 ration [IRR] 2.35, 95%CI 1.53–3.68) [16]. 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 US, found a similarly small but significant increase in risk during the 42 days post pandemic H1N1 vaccination (relative incidence [RI] 2.42, 95% CI 1.58–3.72) [22]. 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) [28]. 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. 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 [2].

Other than influenza vaccines, vaccines routinely used in the US 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 [29]. A review of quadrivalent HPV vaccine safety data published between 2006 and 2015 found no increase in incidence of GBS compared to background rates [30]. Most studies published since this 2006–2015 review have also found no increased risk of GBS following HPV vaccine [31–33], with the exception of one large cohort study in France [34], 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 US [35].

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. [36]. *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 [37, 38]. The mechanism for other infectious agents associated with GBS has not been identified [2, 17, 39].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about GBS?
Step 2: Briefly address specific concerns, if any
• Severe adverse events from vaccines, such as GBS, are very rare. • An older rabies vaccine was associated with GBS. However, based on the best available science, it does not appear that the current rabies vaccine causes GBS, and rabies vaccine is not recommended for most people. • There is a very small risk that influenza vaccine can cause GBS at a rate of about 1–3 cases of GBS per million vaccines administered. Influenza vaccine can also prevent GBS. The very small risk of GBS from the influenza vaccine is outweighed by the protection the vaccine provides to you and your family.

(continued)

Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time. • The flu can cause a sore throat, fever, headache, and cough. It can also cause more severe illness, such as pneumonia and sinus infections. More than 20,000 people die from the flu in the US every year. Pregnant women and infants are at high risk of developing serious complications from the flu and dying from the flu.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Halsey, N.A., et al., *The safety of influenza vaccines in children: An Institute for Vaccine Safety white paper.* Vaccine, 2015. **33**: p. F1–F67.
2. Vellozzi, C., S. Iqbal, and K. Broder, *Guillain-Barre syndrome, influenza, and influenza vaccination: the epidemiologic evidence.* Clin Infect Dis, 2014. **58**(8): p. 1149–55.
3. Schonberger, L.B., et al., *Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977.* Am J Epidemiol, 1979. **110**(2): p. 105–23.
4. Ellenberg, S.S. and M.M. Braun, *Monitoring the safety of vaccines: assessing the risks.* Drug Saf, 2002. **25**(3): p. 145–52.

5. Greene, S.K., et al., *Near real-time surveillance for influenza vaccine safety: Proof-of-concept in the vaccine safety datalink project.* American Journal of Epidemiology, 2010. **171**(2): p. 177–88.
6. Johnson, D.E., *Guillain-Barre syndrome in the US Army.* Arch Neurol, 1982. **39**(1): p. 21–4.
7. Hurwitz, E.S., et al., *Guillain-Barre syndrome and the 1978–1979 influenza vaccine.* New England Journal of Medicine, 1981. **304**(26): p. 1557–61.
8. Kaplan, J.E., et al., *Guillain-Barre syndrome in the United States, 1979–1980 and 1980–1981.* Journal of the American Medical Association, 1982. **248**(6): p. 698–700.
9. Roscelli, J.D., J.W. Bass, and L. Pang, *Guillain-Barre syndrome and influenza vaccination in the US Army, 1980–1988.* American Journal of Epidemiology, 1991. **133**(9): p. 952–5.
10. Lasky, T., et al., *The Guillain-Barre syndrome and the 1992–1993 and 1993–1994 influenza vaccines.* New England Journal of Medicine, 1998. **339**(25): p. 1797–802.
11. Ho, T.Y., et al., *The Impact of Influenza Vaccinations on the Adverse Effects and Hospitalization Rate in the Elderly: A National Based Study in an Asian Country.* PLoS ONE, 2012. **7**(11).
12. Kawai, A.T., et al., *Absence of associations between influenza vaccines and increased risks of seizures, Guillain-Barre syndrome, encephalitis, or anaphylaxis in the 2012–2013 season.* Pharmacoepidemiology and Drug Safety, 2014. **23**(5): p. 548–53.
13. Grimaldi-Bensouda, L., et al., *Guillain-barre syndrome, influenzalike illnesses, and influenza vaccination during seasons with and without circulating A/H1N1 viruses.* American Journal of Epidemiology, 2011. **174**(3): p. 326–35.
14. Galeotti, F., et al., *Risk of Guillain-Barre syndrome after 2010–2011 influenza vaccination.* European Journal of Epidemiology, 2013. **28**(5): p. 433–44.
15. Dieleman, J., et al., *Guillain-Barre syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: Multinational case-control study in Europe.* BMJ, 2011. **343**(7815).
16. Salmon, D.A., et al., *Association between Guillain-Barre syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis.* Lancet, 2013. **381**(9876): p. 1461–8.
17. Stowe, J., et al., *Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenza-like illness using the United Kingdom general practice research*

database. American Journal of Epidemiology, 2009. **169**(3): p. 382–8.
18. Juurlink, D.N., et al., *Guillain-Barre syndrome after influenza vaccination in adults: A population-based study.* Archives of Internal Medicine, 2006. **166**(20): p. 2217–21.
19. Hughes, R.A., et al., *No association between immunization and Guillain-Barre syndrome in the United Kingdom, 1992 to 2000.* Archives of Internal Medicine, 2006. **166**(12): p. 1301–4.
20. Baxter, R., et al., *Lack of association of Guillain-Barre syndrome with vaccinations.* Clinical Infectious Diseases, 2013. **57**(2): p. 197–204.
21. Burwen, D.R., et al., *Evaluation of Guillain-Barre syndrome among recipients of influenza vaccine in 2000 and 2001.* American Journal of Preventive Medicine, 2010. **39**(4): p. 296–304.
22. Dodd, C.N., et al., *International collaboration to assess the risk of Guillain Barre Syndrome following Influenza A (H1N1) 2009 monovalent vaccines.* Vaccine, 2013. **31**(40): p. 4448–58.
23. Huang, W.T., et al., *Safety of Pandemic (H1N1) 2009 Monovalent Vaccines in Taiwan: A Self-Controlled Case Series Study.* PLoS ONE, 2013. **8**(3).
24. Prestel, J., et al., *Risk of Guillain-Barre syndrome following pandemic influenza A(H1N1) 2009 vaccination in Germany.* Pharmacoepidemiol Drug Saf, 2014.
25. Greene, S.K., et al., *Guillain-Barre Syndrome, Influenza Vaccination, and Antecedent Respiratory and Gastrointestinal Infections: A Case-Centered Analysis in the Vaccine Safety Datalink, 2009–2011.* PLoS ONE, 2013. **8**(6).
26. Kwong, J.C., et al., *Risk of Guillain-Barre syndrome after seasonal influenza vaccination and influenza health-care encounters: A self-controlled study.* The Lancet Infectious Diseases, 2013. **13**(9): p. 769–76.
27. McCarthy, N.L., et al., *Evaluating the safety of influenza vaccine using a claims-based health system.* Vaccine, 2013. **31**(50): p. 5975–82.
28. Martin Arias, L.H., et al., *Guillain-Barre syndrome and influenza vaccines: A meta-analysis.* Vaccine, 2015. **33**(31): p. 3773–8.
29. Hansen, J., et al., *Safety of DTaP-IPV/Hib vaccine administered routinely to infants and toddlers.* Vaccine, 2016. **34**(35): p. 4172–9.
30. Vichnin, M., et al., *An Overview of Quadrivalent Human Papillomavirus Vaccine Safety: 2006 to 2015.* Pediatr Infect Dis J, 2015. **34**(9): p. 983–91.

31. Andrews, N., J. Stowe, and E. Miller, *No increased risk of Guillain-Barre syndrome after human papilloma virus vaccine: A self-controlled case-series study in England.* Vaccine, 2017. **35**(13): p. 1729–32.
32. Gee, J., L. Sukumaran, and E. Weintraub, *Risk of Guillain-Barre Syndrome following quadrivalent human papillomavirus vaccine in the Vaccine Safety Datalink.* Vaccine, 2017. **35**(43): p. 5756–8.
33. Grimaldi-Bensouda, L., et al., *Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance.* J Autoimmun, 2017. **79**: p. 84–90.
34. Miranda, S., et al., *Human papillomavirus vaccination and risk of autoimmune diseases: A large cohort study of over 2million young girls in France.* Vaccine, 2017. **35**(36): p. 4761–8.
35. Haber, P., et al., *Vaccines and Guillain-Barre syndrome.* Drug Saf, 2009. **32**(4): p. 309–23.
36. Yuki, N. and H.P. Hartung, *Guillain-Barre syndrome.* N Engl J Med, 2012. **366**(24): p. 2294–304.
37. Mizoguchi, K., *Anti-GQ1b IgG antibody activities related to the severity of Miller Fisher syndrome.* Neurol Res, 1998. **20**(7): p. 617–24.
38. Rees, J.H., et al., *Campylobacter jejuni infection and Guillain-Barre syndrome.* N Engl J Med, 1995. **333**(21): p. 1374–9.
39. Tam, C.C., et al., *Guillain-Barre syndrome and preceding infection with campylobacter, influenza and Epstein-Barr virus in the general practice research database.* PLoS One, 2007. **2**(4): p. e344.

Chapter 37
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 US[1] **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 [1]. A large case-centered analysis published since the IOM report found no association between hearing loss and vaccination [2].

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

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_37

approximately once in every 20,000 cases [1]. 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 [3–5]. 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 [1, 6].

The 2012 IOM report described several cases [7–9] and some experimental evidence [10, 11] 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 [1]. Although spontaneous hearing loss does rarely occur after these vaccinations, the causes are unknown, and the data available have not demonstrated an increased risk.

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about hearing loss?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause hearing loss.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.

(continued)

Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Baxter, R., et al., *Sudden-Onset Sensorineural Hearing Loss after Immunization: A Case-Centered Analysis*. Otolaryngol Head Neck Surg, 2016. **155**(1): p. 81–6.
3. Brookhouser, P.E., D.W. Worthington, and W.J. Kelly, *Unilateral hearing loss in children.* Laryngoscope, 1991. **101**(12 Pt 1): p. 1264–72.
4. Mizushima, N. and Y. Murakami, *Deafness following mumps: the possible pathogenesis and incidence of deafness.* Auris Nasus Larynx, 1986. **13 Suppl 1**: p. S55–7.
5. Unal, M., et al., *Sudden total bilateral deafness due to asymptomatic mumps infection.* Int J Pediatr Otorhinolaryngol, 1998. **45**(2): p. 167–9.
6. Cohen, B.E., A. Durstenfeld, and P.C. Roehm, *Viral Causes of Hearing Loss: A Review for Hearing Health Professionals.* Trends in Hearing, 2014. **18**: p. 2331216514541361.
7. Asatryan, A., et al., *Live attenuated measles and mumps viral strain-containing vaccines and hearing loss: Vaccine Adverse Event Reporting System (VAERS), United States, 1990–2003.* Vaccine, 2008. **26**(9): p. 1166–72.

8. Brodsky, L. and J. Stanievich, *Sensorineural hearing loss following live measles virus vaccination.* Int J Pediatr Otorhinolaryngol, 1985. **10**(2): p. 159–63.
9. Hulbert, T.V., et al., *Bilateral hearing loss after measles and rubella vaccination in an adult.* N Engl J Med, 1991. **325**(2): p. 134.
10. Fukuda, S., et al., *An anti-mumps IgM antibody level in the serum of idiopathic sudden sensorineural hearing loss.* Auris Nasus Larynx, 2001. **28 Suppl**: p. S3–5.
11. Fukuda, S., K. Ishikawa, and Y. Inuyama, *Acute measles infection in the hamster cochlea.* Acta Otolaryngol Suppl, 1994. **514**: p. 111–6.

Chapter 38
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 US[1] **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 Advisory Committee on Immunization Practices (ACIP). Hepatitis A

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_38

and hepatitis B vaccines are specifically recommended for such individuals to protect them from these natural infections leading to more severe disease [1].

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 [2]. No relevant studies of quality have been published since the 2012 IOM 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 [3]. 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 function to amplify the immune response but can damage host cells if not properly regulated, as well as autoantibodies or T cells [2]. 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 [2].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about hepatitis?
Step 2: Briefly address specific concerns, if any
• Studies have concluded that vaccines do not cause hepatitis in immunocompetent persons. • Hepatitis A and B vaccines actually prevent hepatitis.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Alter, M.J., *Vaccinating Patients with Chronic Liver Disease.* Gastroenterology & Hepatology, 2012. **8**(2): p. 120–2.
2. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
3. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, Hamborsky J, Kroger A, Wolfe S, eds. 2015, Centers for Disease Control and Prevention: Washington D.C.

Chapter 39
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 US[1] **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 [1]; however, it did not provide convincing evidence due to a lack of validity and precision [2]. 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 US. Both of these

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_39

serious adverse events[2] were reported as recovered or resolved [3].

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 [4]. 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 [4–23], and concluded that these cases together presented strong mechanistic evidence supporting an association [2]. 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 [24]. In immunodeficient persons, vaccine-strain viral reactivation can result in meningitis [4, 9, 21–23] or encephalitis [11, 20].

[2] 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**

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about vaccine-strain viral reactivation?
Step 2: Briefly address specific concerns, if any
• The varicella vaccine, the vaccine that protects against chicken pox, can cause zoster due to vaccine-strain viral reactivation, but this is very rare.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time. • Varicella can cause skin lesions, pneumonia, and inflammation of the brain and spinal cord membranes. Individuals under the age of 1 year are particularly at risk.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases. • The two-dose series of varicella vaccine is 94% effective against varicella disease.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Donahue, J.G., et al., *Varicella vaccination and ischemic stroke in children: is there an association?* Pediatrics, 2009. **123**(2): p. e228–34.
2. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
3. Prymula, R., et al., *Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine versus one dose of monovalent varicella vaccine: a multicentre, observer-blind, randomised, controlled trial.* Lancet, 2014. **383**(9925): p. 1313–24.
4. Galea, S.A., et al., *The safety profile of varicella vaccine: a 10-year review.* J Infect Dis, 2008. **197 Suppl 2**: p. S165–9.
5. Sharrar, R.G., et al., *The postmarketing safety profile of varicella vaccine.* Vaccine, 2000. **19**(7–8): p. 916–23.
6. Wise, R.P., et al., *Postlicensure safety surveillance for varicella vaccine.* JAMA, 2000. **284**(10): p. 1271–9.
7. Angelini, P., et al., *Aplastic anemia following varicella vaccine.* Pediatr Infect Dis J, 2009. **28**(8): p. 746–8.
8. Bryan, C.J., et al., *Acyclovir-resistant chronic verrucous vaccine strain varicella in a patient with neuroblastoma.* Pediatr Infect Dis J, 2008. **27**(10): p. 946–8.
9. Chaves, S.S., et al., *Safety of varicella vaccine after licensure in the United States: experience from reports to the vaccine adverse event reporting system, 1995-2005.* J Infect Dis, 2008. **197 Suppl 2**: p. S170–7.
10. Ghaffar, F., et al., *Disseminated infection with varicella-zoster virus vaccine strain presenting as hepatitis in a child with adenosine deaminase deficiency.* Pediatr Infect Dis J, 2000. **19**(8): p. 764–6.
11. Goulleret, N., et al., *Safety profile of live varicella virus vaccine (Oka/Merck): five-year results of the European Varicella Zoster Virus Identification Program (EU VZVIP).* Vaccine, 2010. **28**(36): p. 5878–82.
12. Ihara, T., et al., *Viremic phase in a leukemic child after live varicella vaccination.* Pediatrics, 1992. **89**(1): p. 147–9.
13. Jean-Philippe, P., et al., *Severe varicella caused by varicella-vaccine strain in a child with significant T-cell dysfunction.* Pediatrics, 2007. **120**(5): p. e1345–9.

14. Kraft, J.N. and J.C. Shaw, *Varicella infection caused by Oka strain vaccine in a heart transplant recipient.* Arch Dermatol, 2006. **142**(7): p. 943–5.
15. Kramer, J.M., et al., *Disseminated vaccine strain varicella as the acquired immunodeficiency syndrome-defining illness in a previously undiagnosed child.* Pediatrics, 2001. **108**(2): p. E39.
16. Levy, O., et al., *Disseminated varicella infection due to the vaccine strain of varicella-zoster virus, in a patient with a novel deficiency in natural killer T cells.* J Infect Dis, 2003. **188**(7): p. 948–53.
17. Waters, V., K.S. Peterson, and P. LaRussa, *Live viral vaccines in a DiGeorge syndrome patient.* Arch Dis Child, 2007. **92**(6): p. 519–20.
18. Chan, Y., et al., *Herpes zoster due to Oka vaccine strain of varicella zoster virus in an immunosuppressed child post cord blood transplant.* J Paediatr Child Health, 2007. **43**(10): p. 713–5.
19. Ota, K., et al., *Vaccine-strain varicella zoster virus causing recurrent herpes zoster in an immunocompetent 2-year-old.* Pediatr Infect Dis J, 2008. **27**(9): p. 847–8.
20. Chouliaras, G., et al., *Vaccine-associated herpes zoster ophthalmicus [correction of opthalmicus] and encephalitis in an immunocompetent child.* Pediatrics, 2010. **125**(4): p. e969–72.
21. Iyer, S., M.K. Mittal, and R.L. Hodinka, *Herpes zoster and meningitis resulting from reactivation of varicella vaccine virus in an immunocompetent child.* Ann Emerg Med, 2009. **53**(6): p. 792–5.
22. Levin, M.J., et al., *Development of resistance to acyclovir during chronic infection with the Oka vaccine strain of varicella-zoster virus, in an immunosuppressed child.* J Infect Dis, 2003. **188**(7): p. 954–9.
23. Levin, M.J., et al., *Herpes zoster with skin lesions and meningitis caused by 2 different genotypes of the Oka varicella-zoster virus vaccine.* J Infect Dis, 2008. **198**(10): p. 1444–7.
24. Tseng, H.F., et al., *Herpes zoster caused by vaccine-strain varicella zoster virus in an immunocompetent recipient of zoster vaccine.* Clin Infect Dis, 2014. **58**(8): p. 1125–8.

Chapter 40
Do Vaccines Cause Hypersensitivity Reactions?

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** [1].

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 [1]. 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 [2]. 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

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_40

one study assessing influenza vaccination and anaphylaxis [3]; 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 [4]. 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 [5–8], 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 [2]. 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 [9]. 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 egg [10, 11]. 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 [12].

The IOM found no relevant studies of quality in the literature assessing chronic urticaria and diphtheria, tetanus or pertussis vaccines [4]. 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®) [13, 14]. A randomized controlled trial in the US found no association between localized or systemic urticaria and the inactivated influenza vaccine Fluzone® [15]. A randomized controlled trial in the US and South America found no association between quadrivalent meningococcal conjugate vaccine and

urticaria in young infants in the year following vaccination [16]. 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 [17].

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% [18–21]. Extensive swelling reactions in the injected limb after vaccination with DTaP has also been reported [22–24].

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 [25]. Chronic urticaria involves different pathogenic mechanisms [1]. A full list of potential allergens within vaccines can be found at the Johns Hopkins Bloomberg School of Public Health 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 [26–37], varicella [38–45], influenza [40, 46–52], hepatitis B [40], meningococcal conjugate [53] and tetanus toxoid vaccines [54–57], which together present strong mechanistic evidence for a rare causal association with these vaccines. The report also provides several reports for HPV [58, 59] and hepatitis A vaccines [51], for which the mechanistic evidence is less conclusive [4].

Development of acute urticaria is associated with natural infections, including viral hepatitis and many different bacteria [60–62]. 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 [4].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about hypersensitivity reactions?
Step 2: Briefly address specific concerns, if any
• Vaccines can cause hypersensitivity reactions such as anaphylaxis and hives, but these reactions are very rare.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Dreskin, S.C., et al., *International Consensus (ICON): allergic reactions to vaccines.* World Allergy Organ J, 2016. **9**(1): p. 32.
2. Halsey, N.A., et al., *Immediate hypersensitivity reactions following monovalent 2009 pandemic influenza A (H1N1) vaccines: reports to VAERS.* Vaccine, 2013. **31**(51): p. 6107–12.

3. Greene, S.K., et al., *Near real-time surveillance for influenza vaccine safety: Proof-of-concept in the vaccine safety datalink project.* American Journal of Epidemiology, 2010. **171**(2): p. 177–88.
4. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
5. Daley, M.F., et al., *Safety of diphtheria, tetanus, acellular pertussis and inactivated poliovirus (DTaP-IPV) vaccine.* Vaccine, 2014. **32**(25): p. 3019–24.
6. Kawai, A.T., et al., *Absence of associations between influenza vaccines and increased risks of seizures, Guillain-Barre syndrome, encephalitis, or anaphylaxis in the 2012–2013 season.* Pharmacoepidemiology and Drug Safety, 2014. **23**(5): p. 548–53.
7. McCarthy, N.L., et al., *Evaluating the safety of influenza vaccine using a claims-based health system.* Vaccine, 2013. **31**(50): p. 5975–82.
8. Vichnin, M., et al., *An Overview of Quadrivalent Human Papillomavirus Vaccine Safety: 2006 to 2015.* Pediatr Infect Dis J, 2015. **34**(9): p. 983–91.
9. McNeil, M.M., et al., *Risk of anaphylaxis after vaccination in children and adults.* J Allergy Clin Immunol, 2016. **137**(3): p. 868–78.
10. Turner, P.J., et al., *Safety of live attenuated influenza vaccine in young people with egg allergy: multicentre prospective cohort study.* Bmj, 2015. **351**: p. h6291.
11. Turner, P.J., et al., *Safety of live attenuated influenza vaccine in atopic children with egg allergy.* J Allergy Clin Immunol, 2015. **136**(2): p. 376–81.
12. Baxter, R., et al., *Safety of quadrivalent live attenuated influenza vaccine in subjects aged 2–49years.* Vaccine, 2017. **35**(9): p. 1254–8.
13. Ngan, H.Y., et al., *Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in healthy Chinese women from Hong Kong.* Hong Kong Med J, 2010. **16**(3): p. 171–9.
14. Kim, S.C., et al., *Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in 15–25 years old healthy Korean women.* J Gynecol Oncol, 2011. **22**(2): p. 67–75.
15. Greenhawt, M.J., et al., *Safe administration of the seasonal trivalent influenza vaccine to children with severe egg allergy.* Ann Allergy Asthma Immunol, 2012. **109**(6): p. 426–30.
16. Klein, N.P., et al., *Safety and immunogenicity of a novel quadrivalent meningococcal CRM-conjugate vaccine given concomitantly*

with routine vaccinations in infants. Pediatr Infect Dis J, 2012. **31**(1): p. 64–71.
17. Hansen, J., et al., *Safety of DTaP-IPV/Hib vaccine administered routinely to infants and toddlers.* Vaccine, 2016. **34**(35): p. 4172–9.
18. Baylor, N.W., W. Egan, and P. Richman, *Aluminum salts in vaccines–US perspective.* Vaccine, 2002. **20 Suppl 3**: p. S18–23.
19. Bergfors, E., et al., *How common are long-lasting, intensely itching vaccination granulomas and contact allergy to aluminium induced by currently used pediatric vaccines? A prospective cohort study.* Eur J Pediatr, 2014. **173**(10): p. 1297–307.
20. Bergfors, E., B. Trollfors, and A. Inerot, *Unexpectedly high incidence of persistent itching nodules and delayed hypersensitivity to aluminium in children after the use of adsorbed vaccines from a single manufacturer.* Vaccine, 2003. **22**(1): p. 64–9.
21. Netterlid, E., et al., *Persistent itching nodules after the fourth dose of diphtheria-tetanus toxoid vaccines without evidence of delayed hypersensitivity to aluminium.* Vaccine, 2004. **22**(27–28): p. 3698–706.
22. Rennels, M.B., et al., *Safety of a fifth dose of diphtheria and tetanus toxoid and acellular pertussis vaccine in children experiencing extensive, local reactions to the fourth dose.* Pediatr Infect Dis J, 2008. **27**(5): p. 464–5.
23. Rennels, M.B., et al., *Extensive swelling after booster doses of acellular pertussis-tetanus-diphtheria vaccines.* Pediatrics, 2000. **105**(1): p. e12.
24. Sekaran, N.K. and K.M. Edwards, *Extensive swelling reaction associated with diphtheria and tetanus toxoids and acellular pertussis vaccine.* Pediatr Infect Dis J, 2006. **25**(4): p. 374–5.
25. Wood, R.A., *Allergic reactions to vaccines.* Pediatr Allergy Immunol, 2013. **24**(6): p. 521–6.
26. Aukrust, L., et al., *Severe hypersensitivity or intolerance reactions to measles vaccine in six children. Clinical and immunological studies.* Allergy, 1980. **35**(7): p. 581–7.
27. Baxter, D.N., *Measles immunization in children with a history of egg allergy.* Vaccine, 1996. **14**(2): p. 131–4.
28. Bohlke, K., et al., *Risk of anaphylaxis after vaccination of children and adolescents.* Pediatrics, 2003. **112**(4): p. 815–20.
29. Erlewyn-Lajeunesse, M., et al., *Anaphylaxis following single component measles and rubella immunisation.* Arch Dis Child, 2008. **93**(11): p. 974–5.
30. Fasano, M.B., et al., *Egg hypersensitivity and adverse reactions to measles, mumps, and rubella vaccine.* J Pediatr, 1992. **120**(6): p. 878–81.

31. Giampietro, P.G., et al., *Adverse reaction to measles immunization.* Eur J Pediatr, 1993. **152**(1): p. 80.
32. Herman, J.J., R. Radin, and R. Schneiderman, *Allergic reactions to measles (rubeola) vaccine in patients hypersensitive to egg protein.* J Pediatr, 1983. **102**(2): p. 196–9.
33. Kelso, J.M., R.T. Jones, and J.W. Yunginger, *Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin.* J Allergy Clin Immunol, 1993. **91**(4): p. 867–72.
34. Patja, A., et al., *Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow-up.* Pediatr Infect Dis J, 2000. **19**(12): p. 1127–34.
35. Patja, A., et al., *Allergic reactions to measles-mumps-rubella vaccination.* Pediatrics, 2001. **107**(2): p. E27.
36. Pool, V., et al., *Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps rubella vaccine in the United States.* Pediatrics, 2002. **110**(6): p. e71.
37. Puvvada, L., et al., *Systemic reactions to measles-mumps-rubella vaccine skin testing.* Pediatrics, 1993. **91**(4): p. 835–6.
38. Sharrar, R.G., et al., *The postmarketing safety profile of varicella vaccine.* Vaccine, 2000. **19**(7–8): p. 916–23.
39. Wise, R.P., et al., *Postlicensure safety surveillance for varicella vaccine.* JAMA, 2000. **284**(10): p. 1271–9.
40. DiMiceli, L., et al., *Vaccination of yeast sensitive individuals: review of safety data in the US vaccine adverse event reporting system (VAERS).* Vaccine, 2006. **24**(6): p. 703–7.
41. Kumagai, T., et al., *Gelatin-specific humoral and cellular immune responses in children with immediate- and nonimmediate-type reactions to live measles, mumps, rubella, and varicella vaccines.* J Allergy Clin Immunol, 1997. **100**(1): p. 130–4.
42. Ozaki, T., et al., *Safety and immunogenicity of gelatin-free varicella vaccine in epidemiological and serological studies in Japan.* Vaccine, 2005. **23**(10): p. 1205–8.
43. Sakaguchi, M., H. Miyazawa, and S. Inouye, *Sensitization to gelatin in children with systemic non-immediate-type reactions to varicella vaccines.* Ann Allergy Asthma Immunol, 2000. **84**(3): p. 341–4.
44. Sakaguchi, M., et al., *Minimum estimated incidence in Japan of anaphylaxis to live virus vaccines including gelatin.* Vaccine, 2000. **19**(4–5): p. 431–6.
45. Sakaguchi, M., et al., *IgE-mediated systemic reactions to gelatin included in the varicella vaccine.* J Allergy Clin Immunol, 1997. **99**(2): p. 263–4.
46. Chung, E.Y., L. Huang, and L. Schneider, *Safety of influenza vaccine administration in egg-allergic patients.* Pediatrics, 2010. **125**(5): p. e1024–30.

47. Coop, C.A., et al., *Anaphylaxis from the influenza virus vaccine.* Int Arch Allergy Immunol, 2008. **146**(1): p. 85–8.
48. Izurieta, H.S., et al., *Adverse events reported following live, cold-adapted, intranasal influenza vaccine.* JAMA, 2005. **294**(21): p. 2720–5.
49. James, J.M., et al., *Safe administration of influenza vaccine to patients with egg allergy.* J Pediatr, 1998. **133**(5): p. 624–8.
50. Muhammad, R.D., et al., *Adverse Events Following Trivalent Inactivated Influenza Vaccination in Children: Analysis of the Vaccine Adverse Event Reporting System.* Pediatr Infect Dis J, 2010.
51. Peng, M.M. and H. Jick, *A population-based study of the incidence, cause, and severity of anaphylaxis in the United Kingdom.* Arch Intern Med, 2004. **164**(3): p. 317–9.
52. Zheng, W. and S.C. Dreskin, *Thimerosal in influenza vaccine: an immediate hypersensitivity reaction.* Ann Allergy Asthma Immunol, 2007. **99**(6): p. 574–5.
53. Yergeau, A., et al., *Adverse events temporally associated with meningococcal vaccines.* CMAJ, 1996. **154**(4): p. 503–7.
54. Bilyk, M.A. and G. Dubchik, *[Anaphylactic reaction following subcutaneous administration of tetanus anatoxin].* Klin Med (Mosk), 1978. **56**(9): p. 137–8.
55. Mandal, G.S., M. Mukhopadhyay, and A.R. Bhattacharya, *Adverse reactions following tetanus toxoid injection.* J Indian Med Assoc, 1980. **74**(2): p. 35–7.
56. Mansfield, L.E., et al., *Systemic reactions during cutaneous testing for tetanus toxoid hypersensitivity.* Ann Allergy, 1986. **57**(2): p. 135–7.
57. Zaloga, G.P. and B. Chernow, *Life-threatening anaphylactic reaction to tetanus toxoid.* Ann Allergy, 1982. **49**(2): p. 107–8.
58. Brotherton, J.M., et al., *Anaphylaxis following quadrivalent human papillomavirus vaccination.* CMAJ, 2008. **179**(6): p. 525–33.
59. Slade, B.A., et al., *Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine.* JAMA, 2009. **302**(7): p. 750–7.
60. Cribier, B., *Urticaria and hepatitis.* Clin Rev Allergy Immunol, 2006. **30**(1): p. 25–9.
61. Darlenski, R., et al., *Chronic urticaria as a systemic disease.* Clin Dermatol, 2014. **32**(3): p. 420–3.
62. Minciullo, P.L., et al., *Urticaria and bacterial infections.* Allergy Asthma Proc, 2014. **35**(4): p. 295–302.

Chapter 41
Do Vaccines Cause Immune Thrombocytopenic Purpura (ITP)?

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 US[1] **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 [1–3]. 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 [3].

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_41

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 [4].

Studies published since this report have consistently shown an increased risk of thrombocytopenic purpura in children within 6 weeks of measles-containing vaccination [2–6]. However, several studies published since this report have found no association between influenza vaccines and ITP [7–9], and early childhood vaccines other than MMR or MMRV (ProQuad®) have not been shown to cause ITP [2, 3]. One study examining the safety of trivalent inactivated seasonal influenza vaccination in pregnant women reported a null association with thrombocytopenia [10]. 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 [11]. 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 [12].

Proposed biological mechanism: ITP has been associated with natural viral infections such as influenza, varicella, measles, mumps and rubella [3, 13]. 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 [14]. 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 [15]. The IOM also concluded that there was no mechanistic evidence for an association between ITP and diphtheria, tetanus or pertussis vaccines [4].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about ITP?
Step 2: Briefly address specific concerns, if any
• MMR vaccine can very rarely cause ITP in children. However, MMR actually prevents many more cases of ITP than it causes. • Based on the best available science, it does not appear that other vaccines cause ITP.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time. • Measles is one of the most contagious diseases and can cause a high fever, rash, and in some cases inflammation of the brain, seizures, and death. Mumps can cause a fever, and in some cases deafness and inflammation of the brain and spinal cord membranes. Rubella can cause a fever and rash.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases. • Over 99% of children who receive two doses of MMR develop immune protection against measles. The MMR vaccine is also over 90% effective against rubella, and over 66% effective against mumps.

(continued)

(continued)

Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, Hamborsky J, Kroger A, Wolfe S, eds. 2015, Centers for Disease Control and Prevention: Washington D.C.
2. O'Leary, S.T., et al., *The risk of immune thrombocytopenic purpura after vaccination in children and adolescents.* Pediatrics, 2012. **129**(2): p. 248–55.
3. Cecinati, V., et al., *Vaccine administration and the development of immune thrombocytopenic purpura in children.* Hum Vaccin Immunother, 2013. **9**(5): p. 1158–62.
4. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
5. Andrews, N., et al., *A collaborative approach to investigating the risk of thrombocytopenic purpura after measles-mumps-rubella vaccination in England and Denmark.* Vaccine, 2012. **30**(19): p. 3042–6.
6. Bertuola, F., et al., *Association between drug and vaccine use and acute immune thrombocytopenia in childhood: a case-control study in Italy.* Drug Saf, 2010. **33**(1): p. 65–72.
7. Huang, W.T., et al., *Safety of Pandemic (H1N1) 2009 Monovalent Vaccines in Taiwan: A Self-Controlled Case Series Study.* PLoS ONE, 2013. **8**(3).
8. Grimaldi-Bensouda, L., et al., *A case-control study to assess the risk of immune thrombocytopenia associated with vaccines.* Blood, 2012. **120**(25): p. 4938–44.
9. Villa, M., et al., *Safety of MF59-adjuvanted influenza vaccination in the elderly: results of a comparative study of MF59-adjuvanted vaccine versus nonadjuvanted influenza vaccine in northern Italy.* Am J Epidemiol, 2013. **178**(7): p. 1139–45.

10. Nordin, J.D., et al., *Maternal safety of trivalent inactivated influenza vaccine in pregnant women.* Obstet Gynecol, 2013. **121**(3): p. 519–25.
11. Kharbanda, E.O., et al., *Maternal Tdap vaccination: Coverage and acute safety outcomes in the vaccine safety datalink, 2007–2013.* Vaccine, 2016. **34**(7): p. 968–73.
12. Hansen, J., et al., *Safety of DTaP-IPV/Hib vaccine administered routinely to infants and toddlers.* Vaccine, 2016. **34**(35): p. 4172–9.
13. Yenicesu, I., et al., *Virus-associated immune thrombocytopenic purpura in childhood.* Pediatr Hematol Oncol, 2002. **19**(6): p. 433–7.
14. Oski, F.A. and J.L. Naiman, *Effect of live measles vaccine on the platelet count.* N Engl J Med, 1966. **275**(7): p. 352–6.
15. Wise, R.P., et al., *Postlicensure safety surveillance for varicella vaccine.* JAMA, 2000. **284**(10): p. 1271–9.

Chapter 42
Do Vaccines Cause Meningitis or Encephalitis/ Encephalopathy?

Conclusion: Varicella vaccine in routine use in the United States[1] **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[1] 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

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_42

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.

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 [1, 2–7].

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM) [8], 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 [9, 10, 11]. The report also described several studies assessing meningitis, encephalitis or encephalopathy and MMR [9, 12, 13], DTaP [14, 15] or meningococcal [13] 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 [8].

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 [16]. A case-centered analysis of 110 childhood encephalitis cases from California found no association between vaccination and encephalitis [17]. Large Vaccine Safety Datalink studies found no association between meningitis/encephalitis and either 2012-2013 influenza vaccines [18],

the DTaP-IPV combination vaccine (Kinrix®) [19], or MMR, MMRV (ProQuad®) and varicella vaccine (Varivax®) [20]. 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 [21]. A 2017 Norwegian registry study found no increased risk of encephalitis following pH1N1 vaccine [22].

The IOM found no relevant epidemiologic studies of quality in the literature assessing an association between vaccination and MIBE [8].

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 1,000-2,000 patients infected with measles, 400-6,000 patients infected with mumps, or 5000 patients infected with rubella, respectively [8]. 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 [23]. Natural infection with wild-type influenza has also been associated with encephalitis, albeit rarely [8, 24–26].

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 [8]. 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 [8]. 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 [12, 27] 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) [28].

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 [8]. The 2012 IOM report described several cases of encephalitis or encephalopathy after MMR [29–31], influenza [32] and DTaP [33] vaccines, and four cases of meningitis after mumps vaccine [29, 34, 35] but, when considering knowledge about the natural infection, the IOM concluded this mechanistic evidence was weak [8]. However, there is one well documented case of measles vaccine virus isolated from the cerebrospinal fluid of a patient with encephalitis in Canada [36], as well as documented cases of meningitis following reactivation of vaccine-type varicella zoster virus [37–39].

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 [1]. 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 [8]. The 2012 IOM report described several cases of MIBE after measles vaccination in immunodeficient persons [36, 40, 41] and concluded that these cases together presented strong mechanistic evidence supporting an association [8].

Talking Points

Step 1: Establish empathy and credibility

- As your doctor, I know that you want to make the best choices about vaccines for you and your family.
- I also know there is a lot of information out there, and it is difficult to figure out who to trust.
- Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about encephalitis (inflammation of the brain) and meningitis (inflammation of the brain and spinal cord membranes)?

Step 2: Briefly address specific concerns, if any

- The varicella vaccine, the vaccine that protects against chicken pox, can cause meningitis, but this is very rare.
- The measles-containing vaccine can cause encephalitis, but this is very rare.
- The benefit of vaccination in preventing neurologic diseases such as meningitis and encephalitis greatly outweighs the minimal risk of vaccine complications.

Step 3: Pivot to disease risk

- Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
- Measles is one of the most contagious diseases and can cause a high fever, rash, and in some cases inflammation of the brain, seizures, and death. Mumps can cause a fever, and in some cases deafness and inflammation of the brain and spinal cord membranes. Rubella can cause a fever and rash.
- Varicella can cause skin lesions, pneumonia, and inflammation of the brain and spinal cord membranes. Individuals under the age of 1 year are particularly at risk.

(continued)

(continued)

Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases. • Over 99% of children who receive two doses of MMR develop immune protection against measles. The MMR vaccine is also over 90% effective against rubella, and over 66% effective against mumps. • The two-dose series of varicella vaccine is 94% effective against varicella disease.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, K.A. Hamborsky J, Wolfe S Editor. 2015, Centers for Disease Control and Prevention: Washington D.C.
2. Buchanan, R. and D.J. Bonthius, *Measles Virus and Associated Central Nervous System Sequelae.* Seminars in Pediatric Neurology, 2012. **19**(3): p. 107–14.
3. Studahl, M., et al., *Acute viral infections of the central nervous system in immunocompetent adults: diagnosis and management.* Drugs, 2013. **73**(2): p. 131–58.
4. Gilden, D., M.A. Nagel, and R.J. Cohrs, *Chapter 12 - Varicella-zoster*, in *Handbook of Clinical Neurology*, C.T. Alex and B. John, Editors. 2014, Elsevier. p. 265–83.
5. Griffin, D.E., *Chapter 27 - Measles virus and the nervous system*, in *Handbook of Clinical Neurology*, C.T. Alex and B. John, Editors. 2014, Elsevier. p. 577–90.
6. Tyor, W. and T. Harrison, *Chapter 28 - Mumps and rubella*, in *Handbook of Clinical Neurology*, C.T. Alex and B. John, Editors. 2014, Elsevier. p. 591–600.

7. Rubin, S., et al., *Molecular biology, pathogenesis and pathology of mumps virus.* J Pathol, 2015. **235**(2): p. 242–52.
8. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
9. Makela, A., J.P. Nuorti, and H. Peltola, *Neurologic disorders after measles-mumps-rubella vaccination.* Pediatrics, 2002. **110**(5): p. 957–63.
10. Ki, M., et al., *Risk analysis of aseptic meningitis after measles-mumps-rubella vaccination in Korean children by using a case-crossover design.* Am J Epidemiol, 2003. **157**(2): p. 158–65.
11. Black, S., et al., *Risk of hospitalization because of aseptic meningitis after measles-mumps-rubella vaccination in one- to two-year-old children: an analysis of the Vaccine Safety Datalink (VSD) Project.* Pediatr Infect Dis J, 1997. **16**(5): p. 500–3.
12. Ray, P., et al., *Encephalopathy after whole-cell pertussis or measles vaccination: lack of evidence for a causal association in a retrospective case-control study.* Pediatr Infect Dis J, 2006. **25**(9): p. 768–73.
13. Ward, K.N., et al., *Risk of serious neurologic disease after immunization of young children in Britain and Ireland.* Pediatrics, 2007. **120**(2): p. 314–21.
14. Yih, W.K., et al., *An assessment of the safety of adolescent and adult tetanus-diphtheria-acellular pertussis (Tdap) vaccine, using active surveillance for adverse events in the Vaccine Safety Datalink.* Vaccine, 2009. **27**(32): p. 4257–62.
15. Greco, D., *Case-control study on encephalopathy associated with diphtheria-tetanus immunization in Campania, Italy.* Bull World Health Organ, 1985. **63**(5): p. 919–25.
16. Tseng, H.F., et al., *Safety of zoster vaccine in adults from a large managed-care cohort: a Vaccine Safety Datalink study.* J Intern Med, 2012. **271**(5): p. 510–20.
17. Pahud, B.A., et al., *Lack of association between childhood immunizations and encephalitis in California, 1998–2008.* Vaccine, 2012. **30**(2): p. 247–53.
18. Kawai, A.T., et al., *Absence of associations between influenza vaccines and increased risks of seizures, Guillain-Barre syndrome, encephalitis, or anaphylaxis in the 2012–2013 season.* Pharmacoepidemiology and Drug Safety, 2014. **23**(5): p. 548–53.
19. Daley, M.F., et al., *Safety of diphtheria, tetanus, acellular pertussis and inactivated poliovirus (DTaP-IPV) vaccine.* Vaccine, 2014. **32**(25): p. 3019–24.

20. Klein, N.P., et al., *Safety of measles-containing vaccines in 1-year-old children.* Pediatrics, 2015. **135**(2): p. e321–9.
21. Hansen, J., et al., *Safety of DTaP-IPV/Hib vaccine administered routinely to infants and toddlers.* Vaccine, 2016. **34**(35): p. 4172–9.
22. Ghaderi, S., et al., *Encephalitis after influenza and vaccination: a nationwide population-based registry study from Norway.* Int J Epidemiol, 2017. **46**(5): p. 1618–26.
23. Bellini, W.J., et al., *Subacute sclerosing panencephalitis: more cases of this fatal disease are prevented by measles immunization than was previously recognized.* J Infect Dis, 2005. **192**(10): p. 1686–93.
24. Goenka, A., et al., *Neurological manifestations of influenza infection in children and adults: results of a National British Surveillance Study.* Clin Infect Dis, 2014. **58**(6): p. 775–84.
25. Britton, P.N., et al., *Influenza-associated Encephalitis/Encephalopathy Identified by the Australian Childhood Encephalitis Study 2013–2015.* Pediatr Infect Dis J, 2017. **36**(11): p. 1021–6.
26. Hoshino, A., et al., *Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes.* Brain Dev, 2012. **34**(5): p. 337–43.
27. Moore, D.L., et al., *Lack of evidence of encephalopathy related to pertussis vaccine: active surveillance by IMPACT, Canada, 1993–2002.* Pediatr Infect Dis J, 2004. **23**(6): p. 568–71.
28. Berkovic, S.F., et al., *De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study.* Lancet Neurol, 2006. **5**(6): p. 488–92.
29. Bakshi, N., et al., *Fatal mumps meningoencephalitis in a child with severe combined immunodeficiency after bone marrow transplantation.* J Child Neurol, 1996. **11**(2): p. 159–62.
30. Lacroix, C., et al., *Acute necrotizing measles encephalitis in a child with AIDS.* J Neurol, 1995. **242**(4): p. 249–51.
31. Valmari, P., et al., *Measles virus in the cerebrospinal fluid in post-vaccination immunosuppressive measles encephalopathy.* Pediatr Infect Dis J, 1987. **6**(1): p. 59–63.
32. Froissart, M., J.P. Mizon, and J.L. Leroux, *[Acute meningoencephalitis immediately after an influenza vaccination].* Lille Med, 1978. **23**(8): p. 548–51.
33. Schwarz, G., G. Lanzer, and W.F. List, *Acute midbrain syndrome as an adverse reaction to tetanus immunization.* Intensive Care Med, 1988. **15**(1): p. 53–4.

34. Ehrengut, W. and K. Zastrow, *[Complications after preventive mumps vaccination in West Germany (including multiple preventive vaccinations)].* Monatsschr Kinderheilkd, 1989. **137**(7): p. 398–402.
35. Fescharek, R., et al., *Measles-mumps vaccination in the FRG: an empirical analysis after 14 years of use. II. Tolerability and analysis of spontaneously reported side effects.* Vaccine, 1990. **8**(5): p. 446–56.
36. Bitnun, A., et al., *Measles inclusion-body encephalitis caused by the vaccine strain of measles virus.* Clin Infect Dis, 1999. **29**(4): p. 855–61.
37. Iyer, S., M.K. Mittal, and R.L. Hodinka, *Herpes zoster and meningitis resulting from reactivation of varicella vaccine virus in an immunocompetent child.* Ann Emerg Med, 2009. **53**(6): p. 792–5.
38. Han, J.Y., D.C. Hanson, and S.S. Way, *Herpes zoster and meningitis due to reactivation of varicella vaccine virus in an immunocompetent child.* Pediatr Infect Dis J, 2011. **30**(3): p. 266–8.
39. Gershon, A.A., et al., *Varicella zoster virus infection.* Nat Rev Dis Primers, 2015. **1**: p. 15016.
40. Baram, T.Z., et al., *Subacute sclerosing panencephalitis in an infant: diagnostic role of viral genome analysis.* Ann Neurol, 1994. **36**(1): p. 103–8.
41. Poon, T.P., V. Tchertkoff, and H. Win, *Subacute measles encephalitis with AIDS diagnosed by fine needle aspiration biopsy. A case report.* Acta Cytol, 1998. **42**(3): p. 729–33.

Chapter 43
Do Vaccines Cause Multiple Sclerosis (MS)?

Conclusion: Influenza vaccines **do not cause** multiple sclerosis (MS). Other vaccines currently routinely recommended to the general population in the US[1] **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 [1–5] or relapse [6, 7] in adults, or onset [1, 8] or relapse [9] in children; however, these studies did not provide convincing evidence due to a lack of validity and precision [10]. Studies published since the 2012 IOM report focusing on the pandemic H1N1 influenza vaccine Pandemrix [11–13], quadrivalent HPV vaccine (Gardasil®) [14–17] and hepatitis B vaccine [15] 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 evi-

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_43

dence 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 [18]. 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 [19]. Another recent literature review also found no increase in risk of onset or relapse of MS after vaccination [20].

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 [21]. 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 [22, 23]. 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 [24]. 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 [10].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about multiple sclerosis?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause multiple sclerosis.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Ahlgren, C., et al., *A population-based case-control study on viral infections and vaccinations and subsequent multiple sclerosis risk.* Eur J Epidemiol, 2009. **24**(9): p. 541–52.

2. Ascherio, A., et al., *Hepatitis B vaccination and the risk of multiple sclerosis.* N Engl J Med, 2001. **344**(5): p. 327–32.
3. DeStefano, F., et al., *Vaccinations and risk of central nervous system demyelinating diseases in adults.* Arch Neurol, 2003. **60**(4): p. 504–9.
4. Hernan, M.A., et al., *Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study.* Neurology, 2004. **63**(5): p. 838–42.
5. Hocine, M.N., et al., *Hepatitis B vaccination and first central nervous system demyelinating events: reanalysis of a case-control study using the self-controlled case series method.* Vaccine, 2007. **25**(31): p. 5938–43.
6. Confavreux, C., et al., *Vaccinations and the risk of relapse in multiple sclerosis. Vaccines in Multiple Sclerosis Study Group.* N Engl J Med, 2001. **344**(5): p. 319–26.
7. Miller, A.E., et al., *A multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis.* Neurology, 1997. **48**(2): p. 312–4.
8. Mikaeloff, Y., et al., *Hepatitis B vaccination and the risk of childhood-onset multiple sclerosis.* Arch Pediatr Adolesc Med, 2007. **161**(12): p. 1176–82.
9. Mikaeloff, Y., et al., *Hepatitis B vaccine and risk of relapse after a first childhood episode of CNS inflammatory demyelination.* Brain, 2007. **130**(Pt 4): p. 1105–10.
10. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
11. Persson, I., et al., *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): p. 172–90.
12. Bardage, C., et al., *Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden.* Bmj, 2011. **343**: p. d5956.
13. Farez, M.F., et al., *H1N1 vaccination does not increase risk of relapse in multiple sclerosis: a self-controlled case-series study.* Mult Scler, 2012. **18**(2): p. 254–6.
14. Chao, C., et al., *Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine.* J Intern Med, 2012. **271**(2): p. 193–203.

15. Langer-Gould, A., et al., *Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases.* JAMA Neurol, 2014. **71**(12): p. 1506–13.
16. Scheller, N.M., et al., *Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system.* JAMA, 2015. **313**(1): p. 54–61.
17. Vichnin, M., et al., *An Overview of Quadrivalent Human Papillomavirus Vaccine Safety: 2006 to 2015*. Pediatr Infect Dis J, 2015. **34**(9): p. 983–91.
18. Halsey, N.A., et al., *The safety of influenza vaccines in children: An Institute for Vaccine Safety white paper.* Vaccine, 2015. **33**: p. F1–F67.
19. Mailand, M.T. and J.L. Frederiksen, *Vaccines and multiple sclerosis: a systematic review.* Journal of Neurology, 2016: p. 1–16.
20. Frederiksen, J.L. and M. Topsoe Mailand, *Vaccines and multiple sclerosis.* Acta Neurol Scand, 2017. **136**: Suppl 201: p. 49–51.
21. Pena, J.A. and T.E. Lotze, *Pediatric multiple sclerosis: current concepts and consensus definitions.* Autoimmune Dis, 2013. **2013**: p. 673947.
22. Sejvar, J.J., et al., *Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data.* Vaccine, 2007. **25**(31): p. 5771–92.
23. Krupp, L.B., et al., *International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions.* Mult Scler, 2013. **19**(10): p. 1261–7.
24. Fujinami, R.S. and M.B. Oldstone, *Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity.* Science, 1985. **230**(4729): p. 1043–5.

Chapter 44
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 US[1] **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 [1]. The report also described one study assessing stroke and varicella vaccine (Varivax®) [2], but this study did not provide convincing evidence due to a lack of validity and precision [3].

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_44

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 [aOR] 0.81, 95% confidence interval [CI] 0.77-0.85) and receipt of pneumococcal vaccine was not associated with a change in odds of MI in adults [4]. Another matched case-control study of 94,022 persons found that receipt of seasonal influenza vaccine 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 [5]. A self-controlled case-series study of 17,853 persons found a reduction in incidence of stroke after receipt of influenza vaccine [6]. 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) [7]. 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 [IRR] 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) [8]. 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) [9]. Pooled data from several studies examining adults with recent ischemic stroke found no association between influenza vaccination and MI or stroke [10]. 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 [11–13]. Prospective cohorts of older adults found that receipt of pneumococcal polysaccharide vaccine was either not associated with MI or stroke [14, 15] or associated with a decreased risk of acute coronary syndrome events in general [16, 17]. A prospective cohort of 27,204 Spanish individuals initially found a decreased risk of stroke in individuals receiving 23-valent pneumococcal polysaccharide vaccine [18]; however, this association was later refuted by the authors [19]. This study did show that influenza

vaccine was associated with reduced risk of death from stroke [20] and that pneumococcal vaccine was not associated with MI [21]. 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 [22]. Two large Vaccine Safety Datalink studies found no association between stroke and receipt of quadrivalent HPV vaccine (Gardasil®) in females age 9-26 [23] or receipt of the DTaP-IPV combination vaccine (Kinrix®) in children age 4-6 [24], 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 [25]. Herpes zoster vaccine was not associated with an increased risk of stroke or cardiovascular events in numerous safety studies [26]. A 2015 international case-control study concluded that routine vaccinations in childhood appear to be protective against stroke [27]. 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 [28].

Proposed biological mechanism: Potential mechanisms for MI include viral infection and alterations in the coagulation cascade [3]. MI has been associated with natural influenza infection, albeit very rarely [29]. Potential mechanisms for stroke include direct viral infection, viral reactivation, and alterations in the coagulation cascade [3]. Stroke has been associated with natural varicella infection, at an incidence of about 1 in 15,000 cases [30].

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 [3].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about myocardial infarction (heart attack) and stroke?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause heart attack or stroke. • Influenza vaccine actually prevents heart attack, and varicella vaccine prevents stroke.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Smeeth, L., et al., *Risk of myocardial infarction and stroke after acute infection or vaccination.* N Engl J Med, 2004. **351**(25): p. 2611–8.
2. Donahue, J.G., et al., *Varicella vaccination and ischemic stroke in children: is there an association?* Pediatrics, 2009. **123**(2): p. e228–34.
3. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
4. Siriwardena, A.N., S.M. Gwini, and C.A. Coupland, *Influenza vaccination, pneumococcal vaccination and risk of acute myocardial infarction: matched case-control study.* CMAJ, 2010. **182**(15): p. 1617–23.
5. Siriwardena, A.N., Z. Asghar, and C.C. Coupland, *Influenza and pneumococcal vaccination and risk of stroke or transient ischaemic attack-matched case control study.* Vaccine, 2014. **32**(12): p. 1354–61.
6. Asghar, Z., C. Coupland, and N. Siriwardena, *Influenza vaccination and risk of stroke: Self-controlled case-series study.* Vaccine, 2015. **33**(41): p. 5458–63.
7. Lee, K.R., et al., *Effect of Influenza Vaccination on Risk of Stroke: A Systematic Review and Meta-Analysis.* Neuroepidemiology, 2017. **48**(3–4): p. 103–10.
8. Gwini, S.M., C.A. Coupland, and A.N. Siriwardena, *The effect of influenza vaccination on risk of acute myocardial infarction: self-controlled case-series study.* Vaccine, 2011. **29**(6): p. 1145–9.
9. Macintyre, C.R., et al., *Ischaemic heart disease, influenza and influenza vaccination: a prospective case control study.* Heart, 2013. **99**(24): p. 1843–8.
10. Lavallee, P.C., et al., *Influenza vaccination and cardiovascular risk in patients with recent TIA and stroke.* Neurology, 2014. **82**(21): p. 1905–13.
11. Lin, H.C., et al., *Association of influenza vaccination and reduced risk of stroke hospitalization among the elderly: a population-based case-control study.* Int J Environ Res Public Health, 2014. **11**(4): p. 3639–49.
12. Chiang, M.H., et al., *Association between influenza vaccination and reduced risks of major adverse cardiovascular events in elderly patients.* Am Heart J, 2017. **193**: p. 1–7.

13. Hsu, S.Y., et al., *A Matched Influenza Vaccine Strain Was Effective in Reducing the Risk of Acute Myocardial Infarction in Elderly Persons: A Population-Based Study.* Medicine (Baltimore), 2016. **95**(10): p. e2869.
14. Tseng, H.F., et al., *Pneumococcal vaccination and risk of acute myocardial infarction and stroke in men.* JAMA, 2010. **303**(17): p. 1699–706.
15. Hedlund, J., et al., *Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in elderly people: a 1-year follow-up.* Vaccine, 2003. **21**(25–26): p. 3906–11.
16. Eurich, D.T., et al., *Pneumococcal vaccination and risk of acute coronary syndromes in patients with pneumonia: population-based cohort study.* Heart, 2012. **98**(14): p. 1072–7.
17. Vlachopoulos, C.V., et al., *Association between pneumococcal vaccination and cardiovascular outcomes: a systematic review and meta-analysis of cohort studies.* Eur J Prev Cardiol, 2015. **22**(9): p. 1185–99.
18. Vila-Corcoles, A., et al., *Clinical effectiveness of pneumococcal vaccination against acute myocardial infarction and stroke in people over 60 years: the CAPAMIS study, one-year follow-up.* BMC Public Health, 2012. **12**: p. 222.
19. Vila-Corcoles, A., et al., *Ineffectiveness of pneumococcal vaccination in cardiovascular prevention: the CAPAMIS study.* JAMA Intern Med, 2013. **173**(20): p. 1918–20.
20. Vila-Corcoles, A., et al., *Evaluating clinical effectiveness of pneumococcal vaccination in preventing stroke: the CAPAMIS Study, 3-year follow-up.* J Stroke Cerebrovasc Dis, 2014. **23**(6): p. 1577–84.
21. Ochoa-Gondar, O., et al., *Evaluating the clinical effectiveness of pneumococcal vaccination in preventing myocardial infarction: The CAPAMIS study, three-year follow-up.* Vaccine, 2014. **32**(2): p. 252–7.
22. Tseng, H.F., et al., *Safety of zoster vaccine in adults from a large managed-care cohort: a Vaccine Safety Datalink study.* J Intern Med, 2012. **271**(5): p. 510–20.
23. Gee, J., et al., *Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink.* Vaccine, 2011. **29**(46): p. 8279–84.
24. Daley, M.F., et al., *Safety of diphtheria, tetanus, acellular pertussis and inactivated poliovirus (DTaP-IPV) vaccine.* Vaccine, 2014. **32**(25): p. 3019–24.

25. Vichnin, M., et al., *An Overview of Quadrivalent Human Papillomavirus Vaccine Safety: 2006 to 2015.* Pediatr Infect Dis J, 2015. **34**(9): p. 983–91.
26. Keating, G.M., *Shingles (herpes zoster) vaccine (zostavax((R))): a review of its use in the prevention of herpes zoster and postherpetic neuralgia in adults aged >/=50 years.* Drugs, 2013. **73**(11): p. 1227–44.
27. Fullerton, H.J., et al., *Infection, vaccination, and childhood arterial ischemic stroke: Results of the VIPS study.* Neurology, 2015. **85**(17): p. 1459–66.
28. Clar, C., et al., *Influenza vaccines for preventing cardiovascular disease.* Cochrane Database Syst Rev, 2015(5): p. Cd005050.
29. Estabragh, Z.R. and M.A. Mamas, *The cardiovascular manifestations of influenza: a systematic review.* Int J Cardiol, 2013. **167**(6): p. 2397–403.
30. Nagel, M.A., et al., *Virus vasculopathy and stroke: an underrecognized cause and treatment target.* Infect Disord Drug Targets, 2010. **10**(2): p. 105–11.

Chapter 45
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 US[1] **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 [1].

One study published since the 2012 IOM report of 193,083 adults over 50 years of age found no association between zoster vaccine and myocarditis using both case-centered and

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_45

self-controlled case series analyses [2]. 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 [3].

US 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) [4]. 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 [5].

Proposed biological mechanism: Myocarditis often results from a prolonged immune response induced by viral infection [6]. 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 [1].

The IOM concluded that there was no mechanistic evidence for an association between myocarditis and tetanus or pertussis containing vaccines [1].

Talking Points

Step 1: Establish empathy and credibility

- As your doctor, I know that you want to make the best choices about vaccines for you and your family.
- I also know there is a lot of information out there, and it is difficult to figure out who to trust.
- Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about myocarditis (inflammation of the heart) and cardiomyopathy (heart disease)?

(continued)

Step 2: Briefly address specific concerns, if any
• Smallpox vaccine very rarely causes inflammation of the heart and heart disease, but smallpox vaccine is not recommended for most people. • Based on the best available science, it does not appear that other vaccines cause inflammation of the heart and heart disease.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Tseng, H.F., et al., *Safety of zoster vaccine in adults from a large managed-care cohort: a Vaccine Safety Datalink study.* J Intern Med, 2012. **271**(5): p. 510–20.
3. Kharbanda, E.O., et al., *Maternal Tdap vaccination: Coverage and acute safety outcomes in the vaccine safety datalink, 2007-2013*. Vaccine, 2016. **34**(7): p. 968–73.

4. Poland, G.A., J.D. Grabenstein, and J.M. Neff, *The US smallpox vaccination program: a review of a large modern era smallpox vaccination implementation program.* Vaccine, 2005. **23**(17–18): p. 2078–81.
5. Engler, R.J., et al., *A prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination.* PLoS One, 2015. **10**(3): p. e0118283.
6. Biesbroek, P.S., et al., *Diagnosis of myocarditis: Current state and future perspectives.* Int J Cardiol, 2015. **191**: p. 211–9.

Chapter 46
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[1] **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

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_46

[1–3]. 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 [1–14]. The estimated rate was 1 case per 16,000 persons vaccinated between 4 and 19 years of age in Finland [1]. The strength of this association varied depending on the country studied, with an intermediate association in the rest of Europe and a possible association in Canada [8, 15]. This could be explained by differences in population genetics [16]. Studies have not shown any association between narcolepsy and other influenza vaccines, either MF59-adjuvanted or without an adjuvant [17–21]. A cohort study of almost one million adolescent girls in Denmark and Sweden found no association between quadrivalent HPV vaccine and narcolepsy [22]. A 2018 meta-analysis found that during the first year after vaccination with Pandemrix™ 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 [23].

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 [24]. Almost all patients with narcolepsy have HLA DQB1*0602, a genetic marker for predisposition to the disorder [25, 26]. Recent studies have provided further evidence that infections may serve as a potential trigger for the pathogenesis of narcolepsy [27]. 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 [28].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about narcolepsy?
Step 2: Briefly address specific concerns, if any
• A flu vaccine previously used in Europe was associated with an increased risk of narcolepsy; however, based on the best available science, it does not appear that vaccines used in the US cause narcolepsy.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time. • The flu can cause a sore throat, fever, headache, and cough. It can also cause more severe illness, such as pneumonia and sinus infections. More than 20,000 people die from the flu in the US every year. Pregnant women and infants are at high risk of developing serious complications from the flu and dying from the flu.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.

(continued)

(continued)

Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Nohynek, H., et al., *AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland.* PLoS One, 2012. **7**(3): p. e33536.
2. Partinen, M., et al., *Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland.* PLoS One, 2012. **7**(3): p. e33723.
3. Szakacs, A., N. Darin, and T. Hallbook, *Increased childhood incidence of narcolepsy in western Sweden after H1N1 influenza vaccination.* Neurology, 2013. **80**(14): p. 1315–21.
4. Persson, I., et al., *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): p. 172–90.
5. Johansen, K., *The roles of influenza virus antigens and the AS03 adjuvant in the 2009 pandemic vaccine associated with narcolepsy needs further investigation.* Dev Med Child Neurol, 2014. **56**(11): p. 1041–2.
6. Dauvilliers, Y., et al., *Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France.* Brain, 2013. **136**(Pt 8): p. 2486–96.
7. Wijnans, L., et al., *The incidence of narcolepsy in Europe: before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns.* Vaccine, 2013. **31**(8): p. 1246–54.
8. European Centre for Disease Prevention and Control, *Narcolepsy in association with pandemic influenza vaccination (a multi-country European epidemiological investigation)*. ECDC: Stockholm.

9. Miller, E., et al., *Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis.* Bmj, 2013. **346**: p. f794.
10. O'Flanagan, D., et al., *Investigation of an association between onset of narcolepsy and vaccination with pandemic influenza vaccine, Ireland April 2009-December 2010.* Euro Surveill, 2014. **19**(17): p. 15–25.
11. Stowe, J., et al., *Risk of Narcolepsy after AS03 Adjuvanted Pandemic A/H1N1 2009 Influenza Vaccine in Adults: A Case-Coverage Study in England.* Sleep, 2016. **39**(5): p. 1051–7.
12. Heier, M.S., et al., *Incidence of narcolepsy in Norwegian children and adolescents after vaccination against H1N1 influenza A.* Sleep Med, 2013. **14**(9): p. 867–71.
13. Oberle, D., et al., *Retrospective multicenter matched case-control study on the risk factors for narcolepsy with special focus on vaccinations (including pandemic influenza vaccination) and infections in Germany.* Sleep Med, 2017. **34**: p. 71–83.
14. Feltelius, N., et al., *A coordinated cross-disciplinary research initiative to address an increased incidence of narcolepsy following the 2009–2010 Pandemrix vaccination programme in Sweden.* J Intern Med, 2015. **278**(4): p. 335–53.
15. Montplaisir, J., et al., *Risk of narcolepsy associated with inactivated adjuvanted (AS03) A/H1N1 (2009) pandemic influenza vaccine in Quebec.* PLoS One, 2014. **9**(9): p. e108489.
16. Partinen, M., et al., *Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination.* Lancet Neurol, 2014. **13**(6): p. 600–13.
17. McCarthy, N.L., et al., *Evaluating the safety of influenza vaccine using a claims-based health system.* Vaccine, 2013. **31**(50): p. 5975–82.
18. Tsai, T.F., et al., *Explorations of clinical trials and pharmacovigilance databases of MF59(R)-adjuvanted influenza vaccines for associated cases of narcolepsy.* Scand J Infect Dis, 2011. **43**(9): p. 702–6.
19. Ahmed, S.S., et al., *Narcolepsy, 2009 A(H1N1) pandemic influenza, and pandemic influenza vaccinations: what is known and unknown about the neurological disorder, the role for autoimmunity, and vaccine adjuvants.* J Autoimmun, 2014. **50**: p. 1–11.
20. Duffy, J., et al., *Narcolepsy and influenza A(H1N1) pandemic 2009 vaccination in the United States.* Neurology, 2014. **83**(20): p. 1823–30.

21. Baxter, R., et al., *Safety of quadrivalent live attenuated influenza vaccine in subjects aged 2–49years.* Vaccine, 2017. **35**(9): p. 1254–8.
22. Arnheim-Dahlström, L., et al., *Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study.* BMJ : British Medical Journal, 2013. **347**.
23. Sarkanen, T.O., et al., *Incidence of narcolepsy after H1N1 influenza and vaccinations: Systematic review and meta-analysis.* Sleep Med Rev, 2018. **38**: p. 177–86.
24. Han, F., et al., *Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China.* Ann Neurol, 2011. **70**(3): p. 410–7.
25. Matsuki, K., et al., *DQ (rather than DR) gene marks susceptibility to narcolepsy.* Lancet, 1992. **339**(8800): p. 1052.
26. Kadotani, H., J. Faraco, and E. Mignot, *Genetic studies in the sleep disorder narcolepsy.* Genome Res, 1998. **8**(5): p. 427–34.
27. Dye, T.J., N. Gurbani, and N. Simakajornboon, *Epidemiology and Pathophysiology of Childhood Narcolepsy.* Paediatr Respir Rev, 2016.
28. Johansen, K., et al., *Where are we in our understanding of the association between narcolepsy and one of the 2009 adjuvanted influenza A (H1N1) vaccines?* Biologicals, 2016. **44**(4): p. 276–80.

Chapter 47
Do Vaccines Cause Oculorespiratory Syndrome (ORS)?

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 [1].

Epidemiological evidence: 96% of the ORS cases reported in Canada during the 2000–2001 influenza season occurred after vaccination with Fluviral S/F® [2]. The attributable risk of ORS for the 2001–2002 formulation of Fluviral S/F® was estimated to be 2.9 cases per 100 vaccinees [3]. The 2012

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_47

report by the Institute of Medicine (IOM) [4], 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 [3, 5, 6].

Most studies have not demonstrated a causal relationship between ORS and influenza vaccines used in the US [7]. 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 [4]. 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 [8].

Proposed biological mechanism The clinical presentation of ORS indicates that its pathogenesis is most likely immune-based [1]. 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 function to amplify the immune response but can damage host cells if not properly regulated [4]. Possible mechanisms of complement activation by influenza viruses include direct binding of the matrix (M1) protein [9] and immune complex formation with preformed nonprotective antibodies leading to tissue pathology [10]. Host factors involving cytokine production may also predispose some individuals to develop ORS after influenza vaccination [11].

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 [3].

The 2012 IOM report described both experimental and clinical evidence [5, 6, 12–15] supporting a causal relationship between ORS and the aforementioned influenza vaccine [4].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about ORS?
Step 2: Briefly address specific concerns, if any
• Two flu vaccines previously used in Canada did cause ORS; however, these vaccines were never used in the US • Reports of ORS-like symptoms after flu vaccines in the US are rare, and symptoms are generally short-term and mild.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time. • The flu can cause a sore throat, fever, headache, and cough. It can also cause more severe illness, such as pneumonia and sinus infections. More than 20,000 people die from the flu in the US every year. Pregnant women and infants are at high risk of developing serious complications from the flu and dying from the flu.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Horne, Z., et al., *Countering antivaccination attitudes.* Proc Natl Acad Sci U S A, 2015. **112**(33): p. 10321–4.
2. Squires, S.G., et al., *Influenza in Canada--1999–2000 season.* Can Commun Dis Rep, 2001. **27**(1): p. 1–9.
3. Scheifele, D.W., et al., *Ocular and respiratory symptoms attributable to inactivated split influenza vaccine: evidence from a controlled trial involving adults.* Clin Infect Dis, 2003. **36**(7): p. 850–7.
4. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
5. De Serres, G., et al., *Recurrence risk of oculorespiratory syndrome after influenza vaccination: randomized controlled trial of previously affected persons.* Arch Intern Med, 2004. **164**(20): p. 2266–72.
6. Skowronski, D.M., et al., *Randomized, double-blind, placebo-controlled trial to assess the rate of recurrence of oculorespiratory syndrome following influenza vaccination among persons previously affected.* Clin Infect Dis, 2003. **37**(8): p. 1059–66.
7. Hambidge, S.J., et al., *Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old.* JAMA, 2006. **296**(16): p. 1990–7.
8. Grohskopf, L.A., et al., *Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices – United States, 2013–2014.* MMWR Recomm Rep, 2013. **62**(Rr-07): p. 1–43.
9. Zhang, J., et al., *Influenza A virus M1 blocks the classical complement pathway through interacting with C1qA.* J Gen Virol, 2009. **90**(Pt 11): p. 2751–8.
10. Monsalvo, A.C., et al., *Severe pandemic 2009 H1N1 influenza disease due to pathogenic immune complexes.* Nat Med, 2011. **17**(2): p. 195–9.
11. Al-Dabbagh, M., et al., *Elevated inflammatory mediators in adults with oculorespiratory syndrome following influenza immunization: a public health agency of Canada/Canadian Institutes of Health Research Influenza Research Network Study.* Clin Vaccine Immunol, 2013. **20**(8): p. 1108–14.
12. De Serres, G., et al., *Oculo-respiratory syndrome after influenza vaccination: trends over four influenza seasons.* Vaccine, 2005. **23**(28): p. 3726–32.

13. Fredette, M.J., G. De Serres, and M. Malenfant, *Ophthalmological and biological features of the oculorespiratory syndrome after influenza vaccination.* Clin Infect Dis, 2003. **37**(8): p. 1136–8.
14. Skowronski, D.M., et al., *Oculorespiratory syndrome after influenza immunization in children.* Pediatr Infect Dis J, 2005. **24**(1): p. 63–9.
15. Skowronski, D.M., et al., *Low risk of recurrence of oculorespiratory syndrome following influenza revaccination.* CMAJ, 2002. **167**(8): p. 853–8.

Chapter 48
Do Vaccines Cause Opsoclonus Myoclonus Syndrome (OMS)?

Conclusion: Opsoclonus myoclonus syndrome (OMS) is a very rare neurological condition that generally begins at 1-2 years of age and is characterized by uncontrolled, irregular and rapid movements of the muscles and eyes [1].

Vaccines currently routinely recommended to the general population in the US[1] **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 [2]. No relevant studies of quality have been published since the 2012 IOM report.

Proposed biological mechanism: OMS is generally caused by either a tumor or a viral infection [3–6]. Potential mechanisms for OMS include activation of the complement system, in which a cascade of proteolysis and successive release of

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_48

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.

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 [2].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about OMS?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause OMS.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness

(continued)

• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Angel, J.B., et al., *Vaccine-associated measles pneumonitis in an adult with AIDS.* Ann Intern Med, 1998. **129**(2): p. 104–6.
2. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
3. Gorman, M.P., *Update on diagnosis, treatment, and prognosis in opsoclonus-myoclonus-ataxia syndrome.* Curr Opin Pediatr, 2010. **22**(6): p. 745–50.
4. Hero, B. and G. Schleiermacher, *Update on pediatric opsoclonus myoclonus syndrome.* Neuropediatrics, 2013. **44**(6): p. 324–9.
5. Pike, M., *Opsoclonus-myoclonus syndrome.* Handb Clin Neurol, 2013. **112**: p. 1209–11.
6. Pranzatelli, M.R. and E.D. Tate, *Trends and tenets in relapsing and progressive opsoclonus-myoclonus syndrome.* Brain Dev, 2016. **38**(5): p. 439–48.

Chapter 49
Do Vaccines Cause Optic Neuritis or Neuromyelitis Optica (NMO)?

Conclusion: Vaccines currently routinely recommended to the general population in the US[1] **have not been shown to cause** optic neuritis or neuromyelitis optica (NMO).

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM) [1], now called the National Academy of Medicine (NAM), described two studies assessing optic neuritis and MMR, influenza, hepatitis B, diphtheria and tetanus vaccines [2, 3], 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 [1].

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 [4]. A Vaccine Safety Datalink study found no cases of

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_49

optic neuritis in over 200,000 pregnant women within 42 days after receiving trivalent inactivated influenza vaccine [5]. 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 [6]. 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 neuromyelitis optica [7]. A case-centered analysis in a large integrated Californian health plan population did not find an association between vaccines and optic neuritis [8]. A recent literature review found no increase in risk of optic neuritis after vaccination [9].

Proposed biological mechanism: Anti-phosphatidylcholine antibodies have been suggested as a potential cause of optic neuritis [10]. A highly specific immunoglobulin G autoantibody that targets aquaporin-4 is present in up to 80% of patients with NMO [11, 12]. 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 function 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 [1].

The 2012 IOM report described two cases of optic neuritis after MMR [13, 14], two cases of optic neuritis after influenza vaccine showing a reoccurrence of symptoms after vaccine rechallenge [15, 16], and one case of NMO after rubella vaccine [17]; 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 [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about optic neuritis and NMO?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause optic neuritis or NMO.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).

2. DeStefano, F., et al., *Vaccinations and risk of central nervous system demyelinating diseases in adults.* Arch Neurol, 2003. **60**(4): p. 504–9.
3. Payne, D.C., et al., *Anthrax vaccination and risk of optic neuritis in the United States military, 1998–2003.* Arch Neurol, 2006. **63**(6): p. 871–5.
4. Chao, C., et al., *Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine.* J Intern Med, 2012. **271**(2): p. 193–203.
5. Nordin, J.D., et al., *Maternal safety of trivalent inactivated influenza vaccine in pregnant women.* Obstet Gynecol, 2013. **121**(3): p. 519–25.
6. Sridhar, G., et al., *Evaluation of optic neuritis following human papillomavirus vaccination.* Hum Vaccin Immunother, 2017. **13**(7): p. 1705–13.
7. Scheller, N.M., et al., *Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system.* Jama, 2015. **313**(1): p. 54–61.
8. Baxter, R., et al., *Case-centered Analysis of Optic Neuritis After Vaccines.* Clin Infect Dis, 2016. **63**(1): p. 79–81.
9. Frederiksen, J.L. and M. Topsoe Mailand, *Vaccines and multiple sclerosis.* Acta Neurol Scand, 2017. **136 Suppl 201**: p. 49–51.
10. Korematsu, S., et al., *Elevated serum anti-phosphatidylcholine IgG antibodies in patients with influenza vaccination-associated optic neuritis.* Vaccine, 2014. **32**(48): p. 6345–8.
11. Jarius, S., B. Wildemann, and F. Paul, *Neuromyelitis optica: clinical features, immunopathogenesis and treatment.* Clin Exp Immunol, 2014. **176**(2): p. 149–64.
12. Wingerchuk, D.M. and B.G. Weinshenker, *Neuromyelitis optica (Devic's syndrome).* Handb Clin Neurol, 2014. **122**: p. 581–99.
13. Riikonen, R.S., *Retinal vasculitis caused by rubella.* Neuropediatrics, 1995. **26**(3): p. 174–6.
14. Stevenson, V.L., et al., *Optic neuritis following measles/rubella vaccination in two 13-year-old children.* Br J Ophthalmol, 1996. **80**(12): p. 1110–1.
15. Vellozzi, C., et al., *Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring.* Vaccine, 2009. **27**(15): p. 2114–20.
16. Hull, T.P. and J.H. Bates, *Optic neuritis after influenza vaccination.* Am J Ophthalmol, 1997. **124**(5): p. 703–4.
17. Kline, L.B., S.L. Margulies, and S.J. Oh, *Optic neuritis and myelitis following rubella vaccination.* Arch Neurol, 1982. **39**(7): p. 443–4.

Chapter 50
Do Vaccines Cause Primary Ovarian Insufficiency (POI)?

Conclusion: Vaccines in routine use in the US[1] **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 [1]. 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 [2]. Publications of case series include a combined six total case reports of POI that may have had onset at varying times after HPV vaccination [3–5]. 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 pro-

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_50

portion of cases are due to autoimmunity [6]. 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 [7, 8]. However, questions have been raised regarding the validity of the arguments put forth in these publications in several letters to the editor [9, 10] and a special editorial [11]. Major problems with the proposed associations include 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 [12].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about POI?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause POI. • There is really no scientific reason for why HPV vaccine would cause POI – this is basically a myth that has circulated on the internet. What we do know is that HPV disease can lead to several problems that impact fertility, such as cervical incompetence and cervical cancer.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.

(continued)

Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Naleway, A.L., et al., *Primary Ovarian Insufficiency and Adolescent Vaccination*. Pediatrics, 2018.
3. Colafrancesco, S., et al., *Human papilloma virus vaccine and primary ovarian failure: another facet of the autoimmune/inflammatory syndrome induced by adjuvants.* Am J Reprod Immunol, 2013. **70**(4): p. 309–16.
4. Little, D.T. and H.R. Ward, *Adolescent Premature Ovarian Insufficiency Following Human Papillomavirus Vaccination: A Case Series Seen in General Practice.* J Investig Med High Impact Case Rep, 2014. **2**(4): p. 2324709614556129.
5. Little, D.T. and H.R. Ward, *Premature ovarian failure 3 years after menarche in a 16-year-old girl following human papillomavirus vaccination.* BMJ Case Rep, 2012. **2012**.
6. Gordon, C.M., T. Kanaoka, and L.M. Nelson, *Update on primary ovarian insufficiency in adolescents.* Curr Opin Pediatr, 2015. **27**(4): p. 511–9.
7. Gruber, N. and Y. Shoenfeld, *A link between human papilloma virus vaccination and primary ovarian insufficiency: current analysis.* Curr Opin Obstet Gynecol, 2015. **27**(4): p. 265–70.
8. Shoenfeld, Y. and N. Agmon-Levin, *'ASIA' - autoimmune/inflammatory syndrome induced by adjuvants.* J Autoimmun, 2011. **36**(1): p. 4–8.

9. Pellegrino, P., et al., *On the association between human papillomavirus vaccine and primary ovarian failure.* Am J Reprod Immunol, 2014. **71**(4): p. 293–4.
10. Wiznitzer, M., *RE: Human papillomavirus vaccine and primary ovarian failure paper.* Am J Reprod Immunol, 2014. **72**(3): p. 259.
11. Hawkes, D. and J.P. Buttery, *Human papillomavirus vaccination and primary ovarian insufficiency: an association based on ideology rather than evidence.* Curr Opin Obstet Gynecol, 2016. **28**(1): p. 70–2.
12. Hawkes, D., et al., *Revisiting adverse reactions to vaccines: A critical appraisal of Autoimmune Syndrome Induced by Adjuvants (ASIA).* J Autoimmun, 2015. **59**: p. 77–84.

Chapter 51
Do Vaccines Cause Seizures?

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 1,000 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 US. 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.

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_51

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 US[1] **have not been shown to cause** persistent epilepsy or infantile spasms.

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 [1–4].

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 [5–13]. A 2016 summary of 23 post-licensure clinical trials and a 2015 meta-analysis both confirmed these findings [14, 15]. The MMRV combination vaccine (ProQuad®) has a higher risk of febrile convulsions than simultaneous yet separate administration of MMR and varicella vaccine (Varivax®) [16–21]. Febrile seizures occurred at a rate of 26.4 per 1,000 person-years after MMR and 84.6 per 1,000 person-years after MMRV in the 7–10 days after vaccination [16]. There is no increased risk of fever or febrile seizures in children receiving their second dose of measles-containing vaccine at 4–6 years of age, whether given MMR

[1]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).

or MMRV [22–24]. Delaying MMR or MMRV vaccines past 15 months of age results in a higher risk of seizures than vaccinating according to the recommended schedule [25, 26].

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 [4].

Aside from the CSL Biotherapies trivalent vaccine licensed in Australia in 2010 [27–29], 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 [30–35]. 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 [IRR] 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) [4]. 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) [36]. 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 [37]. 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 [38]. 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) [39], 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 [11, 40–43]. A large cohort study published since the 2012 IOM 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 [44]. Two large VSD studies published since the 2012 IOM report found no association between seizures and the DTaP-IPV combination vaccine (Kinrix®) [45] or quadrivalent HPV vaccine (Gardasil®) [46]. 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 [47]. 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 [48].

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 [49], and the report found no relevant studies of quality in the literature assessing an association between infantile spasms and pertussis vaccine [39]. No relevant studies of quality examining infantile spasms and vaccination have been published since the 2012 IOM report.

Proposed biological mechanism: Immunization may induce fever through the release of cytokines from inflammatory cells and fever is associated with febrile seizures [39]. Although an interaction of genetics, brain maturity, and fever is hypothesized, the pathophysiology of febrile seizures is largely unknown [3]. The pathogenesis may be explained by alteration of brain ion channel function due to change in temperature [50, 51], modification of neuronal excitability [52] or fever-

induced respiratory alkalosis [53]. 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 [54–67]. For well-studied vaccines such as influenza vaccines, increases in reactogenicity have been shown to be associated with differences in manufacturing procedures [68–70].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about seizures?
Step 2: Briefly address specific concerns, if any
• Vaccines can cause seizures in infants and young children 7–10 days after vaccination, but these reactions are very rare. • There are no long-term effects of simple febrile seizures, with the possible exception of an increased risk of recurrence. • Many vaccines actually prevent febrile seizures by protecting against natural infections. • The benefits of vaccination greatly outweigh the minimal risk of vaccine complications.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.

Step 5: Give a strong and personalized recommendation

- You and I have the same goal: to keep you and your family healthy.
- You have the power to protect yourself and your family from these diseases through vaccination.
- I strongly recommend vaccination to my patients, my family, and my friends.

References

1. (AAP), A.A.o.P., *Neurodiagnostic evaluation of the child with a simple febrile seizure.* Pediatrics, 2011. **127**(2): p. 389–94.
2. (AAP), A.A.o.P., *Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures.* Pediatrics, 2008. **121**(6): p. 1281–6.
3. Bonhoeffer, J., et al., *Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation.* Vaccine, 2004. **22**(5–6): p. 557–62.
4. Tse, A., et al., *Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011.* Vaccine, 2012. **30**(11): p. 2024–31.
5. Ward, K.N., et al., *Risk of serious neurologic disease after immunization of young children in Britain and Ireland.* Pediatrics, 2007. **120**(2): p. 314–21.
6. Barlow, W.E., et al., *The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine.* N Engl J Med, 2001. **345**(9): p. 656–61.
7. Farrington, P., et al., *A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines.* Lancet, 1995. **345**(8949): p. 567–9.
8. Chen, R.T., et al., *Vaccine Safety Datalink project: a new tool for improving vaccine safety monitoring in the United States. The Vaccine Safety Datalink Team.* Pediatrics, 1997. **99**(6): p. 765–73.
9. Griffin, M.R., et al., *Risk of seizures after measles-mumps-rubella immunization.* Pediatrics, 1991. **88**(5): p. 881–5.
10. Vestergaard, M., et al., *MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis.* JAMA, 2004. **292**(3): p. 351–7.

11. Andrews, N., et al., *Post-licensure safety of the meningococcal group C conjugate vaccine.* Hum Vaccin, 2007. **3**(2): p. 59–63.
12. Miller, E., et al., *Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom.* Am J Epidemiol, 2007. **165**(6): p. 704–9.
13. Gold, M., et al., *Use of the Australian Childhood Immunisation Register for vaccine safety data linkage.* Vaccine, 2010. **28**(26): p. 4308–11.
14. Kuter, B.J., et al., *Safety and Immunogenicity of M-M-RII (Combination Measles-Mumps-Rubella Vaccine) in Clinical Trials of Healthy Children Conducted Between 1988 and 2009.* Pediatr Infect Dis J, 2016. **35**(9): p. 1011–20.
15. Ma, S.J., et al., *Risk of febrile seizure after measles-mumps-rubella-varicella vaccine: A systematic review and meta-analysis.* Vaccine, 2015. **33**(31): p. 3636–49.
16. Klein, N.P., et al., *Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures.* Pediatrics, 2010. **126**(1): p. e1–8.
17. Jacobsen, S.J., et al., *Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting.* Vaccine, 2009. **27**(34): p. 4656–61.
18. Klopfer, S.O., et al., *Analysis of safety data in children after receiving two doses of ProQuad(R) (MMRV).* Vaccine, 2014. **32**(52): p. 7154–60.
19. Macartney, K.K., et al., *Febrile seizures following measles and varicella vaccines in young children in Australia.* Vaccine, 2015. **33**(11): p. 1412–7.
20. MacDonald, S.E., et al., *Risk of febrile seizures after first dose of measles-mumps-rubella-varicella vaccine: a population-based cohort study.* Cmaj, 2014. **186**(11): p. 824–9.
21. Schink, T., et al., *Risk of febrile convulsions after MMRV vaccination in comparison to MMR or MMR+V vaccination.* Vaccine, 2014. **32**(6): p. 645–50.
22. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, K.A. Hamborsky J, Wolfe S Editor. 2015, Centers for Disease Control and Prevention: Washington D.C.
23. Centers for Disease Control and Prevention. *Vaccine Information Statements (VIS)*. August 7, 2015 [cited 2015; Available from: http://www.cdc.gov/vaccines/hcp/vis/current-vis.html.
24. Macartney, K., et al., *Evaluation of Combination Measles-Mumps-Rubella-Varicella Vaccine Introduction in Australia.* JAMA Pediatr, 2017. **171**(10): p. 992–8.

25. Hambidge, S.J., et al., *Timely versus delayed early childhood vaccination and seizures.* Pediatrics, 2014. **133**(6): p. e1492–9.
26. Rowhani-Rahbar, A., et al., *Effect of age on the risk of Fever and seizures following immunization with measles-containing vaccines in children.* JAMA Pediatr, 2013. **167**(12): p. 1111–7.
27. Armstrong, P.K., et al., *Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine.* BMJ Open, 2011. **1**(1): p. e000016.
28. Kelly, H.A., et al., *Adverse events associated with 2010 CSL and other inactivated influenza vaccines.* Med J Aust, 2011. **195**(6): p. 318–20.
29. Li-Kim-Moy, J., et al., *Systematic review of fever, febrile convulsions and serious adverse events following administration of inactivated trivalent influenza vaccines in children.* Euro Surveill, 2015. **20**(24).
30. France, E.K., et al., *Safety of the trivalent inactivated influenza vaccine among children: a population-based study.* Arch Pediatr Adolesc Med, 2004. **158**(11): p. 1031–6.
31. Hambidge, S.J., et al., *Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old.* JAMA, 2006. **296**(16): p. 1990–7.
32. Goodman, M.J., et al., *The safety of trivalent influenza vaccine among healthy children 6 to 24 months of age.* Pediatrics, 2006. **117**(5): p. e821–6.
33. Greene, S.K., et al., *Near real-time surveillance for influenza vaccine safety: proof-of-concept in the Vaccine Safety Datalink Project.* Am J Epidemiol, 2010. **171**(2): p. 177–88.
34. Stowe, J., et al., *Risk of convulsions in children after monovalent H1N1 (2009) and trivalent influenza vaccines: a database study.* Vaccine, 2011. **29**(51): p. 9467–72.
35. Kawai, A.T., et al., *Febrile Seizures After 2010–2011 Trivalent Inactivated Influenza Vaccine.* Pediatrics, 2015. **136**(4): p. e848–55.
36. Li, R., et al., *Post licensure surveillance of influenza vaccines in the Vaccine Safety Datalink in the 2013–2014 and 2014–2015 seasons.* Pharmacoepidemiol Drug Saf, 2016. **25**(8): p. 928–34.
37. Duffy, J., et al., *Febrile Seizure Risk After Vaccination in Children 6 to 23 Months.* Pediatrics, 2016. **138**(1).
38. Bakken, I.J., et al., *Febrile seizures after 2009 influenza A (H1N1) vaccination and infection: a nationwide registry-based study.* BMC Infect Dis, 2015. **15**: p. 506.

39. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
40. Yih, W.K., et al., *An assessment of the safety of adolescent and adult tetanus-diphtheria-acellular pertussis (Tdap) vaccine, using active surveillance for adverse events in the Vaccine Safety Datalink.* Vaccine, 2009. **27**(32): p. 4257–62.
41. Black, S., et al., *Postmarketing evaluation of the safety and effectiveness of varicella vaccine.* Pediatr Infect Dis J, 1999. **18**(12): p. 1041–6.
42. Lewis, E., et al., *Safety of neonatal hepatitis B vaccine administration.* Pediatr Infect Dis J, 2001. **20**(11): p. 1049–54.
43. Huang, W.T., et al., *Lack of association between acellular pertussis vaccine and seizures in early childhood.* Pediatrics, 2010. **126**(2): p. 263–9.
44. Sun, Y., et al., *Risk of febrile seizures and epilepsy after vaccination with diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenzae type B.* JAMA, 2012. **307**(8): p. 823–31.
45. Daley, M.F., et al., *Safety of diphtheria, tetanus, acellular pertussis and inactivated poliovirus (DTaP-IPV) vaccine.* Vaccine, 2014. **32**(25): p. 3019–24.
46. Gee, J., et al., *Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink.* Vaccine, 2011. **29**(46): p. 8279–84.
47. Hansen, J., et al., *Safety of DTaP-IPV/Hib vaccine administered routinely to infants and toddlers.* Vaccine, 2016. **34**(35): p. 4172–9.
48. Duffy, J., et al., *Febrile Seizure Risk after Vaccination in Children One to Five Months of Age.* Pediatr Neurol, 2017. **76**: p. 72–8.
49. Goodman, M., S.H. Lamm, and M.H. Bellman, *Temporal relationship modeling: DTP or DT immunizations and infantile spasms.* Vaccine, 1998. **16**(2–3): p. 225–31.
50. Shibasaki, K., et al., *Effects of body temperature on neural activity in the hippocampus: regulation of resting membrane potentials by transient receptor potential vanilloid 4.* J Neurosci, 2007. **27**(7): p. 1566–75.
51. Thomas, E.A., et al., *Heat opens axon initial segment sodium channels: a febrile seizure mechanism?* Ann Neurol, 2009. **66**(2): p. 219–26.
52. Balosso, S., et al., *A novel non-transcriptional pathway mediates the proconvulsive effects of interleukin-1beta.* Brain, 2008. **131**(Pt 12): p. 3256–65.

53. Schuchmann, S., et al., *Experimental febrile seizures are precipitated by a hyperthermia-induced respiratory alkalosis.* Nat Med, 2006. **12**(7): p. 817–23.
54. Wallace, R.H., et al., *Suggestion of a major gene for familial febrile convulsions mapping to 8q13–21.* J Med Genet, 1996. **33**(4): p. 308–12.
55. Johnson, E.W., et al., *Evidence for a novel gene for familial febrile convulsions, FEB2, linked to chromosome 19p in an extended family from the Midwest.* Hum Mol Genet, 1998. **7**(1): p. 63–7.
56. Peiffer, A., et al., *A locus for febrile seizures (FEB3) maps to chromosome 2q23–24.* Ann Neurol, 1999. **46**(4): p. 671–8.
57. Nakayama, J., et al., *Significant evidence for linkage of febrile seizures to chromosome 5q14–q15.* Hum Mol Genet, 2000. **9**(1): p. 87–91.
58. Nakayama, J., et al., *A nonsense mutation of the MASS1 gene in a family with febrile and afebrile seizures.* Ann Neurol, 2002. **52**(5): p. 654–7.
59. Nabbout, R., et al., *A locus for simple pure febrile seizures maps to chromosome 6q22–q24.* Brain, 2002. **125**(Pt 12): p. 2668–80.
60. Nakayama, J., et al., *Linkage and association of febrile seizures to the IMPA2 gene on human chromosome 18.* Neurology, 2004. **63**(10): p. 1803–7.
61. Hedera, P., et al., *Identification of a novel locus for febrile seizures and epilepsy on chromosome 21q22.* Epilepsia, 2006. **47**(10): p. 1622–8.
62. Audenaert, D., C. Van Broeckhoven, and P. De Jonghe, *Genes and loci involved in febrile seizures and related epilepsy syndromes.* Hum Mutat, 2006. **27**(5): p. 391–401.
63. Poduri, A., et al., *Novel susceptibility locus at chromosome 6q16.3–22.31 in a family with GEFS+.* Neurology, 2009. **73**(16): p. 1264–72.
64. Schlachter, K., et al., *A splice site variant in the sodium channel gene SCN1A confers risk of febrile seizures.* Neurology, 2009. **72**(11): p. 974–8.
65. Saghazadeh, A., M. Mastrangelo, and N. Rezaei, *Genetic background of febrile seizures.* Rev Neurosci, 2014. **25**(1): p. 129–61.
66. Feenstra, B., et al., *Common variants associated with general and MMR vaccine-related febrile seizures.* Nat Genet, 2014. **46**(12): p. 1274–82.
67. Verbeek, N.E., et al., *Etiologies for seizures around the time of vaccination.* Pediatrics, 2014. **134**(4): p. 658–66.

68. Blyth, C.C., et al., *Trivalent influenza vaccine and febrile adverse events in Australia, 2010: clinical features and potential mechanisms.* Vaccine, 2011. **29**(32): p. 5107–13.
69. Rockman, S., et al., *Evaluation of the bioactivity of influenza vaccine strains in vitro suggests that the introduction of new strains in the 2010 Southern Hemisphere trivalent influenza vaccine is associated with adverse events.* Vaccine, 2014. **32**(30): p. 3861–8.
70. Rockman, S., et al., *Role of viral RNA and lipid in the adverse events associated with the 2010 Southern Hemisphere trivalent influenza vaccine.* Vaccine, 2014. **32**(30): p. 3869–76.

Chapter 52
Do Vaccines Cause Serum Sickness?

Conclusion: Vaccines currently routinely recommended to the general population in the US[1] **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 [1]. No relevant studies of quality have been published since the 2012 IOM 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 function to amplify the immune response but can damage host cells if not properly regulated [1].

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_52

The 2012 IOM report described one case of serum sickness after a diphtheria and tetanus vaccine [2]; 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 [1]. Since publication of the 2012 IOM report, a case of serum sickness after H1N1 pandemic influenza vaccine was also described in the literature [3].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about serum sickness?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause serum sickness.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Daschbach, R.J., *Serum sickness and tetanus immunization.* JAMA, 1972. **220**(12): p. 1619.
3. Bonds, R.S. and B.C. Kelly, *Severe serum sickness after H1N1 influenza vaccination.* Am J Med Sci, 2013. **345**(5): p. 412–3.

Chapter 53
Do Vaccines Cause Small Fiber Neuropathy (SFN)?

Conclusion: Vaccines currently routinely recommended to the general population in the US[1] **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 [1]. No relevant studies of quality have been published since the 2012 IOM 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 [2]. 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,

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_53

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 [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about SFN?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause SFN.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Gibbons, C.H., *Small fiber neuropathies.* Continuum (Minneap Minn), 2014. **20**(5 Peripheral Nervous System Disorders): p. 1398–412.

Chapter 54
Do Vaccines Cause Spontaneous Abortion?

Conclusion: Vaccines currently routinely recommended for pregnant women in the US **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 US [1].

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 [2]. SAb is defined in the United States as the loss of a fetus before 20 weeks of gestation (before 24

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_54

weeks in some other countries), and occurs in roughly 15–20% of clinically recognized pregnancies [3].

Donahue et al. 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 [4]. 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 [aOR] 2.0, 95% Confidence Interval [CI] 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) [4].

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 [5]. 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 [4, 5].

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 randomized trial recruited women at 17–34 weeks gestation [6], thirteen other observational studies [7–19], two system-

atic reviews [20, 21], and one meta-analysis [22] assessed the potential association between influenza vaccine and SAb or a related outcome and none 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 [RR] 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) [6]. 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 [aHR] 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) [7].

Chambers et al. also recruited 1,730 American and Canadian women between 2010 and 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) [8].

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 [9].

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 [12].

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%) [13].

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) [14].

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 [15].

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 [19].

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 [23].

Irving et al. found in a 2005–2006 case-control study in the US 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 [16].

Sammon et al. found, in a retrospective cohort study in the UK, 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 [17].

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 [18].

Bratton et al. conducted a systematic review and meta-analysis. Their pooled estimate for SAb was not significant (relative risk [RR] 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) [22].

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 and 20 gestational weeks is inconclusive and requires additional study.

Studies of HPV [24–34] and rubella [35–37] 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 [38] and a meta-analysis of smallpox vaccination in pregnancy [39] 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 [40, 41].

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 [4]. They point out that studies have demonstrated a relationship between vaccination and inflammation, and between inflammation and pregnancy loss [42–44]. 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 [45, 46]. 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 [47, 48]. Significant associations between an increased Th1 response and miscarriage have been reported [42, 43]. 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 [49–51]. 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.

Talking Points

Please note: we suggest using these talking points ONLY if a pregnant patient brings up the recent study that links influenza vaccine to miscarriage risk. After going through the talking points, if the patient still has concerns, you may consider suggesting they receive the influenza vaccine during the second trimester.

Step 1: Establish empathy and credibility

- As your doctor, I know that you want to make the best choices about vaccines for you and your family.
- I also know there is a lot of information out there, and it is difficult to figure out who to trust.
- Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about the recent study about the influenza vaccine and risk of miscarriage?

Step 2: Briefly address specific concerns, if any

- A recent study found a risk of miscarriage among women who received the flu vaccine in consecutive influenza seasons. However, the study does not prove that the flu vaccine was the cause of the miscarriage. Other studies have not found a link between flu vaccination and miscarriage.
- The flu vaccine is very safe. After getting the flu vaccine, one may experience soreness or a fever, but these reactions usually resolve within a few days. Serious complications from the flu vaccine are very rare.

(continued)

(continued)

Step 3: Pivot to disease risk
• Flu is a virus that is spread by droplets in the air – such as through sneezing and coughing. • Flu can cause a sore throat, fever, headache, and cough. It can also cause more severe illness, such as pneumonia and sinus infections. More than 20,000 people die from the flu every year. • Pregnant women and infants are at high risk of developing serious complications from the flu and dying from the flu.
Step 4: Convey vaccine effectiveness
• The good news about the flu is that there are vaccines. • Influenza vaccines are developed every year, to match the seasonal strain. You should receive a flu vaccine every year as soon as it is available to protect yourself.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Grohskopf, L.A., et al., *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices-United States, 2018–19 Influenza Season.* MMWR Recomm Rep, 2018. **67**(3): p. 1–20.
2. *Committee opinion no. 608: influenza vaccination during pregnancy.* Obstet Gynecol, 2014. **124**(3): p. 648–51.
3. Farquharson, R.G., E. Jauniaux, and N. Exalto, *Updated and revised nomenclature for description of early pregnancy events.* Human Reproduction, 2005. **20**(11): p. 3008–11.
4. Donahue, J.G., et al., *Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010–11 and 2011–12.* Vaccine, 2017. **35**(40): p. 5314–22.

5. Chambers, C.D., R. Xu, and A.A. Mitchell, *Commentary on: "Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010–11 and 2011–12".* Vaccine, 2017. **35**(40): p. 5323–4.
6. Steinhoff, M.C., et al., *Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial.* Lancet Infect Dis, 2017. **17**(9): p. 981–9.
7. Chambers, C.D., et al., *Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants.* Vaccine, 2013. **31**(44): p. 5026–32.
8. Chambers, C.D., et al., *Safety of the 2010–11, 2011–12, 2012–13, and 2013–14 seasonal influenza vaccines in pregnancy: Birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants, a study from the cohort arm of VAMPSS.* Vaccine, 2016. **34**(37): p. 4443–9.
9. Chavant, F., et al., *The PREGVAXGRIP Study: a Cohort Study to Assess Foetal and Neonatal Consequences of In Utero Exposure to Vaccination Against A(H1N1)v2009 Influenza.* Drug Safety, 2013. **36**(6): p. 455–65.
10. Huang, W.T., et al., *Safety of inactivated monovalent pandemic (H1N1) 2009 vaccination during pregnancy: a population-based study in Taiwan.* Vaccine, 2014. **32**(48): p. 6463–8.
11. Ludvigsson, J.F., et al., *Maternal vaccination against H1N1 influenza and offspring mortality: population based cohort study and sibling design.* Bmj, 2015. **351**: p. h5585.
12. Ma, F., et al., *Prospective cohort study of the safety of an influenza A(H1N1) vaccine in pregnant Chinese women.* Clin Vaccine Immunol, 2014. **21**(9): p. 1282–7.
13. Oppermann, M., et al., *A(H1N1)v2009: A controlled observational prospective cohort study on vaccine safety in pregnancy.* Vaccine, 2012. **30**(30): p. 4445–52.
14. Pasternak, B., et al., *Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study in Denmark.* BMJ : British Medical Journal, 2012. **344**.
15. Tavares, F., et al., *Pregnancy and safety outcomes in women vaccinated with an AS03-adjuvanted split virion H1N1 (2009) pandemic influenza vaccine during pregnancy: A prospective cohort study.* Vaccine, 2011. **29**(37): p. 6358–65.
16. Irving, S.A., et al., *Trivalent Inactivated Influenza Vaccine and Spontaneous Abortion.* Obstetrics & Gynecology, 2013. **121**(1): p. 159–65.

17. Sammon, C.J., et al., *Evaluating the hazard of foetal death following H1N1 influenza vaccination; a population based cohort study in the UK GPRD.* PLoS One, 2012. **7**(12): p. e51734.
18. Heikkinen, T., et al., *Safety of MF59-adjuvanted A/H1N1 influenza vaccine in pregnancy: a comparative cohort study.* Am J Obstet Gynecol, 2012. **207**(3): p. 177.e1–8.
19. de Vries, L., et al., *Adjuvanted A/H1N1 (2009) influenza vaccination during pregnancy: description of a prospective cohort and spontaneously reported pregnancy-related adverse reactions in the Netherlands.* Birth Defects Res A Clin Mol Teratol, 2014. **100**(10): p. 731–8.
20. McMillan, M., et al., *Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes.* Vaccine, 2015. **33**(18): p. 2108–17.
21. Bednarczyk, R.A., D. Adjaye-Gbewonyo, and S.B. Omer, *Safety of influenza immunization during pregnancy for the fetus and the neonate.* American Journal of Obstetrics & Gynecology, 2012. **207**(3): p. S38–S46.
22. Bratton, K.N., et al., *Maternal influenza immunization and birth outcomes of stillbirth and spontaneous abortion: a systematic review and meta-analysis.* Clin Infect Dis, 2015. **60**(5): p. e11–9.
23. Eaton, A., et al., *Birth outcomes following immunization of pregnant women with pandemic H1N1 influenza vaccine 2009–2010.* Vaccine, 2017.
24. Angelo, M.G., et al., *Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme.* Pharmacoepidemiol Drug Saf, 2014. **23**(5): p. 466–79.
25. Baril, L., et al., *Risk of spontaneous abortion and other pregnancy outcomes in 15–25 year old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom.* Vaccine, 2015. **33**(48): p. 6884–91.
26. Bonde, U., et al., *Is HPV vaccination in pregnancy safe?* Hum Vaccin Immunother, 2016. **12**(8): p. 1960–4.
27. Dana, A., et al., *Pregnancy outcomes from the pregnancy registry of a human papillomavirus type 6/11/16/18 vaccine.* Obstet Gynecol, 2009. **114**(6): p. 1170–8.
28. Forinash, A.B., et al., *Safety of the HPV Bivalent and Quadrivalent Vaccines During Pregnancy.* Ann Pharmacother, 2011. **45**(2): p. 258–62.

29. Garland, S.M., et al., *Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials.* Obstet Gynecol, 2009. **114**(6): p. 1179–88.
30. Goss, M.A., et al., *Final report on exposure during pregnancy from a pregnancy registry for quadrivalent human papillomavirus vaccine.* Vaccine, 2015. **33**(29): p. 3422–8.
31. Panagiotou, O.A., et al., *Effect of bivalent human papillomavirus vaccination on pregnancy outcomes: long term observational follow-up in the Costa Rica HPV Vaccine Trial.* Bmj, 2015. **351**: p. h4358.
32. Scheller, N.M., et al., *Quadrivalent HPV Vaccination and the Risk of Adverse Pregnancy Outcomes.* N Engl J Med, 2017. **376**(13): p. 1223–33.
33. Wacholder, S., et al., *Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomised controlled trials.* Bmj, 2010. **340**: p. c712.
34. Vichnin, M., et al., *An Overview of Quadrivalent Human Papillomavirus Vaccine Safety: 2006 to 2015*. Pediatr Infect Dis J, 2015. 34(9): p. 983–91.
35. Badilla, X., et al., *Fetal risk associated with rubella vaccination during pregnancy.* Pediatr Infect Dis J, 2007. **26**(9): p. 830–5.
36. Sato, H.K., et al., *Rubella vaccination of unknowingly pregnant women: the Sao Paulo experience, 2001.* J Infect Dis, 2011. **204 Suppl 2**: p. S737–44.
37. Tookey, P.A., et al., *Rubella vaccination in pregnancy.* CDR (Lond Engl Rev), 1991. **1**(8): p. R86–8.
38. Makris, M.C., et al., *Safety of hepatitis B, pneumococcal polysaccharide and meningococcal polysaccharide vaccines in pregnancy: a systematic review.* Drug Saf, 2012. **35**(1): 1–14.
39. Badell, M.L., et al., *Risks Associated With Smallpox Vaccination in Pregnancy: A Systematic Review and Meta-analysis.* Obstet Gynecol, 2015. **125**(6): p. 1439–51.
40. Mosby, L.G., S.A. Rasmussen, and D.J. Jamieson, *2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature.* American Journal of Obstetrics and Gynecology, 2011. **205**(1): p. 10–18.
41. Rasmussen, S.A., D.J. Jamieson, and T.M. Uyeki, *Effects of influenza on pregnant women and infants.* American Journal of Obstetrics and Gynecology, 2012. **207**(3, Supplement): p. S3–S8.

42. Calleja-Agius, J., et al., *Pro- and antiinflammatory cytokines in threatened miscarriages.* American Journal of Obstetrics and Gynecology, 2011. **205**(1): p. 83.e8–83.e16.
43. Lissauer, D., et al., *Profile of maternal CD4 T-cell effector function during normal pregnancy and in women with a history of recurrent miscarriage.* Clinical Science, 2014. **126**(5): p. 347–54.
44. Christiansen, O.B., H.S. Nielsen, and A.M. Kolte, *Inflammation and miscarriage.* Seminars in Fetal and Neonatal Medicine, 2006. **11**(5): p. 302–8.
45. Christian, L.M., et al., *Inflammatory responses to trivalent influenza virus vaccine among pregnant women.* Vaccine, 2011. **29**(48): p. 8982–7.
46. Christian, L.M., et al., *Proinflammatory cytokine responses correspond with subjective side effects after influenza virus vaccination.* Vaccine, 2015. **33**(29): p. 3360–6.
47. Yang, J., et al., *CD4+ T cells recognize unique and conserved 2009 H1N1 influenza hemagglutinin epitopes after natural infection and vaccination.* International Immunology, 2013. **25**(8): p. 447–57.
48. Schmidt, T., et al., *CD4+T-cell immunity after pandemic influenza vaccination cross-reacts with seasonal antigens and functionally differs from active influenza infection.* European Journal of Immunology, 2012. **42**(7): p. 1755–66.
49. Belongia, E.A., et al., *Repeated annual influenza vaccination and vaccine effectiveness: review of evidence.* Expert Rev Vaccines, 2017. **16**(7): p. 1–14.
50. Feng, J., et al., *Antibody quantity versus quality after influenza vaccination.* Vaccine, 2009. **27**(45): p. 6358–62.
51. Sasaki, S., et al., *Influence of prior influenza vaccination on antibody and B-cell responses.* PLoS One, 2008. **3**(8): p. e2975.

Chapter 55
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 US[1] **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 [1]. The 2012 IOM report found no new relevant studies of quality in the literature assessing SIDS and DTaP vaccination [2]. Two large randomized controlled trials found no association between SIDS and pentavalent rotavirus vaccine [3, 4]. No increase in the risk of SIDS after immunization with the DTP vaccine was found among a cohort of 129,834 US children born between 1974 and 1984 [5]. 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 [6]. A meta-analysis found that immunizations are actu-

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_55

ally associated with a reduced risk of SIDS; however, this may be attributable to the healthy vaccinee effect [7]. 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 [8]. A retrospective observational study of California infants found no cases of SIDS that were considered to be related to the administration of 46,486 doses of DTaP-IPV/Hib vaccine [9]. Case-control and self-controlled case series analyses of the Taiwanese death registration databases found no association between SIDS and DTaP vaccine [10].

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 [2].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about SIDS?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause SIDS.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.

(continued)

Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine Immunization Safety Review, C., in *Immunization Safety Review: Vaccinations and Sudden Unexpected Death in Infancy*, K. Stratton, et al., Editors. 2003, National Academies Press (US) Copyright 2003 by the National Academy of Sciences. All rights reserved.: Washington (DC).
2. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
3. Armah, G.E., et al., *Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial.* Lancet, 2010. **376**(9741): p. 606–14.
4. Goveia, M.G., et al., *Safety and efficacy of the pentavalent human-bovine (WC3) reassortant rotavirus vaccine in healthy premature infants.* Pediatr Infect Dis J, 2007. **26**(12): p. 1099–104.
5. Griffin, M.R., et al., *Risk of sudden infant death syndrome after immunization with the diphtheria-tetanus-pertussis vaccine.* N Engl J Med, 1988. **319**(10): p. 618–23.
6. Eriksen, E.M., et al., *Lack of association between hepatitis B birth immunization and neonatal death: a population-based study from the vaccine safety datalink project.* Pediatr Infect Dis J, 2004. **23**(7): p. 656–62.
7. Vennemann, M.M., et al., *Do immunisations reduce the risk for SIDS? A meta-analysis.* Vaccine, 2007. **25**(26): p. 4875–9.

8. Kuhnert, R., et al., *Reanalyses of case-control studies examining the temporal association between sudden infant death syndrome and vaccination.* Vaccine, 2012. **30**(13): p. 2349–56.
9. Hansen, J., et al., *Safety of DTaP-IPV/Hib vaccine administered routinely to infants and toddlers.* Vaccine, 2016. **34**(35): p. 4172–9.
10. Huang, W.T., et al., *Vaccination and unexplained sudden death risk in Taiwanese infants.* Pharmacoepidemiol Drug Saf, 2017. **26**(1): p. 17–25.

Chapter 56
Do Vaccines Cause Syncope?

Conclusion: Vaccines currently routinely recommended to the general population in the US[1] **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 [1]. The ACIP recommends that recipients always receive the vaccine while sitting and that providers observe adolescent and adult patients for 15 minutes after vaccination [2, 3]. 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 [4].

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

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_56

unvaccinated comparison group [5]. However, numerous case studies have provided strong mechanistic evidence, as described in the proposed biological mechanism section below.

A study by the US 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 [6].

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 [1].

The 2012 IOM report described a number of cases of syncope after vaccination [1, 7–16]. 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 [5]. Syncope following vaccination has also occasionally been reported via passive surveillance systems [17].

Talking Points

Step 1: Establish empathy and credibility

- As your doctor, I know that you want to make the best choices about vaccines for you and your family.
- I also know there is a lot of information out there, and it is difficult to figure out who to trust.
- Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about fainting?

(continued)

Step 2: Briefly address specific concerns, if any
• Vaccines can cause fainting, but these reactions are rare. • Fainting happens most frequently among teenagers, especially among female teens. • Potential injury from fainting after vaccination can be prevented by careful monitoring of persons receiving vaccines, and by having them sit or lay down if symptoms develop.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Braun, M.M., P.A. Patriarca, and S.S. Ellenberg, *Syncope after immunization.* Arch Pediatr Adolesc Med, 1997. **151**(3): p. 255–9.
2. Kroger, A.T., J. Duchin, and M. Vázquez. *General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)*. 2017 [cited 2017 October]; Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.
3. *Syncope after vaccination--United States, January 2005-July 2007.* MMWR Morb Mortal Wkly Rep, 2008. **57**(17): p. 457–60.

4. Bernard, D.M., et al., *The domino effect: adolescent girls' response to human papillomavirus vaccination.* Med J Aust, 2011. **194**(6): p. 297–300.
5. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
6. Armed Forces Health Surveillance Center, *Syncope, active and reserve components, U.S. Armed Forces, 1998-2012.* MSMR, 2013. **20**(11): p. 5–9.
7. Vellozzi, C., et al., *Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring.* Vaccine, 2009. **27**(15): p. 2114–20.
8. Slade, B.A., et al., *Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine.* JAMA, 2009. **302**(7): p. 750–7.
9. Buttery, J.P., et al., *Mass psychogenic response to human papillomavirus vaccination.* Med J Aust, 2008. **189**(5): p. 261–2.
10. D'Souza, R.M., et al., *Adverse events following immunisation associated with the 1998 Australian Measles Control Campaign.* Commun Dis Intell, 2000. **24**(2): p. 27–33.
11. Keyserling, H., et al., *Safety, immunogenicity, and immune memory of a novel meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine (MCV-4) in healthy adolescents.* Arch Pediatr Adolesc Med, 2005. **159**(10): p. 907–13.
12. Laribiere, A., et al., *Surveillance of adverse effects during a vaccination campaign against meningitis C.* Eur J Clin Pharmacol, 2005. **61**(12): p. 907–11.
13. Meyer, K., et al., *Neurocardiogenic syncope in a 10-year-old boy.* Pediatr Cardiol, 2001. **22**(5): p. 415–6.
14. Miller, E.R. and E.J. Woo, *Time to prevent injuries from postimmunization syncope.* Nursing, 2006. **36**(12 Pt.1): p. 20.
15. Wiersbitzky, S., R. Bruns, and U. Schmidt, *[Cerebral seizures and/or encephalitis after MMR, oral polio, HiB or DPT vaccination?].* Kinderarztl Prax, 1993. **61**(6): p. 232–4.
16. Zimmerman, R.K., et al., *Randomized trial of an alternate human papillomavirus vaccine administration schedule in college-aged women.* J Womens Health (Larchmt), 2010. **19**(8): p. 1441–7.
17. Halsey, N.A., et al., *Immediate hypersensitivity reactions following monovalent 2009 pandemic influenza A (H1N1) vaccines: reports to VAERS.* Vaccine, 2013. **31**(51): p. 6107–12.

Chapter 57
Do Vaccines Cause Systemic Lupus Erythematosus (SLE)?

Conclusion: Vaccines currently routinely recommended to the general population in the US[1] **have not been shown to cause** systemic lupus erythematosus (SLE).

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM) [1], now called the National Academy of Medicine (NAM), described four studies assessing exacerbation of SLE and influenza vaccine [2–5] and one study assessing onset of SLE and hepatitis B vaccine [6]; 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 [1].

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®) [7] and a

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_57

prospective cohort of women receiving quadrivalent HPV vaccine (Gardasil®) [8], 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 [9]. A 2017 clinical trial found that quadrivalent HPV vaccine was safe and well tolerated in patients with SLE [10]. Two 2016 meta-analyses found no difference in adverse event rates after influenza vaccination between SLE patients and healthy controls [11, 12]. A 2015 systematic review did not suggest an increased risk of SLE exacerbation following HPV vaccination [13]. A 2016 meta-analysis found that influenza and pneumococcal vaccines had no impact on SLE disease activity [14]. However, pooled findings from a 2017 meta-analysis suggested that vaccination did increase the risk of SLE (relative risk 1.50; 95% CI 1.05-2.12) [15].

Proposed biological mechanism: There is evidence that natural infection may exacerbate symptoms in SLE patients [16]. 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 function 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 [17]; 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 [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about SLE?
Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause SLE.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).

2. Abu-Shakra, M., et al., *Influenza virus vaccination of patients with systemic lupus erythematosus: effects on disease activity.* J Rheumatol, 2000. **27**(7): p. 1681–5.
3. Del Porto, F., et al., *Influenza vaccine administration in patients with systemic lupus erythematosus and rheumatoid arthritis. Safety and immunogenicity.* Vaccine, 2006. **24**(16): p. 3217–23.
4. Stojanovich, L., *Influenza vaccination of patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).* Clin Dev Immunol, 2006. **13**(2–4): p. 373–5.
5. Williams, G.W., et al., *Influenza immunization in systemic lupus eruthematosus. A double-blind trial.* Ann Intern Med, 1978. **88**(6): p. 729–34.
6. Cooper, G.S., et al., *Risk factors for development of systemic lupus erythematosus: allergies, infections, and family history.* J Clin Epidemiol, 2002. **55**(10): p. 982–9.
7. Baxter, R., et al., *Safety of Zostavax--a cohort study in a managed care organization.* Vaccine, 2012. **30**(47): p. 6636–41.
8. Chao, C., et al., *Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine.* J Intern Med, 2012. **271**(2): p. 193–203.
9. Barbosa, C.M., et al., *Immune response and tolerability of varicella vaccine in children and adolescents with systemic lupus erythematosus previously exposed to varicella-zoster virus.* Clin Exp Rheumatol, 2012. **30**(5): p. 791–8.
10. Dhar, J.P., et al., *The safety and immunogenicity of Quadrivalent HPV (qHPV) vaccine in systemic lupus erythematosus.* Vaccine, 2017. **35**(20): p. 2642–64.
11. Huang, Y., et al., *Is Systemic Lupus Erythematosus Associated With a Declined Immunogenicity and Poor Safety of Influenza Vaccination?: A Systematic Review and Meta-Analysis.* Medicine (Baltimore), 2016. **95**(19): p. e3637.
12. Liao, Z., et al., *Immunogenicity and Safety of Influenza Vaccination in Systemic Lupus Erythematosus Patients Compared with Healthy Controls: A Meta-Analysis.* PLoS One, 2016. **11**(2): p. e0147856.
13. Pellegrino, P., S. Radice, and E. Clementi, *Immunogenicity and safety of the human papillomavirus vaccine in patients with autoimmune diseases: A systematic review.* Vaccine, 2015. **33**(30): p. 3444–9.

14. Puges, M., et al., *Immunogenicity and impact on disease activity of influenza and pneumococcal vaccines in systemic lupus erythematosus: a systematic literature review and meta-analysis.* Rheumatology (Oxford), 2016. **55**(9): p. 1664–72.
15. Wang, B., et al., *Vaccinations and risk of systemic lupus erythematosus and rheumatoid arthritis: A systematic review and meta-analysis.* Autoimmun Rev, 2017. **16**(7): p. 756–65.
16. Doria, A., et al., *Infections as triggers and complications of systemic lupus erythematosus.* Autoimmun Rev, 2008. **8**(1): p. 24–8.
17. Poirriez, J., *A preliminary experiment of absorption of antinuclear antibodies by the hepatitis B vaccine components, in a case of neurolupus.* Vaccine, 2004. **22**(23–24): p. 3166–8.

Chapter 58
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 US[1] **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 [1].

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_58

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 [2] and in over 9,000 pregnant women within 42 days after receiving 2009 H1N1 pandemic influenza vaccine [3]. 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 [4].

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 [1], 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 [5–7], varicella [8], and hepatitis B vaccines [9], 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 [1].

Talking Points

Step 1: Establish empathy and credibility

- As your doctor, I know that you want to make the best choices about vaccines for you and your family.
- I also know there is a lot of information out there, and it is difficult to figure out who to trust.
- Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about transverse myelitis?

(continued)

Step 2: Briefly address specific concerns, if any
• Based on the best available science, it does not appear that vaccines cause Transverse Myelitis.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).
2. Nordin, J.D., et al., *Maternal safety of trivalent inactivated influenza vaccine in pregnant women.* Obstet Gynecol, 2013. **121**(3): p. 519–25.
3. Nordin, J.D., et al., *Monovalent H1N1 influenza vaccine safety in pregnant women, risks for acute adverse events.* Vaccine, 2014. **32**(39): p. 4985–92.
4. Scheller, N.M., et al., *Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system*. Jama, 2015. **313**(1): p. 54–61.
5. Holt, S., et al., *Diffuse myelitis associated with rubella vaccination.* Br Med J, 1976. **2**(6043): p. 1037–8.

6. Joyce, K.A. and J.E. Rees, *Transverse myelitis after measles, mumps, and rubella vaccine.* BMJ, 1995. **311**(7002): p. 422.
7. Lim, S., et al., *Transverse myelitis after measles and rubella vaccination.* J Paediatr Child Health, 2004. **40**(9–10): p. 583–4.
8. LaRovere, K.L., G.P. Raju, and M.P. Gorman, *Postvaricella acute transverse myelitis in a previously vaccinated child.* Pediatr Neurol, 2008. **38**(5): p. 370–2.
9. Tartaglino, L.M., et al., *MR imaging in a case of postvaccination myelitis.* AJNR Am J Neuroradiol, 1995. **16**(3): p. 581–2.

Chapter 59
Do Vaccines Cause Vasculitis or Polyarteritis Nodosa (PAN)?

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 US[1] **have not been shown to cause** vasculitis or PAN.

Epidemiological evidence: The 2012 report by the Institute of Medicine (IOM) [1], now called the National Academy of Medicine (NAM), described two studies assessing exacerbation of vasculitis and influenza vaccine [2, 3], 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 [1].

[1] 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).

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8_59

Since the IOM report, a randomized trial found that influenza vaccine was safe for patients in remission with antineutrophil cytoplasmic antibody-associated vasculitis [4], and a prospective observational study found that vaccinations had no significant clinical impact on patients with systemic necrotising vasculitis [5]. 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) [6]. A large VSD study found that vaccination was associated with a decrease in incidence of the vascular disorder known as Kawasaki disease [7], and a 2017 systematic review concluded that evidence is lacking for a causal relationship between immunization and Kawasaki disease [8].

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 function 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 [1].

The 2012 IOM report described two cases of exacerbation of vasculitis after influenza vaccine that showed recurrence of symptoms after vaccine re-challenge [9], and three cases of PAN after hepatitis B vaccine [10–13]; 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 [1].

Talking Points

Step 1: Establish empathy and credibility
• As your doctor, I know that you want to make the best choices about vaccines for you and your family. • I also know there is a lot of information out there, and it is difficult to figure out who to trust. • Would it be okay if I share with you what I have learned from my experience and what I share with my patients, my family and my friends about vasculitis and PAN?
Step 2: Briefly address specific concerns, if any
• Studies have not concluded that vaccines have been shown to cause vasculitis or PAN.
Step 3: Pivot to disease risk
• Vaccine-preventable diseases are real and have very real dangers associated with them, including illness, and even death. They are also equal opportunity diseases, as they can infect anyone at any time.
Step 4: Convey vaccine effectiveness
• Vaccines are highly effective at protecting you and your family from vaccine-preventable diseases.
Step 5: Give a strong and personalized recommendation
• You and I have the same goal: to keep you and your family healthy. • You have the power to protect yourself and your family from these diseases through vaccination. • I strongly recommend vaccination to my patients, my family, and my friends.

References

1. Institute of Medicine, in *Adverse Effects of Vaccines: Evidence and Causality*, K. Stratton, et al., Editors. 2012, National Academies Press (US): Washington (DC).

2. Stassen, P.M., et al., *Influenza vaccination does not result in an increase in relapses in patients with ANCA-associated vasculitis.* Nephrol Dial Transplant, 2008. **23**(2): p. 654–8.
3. Holvast, A., et al., *Wegener's granulomatosis patients show an adequate antibody response to influenza vaccination.* Ann Rheum Dis, 2009. **68**(6): p. 873–8.
4. Jeffs, L.S., et al., *Randomized trial investigating the safety and efficacy of influenza vaccination in patients with antineutrophil cytoplasmic antibody-associated vasculitis.* Nephrology (Carlton), 2015. **20**(5): p. 343–51.
5. Kerneis, S., et al., *Do vaccinations affect the clinical course of systemic necrotising vasculitis? A prospective observational web-based study.* Clin Exp Rheumatol, 2016. **34**(3 Suppl 97): p. S89–92.
6. Da Dalt, L., et al., *Henoch-Schonlein purpura and drug and vaccine use in childhood: a case-control study.* Ital J Pediatr, 2016. **42**(1): p. 60.
7. Abrams, J.Y., et al., *Childhood vaccines and Kawasaki disease, Vaccine Safety Datalink, 1996–2006.* Vaccine, 2015. **33**(2): p. 382–7.
8. Phuong, L.K., et al., *Kawasaki disease and immunisation: A systematic review.* Vaccine, 2017. **35**(14): p. 1770–9.
9. Vellozzi, C., et al., *Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring.* Vaccine, 2009. **27**(15): p. 2114–20.
10. Begier, E.M., et al., *Polyarteritis nodosa reports to the vaccine adverse event reporting system (VAERS): implications for assessment of suspected vaccine-provoked vasculitis.* J Rheumatol, 2004. **31**(11): p. 2181–8.
11. Bourgeais, A.M., et al., *[Cutaneous polyarteritis nodosa following hepatitis B vaccination].* Ann Dermatol Venereol, 2003. **130**(2 Pt 1): p. 205–7.
12. De Keyser, F., et al., *Immune-mediated pathology following hepatitis B vaccination. Two cases of polyarteritis nodosa and one case of pityriasis rosea-like drug eruption.* Clin Exp Rheumatol, 2000. **18**(1): p. 81–5.
13. Ventura, F., et al., *Cutaneous polyarteritis nodosa in a child following hepatitis B vaccination.* Eur J Dermatol, 2009. **19**(4): p. 400–1.

Index

M. Z. Dudley et al., *The Clinician's Vaccine Safety Resource Guide*, https://doi.org/10.1007/978-3-319-94694-8