Best Practices for Physicians Recommending a Medical Exemption to Vaccination

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The goal of this presentation is to assist physicians and their staff with the evaluation of patients for medical exemption from vaccination. At the end of this presentation, the participant will be able to meet the following four learning objectives:

1. Understand the difference between vaccine warnings, precautions, and contraindications to vaccination, and the medicolegal definition of a medical exemption.
2. Become familiar with vaccine warnings and precautions described in vaccine package inserts (PIs), contraindications and precautions recognized by the Centers for Disease Control and Prevention (CDC), vaccine injuries listed in the National Vaccine Injury Compensation Program's (VICP) Vaccine Injury Table, and other known and emerging vaccine adverse events.[1-3]
3. Recognize current medical problems, personal medical histories, family medical histories, and other circumstances that may increase the risk of vaccine adverse events.
4. Consider the administrative procedures and best practices involved in writing a medical exemption.

In June 2015, California enacted a mandatory vaccination law (SB277) for both private and public-school attendance.[4] As personal belief exemptions and religious exemptions were no longer available to parents who had particular concerns about a vaccine's safety for their children, the law triggered a rapid increase in requests for physicians to evaluate potentially at-risk children for medical exemptions.[5] The new law revealed a population of chronically ill children whose parents had previously exercised a personal belief exemption for school attendance, as that was all that was required before SB277 was enacted into California law.

The new law emphasizes the need for physicians to understand the science of medical exemptions to vaccination. Most physicians understand that the risk of a vaccine side effect should always be weighed against the risk (e.g., severity and frequency of occurrence) of the corresponding infectious disease, since vaccination is intended as a preventative medical procedure. For example regarding the measles, a

pre-vaccination fatality rate of about 1 in 1,000 reported cases has been publicized by public health departments, even though in reality only 10% of cases were *reported* to public health departments, such as the Centers for Disease Control and Prevention (CDC).[97,98] Since nearly 90% of measles cases were not reported to the CDC, the result was a case-fatality rate of 1 in 10,000 for all measles cases,[97,98] which emphasizes the importance of reviewing available medical literature and data to measure disease risks based on *total* cases, not just the percentage of cases that are reported.

A similar analysis can be done on the risk of seizure. Measles surveillance between 1985 and 1992 showed that measles seizures are 3-times more common than measles deaths; therefore, about 3 in 10,000 (or 1 in 3,333) measles cases result in seizure.[97,98] In contrast, the risk of seizure from MMR has been measured to be 1 in 641, about 5 times greater than the seizure risk from measles.[8,17] In addition, studies show that pre-existing medical conditions significantly elevate the risk of suffering an adverse reaction from MMR. The risk of seizure from MMR in siblings of children with a history of febrile seizures is 1 in 252, and the risk of seizure from MMR in children with a personal history of febrile seizures is 1 in 51.[8,17]

In the United States, many physicians and their staff have not been trained or experienced with how to evaluate a patient for an increased risk of vaccine side effects, beyond general contraindications recognized by the CDC. The goal of this presentation is to fill the knowledge gap in physicians' training to evaluate a patient for a medical exemption to vaccination.

WHAT IS A MEDICAL EXEMPTION TO VACCINATION?

A medical exemption to vaccination is a medicolegal document that is required specifically for school attendance when a patient is at increased risk of harm from any state-mandated vaccine. It is important to recognize that a medical exemption must be based on one or more medical issues, such as contraindication, precaution, warning, or perceived risk of an adverse event from the physician's point of view.

In some states, a medical exemption must be based on specific contraindications or a state-determined standard. While in other states a medical exemption is not limited to contraindications or state-determined guidelines, but rather is based on a physician's professional recommendation to exempt a child from vaccination for school attendance for medical reasons. In California, for example, a medical exemption is "a written statement by a licensed physician to the effect that the physical condition of the child is such, or medical circumstances relating to the child are such, that immunization is not considered safe." [4] Thus, in California, licensed physicians are allowed by law to make individualized and up-to-date recommendations for at-risk children, after weighing the benefits versus the risks of a vaccine.

The ethical implications of requiring a medical exemption, such as for school attendance, is beyond the scope of this presentation. Also beyond the scope of this presentation is the worldwide vaccine debate/conversation among medical professionals comparing, for example, the benefits of lifelong naturally-acquired immunity versus temporary pharmaceutical-based immunity.[46] The notion of a one-size-fits-all vaccination schedule has also recently come under scrutiny as potentially outdated science due to the known and unknown variety of immune system responses among diverse individuals.[92]

WHAT ARE VACCINE CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, AND ADVERSE EVENTS?

As defined by the CDC, a vaccine contraindication is a condition that "increases the risk of a serious adverse reaction," and when such condition is present, a vaccine should not be administered.[2] For example, a contraindication to any vaccine is a severe allergic reaction to a prior dose or hypersensitivity to a vaccine component.

The CDC defines vaccine precautions as conditions that "might increase the risk for a serious adverse reaction, might cause diagnostic confusion, or might compromise the ability of the vaccine to produce immunity," and therefore, when present, should also cause deferment of vaccine administration.[2] The CDC explains, "In general, vaccinations should be deferred when a precaution is present." Although the risk of a serious adverse reaction occurring in the presence of a precaution is considered to be smaller than that in the presence of a contraindication, the recommendation to vaccinate or not in the presence of a precaution "should be decided on a case-by-case basis" by the physician.[2] The latter requires weighing the necessity or urgency of administering the vaccine (e.g., the imminence of an outbreak or severity of disease) against the severity of a possible vaccine side effect. For example, a precaution to administering any vaccine is a "moderate or severe acute illness, with or without fever."[2]

In some cases, drug manufacturers' package inserts (PIs) identify certain conditions as contraindications, even though the CDC considers those conditions as precautions. Also, PIs include warnings to vaccination—situations where "due caution" should be exercised when determining the appropriateness of administering a vaccine.[1]

Vaccine adverse events (AEs) are side effects or health complications that occur after vaccination. AEs are identified during clinical trials and post-marketing surveillance and are usually listed in PIs in decreasing order of severity. For example, the measles, mumps, and rubella (MMR) vaccine PI lists panniculitis, vasculitis, pancreatitis, diabetes mellitus, thrombocytopenia, anaphylaxis, arthritis, encephalitis, and pneumonia amongst the most severe AEs.[7] Other severe adverse reactions include deafness, long-term seizures, coma, lowered consciousness, permanent brain damage, and death.[7,8]

In addition, the Vaccine Injury Table lists specific adverse events, including deaths, that are awarded compensation by the Vaccine Injury Compensation Program (VICP).[3] Notably, if an AE listed on the Vaccine Injury Table or a contraindication listed in a vaccine manufacturer's PI occurs, healthcare providers are required by law to report it to the Vaccine Adverse Event Reporting System (VAERS).[9]

Both the VICP and VAERS were enacted by the National Childhood Vaccine Injury Act of 1986 in order to provide a no-fault alternative to the traditional court system for resolving vaccine injury or death claims; and to conduct passive surveillance of adverse events occurring after vaccination, respectively.[10] With only limited exception, healthcare providers and vaccine manufacturers are not liable for damages from vaccines they produce or administer. And, generally, VICP claims of injury must be filed "within three years after the first symptom or manifestation of onset or of the significant aggravation of the injury," and within two years if the vaccination resulted in death.[11]

Select vaccine contraindications, warnings and precautions, and adverse events are tabulated in Table 1 provided with this presentation.

MEDICAL CIRCUMSTANCES THAT INCREASE THE RISK OF VACCINE ADVERSE EVENTS

In evaluating a patient for a medical exemption to vaccination it is important that a physician consider medical circumstances that increase the risk of vaccine adverse events.

Chief Complaint

If a patient is currently experiencing any of the following complaints, a medical exemption may be indicated for several months or longer until the problem is resolved:

- Any moderate or severe acute illness, with or without fever (See Table 1)
- Progressive neurologic disorder, until a treatment regimen is established, and the condition has stabilized—listed as a precaution in the PI of DTaP and on the CDC list of precautions (See Table 1)
- Cerebral injury or seizure disorder—listed as a contraindication in the PI of MMR and on the CDC list of precautions. (See Table 1)
- Severe immune deficiency states—listed as a contraindication in the PIs for live vaccines and on the CDC list of contraindications. (See Table 1)
- Prematurity in the early months—some PIs warn of the risk of apnea and other life-threatening events following intramuscular injections of premature infants (See Table 1)
- Developmental delay or regression[12]

In practice, a patient's current medical condition could deteriorate in response to vaccination. The physician must weigh the likelihood and consequences of worsening the patient's medical condition due to vaccination against the likelihood of acquiring and incurring permanent damage from the corresponding infectious disease(s).

Personal Medical History

If a patient's past medical history includes any of the following, a medical exemption may be indicated:

- History of previous vaccine adverse event (See Table 1)
- Latex allergy—listed as a precaution in some PIs (See Table 1)
- Mild to moderate (non-anaphylactic) egg allergy—listed as a precaution in the PI of the MMR and influenza vaccines (See Table 1)
- History of seizure disorder now resolved—listed as a warning in the PI of the MMR vaccine (See Table 1)
- History of significant neurodevelopmental regression requiring extensive therapy to resolve (See Table 1)
- History of inflammatory bowel disorder[14, 15]
- History of thrombocytopenia—listed as a warning in the PI of the MMR vaccine (See Table 1)
- History of severe immunodeficiency (See Table 1)
- History of intussusception (See Table 1)
- History of receipt of antibody-containing blood product within the past 11 months[2]

The physician must consider the possibility that a medical condition may be exacerbated as an adverse event to vaccination,[14,16,17] and weigh it against the likelihood of acquiring and incurring damage from the corresponding infectious disease(s).

Table 1: Select Vaccine Contraindications, Warnings and Precautions, and Compensated Adverse Events[1-3]

Vaccine	**Contraindications**	**Warnings and Precautions**	**Adverse Events** From Vaccine Injury Compensation Program (VICP)
Most vaccines	Severe allergic reaction (e.g., anaphylaxis) after a prior dose or hypersensitivity to a vaccine component	Moderate or severe acute illness with or without a fever	Anaphylaxis Shoulder injury related to vaccination Vasovagal synope
Inactivated Polio Vaccine [o]	History of hypersensitivity to any component of the vaccine, including 2-phenoxyethanol, formaldehyde, neomycin, streptomycin, and polymyxin B	Pregnancy Immunodeficient patients or patients under immunosuppressive therapy may not develop a protective immune response against paralytic poliomyelitis after administration of IPV	Anaphylaxis Shoulder injury related to vaccination Vasovagal syncope
Influenza (Inactivated) [p]	Severe allergic reaction (e.g., anaphylaxis) after previous dose of influenza vaccine, to egg protein, or other vaccine component	GBS <6 weeks after previous dose of tetanus-toxoid-containing vaccine Syncope warning Egg allergy other than hives, e.g., angioedema, respiratory distress, lightheadedness, recurrent emesis; or required epinephrine or another emergency medical intervention (IIV may be administered in an inpatient or outpatient medical setting and under the	Guillain-Barré syndrome Anaphylaxis Shoulder injury related to vaccination Vasovagal syncope

		supervision of a health care provider who is able to recognize and manage severe allergic conditions) [2]	

Diphtheria, tetanus and pertussis (DTaP)[a,b,c,d,e]	Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP or DTaP Progressive neurological disorders Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria-toxoid-, tetanus-toxoid-, or pertussis-containing vaccine, or any vaccine component Severe allergic reaction to any component including neomycin and polymyxin[b]	Temperature of ≥105°F (≥40.5°C) within 48 hours after vaccination with a previous dose of a pertussis-containing vaccine Collapse or shock-like state (i.e., hypotonic-hyporesponsive episode) within 48 hours after receiving a previous dose of a pertussis-containing vaccine Seizure ≤3 days after receiving a previous dose of a pertussis-containing vaccine Persistent, inconsolable crying lasting ≥3 hours within 48 hours after receiving a previous dose of a pertussis-containing vaccine Guillain-Barré syndrome (GBS) <6 weeks after previous dose of tetanus-toxoid-containing vaccine History of Arthus-type hypersensitivity reactions[2] Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy Premature infants (due to risk of apnea with intramuscular vaccines) Latex sensitivity[a,b,c] Immunocompromised persons may have a diminished response[d,e]	Encephalopathy or encephalitis Brachial neuritis Anaphylaxis Shoulder injury related to vaccination Vasovagal syncope

***Haemophilus influenza* type b (Hib)** [f,g,h]	Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any *H. influenzae* type b- or tetanus-toxoid-containing vaccine or any component of the vaccine [f,g] Hypersensitivity to any component of the vaccine [f,g] or diluent [h]	Latex sensitivity [h] Special care should be taken to ensure that the injection does not enter a blood vessel [h] GBS <6 weeks after previous dose of tetanus-toxoid-containing vaccine [f,g] Premature infants—risk of apnea with intramuscular vaccines [g] Syncope warning [h] Safety and effectiveness in immunosuppressed children have not been evaluated [g] Immunocompromised persons may have a diminished response [f,h] Cases of Hib disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines [h]	Shoulder injury related to vaccination Vasovagal syncope

Hepatitis A [i]	A history of immediate and/or severe allergic or hypersensitivity reactions (e.g., anaphylaxis) after a previous dose of any hepatitis A vaccine or with an anaphylactic reaction to neomycin	Latex sensitivity Vaccination may not prevent hepatitis A infection in individuals who have an unrecognized hepatitis A infection at the time of vaccination Immunocompromised persons may have a diminished response	Shoulder injury related to vaccination Vasovagal syncope
Hepatitis B [j,k,l]	Severe allergic or hypersensitivity reactions (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing vaccine, or to any vaccine component including yeast. [j,k,l] Hypersensitivity to yeast [j,k,l]	Latex sensitivity [j,k] Syncope warning [k] Premature infants—risk of apnea with intramuscular vaccines [j,k] Vaccination may not prevent hepatitis A or hepatitis B infection in individuals who have an unrecognized hepatitis A or hepatitis B infection at the time of vaccination [j,k,l] Immunocompromised persons—diminished response [k,l]	Anaphylaxis Shoulder injury related to vaccination Vasovagal syncope
Human Papillomavirus (HPV) [m,n]	Hypersensitivity, including severe allergic reactions to yeast [m] (a vaccine component) or after a previous dose [m,n]	Pregnancy [n] Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity [m,n] Latex warning sensitivity [n]	Anaphylaxis Shoulder injury related to vaccination Vasovagal syncope

Influenza **(Live, Intranasal)** [q]	Severe allergic reaction (e.g., anaphylaxis) after previous dose of influenza vaccine, to egg protein, or other vaccine component Concomitant use of aspirin or aspirin-containing medication in children and adolescents Should not be administered to persons who have taken influenza antiviral medications within the previous 48 hours Pregnancy [2]	GBS <6 weeks after a previous dose of influenza vaccine Asthma in persons aged 5 years old or older Children younger than 5 years of age with recurrent wheezing and persons of any age with asthma may be at increased risk of wheezing Medical conditions which might predispose to higher risk of complications attributable to influenza The effectiveness has not been studied in immuno-compromised persons May not protect all individuals receiving the vaccine	Guillain-Barré syndrome Anaphylaxis Vasovagal syncope
Measles, mumps and rubella (MMR)[r]	History of anaphylaxis to neomycin Hypersensitivity to any component of the vaccine, including gelatin Immunodeficiency states Immunosuppressive therapy Febrile illness (>101.3°F or 38.5°C) Pregnancy Family history of congenital or hereditary immunodeficiency A parent, brother, or sister with a history of immune system problems [42]	Personal or family history of febrile seizures Personal of family history of cerebral injury History of anaphylaxis or hypersensitivity to eggs Thrombocytopenia History of thrombocytopenia or thrombocytopenic purpura Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product) [2] Need for tuberculin skin testing or interferon-gamma release assay (IGRA) testing [2]	Encephalopathy or encephalitis Chronic arthritis Vaccine-strain measles viral disease in an immune-deficient recipient Thrombocytopenic purpura Anaphylaxis Shoulder injury related to vaccination Vasovagal syncope

		Any other vaccines in the past 4 weeks.[42]	
Measles, mumps, rubella, and varicella (MMRV) [s]	History of anaphylaxis to neomycin Hypersensitivity to any component of the vaccine, including gelatin Immunodeficiency states Immunosuppressive therapy Active untreated tuberculosis Febrile illness (>101.3°F or 38.5°C) Pregnancy Family history of congenital or hereditary immunodeficiency A parent, brother, or sister with a history of immune system problems [42]	Personal or family history of febrile seizures Personal or family history of cerebral injury History of anaphylaxis or hypersensitivity to eggs Thrombocytopenia The safety and efficacy for use after exposure to measles, mumps, rubella, or varicella have not been established Any other vaccines in the past 4 weeks.[42]	Encephalopathy or encephalitis Chronic arthritis Vaccine-strain measles viral disease in an immune-deficient recipient Thrombocytopenic purpura Anaphylaxis Shoulder injury related to vaccination Vasovagal syncope
Meningococcal [t,u,v,w]	Severe allergic reaction (e.g., anaphylaxis) after a previous dose of or any component of this vaccine, or any other CRM197-, diphtheria-toxoid- or meningococcal-containing vaccine [t,u]	Premature infants may experience apnea [t] Guillain-Barré syndrome [t,u] Latex sensitivity [v,w] Altered immunocompetence, safety and effectiveness have not been evaluated in immunocompromised persons [t,v,w] Altered immunocompetence, immunosuppressant therapy, may have reduced immune responses [u,v,w]	Anaphylaxis Shoulder injury related to vaccination Vasovagal syncope

Pneumococcal [x,y]	Severe allergic reaction (e.g., anaphylaxis) after a previous dose of PCV13 or any diphtheria-toxoid-containing vaccine or to a component of a vaccine (PCV13 or any diphtheria-toxoid-containing vaccine) [2,x]	Apnea following intramuscular vaccination has been observed in some infants born prematurely [x] Individuals with altered immunocompetence, including those at higher risk for invasive pneumococcal disease (e.g., individuals with congenital or acquired splenic dysfunction, HIV infection, malignancy, hematopoietic stem cell transplant, nephrotic syndrome), may have reduced antibody responses to immunization [x] Persons with severely compromised cardiovascular or pulmonary function [y] Persons with chronic cerebrospinal fluid leakage [y] Immunocompromised persons may have a diminished response [y]	Shoulder injury related to vaccination Vasovagal syncope
Rotavirus [z]	Severe combined immunodeficiency (SCID) History of intussusception History of uncorrected congenital malformation of the gastrointestinal tract that would predispose to intussusception	Altered immunocompetence other than SCID (e.g., HIV/AIDS) Delay administration in infants suffering from acute diarrhea or vomiting. Chronic gastrointestinal disease [2,z] Spina bifida or bladder exstrophy [2] Latex sensitivity Safety and effectiveness in infants with known primary or secondary immunodeficiencies have not been established	Intussusception

		Safety and effectiveness of ROTARIX when administered after exposure to rotavirus have not been evaluated. Rotavirus shedding in stool occurs after vaccination with peak excretion occurring around Day 7 after Dose 1	
Tetanus, diphtheria, and pertussis (Tdap) [aa]	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP, DTaP, or Tdap [2]	GBS <6 weeks after a previous dose of tetanus-toxoid-containing vaccine Progressive or unstable neurological disorder, uncontrolled seizures, or progressive encephalopathy [2] History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid- or tetanus-toxoid-containing vaccine Latex sensitivity If vaccine is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained.	Encephalopathy or encephalitis Brachial neuritis Anaphylaxis Shoulder injury related to vaccination Vasovagal syncope

Varicella [bb]	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component including neomycin and gelatin. Any febrile illness or active infection Active, untreated tuberculosis Pregnancy [2,bb] Immunosuppressed states; immunodeficiency states Family history of altered immunocompetence [2,bb] A parent, brother, or sister with a history of immune system problems [42] Immunoglobulins should not be given concomitantly Blood or plasma transfusions, or administration of immune globulin(s)	Recent (≤11 months) receipt of antibody-containing blood product [2,bb] Receipt of specific antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination (avoid use of these antiviral drugs for 14 days after vaccination) [2] Use of aspirin or aspirin-containing products [2,bb] Premature infants Transmission of vaccine virus may occur between vaccinees and susceptible contacts Any other vaccines in the past 4 weeks. [42]	Anaphylaxis Shoulder injury related to vaccination Vasovagal syncope Disseminated varicella vaccine-strain viral disease Varicella vaccine-strain viral reactivation
Zoster [cc]	Known severe immunodeficiency Pregnancy History of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine	Receipt of specific antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination (avoid use of these antiviral drugs for 14 days after vaccination) [2] Transmission of vaccine virus may occur between vaccinees and susceptible contacts	

The information in this table is extracted from the CDC Vaccine Recommendations and Guidelines of the ACIP on Contraindications and Precautions [2], Vaccine Information Statements,[42] manufacturers' package inserts (PI) current as of February 2019, and from the FDA's website.[1] To query whether a PI has been updated since this table was prepared, check the FDA's website.[1]

PIs referenced: [a] Infanrix, [b] Kinrix, [c] Pediarix, [d] Quadracel, [e] Pentacel, [f] ActHIB, [g] HIBERIX, [h]PedvaxHIB, [i] VAQTA, [j] Recombivax HB, [k] Engerix-B, [l] Hepislav B, [m] Gardasil 9, [n] Cervarix, [o] IPOL IPV, [p]Flulaval, [q] Flumist Quadrivalent, [r] MMR II, [s] Proquad, [t]MENVEO, [u] Menactra , [v]BEXSERO, [w]Menomune, [x] Prevnar 13, [y] PNEUMOVAX 13, [z] Rotarix oral suspension, [aa] TENIVAC, [bb] Varivax, [cc]Zostavax

EMERGING DATA FOR RISK ASSESSMENT REGARDING VACCINE ADVERSE EVENTS

Family Medical History

Emerging data is available on familial predispositions to adverse events to vaccination.[42] If a family has already experienced severe vaccine adverse events in several distant relatives, or a moderate to severe reaction in one or more close family members, a family member may express hesitation to receiving vaccines. The doctor should use discretion and judgment in weighing this factor in the consideration of a medical exemption.

A doctor must utilize clinical judgment and consider the health and well-being of children in families whose medical history includes numerous health problems. Health conditions in the immediate family (sibling, parent) may potentially have a bigger impact on the patient than conditions in more distant relatives.[17]

Medical conditions can be grouped into several categories, with an extensive body of medical research that has examined certain categories. In some, there are considerable data to support a possible link between vaccination and an acute or chronic medical condition; in others, the data are generally lacking.

Following are six categories of acute and chronic illnesses that physicians may encounter as they take familial medical histories of their patients, which could play a role in the consideration of medical exemption from vaccination. These are listed in a descending order of medical certitude (categories with the largest body of research are listed first). It is important to realize that medical research has not conclusively proven that these disorders increase the risk of a severe adverse reaction to vaccines (thus, they are not yet considered contraindications). However, an indicated relationship has been determined in some cases, which may be taken into account when evaluating a patient for a medical exemption.

1. **Autoimmune Disorders**[16,18-23]
    - Systemic lupus erythematosis[24-26]
    - Rheumatoid arthritis[24,26-28]
    - Hashimoto's thyroiditis[25]
    - Psoriasis[29-34]
    - Fibromyalgia/Chronic fatigue[35-38]

- Multiple sclerosis[24,39,40]
- Type 1 diabetes[41,43]
- Sjögren's syndrome[44]
- Vitiligo[35,47]
- Celiac disease[25]
- Addison's disease[25]
- Alopecia areata[24]
- Other autoimmune states[16]

2. **Asthma/Allergy/Atopic Disorders** [48-56]
   - Anaphylaxis[48,56]
   - Asthma and allergy [45,49,54-56]
   - Atopic disorders [50-52]
   - Eczema/Atopic dermatitis[57]
   - Severe food allergies[42,58,59]

3. **Neurological Disorders**[60,61]
   - Seizures or epilepsy[7,42,61,62]
   - Bell's palsy[63,64]
   - Alzheimer's disease[65,66]
   - Parkinson's disease[65,66]
   - Obsessive compulsive disorder/Tic disorder/Tourette's syndrome[67,68]
   - Mitochondrial dysfunction[12]
   - Guillain-Barré syndrome[69]
   - Demyelinating inflammatory disorders[70,71]
   - Other[24]

4. **Inflammatory Bowel Disorders**[14,15]
   - Crohn's disease[14]

- Ulcerative colitis[14]
- Celiac disease[25]

5. **Developmental or Learning Disorders**[73]
    - Autism[74]
    - Speech or language impairment[74]
    - Attention deficit disorder/Attention deficit and hyperactivity disorder[67,75 80, 94-96]
    - Learning disabilities[75]

6. **Psychiatric or Mental Health Disorders**[67]
    - Schizophrenia[76]
    - Depression[77-79]

Genetic Susceptibility That May Increase the Risk of Vaccine Adverse Events

Certain individuals are at a higher risk of having unique neurological, autoimmune, allergic, and inflammatory reactions to vaccine antigens and other ingredients. As part of the National Vaccine Injury Compensation Program (VICP) established in 1986, potential vaccine recipients "who may be at significantly higher risk of major adverse reactions" to vaccines were to be identified,[10] yet they remain unidentified because the population isn't being routinely screened. Certain genetic and immunological tests, some of which are highlighted below, are able to identify an increased risk of a vaccine adverse event based on personal genetic or immunological susceptibility. While more research is needed, preliminary data are available, and the growing body of literature is significant.[81-90]

The practice of performing genetic evaluations to determine the presence of increased risk to a vaccine adverse event has been named several terms, including genetic adversomics,[81] pharmacogenomics,[82,83] and vaccinomics.[84] Several gene polymorphisms (or SNPs) have been noted in the medical literature as having the potential to increase the risk of an adverse reaction to vaccination, for example, *MTHFR*,[85] *IRF1*,[85] *ICAM1*,[86] *IL4*,[87] *HLA-DBR1*,[88] *HLA-DQB1*,[88] and *SCN1A*.[89,90] Until further research is conducted, the degree to which these genetic variants increase vaccine risk cannot be claimed with certainty, but it is currently known that the risk is present. A physician may elect to perform a genetic evaluation for a patient and, for those with one or more genetic variants that are currently known to increase the risk of a vaccine adverse event over that in the general population, may follow the precautionary principle and issue a medical exemption.

The candidate genes noted to have the strongest association with adverse events following vaccination (AEs) include a metabolism gene previously associated with adverse reactions to a variety of pharmacologic agents*, MTHFR*, and an immunological transcription factor, *IRF1* gene. The statistical results from the medical literature carry strong biological plausibility and are in agreement with previous work on the immune response to poxviruses.[85]

Genetic polymorphisms related to inappropriate regulation of *IL4* expression and/or activity of IL-4 cytokine could be associated with altered brain function leading to the development of clinical AEs.[87]

Physicians need to be aware that in certain individuals, vaccinations can trigger serious and potentially disabling and even fatal autoimmune manifestations. These reactions are most often associated with the HLA class of genes. Individuals who carry certain genetic profiles are at increased risk.[16,88]

"Presence of the HLA class I allele A2 can result in heavy cytotoxic T-cell activation and vaccine/self-peptide presentation to immune cells. If HLA autoimmune susceptibility alleles/haplotypes are present that control other immune response components, the probability is elevated that these will activate cross-reactive immune cells; the cells, their inflammatory secretions and/or auto-antibodies may initiate adverse events reflecting those susceptibilities."[88]

The situation with HLA genes is very nuanced because the lack of *HLA-DRB1*13* is associated with being a vaccine non-responder but the presence of *HLA-DRB1*07* does as well.[72] Being a vaccine non-responder is not about calculating AE risk, but rather being able to assess risk versus benefit of a proposed vaccine.

The genetic variants of *IFI44L*, *CD46*, *SCN1A*, *SCN2A*, and *ANO3* are all related to seizure activity following the MMR vaccine.[89] The risk of developing febrile seizures from the MMR vaccine is five times greater than the risk of developing febrile seizures from the measles itself; it is estimated that there are 5,700 MMR-induced febrile seizures every year in the United States.[8] And a portion of febrile seizures have permanent sequelae, as shown for example in a large 2007 epidemiological study finding that 5% of febrile seizures resulted in epilepsy.[6,8]

SUGGESTED POLICIES AND ADMINISTRATIVE PROCEDURES FOR DOCTORS WHO EVALUATE PATIENTS FOR MEDICAL EXEMPTION TO VACCINATION

The authors of this presentation hold the professional opinion that it is in the best interest of the patient for the physician to consider the factors below in a manner most protective of the current and future health and well-being of the individual patient.

1. An adverse event to one or more vaccines should factor into the recommendation regarding exemption to other and all vaccines, due to common vaccine ingredients and excipients.
2. There are no data establishing an age at which a child might outgrow a propensity to suffer a repeat vaccine adverse event, and a physician is justified in providing an exemption for any length of time which he or she decides is warranted in each clinical situation.
3. Extending an exemption beyond the patient's age in which a pediatrician practices medicine (age of 18 years) may not be within the scope of care of a pediatrician, but the severity of an adverse event or condition may be factored into this decision (e.g., a severe allergic reaction or neurological injury).

Best practices include the following:

1. **Asking patients to make a separate appointment for vaccine and immunity evaluation.** A thorough evaluation regarding vaccination and immunity takes time, and an ordinary checkup may not allow adequate time for full consideration of a patient's case. Alternatively, provide a longer appointment to cover both a checkup and an exemption evaluation. In certain cases, a patient's current medical provider may not provide such evaluations, or the patient may want to seek a second opinion.

2. **Providing pre-appointment personal and family history questionnaires so that all required information is available for the appointment.** A thorough personal and family history is most readily obtained if the patient has had adequate time beforehand to gather medical information and come to the appointment prepared with all necessary information written into a questionnaire. Where applicable, the patient should also bring documentation of previous vaccines, any medical records that substantiate a moderate to severe vaccine reaction in the patient history (if available), and medical records that document any past and current medical problems in the patient history (if available).

3. **Seeking to obtain informed consent from *both* parents/legal guardians.** It may generally be acceptable to consult with only one parent if both parents are known to a practice and if the parent who is present confirms that the other parent is in agreement. In the case of a difference of opinion, or (especially) if there is a current custody dispute, it is important to involve both parents in the evaluation process and, where appropriate, to obtain a written consent to the evaluation from both parents before providing an exemption. This respects the authority of both parents and avoids disruption of the doctor-parent relationship. Where one parent has full medical custody of a child, providing an evaluation and exemption irrespective of the consent of the absent parent is appropriate.

4. **Performing a complete physical exam.** It is standard practice to perform a complete physical exam during an evaluation for vaccination and immunity. For physicians who practice telemedicine, consult state laws regarding requirements for an in-person visit.

Discussing the Implications of a Medical Exemption with Patients/Guardians

If a patient is granted a medical exemption the key points that should be discussed with the patient and/or guardian are as follows:

• The medical exemption was granted because the risk of an adverse reaction may be higher for the patient than for the general population. The risks to vaccination outweigh the benefits.

• A medical exemption implies that the patient may attend school without receiving those vaccines.

• According to conventional medical opinion, being exempted from a vaccine or vaccines may leave the patient more susceptible to the associated disease and also more likely to be contagious. Conventional medical opinion also highlights that the patient may be more likely to contract a more severe form of the disease thus increasing the risk of harm or death.

• If necessary, ask the patient/guardian to return periodically or as needed for a re-evaluation of the patient's health and circumstances.

• In the event of an outbreak, a patient with a medical exemption may be requested or required to avoid entering certain areas until the increased risk has cleared.

SUMMARY

There are warnings, precautions, and contraindications associated with every vaccine. These are primarily described on the CDC website, PIs, and in the VICP Vaccine Injury Table. A vast body of medical literature further describes and clarifies the science of vaccination and immunity. To minimize the risk of an adverse event occurring, careful consideration should be given to a patient's personal medical history and family history.

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Self-Assessment Test

Best Practices for Physicians Recommending a Medical Exemption to Vaccination

1. Which of the following is not listed amongst the most severe adverse events on the MMR package insert?

a. Pancreatitis

b. Death

c. The common cold

d. Pneumonia

2. Which of the following is a true statement about medical exemption to vaccination?

a. All States have the same laws governing medical exemptions

b. Medical exemptions can only be written for an immunocompromised patient

c. In all States, a medical exemption must refer to a contraindication specified in the manufacturers' product insert

d. The physician's recommendation to vaccinate or not in the presence of a precaution should be decided on a case-by-case basis

3. Which category of chronic health conditions has the largest body of medical literature indicating a possible link to vaccination?

a. Psychiatric conditions

b. Allergic disorders

c. Autoimmune disorders

d. Inflammatory bowel disease

4. Which of the following statements regarding making a recommendation for a medical exemption from vaccination is true?

a. Family history of a vaccine reaction is not a factor

b. Contraindications are not the only considerations

c. Patients must provide written proof of a previous severe vaccine reaction in order for a doctor to consider it as a factor

d. A physical exam is not a factor in a medical exemption evaluation

5. Once a medical exemption is provided, a patient is unable to receive any more vaccines, even in the event of an outbreak or epidemic.

a. True

b. False

6. What is the statute of limitations for reporting a death after vaccination to the Vaccine Injury Compensation Program?

a. One year

b. Two years

c. Three years

d. Ten years

7. Which of the following medical circumstances prior to vaccination is NOT a precaution to repeat vaccination according to the CDC?

a. Seizure (with or without fever) within three days of a vaccine

b. Encephalitis (three or more hours of persistent, inconsolable crying)

c. Fever of 105 degrees F or higher

d. Hypotonic-hyporesponsive episode or shock-like state

e. None of the above (i.e., they are all precautions)

Correct answers: 1:c, 2:d, 3:c, 4:b, 5:b, 6:b; 7:e