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Immunization

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SUMMARY

Immunization programs are most perhaps the most important public health initiative in which a country can invest as they are designed to protect children, the most vulnerable members of our population. As parents it is important to have a full understanding of the possible complications of vaccines, less we allow fear to guide us. Herein, I provide a framework that will provide information to guide parents in this endeavor.

INTRODUCTION

Immunization programs have been effective in protecting children against infectious disease thus, playing a crucial role in eradicating previously deadly diseases. The main example is smallpox, a formerly deadly childhood disease that was removed worldwide in 1980 as a result of a World Health Organization (WHO) program. However, in order for such programs to be effective they have to be able to reach over 80% of the community at risk (i.e., unvaccinated children). High vaccination rates in turn protect even

unvaccinated people by lowering the level of infectious disease in the community. This phenomenon is known as herd immunity. Table 1 depicts the vaccination schedule recommended for healthy children in the United States (U.S.).

Table 1. Approximate Schedule of Routine Immunization of Healthy Infants and Children.

Recommended Age	Immunizations
Birth	HBV
2 months	DTaP, HBV, Hib, eIPV, RV, PC
4 months	DTaP, Hib, eIPV, RV, PC
6 months	DTaP, Hib, eIPV, RV, PC
12-15 months	DTaP, Hib, MMR, eIPV, Var, PC,HBV (6-18 months) HepA (2 dose series 12-24 months)
15-18 months	RV
4-6 years	DTaP, MMR, eIPV, RV, Var
11-12 years	TDap, MV (with or without Hib), HPV (3 dose series)
16-18 years	MV
Yearly 6-23 Months > 2 Years	Influenza IIVLAIV or IIV

Modified from http://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-schedule.pdf.

HBV, Hepatitis B virus; DTaP, acellular pertussis vaccine combined with diphtheria and tetanus toxoids; eIPV, enhanced-potency trivalent inactivated polio vaccine; Hib, Haemophilus influenzae type b; RV, Rotavirus; MMR, measles, mumps, and rubella vaccine; Var, live-attenuated varicella vaccine; MV meningococcal vaccine; Tdap, tetanus, diphtheria, pertussis vaccine; IIV, Influenza inactivated virus; LAIV (Live attenuated influenza virus); HPV, Human papilloma virus vaccine (boys receive HPV2; girls HPV4 or HPV2)

In the past, countries with strong vaccination programs were able to eradicate disease. However, in less wealthy countries, public health initiatives fell short in vaccinating all at risk children. This resulted in high base rates of specific infectious disease (e.g. polio and measles in Asia and Africa). These countries used to be the primary source of imported infectious disease cases in the U.S. However, thanks to the increased popularity of anti-vaccine movements in developed countries, it is just as likely measles will be imported from Europe than from Africa or Asia. In fact, in 2011 most cases of measles in the U.S. were imported from France. Anti-vaccine sentiment is the driving force behind the return of infectious diseases in these countries.

This article discusses the neurological complications of immunizations, and provides an overview of the current challenges and consequences posed by anti-vaccine movements and vaccine exemptions. By providing the reader with an understanding of the methodological principles involved in determining vaccine safety and critically dissecting complications associated with vaccination, the reader will be better equipped to distinguish fact from

myth.

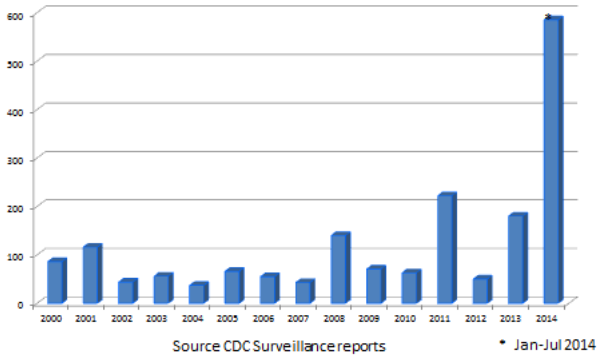
ANTIVACCINE MOVEMENTS

The first objections to vaccination were religious in nature. In 1722, Rev Edward Massey, an English theologian, said small pox inoculation was “dangerous and sinful” and equated it with “a diabolical operation”. Mandatory vaccination policy in Great Britain in 1853 for all infants and later to children up to age 14 years resulted in public outcry, as the policy was viewed as an violation of individual liberties. Eventually the law was changed in 1898 to allow conscientious exemptions to mandatory vaccinations. In the U.S. anti-vaccine movements surfaced in the late 19th century [Porter & Porter 1988]. Anti-vaccine groups founded at the time doubted the science behind vaccination, such as the existence of the concept of immunity. They feared the introduction of “impurities” into their bodies. This concept is similar to the fears espoused by some of today’s vaccine opponents.

Anti-vaccine sentiments unfortunately are global. In Africa, vaccine mistrust brought to a near halt in 2003, a WHO polio eradication program because of rumors that vaccination spread AIDS or sterilized Muslim girls. In developed countries, the inroads made by anti-vaccine movements are reflected in the growing number of vaccine exemptions. These exemptions fuel the return of previously eliminated diseases. In countries that have strong anti-vaccine movements (e.g. U.S.) the rates of pertussis are 10 to 100 times higher than rates in countries without such anti-vaccine movements, where levels of vaccination are very high (e.g. Hungary) (Gangarosa et al. 1998).

Nowhere is the impact of vaccine exemptions more apparent than with measles. With multiple measles outbreaks crisscrossing the nation recently, U.S. faces the worst measles epidemic in over 2 decades (see Fig. 1). The CDC reports a 10-fold increase for the first half of 2014 alone [Gastañaduy et al., 2014]. Outbreaks typically originate from an unvaccinated U.S. citizen who contracts measles while traveling abroad and brings it home where it spreads primarily to children under the age of 5 years. Most individuals contracting imported measles (80%) are susceptible due to vaccine exemptions. The remainders are either too young or too ill to be vaccinated. In 2013, religious exemptions accounted for a measles outbreak of 58 in Brooklyn, New York imported from Britain. Most of those infected were young children, about half under the age 12 months (too young to be vaccinated) [CDC, 2013].

Fig.1. Measles cases in the U.S. 2000-2014



The reasons behind the growth of anti-vaccine sentiments in the United States and other industrialized nations are not clear. A combination of factors are likely contributing to the sentiment including fear, ignorance, celebrity endorsement of such practices (e.g. Jenny McCarthy, Kristen Cavallari), and media sensationalism. The internet, with its lack of scientific scrutiny, has expanded the reach of anti-vaccine movements via seemingly authoritative Web sites that disseminate misinformation about vaccine injuries. For example, such sites can make claims of vaccine injury without needing to show any proof.

Further fueling this anti-vaccine sentiment is the fear generated by the lack of defined etiologies to explain neurological or developmental disorders (e.g. autism) that may temporally coincide with vaccination. This fear, termed risk perception, refers to the manner in which people perceive the severity of a specific risk. Paul Slovic (1987) discussed risk perception is not rational. Therefore, it is not lessened by rational arguments or compelling scientific information. Instead, the judgment of risk severity is curbed by psychological factors, such as whether risks are perceived as being uncontrollable, having catastrophic potential, or having fatal consequences. These key factors apply to autism (an uncontrollable risk with catastrophic potential). A disease that for unknown reasons has reached epidemic proportions, and that is temporally associated with measles vaccination. The spark lighting the fuse of the measles/autism hype was Wakefield's report of an association between autism and measles vaccination (see Combination Vaccines and Additives) [1998]. Wakefield was forced to retract the report as flawed [Anonymous 2010], unfortunately, not before the report influenced measles vaccination practices first in Europe and then in the U.S. The report was later discovered to be fraudulent [Godlee 2011].

CONSEQUENCES OF VACCINE EXEMPTIONS

The loss of herd immunity is the most detrimental consequence of vaccine exemptions. Over the last decade an increasing number of educated parents are choosing vaccine exemptions in the U.S. (6% of children in Seattle and 4% in Colorado are unvaccinated). These high rates of vaccine exemptions are mirrored by an increase in base rates of pertussis (3-fold increase) and measles (10-fold increase). These increased rates have tragic implications, as susceptible children succumb to preventable diseases. In the case of pertussis,

half of infected infants under a year of age are hospitalized and most deaths happen in infants < 3 months of age. Another example is the devastating consequence of meningitis in an Oklahoma boy that tragically resulted in the loss of 4 limbs and facial deformities [Alcindor 2014]. This outcome underscores how personal actions, such as vaccine exemptions, have important public health consequences on children too young to be vaccinated. Hence, children contract diseases they never would have been in contact with had there been proper levels of vaccination in their community. It is these public health considerations that have prompted some States to require parental education prior to granting vaccine exemptions. This requirement is intended to create greater knowledge of the implications of vaccine exemptions for parents' own children, and the children in their community prior to making such decisions.

ASSESSING CAUSALITY

Temporal association is a requirement when assessing causality. However, events that are temporally associated are not necessarily causally linked. Determining causal relationships between vaccinations and specific disorders with certainty is difficult. It requires additional factors to increase the level of certainty. A temporal association may be taken as causally related when it may be linked by simple chance, especially when the biological phenomenon (e.g. onset for a specific neurological outcome) overlaps with the timing of infant vaccinations. The role of chance becomes an even more likely occurrence when the factors being linked occur frequently in the population. Associations by chance between these two common events (developmental disorder and vaccines) are to be expected and do not denote causality.

The role of the coincidence between timing of vaccine and disease onset was the focus of the Melchior study. In the 1970s the DPT (diphtheria, pertussis and tetanus) vaccine was going through media hype. Similar to current scrutiny of the relationship between autism and MMR, early DPT vaccination was linked with claims of vaccine-induced neurological injury, because of the onset of infantile spasms (IS), an epileptic syndrome of childhood.. To dispel this temporal link, Melchior and colleagues sought to examine the effect on the onset of infantile spasms in Denmark by changing the timing of initiating DPT vaccine from 5 months to 5 weeks. The study found that the mean age of onset of IS did not change together with the change in DPT administration. This proved IS was independent of vaccine administration [Melchor 1977]. With greater medical understanding, a greater proportion of IS cases were found to have specific causes (genetic or metabolic). This helped further break the perception of a link with vaccination. As the mystery of autism and a better understanding of its biology is revealed, it is intended that the perception of its risk linked to measles vaccines will also end.

Determining causal relationships between vaccinations and specific disorders with certainty is difficult. There are several methods by which to assess the strength of an association between vaccine and an adverse outcome. The least helpful manner to determine the role of vaccines in causing harm is the anecdotal report. Anecdotal reports are commonly employed by anti-vaccine movements to support claims. A good example of the lack of scrutiny of this type of report is the case in 2013 of a teenage girl in Britain who died shortly after receiving a human papilloma vaccine (HPV) vaccine. The media, as well as anti-vaccine websites, were quick to blame the HPV vaccine [Kotz, 2009]. It was only after the autopsy was performed that the true cause of death was

revealed and the girl was found to have an undiagnosed metastatic cancer surrounding her heart. This example illustrates the limitations of the anecdotal report and highlights the need to employ more rigorous methods in linking causality.

The case report is not much better than the anecdotal report, with one exception: the peer-review process. This is an important safeguard found in medical journals and missing from Web sites. Any publication in medical journals is reviewed by experts in the field who hold the author accountable for the content. This ensures the report does not overstate the findings or associations. These reports play an important role in alerting of a possible association that may prompt further study.

The other two study types:

- clinical trials
- population studies

Clinical trials are experiments in which two comparable groups of people are tested. The primary difference between the groups is the agent under study: one group receives the test agent and the other group receives placebo (a sugar pill or sham injection). Although invaluable for drug studies, clinical trial studies are usually too small in size to test vaccines, especially if adverse outcomes are rare.

Population-based studies are useful, especially if large, because they can assess even rare outcomes. For instance, rates of a naturally occurring disease in an unvaccinated population can be compared to the rates of disease found among people who have been vaccinated. If rates are significantly higher in the vaccinated population, the vaccine may be suspected as being the cause of the increase. Unless there is a biologic marker that links changes in disease frequency to the vaccine, causality cannot be determined with certainty, only suspected. Hence, the value of using such markers to cement as causal the link between vaccine and outcome (e.g. finding a vaccine strain linked to disease symptoms).

A team of experts was called to the task of analyzing existing information with a critical, unbiased viewpoint. Hence, the IOM was charged with reviewing vaccine-related complications and vaccine safety taking into account level of proof. The IOM does not make determination based on lack of evidence. Instead, the literature is reviewed, biologic mechanisms are taken into account, and causality is classified into one of five levels of proof:

1. no evidence bearing on a causal relationship
2. evidence is inadequate to accept or reject a causal relationship
3. evidence favors rejection of a causal relationship
4. evidence favors acceptance of a causal relationship
5. evidence establishes a causal relationship [IOM, 1993, 2012]

In determining causality, the first factor taken into account is the biologic mechanism – *(or is there a plausible mechanism by which the vaccine could cause the complication or disease in question?)* For example, a measles vaccine cannot give polio.

Next, the method of vaccine preparation should be considered. Four types of vaccines are available:

1. vaccines composed of whole-killed organisms

2. vaccines composed of live-attenuated viruses
3. vaccines composed of components of organisms
4. recombinant vaccines

The adverse events should be consistent with the vaccine preparation. For example, vaccines made of components of organisms cannot cause the disease being vaccinated against, but live-attenuated viruses can do so in the right host (e.g., vaccine-associated polio).

As discussed earlier, temporal association is a necessary factor. The disease in question must be temporally linked to the vaccine in question. This means vaccine must be given shortly before or around the time of the onset of the adverse outcome (less than 4 weeks but no more than 90 days of onset in order to be a relevant factor.)

VACCINE INJURY COMPENSATION PROGRAM

The U.S. Vaccine Injury Compensation Program (VICP) came into being in 1988. This was a time in which vaccines became scarce because pharmaceutical companies, fearing the cost of litigation, were ceasing the manufacture of vaccines. By providing a no-fault alternative to the traditional tort system for resolving vaccine injury claims, the VICP was instrumental in fostering the production of a full, steady supply of vaccines. Vaccines covered under the VICP are:

- Diphtheria,tetanus, , and pertussis (DTP, DTaP, DT, TT, or Td)
- measles, mumps, and rubella (MMR or any components)
- polio (OPV or IPV)
- hepatitis B
- hepatitis A
- Haemophilus influenzae type b
- varicella (chickenpox)
- rotavirus
- human papillomavirus
- trivalent influenza
- meningococcal and pneumococcal conjugate *(whether administered individually or in combination)*

The U. S. Court of Federal Claims decides who will be paid based on a table of injuries that outlines known injuries to covered vaccines [HSRSA, 2014]. The injuries listed are presumed to be caused by the vaccine unless an alternate cause is established. If an outcome is not listed in the table additional medical documentation will need to be submitted for the claim to be reviewed by the court.

TYPES OF VACCINES

Vaccines Composed of Whole-Killed Organisms

Vaccines composed of whole-killed organisms were the first laboratory-produced vaccines. They provoke an antibody response that provides temporary immunity. Some vaccines made from whole-killed organisms may cause immune-mediated disorders.

Inactivated Polio Vaccine

Licensed in 1955, the Salk inactivated polio vaccine (IPV) immediately led to a drop in the cases of paralytic poliomyelitis. The Salk vaccine has been highly effective, with a 70% to 90% protection rate. It was replaced in 1963 by Sabin's oral poliovirus vaccine (OPV), which by 1979 had eradicated polio (wild type) in the U.S. Because OPV is prepared with a live-attenuated virus, it is associated with a low risk of eliciting polio in healthy individuals and a larger risk among immune-suppressed individuals (see "Vaccines Composed of Live-Attenuated Viruses"). OPV was replaced by an easier to administer, enhanced-potency trivalent polio vaccine (eIPV) in 1997. No cases of vaccine-associated poliomyelitis have been identified in the U.S. since 1999 [Alexander et al., 2004].

Influenza Virus Vaccine

Epidemic human influenza illness is caused by influenza A and B. Influenza A viruses are categorized into subtypes based on two surface antigens:

1. hemagglutinin (H)
2. neuraminidase (N).

Influenza B viruses are separated into two distinct genetic lineages (Yamagata and Victoria). Viral replication results in DNA changes (mutations) of surface antigens, a phenomenon known as antigenic drift. Each year, a new influenza vaccine is developed to protect against the prevalent virus strains that are expected to appear in the U.S. the following winter. Two types of flu vaccines are available:

1. inactivated flu vaccine
2. the nasal-spray flu vaccine (i.e., live-attenuated influenza vaccine [LAIV])

The "flu shot" vaccine is prepared from inactivated flu virus and is approved for use in all high-risk groups. There are 2 types of inactive vaccine:

1. the trivalent flu vaccine that contains three influenza viruses (one A (H3N2) virus, one A (H1N1) virus, and one B virus)
2. the new quadrivalent flu vaccine that includes 4 different flu viruses (two influenza A viruses and two influenza B viruses)

The CDC does not endorse any specific inactive flu vaccine. The LAIV is prepared from live, attenuated flu viruses that do not cause disease in humans. Annual vaccination against influenza is recommended for both extremes of life: children age 6 to 23 months (as of 2002) and the elderly (>65 years). It is also recommended for people of all ages with chronic diseases. LAIV is more effective than inactivated flu vaccine in younger children and is now recommended for children age 2 to 8 years of age. It has no reported neurological complications in children.

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome (GBS) is an immune-mediated disorder affecting peripheral nerves that causes a flaccid paralysis (varying severity of limb weakness) and, when severe, can affect breathing. The disease is associated with respiratory or gastrointestinal infections through a mechanism termed molecular mimicry- the infectious organism the body is fighting looks immunologically a lot like nerve tissue. The antibodies the body makes to defend itself against the infection cross react with nerve tissue. This causes

weakness. Naturally occurring influenza accounts for about 40% of all GBS cases. In 1976, swine flu vaccine was associated with a slight increase in GBS. It was estimated to add 1 case of GBS per 100,000 people [IOM 2003]. No other strains have been linked to GBS. In fact, compared to the 7- fold increase risk of GBS found with naturally occurring influenza infection, influenza vaccination has a protective effect [Stowe et al., 2009]. A recent IOM review found no causal relationship between GBS and subsequent influenza vaccinations [IOM 2012]. Nevertheless, because individuals with a history of GBS have a greater likelihood of subsequently experiencing GBS than individuals without such a history, it has been recommended that influenza vaccination be avoided among individuals with a history of GBS and who are known to have experienced GBS within 6 weeks of a previous influenza vaccination (http://www.cdc.gov/flu). No cases of GBS are reported in vaccinated children [IOM, 2003].

MULTIPLE SCLEROSIS

There is no evidence that influenza vaccination increases the risk of multiple sclerosis relapse. Multiple studies and a recent IOM review have failed to find an association between multiple sclerosis relapse and vaccination. Influenza vaccination does not induce relapse and should be used in affected individuals.

BELL'S PALSY

Higher rates of Bell's palsy, a cranial nerve demyelinating disorder resulting in unilateral facial weakness, were reported after intranasal vaccination with inactivated influenza virus in a case-control study in Switzerland with a strain no longer in use [Mutsch et al., 2004]. The IOM has undertaken a recent review of topic and rejected an association between Bell's palsy and influenza vaccine, both with inactivated and attenuated vaccines [IOM 2012].

Rabies Vaccine

Rabies was the first manufactured vaccine to be used in humans. Early vaccines were grown in the central nervous system of animals and contained myelin basic protein (Semple vaccine). Additionally, they were associated with, by today's standards, unacceptable immune-mediated side effects, such as:

- demyelination of brain and spinal cord (encephalomyelitis);
- nerve roots (polyradiculitis);, and
- peripheral nerves (polyneuritis) [Hemachudha et al., 1987].

The rabies vaccine licensed for use in the U.S. is prepared from rabies virus grown on human diploid cells, and it has an excellent safety record. Although this rabies vaccine does have a high rate of side effects, they are generally mild:

- sore arm (15 to 25 of 100 recipients);
- headache (5 to 8 of 100 recipients; or
- nausea and vomiting (2 to 5 of 100 recipients)

Given the lethality of rabies (100% deadly), these are clearly acceptable side effects. In developing countries, a less expensive rabies vaccine prepared with chick embryo (Vero cell line) is reported to have a safety profile similar to the diploid cell lines [Toovey 2007].

Whole-Cell Pertussis Vaccine

No longer in use today, the whole-cell pertussis vaccine was combined with diphtheria and tetanus toxoids (DTwP). It contained an endotoxin that causes fever and pain at the site of injection. It also has been associated with seizures, especially febrile and hypotonic hyporesponsiveness (1 case per 1750 doses and acute encephalopathy with a rare (0 to 10.5 cases per 1 million doses administered) with onset within 7 days of vaccination. Encephalopathy is characterized by persistent crying [Cody et al., 1981]. The IOM has determined that evidence was consistent with a causal, yet rare, association with these 2 outcomes, but not with a chronic encephalopathy. However, a large retrospective study in 2006 found no link between whole cell pertussis and acute encephalopathy [Ray 2006].

Vaccines Composed of Live-Attenuated Viruses

Live-attenuated virus vaccines are intended to cause an asymptomatic infection. However, properly constituted vaccines can cause symptomatic infection and the expected complications of the natural disease. The immunity provided by live-attenuated virus vaccines is similar to that from natural diseases, and it may persist for life.

Measles: Rubeola

Measles is a serious childhood disease that can result in pneumonia, encephalitis (1 per 1000 cases) and death. Before the measles vaccine was introduced in 1963, there were about 3 to 4 million cases of measles and 450 deaths annually in the U.S. [CDC 2008]. Subsequently, rates of measles fell and by 2000 endemic measles (i.e., cases arising from within the U.S.) was eliminated. Those measles cases were largely imported, a trend that continues today at alarmingly high rates. Because imported measles infect mainly young children, there is a heightened risk for it turning into a slow virus infection, termed subacute sclerosis panencephalitis (SSPE). This infection can lay dormant in the brain for close to a decade and then present with dementia and seizures.

The licensed measles vaccine uses the Edmonton B measles virus attenuated by prolonged passage in chick embryo cell culture that is combined with mumps and rubella vaccines (MMR). Children who receive live-attenuated measles vaccines are expected to develop an asymptomatic case of measles. Some children develop fever, rash, and conjunctivitis in the second week after immunization (i.e., the incubation period is at least 5 days).

Children with vaccine-induced measles can develop any of the known complications of natural infection except SSPE. In developed countries with scant or no endemic measles, SSPE has disappeared together with the disappearance of measles. Cases of SSPE among measles vaccinated children, when studied, are found to be due to wild type measles infection [Campbell 2007]. The main neurologic complication of measles immunization is a febrile seizure during the second week after immunization [Griffin et al., 1991].Even among high-risk children, the risk of this outcome is low. Children with measles-associated febrile seizures are not at increased risk of epilepsy [Vestergaard et al., 2004]. In immunocompromised children, measles vaccination can result in measles inclusion body encephalitis. This subacute encephalitis is typically lethal [Bitnum et al. 1999].

Mumps

The mumps vaccine is administered with MMR vaccination. It is prepared by

passage of the Jeryl Lynn strain of mumps virus in chick embryo cell culture. Mumps vaccine has eliminated natural mumps infection, including mumps encephalitis that pre-vaccination accounted for 36% of all cases of encephalitis in the U.S. No adverse neurologic events are associated with the mumps vaccine used in the U.S.

Rubella

Earlier rubella vaccines that were grown in various animal kidneys were associated with high rates of nerve (neuropathy) and joint (arthritis) complaints. Since 1979, the rubella vaccine used in the U.S. is prepared from human diploid cells. The immunologic response it produces equals that of the natural infection. Up to 25% of people receiving the current rubella vaccine may develop transient joint pains (arthritis) and tingling of skin (paresthesias). In 2012, the IOM reviewed the available scientific evidence and determined it to be consistent with a causal relationship between rubella vaccination and transient acute arthritis, but not with chronic arthralgias in women and children [IOM, 2012]. Rubella virus vaccine has been successful and has nearly eradicated rubella embryopathy.

Oral Polio Vaccine

Sabin's OPV, introduced in 1963, eradicated polio in the U.S. Since 1997, it has been replaced with the enhanced-potency trivalent IPV (eIPV) (see inactivated vaccines page 9) because the greatest risk of contracting polio in the U.S. was vaccine associated (rate about 1 case per 2.4 million doses and higher among immune suppressed children), while the risk of wild polio is nil.

Varicella

A live-attenuated varicella virus (Oka strain) vaccine was licensed in 1995 in the U.S., and it is currently recommended for routine childhood immunization for susceptible children between 12 and 15 months of age. The vaccine produces a mild case of chickenpox. It is safe and effective in normal and mild to moderately immunocompromised children (e.g. with leukemia and HIV infection), but not recommended in severely immunocompromised children. Varicella vaccination can cause herpes zoster (HZ) (a form of viral reactivation) among vaccine recipients, but incidence rates are 79% lower than among unvaccinated children (48 vs 230 per 100,000 person-years, respectively) [Weinmann 2013]. About half of HZ cases among vaccine recipients may be due to wild type reactivation. Serious adverse events, such as acute encephalitis, ataxia, seizures, neuropathy, and death, have been reported in temporal association with varicella vaccine. In some cases, the wild type of varicella-zoster virus or another causal agent has been identified. In most cases, data are insufficient to determine a causal association. The IOM, however, has determined that, although rare, varicella vaccine is causally related to virus reactivation. This results is an infection leading to meningitis and encephalitis, based on 6 cases found to have the Oka strain.

Component Vaccines

Acellular pertussis vaccine and Haemophilus influenzae type b vaccine are made from components of the bacteria. Toxoids are composed of denatured bacterial toxins. Toxoids prevent disease but not infection.

Acellular Pertussis Vaccine

Since 1997, whole cell pertussis vaccines have been replaced by acellular

pertussis vaccines, that contain fewer proteins (five) and less endotoxin. Acellular pertussis vaccination is associated with fewer local adverse events and systemic and neurological adverse events compared with DwPT.

Haemophilus influenzae Type b

Following the introduction of Hib conjugate in 1990, the incidence of invasive H. influenzae disease in children dropped 99% decreasing from 41 cases to less than 1 case per 100,000 child-years by 2007 [Thigpen 2012]. Hypersensitivity to the vaccine components is the only contraindication to its administration. No neurologic adverse events have been attributed to the vaccine in the U.S.

Pneumococcal Conjugated Vaccine

Licensed in the U.S. in 2000, the conjugated pneumococcal vaccine is comprised of the capsular polysaccharide of seven serotypes of streptococcal pneumonia. Before routine vaccination, Streptococcus pneumonia was responsible for invasive disease in 188 per 100,000 children younger than 2 years, accounting for 20% of all invasive pneumococcal disease. Rates of invasive disease have fallen 95% after vaccination. The vaccine produces local side effects, fever, and muscle aches. No serious neurologic side effects have been attributed to pneumococcal conjugated vaccine.

Tetanus and Diphtheria

Tetanus and diphtheria are toxoids that are produced by formalin inactivation of the toxins elaborated by the two organisms. Both have low rates of complications [Lloyd et al., 2003]. Tetanus toxoid is given alone to children and adults after injury or burn exposure. The only contraindication for either toxoid is a history of a neurologic or severe hypersensitivity reaction after a previous dose.

A temporal association has been reported in infants between DPT and brachial neuritis in which the tetanus toxoid was implicated. The IOM concluded in 1993 that a weak but causal relationship exists in adults between tetanus toxoid and brachial neuritis based on repeated reports (class III).

Recombinant Vaccines

Recombinant vaccines are genetically engineered vaccines. Hepatitis B and HPV are the only recombinant vaccines in use.

Hepatitis B Vaccine

Hepatitis B vaccine is prepared by introducing DNA coding for the hepatitis B surface antigen into yeasts for cloning. Acute disseminated encephalomyelitis (ADEM), a rare acute demyelinating disorder, was reported in 2 cases temporally associated with hepatitis B vaccination. The cases were suggestive of a causal relationship because of disease recurrence on repeat dosing with the hepatitis vaccine. However, it was not definitively causal given the lack of a biological markers linking hepatitis vaccine to ADEM (i.e., hepatitis specific antibodies). Multiple sclerosis has been temporally associated with hepatitis B vaccine, yet numerous studies have failed to show a link between MS and hepatitis. A few cases of GBS, Bell's palsy, acute cerebellar ataxia, and brachial plexitis have been temporally associated with hepatitis. The IOM finds, however, that the evidence is insufficient to support a cause-and-effect association with these outcomes [IOM 2012].

Human papilloma virus

HPV vaccines are developed from a subset of human papilloma viruses. Two HPV vaccines are currently licensed in the U.S..

HPV4 (Gardasil) is a quadrivalent vaccine indicated for females 9 through 26 years of age for the prevention of genital and cervical cancers. It is also recommended for males 9 through 26 years of age for the prevention of anal cancer and genital warts caused by human papillomavirus (HPV) Types 6, 11, 16, and 18.

HPV2 (Cervaxis) is a divalent vaccine indicated for adolescent girls and protects against human papillomavirus 16 and 18. Much criticized by the media as risky [Abdelmutti & Hoffman-Goetz, 2010], the HPV vaccine has a strong safety record. Most side effects are attributed to the local injection. A surveillance report found a slight increase in risk for syncope (the act of fainting) linked to HPV (see Vaccination Procedure Outcome section). However, there was no difference from population rates for immune-mediated disorders, including GBS and ADEM (Slade et al., 2009). Two recent controlled studies have also found no link between HPV and immunological or neurological [Grimaldi-Bensouda et al., 2014; Arnheim-Dahlstrom et al., 2013].

COMBINATION VACCINES AND ADDITIVES

Most vaccination preparations involve combination vaccines. Concerns have been raised that combination vaccines (e.g., MMR) or vaccine additives (e.g., thimerosal) could elicit specific developmental disorders of childhood.

Mumps, Measles, and Rubella Vaccine and Autism

A major debate arose after publication of a small gastroenterology study in Britain of a link between the MMR vaccine and autism. The study of 12 patients found gastrointestinal complaints among patients with autistic regression. Eight of these patients had been vaccinated with MMR as determined retrospectively [Wakefield et al., 1998]. Of note, these results have not been replicated by any other center. The authors have since retracted their conclusion of a causal link with autism [Anonymous, 2010] but not before causing broad repercussions throughout Europe and the U.S. Wakefield's claims were discredited when it became known that he received more than 435,000 pounds ($674,000) from lawyers suing the vaccine company and that he had fabricated data. Of the 12 cases, Wakefield examined in his paper, five showed developmental problems before receiving the MMR vaccine and three never had autism. Because of his fraudulent activities Wakefield lost his medical license. Since Wafefield's infamous report was published, several large studies [Chen et al., 2004; Madsen et al., 2002; Maglione et al. 2014] have found that MMR is not associated with pervasive developmental delay or autistic regression. The IOM has concluded after a careful review of existing studies that data do not support a causal relationship between MMR and autism [IOM, 2004].

Thimerosal-Containing Vaccines and Developmental Disorders of Childhood

Thimerosal is an organic mercury compound preservative that has been in use since the 1930s. It was contained in more than 30 vaccines licensed and marketed in the U.S., including some of the vaccines administered to infants for protection against diphtheria, tetanus, pertussis, Haemophilus influenzae type b, and hepatitis B. Thimerosal is metabolized to ethylmercury and thiosalicylate. A congressional bill in 1997 added mercury to the FDA

surveillance activities regarding additives. The dose of mercury the agency found in vaccines raised theoretical concerns that cumulative exposure to ethylmercury, a known neurotoxin, could have developmental side effects [Thimerosal in vaccines, 1999]. In 1999, out of caution, thimerosal was removed from vaccines to trace amounts (<3 µg). Although no study had determined any such link, this precautionary measure had the unintended effect of alarming parents of children with autism. Some concerned parents formed advocacy groups, and desperate for a cure for what they believed to be "mercury-induced autism" sought harmful chelation treatments. Several subsequent studies [Hviid et al., 2003; Price et al. 2010] have found no association between thimerosal-containing vaccines and autism. Ecologic (population based) studies reported that after discontinuation of thimerosal-containing vaccines, rates of autism remained unchanged or increased [Madsen et al., 2003; Stehr-Green et al., 2003]. The IOM has concluded that thimerosal-containing vaccines are not associated with neurodevelopmental disorders, including autism, attention-deficit–hyperactivity disorder, and developmental delay [IOM, 2004].

VACCINATION PROCEDURE AND OUTCOMES

Bursitis and syncope are vaccine-associated outcomes that can occur independently of vaccine type. Not specific to any individual vaccine, they occur either because of a misapplication of a vaccine or because the vaccine recipient is more susceptible to a certain outcome.

Bursitis is the inflammation of the synovial bursa (i.e., the covering of joints) that can develop when a vaccine is misapplied. Instead of being injected into the deltoid muscle, the needle is inadvertently inserted into the bursa. This could occur if the vaccine is applied too high up in the shoulder or if the deltoid has low muscle mass. The resulting inflammation can result in a frozen shoulder. Although rare, this outcome has been reported with a variety of vaccines, including tetanus and diphtheria.

Syncope, the act of fainting, is not an uncommon reaction to a sudden fright, such as the sight of blood or application of a needle. Rates of syncope peak around the age of 15 years, with girls having more than twice the rates of boys [Driscoll et al. 1997]. Because of the age at which it is administered, understandably HPV is linked to this outcome. Vaccine recipients should be observed for 15 minutes after vaccination to prevent syncope, especially if belonging to a high risk group.

In summary, the proper vaccination of healthy children is the most important health care activity a nation can engage in to keep our children safe. There are many myths linked to vaccines that this article hopes to have helped dispel. As discussed, any potential risk associated with vaccines administered to healthy children is small and outweighed by the risk of the naturally occurring disease. Maintenance of herd immunity and avoidance of vaccine exemptions are critical. Both of these practices disproportionately affect, at times with deadly consequences, our youngest and most vulnerable citizens.

GLOSSARY

Acellular vaccine: A vaccine containing partial cellular material as opposed to complete cells

Acute disseminated encephalomyelitis (ADEM). A rare, usually isolated immune-mediated demyelinating brain disorder.

Adjuvant: A substance (e.g. aluminum salt) that is added during production to increase the body's immune response to a vaccine.

Adverse events: Any undesirable event occurring after immunization, not necessarily caused by the immunization.

Anaphylaxis: An immediate and severe and possibly fatal allergic reaction to a substance (e.g. food or drugs).

Antigens: Substances (e.g. bacteria or viruses) that the body recognizes as foreign and elicit an immune response, usually the production of antibodies.

Association: The degree to which the occurrence of two variables or events is linked.

Attenuated vaccine: A vaccine in which live virus is weakened through chemical or physical processes in order to produce an immune response without causing the severe effects of the disease.

Autism: A developmental brain disorder often presenting between 18 and 30 months of age that impairs communication and social interaction. Believed to be genetic and present prior to birth

Bell's palsy: Partial or complete dysfunction of facial nerve resulting in a facial droop or weakness on one side of the face.

Biological plausibility: A causal association (or relationship between two factors) is consistent with existing medical knowledge.

Brachial neuritis: Inflammation of nerves in the arm causing muscle weakness and pain.

Causal association: A factor that is responsible for a change in another variable, e.g. smoking and cancer.

Cerebellar ataxia: Dysfunction of the cerebellum that results in poor balance and coordination (ataxia)

Demyelinating disorders: Disorders that damage the myelin sheath surrounding nerves and impairs transmission of impulses to the brain. The condition results in muscle weakness, poor coordination and possible paralysis. Multiple Sclerosis (MS), optic neuritis, transverse neuritis and Guillain-Barré Syndrome (GBS) are examples of demyelinating disorders.

Encephalitis: Inflammation of the brain caused by a virus. Encephalitis can result in permanent brain damage or death.

Etiology: The cause of a disease.

Epidemic: An increase in the rate of disease in an area or population above the level that is is normally expected.

Endemic: A continual, low-level disease process in a community.

Guillain-Barré Syndrome (GBS): A rare neurological disease characterized by loss of reflexes and temporary paralysis caused by immune damage to the peripheral nerves.

Hepatitis (A,B,C,D,and E) are viral infection of the liver.

Herd Immunity (also known as community immunity) The degree of immunity required in a population to prevent easy spread of the infection from person to person.

Hypotonic: Low muscle tone or floppy

Infantile Spasms: an epileptic syndrome of childhood characterized by spasms and possible developmental regression.

Influenza**:** (also known as the flu) A highly contagious viral respiratory infection characterized by sudden onset of fever, severe aches and pains, and cough.

Meningitis**:** Inflammation of the covering (meninges) of the brain and spinal cord, usually infectious, that can cause permanent brain damage and death.

Multiple Sclerosis: Multiple sclerosis (MS) is an immune mediated disease of the central nervous system that results in destruction of the myelin sheath surrounding neurons. It is often remitting and relapsing yet progressive and may result in permanent disability.

Neuritis: inflammation of the nerves.

Pertussis**:** (whooping cough) An infectious disease causes by the bacteria pertussis characterized by a spasmodic cough.

Polyneuropathy: A general term for a widespread disease process of the nerve resulting in include pain, muscle weakness, numbness, loss of coordination and paralysis.

Rotavirus**:** A group of viruses that cause diarrhea in children.

Rubella: (German measles) A milder viral infection than measles but highly damaging to the fetus when it occurs in early pregnancy.

Seizure: Irritability of the brain that results in sudden onset of jerking and staring. Also known as fits or convulsions.

Side Effect: Untoward reaction resulting from immunization

Syncope: A fainting episode.

Temporal association: Two or more events that occur around the same time but may be unrelated, chance occurrences.

Susceptible: Capable of being infected.

Thimerosal: a mercury-containing preservative previously used in some vaccines that was removed from vaccines to minute traces in 1999.

Virus: A minute organism that can multiply in cells and cause disease.

Vaccine Adverse Event Reporting System (VAERS): A database managed by the Centers for Disease Control and Prevention and the Food and Drug Administration that collects such reports from various sources.

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