### Vaccines An Educational Module

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For

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# Introduction

This module engages students in learning about association and causation in the context of vaccines, their side effects, and legal issues that could arise as a result of side effects associated with vaccinations.

The module employs five case studies. In the first two case studies, a child receives a vaccination, and students must determine whether an event (vaccination) causes a side effect in the child. In the third case study, a child who has not been vaccinated transmits a disease to another child whose vaccination likely "has not taken." The fourth case study involves a vaccine-related death and considers whether more should have been done to screen the patient. The final case presents a hypothetical situation wherein an expanded use of a vaccine may be the causal factor in an increased prevalence of a certain disease.

The module discusses side effects associated with vaccines and conditions which have been associated with the administration of vaccines, but which are not supported by scientific evidence. The module illustrates the fact that association is not causation and explores how causation is established in the scientific realm.

#### CORE COMPETENCIES THAT STUDENTS WILL ACQUIRE

- a. Recognize the difference between association and causation and be able to articulate the difference between these two terms.
- b. Recognize some of the scientifically accepted methods to establish causation and be able to discuss what is meant by temporal and mechanistic causation.
- c. Become aware that vaccines have complications and be familiar with routine complications.
- d. Learn about the National Childhood Vaccine Injury Act and how this legislation has affected vaccine-related litigation in the United States. See <a href="http://en.wikipedia.org/wiki/National Childhood Vaccine Injury Act">http://en.wikipedia.org/wiki/National Childhood Vaccine Injury Act</a>.
- e. Learn about the "vaccine court" and be able to discuss what cases are referred to this court. See <a href="http://en.wikipedia.org/wiki/Vaccine\_court">http://en.wikipedia.org/wiki/Vaccine\_court</a>.
- f. List the known complications for these common childhood vaccines: Varicella, MMR, DTP, influenza, hepatitis B, and meningococcal.

#### **ESTIMATE OF THE TIME REQUIREMENT**

A 1-hour class per case or 5 total hours. Students and instructors are expected to read the cases before the class.

#### FORMAT

A brief introduction to vaccines and five cases studies with commentary.

# SUPPORTING MATERIALS

- 1. Introduction to Vaccines (see below)
- 2. Five Case Studies (see below)
- Institute of Medicine, Adverse effects of Vaccines: Evidence and Causality (August 2011). Available at <u>http://www.nationalacademies.org/hmd/~/media/Files/Report%20Files/2011/Adve</u> rse-Effects-of-Vaccines-Evidence-and-Causality/Vaccine-report-brief-FINAL.pdf.
- 4. Useful Websites: "Vaccine Safety," Centers for Disease Control and Prevention. Available at <u>http://www.cdc.gov/vaccines/vac-gen/safety/default.htm.</u>

# HOW THIS MODULE SHOULD BE EVALUATED AND ASSESSED

Discussion points are provided for the teacher and the student. Some of the discussion points raise questions that do not have clear answers and are reflective of the type of decisions that patients and physicians must make when considering vaccines. Thematically, the five cases are linked in that they seek to demonstrate causative links among a temporal series of events.

- Explain what is meant by the principle that "association is not causation". Provide an example from everyday life that illustrates this principle. For example, since the 1980s both the national debt and the speed of computers have each increased dramatically. Hence, if one was to plot the national debt versus the speed of computers, an association between these two variables is likely to be apparent. However, neither the increase in the national debt influenced computer speed nor computer speed caused the national debt. Hence, these two variables could be correlated, even though there is no causal link between them.
- Explain the methods that can be used to establish how two events are causally related. For example, if event A is both associated with and causally related to event B it is important to establish the following: temporal causality (e.g., event A must precede event B), mechanistic causality (e.g., the mechanism of A results in B). Case 5 takes the reader on an exercise to establish how association and causation are established.

#### VACCINES

The modern era of vaccination began in the late 18th century with the work of Edward Jenner, who followed up the observation that milkmaids seldom developed smallpox presumably because they were infected with cowpox, which conferred protection against the human virus. Jenner used this observation to develop a preparation from cowpox lesions that contained the cowpox virus as a vaccine to prevent smallpox in humans. This approach worked because smallpox and cowpox were sufficiently similar that an immune response to one protected against the other, but cowpox did not cause significant human disease because it was a cow virus. The word vaccine is derived from the Latin word for cow, *vacca*, which denotes the connection to the early cowpox vaccines. The word *vaccination* denotes the act of giving a vaccine and is different from the word *immunization*, with the latter denoting the concept of an immune response that confers immunity. Although the words *vaccination* and *immunization* are often used interchangeably in common parlance these terms are not synonymous in the sense that not all individuals who are vaccinated are immunized.

In general, vaccines are safe and effective for the majority of the population. For example, the current hepatitis B vaccine is highly effective and safe. Approximately 90% percent of those who are vaccinated with the hepatitis B vaccine become immunized and are protected from hepatitis B virus. However, 10% of the population fails to develop a protective immune response and is not protected. This lack of responsiveness may reflect genetic differences that affect the response to a vaccine. Nevertheless, in some instances, the administration of a vaccine can result adverse side effects.

All effective vaccines contain an essential component known as an antigen that can elicit a protective immune response. Most antigens are microbial components that are recognized by the immune system as foreign, and the resulting immune response protects against the invading microbe. In general, antigens elicit microbe-specific immune responses such that a vaccine against measles protects against the measles virus, but not the mumps virus. In fact, this is the reason that children must receive so many different vaccines. There is hope that one day it will be possible to generate vaccines that contain many different antigens and thus protect against many diseases simultaneously, but no such vaccine is available today. Many vaccines require multiple inoculations (shots) to elicit strong protective immunity, since the immune system learns with each inoculation and responds by producing ever greater immune responses. The length of immunity after vaccination depends on the vaccine. Some vaccines that rely on attenuated microbes (see below) can elicit protective immunity for decades, while others, such as the vaccine for tetanus, need to be given every decade because immunity abates over time. Hence, each vaccine has a different schedule for immunization.

#### Vaccine Types

In approaching the topic of vaccines and their complications, it is imperative to understand that different vaccines contain very different formulations. The major types of vaccines are:  Live Attenuated Vaccine. Live attenuated vaccines use a live organism to cause an infection in the host that elicits protective immunity, but results in no disease. Jenner's cowpox vaccine was an example of a live attenuated vaccine, as it was composed of the cow virus, which was attenuated in humans by virtue of the fact that humans were not its natural host species.

The advantage of live attenuated vaccines is that they can elicit strong and sometimes lifelong immunity because they provide strong stimulation to the immune system by virtue of inducing an infection. The disadvantage of live attenuated vaccines is that in some hosts with weakened immune systems these can disseminate and cause serious disease. Hence, most live attenuated vaccines are contraindicated in individuals with impaired immunity. However, some individuals with impaired immunity do not display any symptoms, and because they are not diagnosed as having impaired immunity, they are occasionally given live vaccines inadvertently. That can result in a serious vaccine-caused infection, as the attenuated virus behaves like a fully virulent virus in the setting of a weak immune response.

From a legal viewpoint, live attenuated vaccines have two particular angles of interest. First is the inadvertent administration of a live attenuated vaccine to an individual who has an undiagnosed immune impairment condition and subsequently develops a potentially life-threatening condition that is clearly vaccine related. The small number of individuals in the population with immune impairment raises questions about due diligence: What steps should a physician take to rule out a hidden immunosuppressive condition before a vaccine is administered? Second, healthy individuals who receive such a vaccine can shed the attenuated microbe (usually a virus) and constitute a potential threat to immune-suppressed individuals with whom they come into contact, and those individuals can develop severe infections. Examples of live attenuated vaccines currently in use are the vaccines against yellow fever, measles, rubella, and mumps.

- 2. Inactivated Vaccine. An inactivated vaccine uses a dead microbe to elicit a protective immune response. In general, inactivated vaccines do not elicit the type of strong immune responses that are associated with live attenuated vaccines, and consequently, vaccine-related immunity tends to be short lived. Since the vaccine is inactivated it does not pose a risk to individuals with impaired immunity. Depending on the vaccine, the microbe is killed with heat, chemicals, or some other sterilization procedure. Examples of inactivated vaccines in clinical use are those to prevent influenza, cholera, bubonic plague, polio, hepatitis A, and rabies.
- 3. *Toxoid Vaccine*. Toxoid vaccines are composed of a chemically inactivated bacterial toxin. Some bacteria, such as those that cause tetanus and diphtheria, produce toxins that are necessary for disease causation. If the toxin is isolated from the bacteria and inactivated, it can be used as a vaccine. The word toxoid denotes that the vaccine is derived from a toxin. Toxoid vaccines are safe and highly effective. Toxoid vaccines induce long-lasting immunity, but revaccination is recommended each decade. Currently used toxoid vaccines are used for the prevention of tetanus and diphtheria.

- 4. Subunit Vaccine. A subunit vaccine uses a single antigen to elicit immunity. Most microbes contain many proteins, each of which is a potential antigen. Hence, when an individual receives a live attenuated or inactivated vaccine, the person is being given an antigen cocktail. However, very few of the antigens are useful in the sense that they elicit a protective response. Hence, a subunit vaccine focuses on that very important antigen and is delivered singly to elicit a protective response. For example, hepatitis B virus has many proteins that serve as antigens. However, there is one in the coat of the virus that elicits protective antibodies. The current hepatitis B vaccine is generated by recombinant DNA technology in a procedure where only the critical coat protein is produced. This vaccine is a "subunit vaccine" because it contains only the relevant subunit (antigen) needed to elicit protective immunity.
- 5. Conjugate Vaccine. Many pathogenic bacterial species are covered in thick layers of polysaccharides in the form of polysaccharide capsules. These can protect the bacteria from the immune system. These polysaccharides prevent white cells from engulfing, ingesting, and killing the bacteria (the process of phagocytosis). However, when antibodies to the polysaccharide are present, they neutralize the effects of the polysaccharide and provide immunity. Consequently, many vaccines have been made containing only polysaccharides, but these have the problem that polysaccharides are poorly immunogenic in general and fail to elicit any immune responses in children before the age of 2 years. Hence, children under 2 years are very vulnerable to disease from these polysaccharide-encapsulated bacteria. Decades ago it was discovered that if the polysaccharides could be conjugated to bacteria, they would trigger an immune response even in young children and this is the premise of conjugate vaccines. Haemophilus influenza type B was a major cause of death and neurological disability in children younger than 2 years, but a conjugate vaccine introduced in the late 1980s has essentially eliminated this disease. Today, there are conjugate vaccines available against *H. influenza* type b and against Streptococcus pneumoniae (pneumococcus). These are both highly effective and safe.

#### **Prophylactic and Therapeutic Vaccines**

All vaccines except one (rabies) are given to prevent disease and thus function in a prophylactic mode and must be administered before infection. For vaccines to be effective, the timing between vaccination and disease must be sufficiently long to allow for the immune response to respond to the vaccine and develop protective immunity. For example, travelers to regions where certain infectious diseases are endemic must be vaccinated some time before they actually travel to the area if they are to benefit from vaccine protection. The rabies vaccine is the exception to the rule, since it can be used both as a prophylactic and therapeutic vaccine. Veterinarians and individuals who are expected to come into contact with wild animals can receive the vaccine in a prophylactic mode, where vaccination elicits an immune response that protects against infection. However, this vaccine can also be used in a therapeutic mode for nonimmune individuals who come into contact with a rabid animal and receive the vaccine after exposure and possible infection. The reason rabies can be treated

with a vaccine is because the infection takes time to progress to clinical rabies, and vaccination shortly after infection such as would occur from the bite of rabid animal can elicit a protective response before symptoms develop. However, this is not possible for other infectious diseases where the time from infection to disease is much shorter than the time required for a vaccine to elicit a protective immune response.

#### Adjuvants

The antigens in many vaccines are often poorly immunogenic, and adjuvants are used to enhance their immunogenicity. An adjuvant is a chemical compound that is added to the vaccine preparation to increase its efficacy. In the United States, the only licensed adjuvant compounds are aluminum salts, which are widely used in vaccine preparations. Although some people have voiced concerns about the use of this metal in vaccines, there is no evidence for toxicity and aluminum salts are considered safe adjuvants.

#### Preservatives

Vaccine preparations are biological solutions, and as such, they are vulnerable to microbial contamination, such as the growth of bacteria in vaccine vials. In 1928, contamination of a diphtheria vaccine with *Staphylococcus aureus* led to the death of 12 of 21 inoculated children. Consequently, some if not most vaccine preparations include preservatives to prevent bacterial growth. Until recently, the mercury-containing compound thimerosal was used as an antimicrobial preservative in vaccines. However, highly controversial claims that the mercury in thimerosal was contributing to autism led to the discontinuation of this preservative in vaccines used in developing countries.

#### **Vaccine Side Effects**

Complications from vaccines can range from trivial (e.g., sore arm) to life threatening (e.g., Guillain-Barré syndrome, disseminated infection with vaccine strain). For the overwhelming number of people who receive vaccines, the benefits of vaccination far outweigh any debits, and it is important to realize that no matter how safe a vaccine is, there are likely to be some serious complications when the vaccine is administered to large numbers of people. Vaccine benefits not only the individual who is vaccinated but also society, since immune individuals do not become ill and cannot be vectors for spreading disease. Vaccine side effects are generally related to one of three factors: (1) the injection procedure, (2) the possibility of disseminated infection with a live attenuated microbe that is part of a vaccine, and (3) the immune system reaction to the vaccine and/or contaminants in the vaccine preparation.

1. *Injection Procedure*. Puncturing the skin with a needle to inject a volume of fluid necessarily injures tissue. Although for most people this is minor and results in at most a sore arm, there are instances where the injection procedure can have significant complications. Vaccine injections occasionally cause a skin infection known as cellulitis. This infection is almost always self-limited and can be easily

treated with antibiotics, but on rare occasions these can be serious and require hospitalization. The act of injection can damage nerves, and health care providers generally avoid injections near major nerves.

2. Disseminated infection. This is a risk only for live attenuated vaccines, and this complication is almost always associated with an underlying immune disorder. In general, physicians avoid giving vaccines to individuals with impaired immunity, although one vaccine, that against varicella virus, was developed specifically for use in children with leukemia, given that natural infection was such a devastating disease.

Disseminated infection from a vaccine organism is a very rare complication of vaccine use. Occasional cases occur when the immune disorder has not been diagnosed, and disseminated infection from the vaccine is the first hint that the individual had impaired immunity. Rare instances of disseminated infection can occur when there is a breakdown in the vaccine manufacturing process and the vaccine preparation becomes contaminated with microbes that can cause disease. Bacterial contamination is very rare with modern manufacturing practices, but occasional problems occur. For example, in 2014 the Food and Drug Administration forced the drug giant GlaxoSmithKline to review its manufacturing practices after chronic problems of bacterial contamination of vaccine batches. See http://www.theguardian.com/business/2014/jun/24/glaxo-fda-flu-vaccines-reviewmanufacturing.

3. Immune-related Complications. The fact that immunizations trigger an immune response means that occasionally individuals the immune response causes host damage. Although the mechanism for immune-related complications is not well understood, the possibility of such occurrences is a well-recognized complication of vaccine administration. One of the most severe complications is a neurological syndrome known as Guillain-Barré syndrome, which can result in a constellation of symptoms ranging from muscle weakness to paralysis.

The associations between Guillain-Barré and vaccination remains circumstantial, but many authorities are more apt to consider the two causally related if the symptoms occur within 30 days of vaccination and if no other cause can be identified. A study of vaccine complications in Canada found only 24 cases from 1996 to 2012 (Top et al., 2015). In 1976 a marked increase in cases of Guillain-Barré was reported among recipients of the swine flu vaccine and with an estimated rate of 8.8 cases per million people vaccinated. However, it is important to note that viral diseases themselves can cause the syndrome of Guillain-Barré, and making an unequivocal causative association in an individual patient can be very difficult.

#### Vaccine Efficacy

When approaching legal aspects of vaccination it is important to also consider the topic of vaccine efficacy. Although the public generally assumes vaccination with specific vaccines implies protection against certain diseases, no vaccine is 100% effective. Hence, a history of vaccination is no guarantee that the individual is protected against a specific disease. Here, it is

important to note that vaccine efficacy is measured on the basis of population, rather than on the basis of the individual receiving a vaccine. Vaccine efficacy can depend on host factors, intrinsic vaccine characteristics, and even mundane variables such as the expertise of the person administering the vaccine and the location of vaccine injection.

*Host variables* are those associated with the individual receiving the vaccine and include age, health status, nutritional status, genetics, and history of prior vaccinations. For example, vaccines are generally less effective with increasing age, presumably as a consequence of a senescent immune system. However, some groups have suboptimal responses to vaccines, including the very young, due to an immature immune system, and those who have impaired immunity resulting from disease (e.g., HIV infection) or immunosuppressive therapies (e.g., transplant and cancer patients). As noted above, even highly effective and safe vaccines like that for hepatitis B virus elicit protective immune responses in only 90% of those vaccinated.

Intrinsic vaccine characteristics are those associated with the antigens and adjuvants in the vaccine preparation itself. For example, vaccines composed of polysaccharide antigens tend to elicit weaker immune responses than compared with those composed of protein antigens such as tetanus and diphtheria toxoids. Vaccine efficacy can also vary depending on how good the match is between the pathogenic microbe and the antigens used in the manufacture of the vaccine. For example, the efficacy of the influenza vaccine varies from year to year depending on how well vaccine manufacturers anticipate the type of virus expected to circulate during the flu seasons. Vaccine efficacy can also vary depending on how the vaccine is administered. The hepatitis B vaccine is usually administered in the deltoid muscle of the upper arm because injection in that location is much more likely to elicit an effective immune response than injection into the gluteal area, where presumably it can easily go into fat deposits and be less immunogenic.

Students should also be familiar with the concept of *herd immunity*, which refers to the fact that when a large portion of the population is vaccinated, the vaccines protect those who are susceptible. In other words, epidemics require the existence of a significant fraction of the population to be susceptible to disease to maintain person-to-person spread. When a microbe spreads to an individual who is immune, infection does not take hold and the spread is a dead-end event. If enough individuals are immune, large epidemics do not occur because many person-to-person transmissions become dead-end events. Although the exact percentage of resistant individuals needed to achieve herd immunity depends on the particular pathogen, most vaccines that are used universally in a population achieve this effect: immunized individuals protect those who are not immunized and those who did not make a protective response to vaccination by creating a large fraction of resistant individuals such that epidemics cannot occur. Herd immunity allows immunocompetent individuals who take a vaccine to protect the immunocompromised, who cannot mount an effective response, by greatly reducing the chance for transmission.

# **Case Studies**

# CASE 1: NEUROLOGICAL PROBLEMS FOLLOWING VACCINATION

#### Goal

To discuss the existence of anti-vaccination movements and how they shape vaccine acceptance, practice, and law.

# **Instructor Discussion Points**

- Anti-vax and anti-vaxxer are 21st century terms associated with the movement against vaccines. An anti-vaxxer is "a person who is opposed to vaccination, typically a parent who does not wish to vaccinate their child".\*
- Anti-vaccine movements have existed since the dawn of vaccination. For example, in the United States, anti-vaccination movements have existed since the early 18th century. In the 1720s, Benjamin Franklin campaigned against the then new smallpox vaccination practices, but changed his views after a son died of the disease in 1736.
- Anti-vaxx movements are motivated by apprehensions ranging from fear that vaccines cause different diseases (e.g., autism) to concerns about immune system exhaustion by vaccines. Anti-vaxx movements are heterogeneous in the belief systems used to oppose vaccinations.
- In general anti-vaxxer movements are resistant to scientific information indicating that vaccines are safe and effective.

# **Case 1 Description**

A 36-year-old mother takes her baby boy to the doctor where he receives the measles vaccine at age 1 year. After the vaccine is administered, the boy develops a fever that lasts for 2 days, but then recovers. In the months afterward, she becomes increasingly concerned, since the child is not making any effort to speak and sometimes engages in repetitive movements for no obvious reason. The child crawls for months and is a late walker. By age 2 he has been diagnosed to have a delayed developmental disorder and is feared to have autism. The mother claims that the child was developing normally until he received the measles vaccine and feels that vaccination has caused him to become autistic. She begins to do Internet research on autism and finds numerous websites that warn against vaccination because of the risk of autism. She feels that the child has been harmed by the vaccine and approaches a lawyer to discuss the possibility of bringing legal action against the physician and vaccine manufacturer.

#### **Background and Analysis**

<sup>&</sup>lt;sup>\*</sup> See <u>http://www.oxforddictionaries.com/us/definition/american\_english/anti-vaxxer</u>.

Autism is a devastating developmental disorder in children that ranges from highly functional to severe neurological, emotional, and intellectual impairment. The cause(s) of autism is poorly understood. Autism is a devastating diagnosis because there is no effective treatment, and the condition results in life-long deficits that are catastrophic for the individual, their families, and society at large.

In 1998, Andrew Wakefield and others authored a paper in the prestigious British medical journal The Lancet, reporting an association between administration of a combination vaccine against mumps, measles, and rubella and the onset of autistic signs (Wakefield et al., 1998). The paper was immediately controversial and led to a barrage of criticism from medical authorities, but the association between vaccination and autism took hold in the popular consciousness. Vaccine rates declined measles returned as an endemic disease after it had essentially disappeared as vaccine-preventable disease. However, by 2004, enough concerns had been raised about the original study, concerns that, combined with epidemiological evidence showing no association between vaccines and autism, led to a partial retraction of the study. In 2010 the journal retracted the paper amid further allegations of scientific misconduct and the possibility of outright scientific fraud (Eggertson, 2010). The consequences of this study continue to reverberate to this day with low prevalence of vaccination in certain areas, which has led to measles outbreaks. Societal vulnerability to measles outbreaks was exemplified by the 2015 Disneyland outbreak, which began when a foreign traveler with incubating measles infected non-vaccinated children in the amusement park, who, in turn traveled back to their communities and triggered outbreaks in several states. There is no credibility for the association of measles and autism based on scientific or medical facts.

#### Autism and Vaccine: Neither Association Nor Causality

The assertion that some cases of autism are related to vaccines has now been established to be erroneous. That assertion was not supported by epidemiological studies showing no linkage between vaccination and autism. Furthermore, no conceivable mechanism could be identified to explain how vaccination could cause a neurological disorder. Recent evidence shows that the neurological processes responsible for autism begin during gestation. In this regard, a recent autopsy study showed that autistic children have malformations in a brain region that matures during the second trimester (Stone et al., 2014). If confirmed, this finding would rule out any connection between childhood vaccines and autism, since the problem would occur before birth. This information means that there is no temporal causality between vaccines and autism, since vaccines are given after birth and the neurological defects occurred during pregnancy. The original assertion linking vaccination and autism has now been discredited as fraudulent, and the original publication retracted by the journal.

#### Outcome

Given the preponderance of data arguing against both association and causation between vaccination and autism, it is unlikely that the case can be made that vaccination caused autism in this boy.

### **Student Discussion Points**

- Why do so many educated people and celebrities join anti-vaxxer movements?
- Explain how anti-vaxxer movements reduce the protective efficacy of vaccines by reducing herd immunity.
- Discuss how the western intellectual tradition of skepticism relates into anti-vaxxer positions.
- Given that most vaccines are safe and effective and that vaccination is a public good, how can society improve those messages to reduce the influence of the anti-vaxx movements?

# **CASE 2: CELLULITIS AFTER VACCINATION**

#### Goal

To discuss the reality that even safe vaccines and good vaccination practices are sometimes associated with untoward effects.

#### **Instructor Discussion Points**

- All medical procedures carry some risk.
- Risk can only be assessed after a certain number of individuals undergo the procedure, which in this case is vaccination.
- Those who go first take the risk, but in doing so also bequeath knowledge that can be used in guidelines for risk-benefit calculations and for improving products.
- For all recommended vaccines, the risk-benefit calculation shows that risks from vaccines are much lower than risks from vaccine-preventable disease.
- How are risk-benefit calculations done and by whom?

# **Case 2 Description**

A 36-year-old mother takes her 5-year-old preschool boy to the doctor where he receives a booster with the diphtheria-pertussis-tetanus (DPT) vaccine. After the vaccine is administered, the boy develops a fever that lasts for 2 days. The mother notices that the site of vaccination is red and hot, and the child screams whenever she touches it. She calls her physician, who provides reassurance over the phone by telling her that local reactions to the DPT vaccine are common and suggests close observation. Three days after vaccination, the child is taken to the emergency room with high fever, lethargy, and a rapidly spreading rash that appears centered at the site of a vaccination. The child is diagnosed to have cellulitis, a bacterial infection of the skin and tissues beneath the skin, and is admitted to the hospital and treated with intravenous antibiotics. Bacterial culture of the site reveals infection with group A streptococcus. The subsequent hospital course is complicated, as the boy develops a catheter-related infection with methicillin-resistant *Staphylococcus aureus*, requiring 2 weeks of

additional antibiotic therapy. The boy recovers, but the parents feel that this entire episode was caused by the vaccine and approach a lawyer to consider suing for damages related to medical bills, lost work time, and pain and suffering.

#### **Background and Analysis**

DPT vaccine is known to be associated with skin reactions, which are usually self-limited and resolve spontaneously. However, skin reactions to the vaccine can be similar to cellulitis, making it hard to distinguish between these two entities. Vaccine-associated cellulitis is an extremely rare complication of vaccine administration. Cellulitis can result from the pricking of the skin and the insertion of skin-associated microbes into deeper tissues. This type of infection can occur even when the best practices are followed. Although most cases of cellulitis respond rapidly to antimicrobial therapy and have no consequences, some can evolve to a life-threatening disease. For example, when cellulitis is caused by the so-called "meat eating" bacteria,<sup>†</sup> the situation is a medical emergency, for the infection can led to massive tissue necrosis. Fortunately, those cases are extremely rare.

In this case the cellulitis was treated with intravenous antimicrobial therapy that in turn was complicated by catheter-related sepsis, which is a well-known complication of placing intravenous catheters. Catheter-related sepsis involves an infection of the catheter and occurs in 1–3% of all patients who have an intravenous line. Although good catheter care can reduce the incidence of catheter-related sepsis, all catheters carry some risk of infection, which in turn necessitates additional antibiotic therapy and prolonged hospital stays.

#### Vaccine-associated Cellulitis: Association and Causation

In this case there is an association between the event of vaccination and the subsequent cellulitis that is almost certainly causative. Vaccination preceded the cellulitis, providing the criterion of temporal causation. Vaccination requires a piercing of skin that is known to create a small wound through which microbes can access the deeper tissues, providing a mechanism to associate event A (vaccination) with event B (cellulitis). The cellulitis began at the site of vaccination and this provides a spatial relationship between the two events. This relationship further solidifies the case for causality (i.e., vaccination caused cellulitis). The cellulitis was caused by a microbe that is frequently associated with such infection. Furthermore, the phenomenon of vaccine-associated cellulitis is a known medical entity (Lapphra and Scheifele, 2009). In this case, most authorities will agree that vaccination caused the cellulitis, since it preceded it, the cellulitis began at the site of vaccination, the infection was caused by a microbe frequently associated with cellulitis; also, there is a large body of experience that such mishaps can occur.

#### Assessment

<sup>&</sup>lt;sup>†</sup> Streptococcus pyogenes.

A strong case can be made that this child had the misfortune to suffer a very rare complication of vaccination that was followed up by an additional misfortune in acquiring a hospital-associated infection. There is no evidence for malpractice in the case history. This case would meet the criteria for a vaccine-related complication and could be referred to the "vaccine court."

# **Student Discussion Points**

- What other information could be obtained to better understand whether this was an isolated case or one resulting from a pattern of problems with the vaccine manufacture and/or administration?
- What questions would one pose to the physicians caring for child, to hospital infection-control physicians, and to hospital administrators?
- Do the parents bear any responsibility in the bad outcome from this vaccination? What information would bear on this question?
- How does one decide what is a routine adverse event from an unusual vaccine untoward event?

# **CASE 3: RESPONSIBILITY TO OTHERS**

#### Goal

To discuss how individual decisions to vaccinate or not vaccinate can affect others in the community and to dissect the legal implications and consequences of such decisions, if any.

# **Instructor Discussion Points**

- Introduce and discuss the concept of herd immunity.
- Discuss reduced efficacy of vaccines in individuals with immune disorders.
- Discuss danger posed to immunocompromised individuals by children who are not immunized and thus susceptible to infection.
- Discuss responsibility of parents to inform others when they rear non-vaccinated children.
- Discuss responsibility to individuals and society when making vaccination choices.

# **Case 3 Description**

A child is born with a congenital immune disorder and responds poorly to vaccines. He receives the recommended sequence of childhood vaccines, but his pediatrician warns the parents that he could not be sure that "the vaccines have taken" and that the child is protected against such diseases as measles, mumps, and rubella. The family lives in an affluent neighborhood. Apart from occasional prolonged colds and upper respiratory infections the child lives a relatively normal life. One spring day the child is invited to a birthday party where

he plays with other children and appears to enjoy the event. One week later the parents note a rash covering his body, and he is brought to the emergency room, where he is diagnosed to have measles. The disease is progressive, and the child is subsequently diagnosed to have sclerosing panencephalitis (chronic measles encephalitis). As part of the epidemiological investigation carried out by public health authorities into the acquisition of measles, the parents learn that the likely source of infection was a non-vaccinated child at the birthday party who subsequently developed measles. Several other children who attended the birthday party have also been diagnosed with measles, but they recover quickly and without consequences. However, the child with immune deficiency and measles complicated by sclerosing panencephalitis deteriorates neurologically and is likely to require long-term care. With medical bills escalating, the parents of the affected child consult a lawyer to explore options from lack of efficacy of the vaccine to the responsibility of others who did not vaccinate their children.

#### **Background and Analysis**

The efficacy of vaccines in individuals with immunosuppressive disorders is known to be less than in the general healthy population. Despite this lowered efficacy, health authorities routinely recommend vaccinations in many individuals with immunosuppressive disorders on the grounds that some immunity is better than none. Sclerosing panencephalitis is a rare complication of measles that is thought to be caused by persistence of infection. The disease can be progressive and is often fatal. The acquisition of measles in this child is consistent with reduced efficacy in immunocompromised populations and the complication of sclerosing panencephalitis is also likely to be the result of this underlying condition. Measles outbreaks in recent years have been associated with low vaccination rates, where the prevalence of vaccination is not sufficient to provide protection through the so-called "herd effect."

#### Measles in the Immunocompromised: Association and Causation

The epidemiologic investigation carried out by the health department associated attendance at the party with exposure to measles on the basis that some of the other children who attended the party were not immune and subsequently developed measles. Although this is the most likely scenario, there are some caveats that should be considered. First, epidemiologic investigations are by definition not all inclusive, and it is possible that the site of the infection was at a time and place other than the party. For example, it is possible that the child was infected through a contact that was not identified because the infecting individual had a mild case and did not report the disease. Second, it is conceivable that the child in question was in fact the index case who brought the virus to the party. Distinguishing among these possibilities may be possible by analyzing the timing of disease symptoms among the affected children. Molecular analysis the virus could provide additional important information. For example, a finding that the virus from the immunosuppressed child was different from that isolated from his playmates who attended the party would effectively rule out the possibility that the infection occurred at the party. In contrast, a finding that the virus isolates were the same would provide strong suggestive evidence for infection at the party, but the finding would

still not be conclusive, since a third source could have still infected both. The strength of the association in this case depends on how thorough the epidemiologic investigation was and the potential for additional information in the form of molecular evidence from the virus itself.

#### Assessment

All aspects of this case fall within existing medical knowledge. The absence of effective vaccine immunity in individuals with impaired immunity is a known limitation of vaccines. The progressive course of measles in this boy is a complication of his known immune deficiency. The question of responsibility by the parents is another matter: should they have informed other parents that their children were not vaccinated?

# **Student Discussion Points**

- Who is responsible in this situation?
- Given that measles infection outside the party celebration cannot be ruled out, how should that uncertainty bear in the assignment of responsibility?
- What is the apportionment of responsibility: to the child's parents for placing the child in a potentially dangerous situation, to the parents of non-vaccinated children for placing other children at risk, or to the medical professionals for not making a safer life plan for the child with an immune disorder?

# **CASE 4: A DEATH FROM VACCINATION**

#### Goal

To discuss the extent of appropriate due diligence by medical providers when contemplating vaccination with potential side effects on specific individuals who may be at greater risk.

#### **Instructor Discussion Points**

- Introduce the concept of standard of care in a community with regard to who should be vaccinated. What does this mean?
- Are physicians who follow vaccine-recommended guidelines exonerated from responsibility in the case of untoward outcomes?
- Should vaccination for elective activities, such as those that include entertainment and adventure, be held to a higher standard than vaccination for routine diseases?

# **Case 4 Description**

A 65-year-old physician plans to travel to Africa to visit wildlife reservations and observe lions in the wild. He is aware that he needs to be concerned about certain infectious diseases and, given his medical expertise, does research, including reading the recommendations from

the Centers for Disease Control and Prevention (CDC) on vaccination for travelers. The area that he plans to visit is endemic with yellow fever, and there have been several reported cases among travelers, and the CDC recommends vaccination for all travelers. He is aware that yellow fever is a severe disease with a mortality of 20–50%. He is also aware that the vaccine is not without risks and is associated with a fatal syndrome known as vaccine-associated viscerotropic disease in approximately 1 in 250,000 people who are vaccinated. He decides that the risk of yellow fever is much greater than the risk of the vaccine, and he has his personal physician administer the vaccine. Before vaccination, his personal physician discusses the potential risk and benefits of vaccination. The traveler receives the 17D live attenuated vaccine, and apart from a sore arm, there are no immediate complications. However, several days later he develops fever and muscle aches, and he rapidly deteriorates. He is admitted to the hospital with multiple organ failure, and blood tests reveal the 17D attenuated virus in the blood. He is diagnosed with yellow fever vaccine-associated viscerotropic disease. He dies several days later. An autopsy reveals widespread virus infection with the vaccine-attenuated virus and a small tumor on the thymus. The family of the diseased doctor contemplates a malpractice suite on the grounds that he had a preexisting condition and should not have received the yellow fever vaccine.

#### **Background and Analysis**

The yellow fever vaccine is the one vaccine that is known to kill a small proportion of those who receive it. The vaccine is composed of an attenuated virus that replicates in vaccinated individuals where it elicits a strong immune response that protects against the yellow fever virus. Yellow fever vaccine-associated viscerotropic disease is a well-known complication of yellow fever vaccination that results from unchecked replication of the vaccine virus in the body of those vaccinated. This complication is extremely rare, occurring in approximately 1 in 250,000 people who receive the vaccine. The likelihood of viscerotropic disease increases significantly with age and is thought to be related to an inability of the immune system to control the attenuated virus such that it undergoes unchecked replication and damages host tissues. Given the rarity of this syndrome, the predisposing factors are not well understood. However, yellow fever viscerotropic disease has been associated with diseases of the thymus, which is an organ involved in the development of the immune system. Diseases of the thymus are themselves relatively rare, and for that reason there is no recommendation that individuals be screened for such conditions prior to vaccination. Given that diseases of the thymus and yellow fever viscerotropic disease are rare, that medical screening carries some risk, and that the vaccine is effective against a viral disease with high mortality, travelers to areas where yellow fever is prevalent are advised to receive the vaccine. In fact, proof of vaccination is a requirement in certain countries.

#### Yellow Fever Vaccine-associated Mortality: Association and Causation

In this case the association between the event of vaccination and the subsequent death are causative. Vaccination preceded disease by several days, and the recovery of the virus from

the blood and tissues indicates unchecked replication, resulting in extensive tissue damage leading to death. Hence, this case meets criteria for temporal and mechanistic causality.

#### Assessment

All facts of this case fall within existing medical knowledge. This individual developed a known complication of yellow fever vaccination after receiving the vaccine in a situation where he had an undiagnosed medical condition (thymus tumor) that predisposed to that vaccine complication. The medical-legal question is whether this individual should have been more extensively screened prior to receiving the vaccine, since the detection of a thymus abnormality would have suggested a contraindication to vaccination, and without vaccination perhaps the trip to Africa would have been canceled. Arguing for additional screening is the fact that he was older, and perhaps more consideration of complications should have been done for an elective vaccination in preparation for a vacation. However, the case does not reveal a deviation from medical care standards, since immunological screening is not currently recommended prior to yellow fever vaccine administration. In the United States there has been only one case of fatal yellow fever vaccine-associated viscerotropic disease in a patient with an undiagnosed tumor of the thymus (DeSilva et al., 2015). Whether this case would be referred to the vaccine court or be handled by a regular court is uncertain given the rarity of the complication and the details of the case. In essence, this was an instance of terrible luck for an individual who was informed and chose to follow current medical recommendations that overwhelmingly favor the high value of vaccination against a very dangerous viral illness over the low risk of serious complications.

# **Student Discussion Points**

- How does one determine community standards of medical care?
- When is enough "enough" when it comes to searching for obscure conditions that could predispose to vaccine-adverse events?
- Is there a different bar for investigating preexisting conditions when considering routine life-saving vaccinations versus elective vaccinations recommended for an individual going on safari?

# **CASE 5: A REGULATOR'S DILEMMA<sup>‡</sup>**

#### Goal

To describe situations that can arise after a vaccine is licensed when recommendations are expanded into other groups.

<sup>&</sup>lt;sup>+</sup> All aspects of this case are fictional.

#### **Instructor Discussion Points**

- Introduce the concept of postmarketing monitoring for licensed vaccines, devices, and drugs. The United States has mechanisms for monitoring and identifying rare complications for licensed products that may become apparent only after clinical trials are complete and the product is administered to large numbers of people.
- Are there sex differences in the response to vaccines and complication rates?
- Where does the threshold lie between recommending a safe vaccine in girls that is untested in boys and yet can potentially protect a terrible cancer later in life?

#### **Case 5 Description**

The vaccine against human papilloma virus (HPV) has proven safe and successful in girls. The success of the vaccine has given momentum to the notion of making it gender neutral and giving it to boys. Some provinces in Canada have now moved to adopt universal vaccination against HPV-related disease by offering it to both boys and girls. However, to date, most of the safety and efficacy data has been obtained in clinical trials involving girls. The health department in a progressive state in the U.S. decides to offer the vaccine to all boys and girls and begins a public information campaign to inform the public about the benefits of the vaccine in preventing future cancers. The campaign is so successful that over 90% of all children in the state are vaccinated. One year after the universal vaccination campaign begins, the state health department begins to receive reports of orchitis (testicular inflammation) in teenagers vaccinated with the HPV vaccine.

#### **Background and Analysis**

This situation would demand an investigation to attempt to establish causality between giving an HPV vaccine to boys and cases of orchitis among some vaccine recipients. Occurrence of orchitis only among vaccinated boys would imply a link, but only if there was a significant number of boys who were not vaccinated and did not have orchitis. The fact that the cases of orchitis occurred after the introduction of HPV vaccination would imply temporal causation, but the fact that a year elapsed between making the vaccine available and the cases of orchitis may unusually long for a vaccine side effect. To conclude that there was temporal causation would require an extensive investigation to ascertain that orchitis was in fact a new phenomenon in that community. It would also be important to ascertain the cause of the orchitis. For example, if the cause of the orchitis was shown to be a viral illness unrelated to human papilloma virus, it would provide strong evidence against direct causation. On the other hand, if a laboratory investigation revealed that the immune response in boys to HPV vaccine contained antibodies with cross-reactivity to testicular tissue, that would point to the vaccine as the culprit, provided that similar antibodies were missing in boys without orchitis. Administration of the HPV vaccine to male animals could be used to further explore mechanistic causality. For example, if HPV vaccination elicited orchitis in some animals, that would also provide strong evidence for a causative link between HPV administration and testicular inflammation.

#### Assessment

The investigation revealed that (1) all children with orchitis had received the HPV vaccine, and no cases of orchitis were found among children who had not received the vaccine; (2) all children were connected by attending the same school, which was highly proactive in having their students immunized; (3) the cause of orchitis was mumps virus. The investigation found that all had received the appropriate mumps vaccine on schedule and that an immigrant child who had never received the mumps vaccine and was recently admitted to their school had developed mumps. The mumps vaccine has an efficacy of only 85%. Hence, the cause of the outbreak was traced to mumps in children who had been vaccinated, but unfortunately fell into the group that was not protected by the vaccine. No causative link to the HPV vaccine was made.

#### **Student Discussion Points**

- Vaccination does not prevent all cases of the disease.
- Some individuals are not protected even when vaccinated.
- Even when a complication is temporally related to a vaccine (all children had recently been vaccinated against HPV), the two events are not necessarily causally related.

# References

- M. DeSilva, A. Sharma, E. Staples, B. Arndt, W.J. Shieh, J. Shames, and P. Cieslak, "Notes from the field: fatal yellow fever vaccine-associated viscerotropic disease–Oregon, September 2014." MMWR Morb Mortal Wkly Rep (2015) 64:279–281.
- L. Eggertson, "Lancet retracts 12-year-old article linking autism to MMR vaccines," CMAJ (2010) 182:E199–E200.
- K. Lapphra and D. Scheifele, "Vaccination site reaction or bacterial cellulitis?" *Paediatr Child Health* (2009) 14:245.
- R. Stoner, M.L. Chow, M.P. Boyle, S.M. Sunkin, P.R. Mouton, S. Roy, A. Wynshaw-Boris, S.A. Colamarino, E.S. Lein, and E. Courchesne, "Patches of disorganization in the neocortex of children with autism," *N Engl J Med* (2014) 370:1209–1219.
- K.A. Top, S. Desai, D. Moore, B.J. Law, W. Vaudry, S.A. Halperin, and J.A. Bettinger, "Guillain-Barre Syndrome after Immunization in Canadian Children (1996–2012)," *Pediatr Infect Dis J* (2015).
- A.J. Wakefield, S.H. Murch, A. Anthony, J. Linnell, D.M. Casson, M. Malik, M. Berelowitz, A.P. Dhillon, M.A. Thomson, P. Harvey, A. Valentine, S.E. Davies, and J.A. Walker-Smith, "Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children," *Lancet* (1998) 351:637–641.