The history of vaccine development and the diseases vaccines prevent

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Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CDC</td>
<td>US Centers for Disease Control and Prevention</td>
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<tr>
<td>CMI</td>
<td>Cell mediated immunity</td>
</tr>
<tr>
<td>CRS</td>
<td>Congenital rubella syndrome</td>
</tr>
<tr>
<td>HAV</td>
<td>Hepatitis A virus</td>
</tr>
<tr>
<td>HBIG</td>
<td>Hepatitis B immunoglobulin</td>
</tr>
<tr>
<td>HBSAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>Hib</td>
<td>Haemophilus influenzae, Type b</td>
</tr>
<tr>
<td>HPV</td>
<td>Human papillomaviruses</td>
</tr>
<tr>
<td>IPD</td>
<td>Invasive pneumococcal disease</td>
</tr>
<tr>
<td>LAIV</td>
<td>Live attenuated influenza vaccine</td>
</tr>
<tr>
<td>MMR</td>
<td>Measles, mumps, and rubella</td>
</tr>
<tr>
<td>MMRV</td>
<td>Measles, mumps, rubella, and varicella</td>
</tr>
<tr>
<td>MVA</td>
<td>Modified Vaccinia Ankara</td>
</tr>
<tr>
<td>PCV7</td>
<td>Heptavalent pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>PHN</td>
<td>Postherpetic neuralgia</td>
</tr>
<tr>
<td>PPS23</td>
<td>23-valent pneumococcal polysaccharide vaccine</td>
</tr>
<tr>
<td>PRP</td>
<td>Polyribosylribitol phosphate</td>
</tr>
<tr>
<td>SSPE</td>
<td>Subacute sclerosing panencephalitis</td>
</tr>
<tr>
<td>TIV</td>
<td>Trivalent inactivated influenza vaccine</td>
</tr>
<tr>
<td>VAPP</td>
<td>Vaccine-associated paralytic poliomyelitis</td>
</tr>
<tr>
<td>VZIG</td>
<td>Human anti-varicella immunoglobulin</td>
</tr>
<tr>
<td>VZV</td>
<td>Varicella zoster virus</td>
</tr>
</tbody>
</table>

The 18th century: vaccines for smallpox

“In 1736 I lost one of my sons, a fine boy of 4-years-old, by the smallpox... I long regretted bitterly and I still regret that I had not given it to him by inoculation; this I mention for the sake of parents, who omit that operation on the supposition that they should never forgive themselves if a child died under it; my example showing that the regret may be the same either way, and that therefore the safer should be chosen.”

Benjamin Franklin, Autobiography, 1791

Attempts to prevent infectious diseases date to antiquity. The first successful prevention strategy was “variolation,” the deliberate inoculation of people in the 16th century in India and China with the pus from smallpox sufferers. This was observed by Lady Mary Wortley Montague in 1716–1718 in Turkey, who had her children inoculated and introduced the method to England.

In 1721, Cotton Mather, an evangelical minister, persuaded a young physician named Zabdiel Boylston (the great-uncle of US President John Adams) to variolate 240 people in Boston, all but six of whom survived the procedure. In contrast, more than 30% died of naturally acquired smallpox. Although the two men were driven out of town and threatened with violence, ultimately variolation was widely used in Boston in the 18th century.
health was found to be constitutional by the US Supreme Court. The successful demonstration of “ring immunization” (the identification, immunization, and quarantine of all contacts of cases and the contacts of contacts) as a tool permitted the elimination and ultimately the eradication of smallpox, which was officially declared by the World Health Organization in 1980, 4 years after the last case. In 2001, because of concerns of bioterrorism, the US government embarked on the development of smallpox vaccines employing modern techniques: the development of a new plaque purified seed virus, cultivated in tissue cultures and then the development and testing of a safer human replication deficient strain of virus in 2010, termed “modified vaccinia Ankara,” or MVA.

The 19th century: new understanding of infectious diseases and immunity

The concept of attenuation (weakening the virulence of the bacterium or virus) preceded Louis Pasteur’s observations with hog cholera, anthrax, and rabies attenuation and vaccination, but those observations began the quest by many scientists to identify and prevent infectious diseases in animals and humans by using killed or inactivated vaccines (normally by chemicals such as formalin) and live attenuated vaccines for hog cholera, cholera, typhoid fever, and plague. At about the same time, late in the 19th century and early in the 20th century, great strides were also made in recognizing serum and cellular immunity, which led to the development of the concepts of passive and active immunity.

Diphtheria and tetanus toxins were recognized as the causes of those diseases and that antiserum made in horses against the toxins (“antitoxin”) could neutralize the toxin effects; antitoxin was first used to prevent diphtheria in a child in 1891 and early vaccines against diphtheria and tetanus were developed at the beginning of the 20th century, which combined toxin with antitoxin.

The 20th century: the control of diseases using vaccines

During the 20th century, many infectious diseases came under control in many countries because of

\[
\begin{array}{|l|}
\hline
\textbf{Diseases caused by bacteria and viruses where the name of the organism and the disease is not the same} \\
\hline
\textbf{Chickenpox (varicella):} Varicella zoster virus \\
\textbf{Diphtheria:} Corynebacterium diphtheriae \\
\textbf{Intestinal tuberculosis:} Mycobacterium bovis \\
\textbf{Pertussis (“whooping cough”):} Bordetella pertussis \\
\textbf{Q fever:} Coxiella burnetii \\
\textbf{Shingles:} Varicella zoster virus \\
\textbf{Syphilis:} Treponema pallidum \\
\textbf{Tetanus (“lockjaw”):} Clostridium tetani \\
\textbf{Typhoid fever:} Salmonella typhi \\
\hline
\end{array}
\]
clean water, improved sanitation, and pasteurization of milk, which reduced exposure to *Brucella* sp. (the cause of brucellosis, a disease of animals transmissible in milk to humans), *Mycobacterium bovis* (the cause of most cases of intestinal tuberculosis), and *Salmonella typhi* (the cause of typhoid fever). Unfortunately, paralytic poliomyelitis also arose during this same period because of these same reasons—improved sanitation had the indirect effect of children acquiring the viruses that cause polio at later ages, causing about 1% to develop paralytic disease.

But the greatest change to the occurrence of infectious diseases occurred when vaccines were developed and became widely used. In the second half of the 20th century, vaccines substantially increased the life expectancy of children and prolonged life throughout society. For example, in the USA alone, before vaccines, there were half-a-million cases of measles with about 500 deaths each year. In 1964–1965, about 4 years before the rubella vaccine became available, there were more than 12,5 million people infected, causing 20,000 babies with congenital rubella infection to be born; of the children born with congenital rubella, 11,600 were born blind, and 1,800 were mentally retarded. In 1952, there were more than 21,000 individuals paralyzed by poliomyelitis in the USA. An overview of the reduction of vaccine-preventable illnesses in the 20th century is shown in Table 1.1.

### Table 1.1 Vaccine-Preventable Illnesses Before and Since Routine Childhood Vaccination in the USA

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of Cases Before Vaccine</th>
<th>Year Vaccine Recommended for Routine Use in Children</th>
<th>Number of Cases in 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>48,164</td>
<td>Early 1900s</td>
<td>0</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>175,885</td>
<td>Mid-1940s</td>
<td>0</td>
</tr>
<tr>
<td>Pertussis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>142,271</td>
<td>Mid-1940s</td>
<td>16,858</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1,314</td>
<td>Mid-1940s</td>
<td>18</td>
</tr>
<tr>
<td>Paralytic polio</td>
<td>16,316</td>
<td>1955</td>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Measles</td>
<td>503,282</td>
<td>1963</td>
<td>71&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209</td>
<td>1967</td>
<td>1,981</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>1969</td>
<td>3</td>
</tr>
<tr>
<td>Congenital rubella</td>
<td>823</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Invasive <em>H. influenzae</em>, type b&lt;sup&gt;e&lt;/sup&gt;</td>
<td>20,000</td>
<td>1985</td>
<td>38</td>
</tr>
<tr>
<td>Invasive <em>S. pneumoniae</em></td>
<td>17,240</td>
<td>2000</td>
<td>583</td>
</tr>
<tr>
<td>Hepatitis A (acute illness)</td>
<td>26,796</td>
<td>2009&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1,987</td>
</tr>
<tr>
<td>Hepatitis B (acute illness)</td>
<td>26,107</td>
<td>1991&lt;sup&gt;g&lt;/sup&gt;</td>
<td>3405</td>
</tr>
<tr>
<td>Varicella</td>
<td>4,000,000</td>
<td>1995</td>
<td>20,480</td>
</tr>
<tr>
<td>Deaths</td>
<td>105</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

Adapted from Myers MG and Pineda D (2008). Do Vaccines Cause That?!. I4PH Press, Galveston (with permission).


<sup>b</sup>Numbers of cases of pertussis were at a historic low of 1,010 in 1976. The rise in cases since then probably involves reduced immunity over time, plus an increased awareness of whooping cough in adolescents and adults for whom there is now a booster dose of vaccine.

<sup>c</sup>Vaccine-associated in an immunodeficient person.

<sup>d</sup>Measles has been largely eliminated from the USA. However, there were 21 importations of measles into the USA in 2009 (14 of whom were US residents traveling abroad), which spread to others in the community.

<sup>e</sup>Children younger than 5 years of age.

<sup>f</sup>Introduced incrementally after licensure in 1995.

<sup>g</sup>Introduced incrementally after licensure in 1986.
In 2005, the total savings from direct costs saved (such as hospitalizations, clinic visits, lost ability from illness or death to fully function in society) from the routinely recommended childhood vaccines in the USA were estimated to be $9.9 billion per year. If the indirect health costs were also included (such as parents’ time off from work or the need for caregivers), those vaccines saved $43.3 billion.

Vaccines

The term vaccine is derived from the Latin word, vacca (meaning cow), because cowpox was used to prevent smallpox. Vaccination is the deliberate attempt to prevent disease by “teaching” the immune system to employ acquired immune mechanisms. In the 21st century, vaccines are also being used to enhance existing immune mechanisms with the development of vaccines as treatments, so-called therapeutic vaccination. The properties of a vaccine are shown in Table 1.2.

Vaccines developed by trial and error

The smallpox vaccines were developed because of direct observation, first with the use of variolation, which, although sometimes a fatal procedure, was of lower risk than when smallpox was acquired in an epidemic, and then by the recognition that cowpox could provide immunity to smallpox. The vaccines for tetanus, diphtheria, and pertussis were prepared by trial and error in the early 1900s, but many other vaccines were also tested in this manner; however, many of these either failed to prevent disease or had severe adverse consequences.

Diphtheria

Diphtheria is a serious disease that can cause death through airway obstruction, heart failure, paralysis of the muscles used for swallowing and pneumonia. It is caused by the bacterium Corynebacterium diphtheriae, which produces toxins that cause cell death both at the site of infection and elsewhere in the body. Diphtheria usually begins with a sore throat, slight fever, and swollen neck. Most commonly, bacteria multiply in the throat, where a grayish membrane forms. This membrane can choke the person—the source of its common name in the late 19th century as the “strangling angel.”

Sometimes, the membrane forms in the nose, on the skin, or other parts of the body. The bacteria also release a toxin that spreads through the bloodstream that may cause muscle paralysis, heart and kidney failure, and death.

Approximately 5% of people who develop diphtheria (500 out of every 10,000) die from the disease and many more suffer permanent damage.

“Baby” Ruth Cleveland, first child of President and Mrs. Grover Cleveland died of diphtheria in 1904, at the age of 12 (see Figure 1.1). In the 1920s, before the diphtheria vaccine, there were 100,000 to 200,000 reported cases in the USA each year. For example, in

<table>
<thead>
<tr>
<th>Table 1.2 Properties of Infectious Disease Preventive Vaccines</th>
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<tr>
<td>The following are properties of preventive infectious disease vaccines:</td>
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<tr>
<td>• An antigenic stimulus that elicits a specific adaptive immune response that can be recalled upon exposure to a specific agent</td>
</tr>
<tr>
<td>• Intentionally delivered</td>
</tr>
<tr>
<td>• Usually given to healthy individuals</td>
</tr>
<tr>
<td>This classic definition of a vaccine now needs to be enlarged to include therapeutic vaccines, such as:</td>
</tr>
<tr>
<td>• Herpes zoster vaccine, which restimulates immunity to varicella zoster virus in order to prevent reactivation of latent virus as shingles</td>
</tr>
<tr>
<td>• Cancer vaccines</td>
</tr>
<tr>
<td>• Vaccines for addiction</td>
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</tbody>
</table>

Diphtheria: The “Strangling Angel”

Brown County, MN, early 1880s:
“Louis Hanson lived southeast of town about five miles. He and his wife had five children. The scourge came and took all five. It was a sad sight to see Hanson driving up the road every day or two on his way to the cemetery, alone with his dead. All their children died between August 26 and September 5.”

With permission: Minnesota Historical Society.
1921 there were 206,000 cases of diphtheria and 15,520 diphtheria-caused deaths, mostly among children.

Early in the 20th century, diphtheria antitoxin became a powerful new tool for the prevention of diphtheria. Unfortunately, there was no oversight as to how it was produced and used, which led to the great tragedy of the St. Louis, Missouri, diphtheria epidemic in 1901. Equine diphtheria antiserum—made from a horse that had died from tetanus—was given to children, causing fatal tetanus. Also, that year there were cases of tetanus among recipients of contaminated smallpox vaccine in Camden, New Jersey. These outbreaks led Congress to enact the Biologics Control Act of 1902, the predecessor to the Centers for Biologics Evaluation and Research of the US Food and Drug Administration, the beginning of vaccine regulatory control.

Active immunization employing diphtheria toxin and antiserum (so-called TaT) was effective but also associated with many adverse events, such as “serum sickness.” However, in the early 1920s it was shown that toxin treated with heat and formalin lost its toxicity but was immunogenic. The production of diphtheria toxoid has evolved since then, but the process remains highly effective in providing protection against disease. However, the fully immunized person who is exposed to the bacterium can, in rare circumstances, still be infected as a “carrier” who usually only develops a mild case, or may not get sick at all. But if they are not fully vaccinated, the risk of getting severely ill after exposure is 30 times higher.

Because of the high level of immunizations now in the USA, only one case of diphtheria (or fewer) occurs each year. However, in areas where the immunization rate has fallen (such as Eastern Europe and the Russian Federation in the 1990s, as shown in Figure 1.2), tens of thousands of people suffered from diphtheria. Even

Figure 1.1 “Baby” Ruth Cleveland, first child of President and Mrs. Grover Cleveland, who died of diphtheria in 1904, aged 12 years. The former president and the remainder of the family were treated with diphtheria antitoxin and remained symptom free.

Figure 1.2 Cases of diphtheria in the Russian Federation per 100,000 population 1992–2006. The bars demonstrate the immunization coverage rate for children as measured by the Department of Sanitation, Russian Federation. Data provided by Dr. Olga Shamshava, 2007.
though we do not see many cases, the potential for diphtheria to reemerge is real.

**Tetanus**

Unlike the other vaccine preventable diseases, tetanus is not communicable person to person. Tetanus (“lockjaw”) is caused by a potent neurotoxin produced by the anaerobic bacterium *Clostridium tetani*. The bacterium is a ubiquitous organism found in soil and the intestines of animals and humans. The organism multiplies in wounds—particularly dirty wounds with devitalized tissues—elaborating a plasmid-encoded exotoxin that binds to skeletal muscle and to neuronal membranes without causing an inflammatory response.

Generalized tetanus, the most common form of disease, usually begins with spasms of the face and chewing muscles causing trismus—or as it is popularly called “lockjaw”—causing a characteristic facial expression, the risus sardonicus or sardonic grin (see Figure 1.3). As the illness progresses, trismus is often accompanied by intense muscle spasms.

In the late 1890s it was recognized that passive prophylaxis with equine antiserum could prevent tetanus. This, plus aggressive surgery, was the only means to combat tetanus in World War I. Chemical inactivation of tetanus toxin in the early 1920s permitted the active immunization with tetanus toxoid to prevent tetanus by the US Army in World War II. The prophylactic use of vaccine plus post-injury management (a booster dose of tetanus toxoid, aggressive surgery, and passive prophylaxis with antiserum) dramatically reduced the occurrence—and therefore the mortality—of tetanus among the US Army in World War II compared to WWI (see Table 1.3).

*Figure 1.3* A 7-day-old infant with neonatal tetanus. Intense spasmodic muscle contractions shown as clenching of the feet (left) and of the facial muscles causing risus sardonicus, literally a “sardonic grin” (right). The child’s mother had not previously been immunized. © Martin G. Myers

<table>
<thead>
<tr>
<th>Table 1.3 The Impact of Tetanus Toxoid Among US Soldiers</th>
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<tbody>
<tr>
<td>Admission for Wounds</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>World War I 523,158</td>
</tr>
<tr>
<td>World War II 2,734,819</td>
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</tbody>
</table>


*Six of whom were unimmunized.*

Neonatal tetanus (Figure 1.3)—generalized tetanus in newborn infants—occurs in infants whose mothers are not immune because they have not received vaccine. Because of nearly universal immunization with tetanus toxoid, neonatal tetanus is now rare in the USA but remains an important cause of neonatal mortality in developing countries.

In the late 1940s, routine tetanus toxoid immunization of children started in the USA. There has been a steady decline in cases from about 500 to 600 cases a year to the all-time low in 2009 of 18 cases—that is, from 0.4 cases/100,000 population to 0.01 cases/100,000 population. Mortality because of better wound care and the use of human tetanus immunoglobulin (which has now replaced horse antiserum) has decreased from 30% to 10%. Persons who recover from tetanus still need to be immunized against tetanus, however, as immunity is not acquired after tetanus. That is, so-called natural immunity to tetanus does not occur.
Almost all cases of human tetanus that occur in the USA now occur in adults who have either not been immunized or have not had a booster dose within 10 years.

Pertussis

Pertussis ("whooping cough") is a bacterial infection caused by Bordetella pertussis. It is spread in respiratory secretions when infected people cough or sneeze.

Children with pertussis have decreased ability to cough up respiratory secretions, and they develop thick, glue-like mucus in their airways. This causes severe coughing spells that make it difficult for them to eat, drink, or breathe. The child may suffer from coughing spells for 2 to 3 weeks or longer. Sometimes the child coughs several times before breathing; when the child finally does inhale, there may be a loud gasp or "whooping" sound. The disease is most severe when it occurs early in life when it often requires hospitalization; most of the deaths due to pertussis occur in very young infants.

Unlike many other vaccine preventable diseases, the bacterium that causes pertussis, B. pertussis, continues to circulate in the population even though most people have been immunized. Because pertussis is one of the most contagious human diseases, it is a great risk to those who are not vaccinated. Pertussis will develop in 90% of unvaccinated children living with someone with pertussis, and in 50% to 80% of unvaccinated children who attend school or daycare with someone with pertussis.

In the pre-vaccine era, pertussis was a universal disease, almost always seen in children. Between 1940 and 1945, before widespread vaccination, as many as 147,000 cases of pertussis were reported in the USA each year, with approximately 8,000 deaths caused by the disease. It is estimated that at the beginning of the 20th century as many as 5 of every 1000 children born in the USA died from pertussis.

In 1976, there were 1,010 case of pertussis in the USA, the lowest number of cases ever reported. Over the past few years the number of reported cases of pertussis has increased, reaching 25,827 in 2004; worldwide, there are an estimated 300,000 annual deaths due to pertussis. In 2009, there were 16,858 cases of pertussis in the USA with the greatest rate occurring in infants younger than 6 months of age but with about half of the cases occurring in adolescents and adults.

- The majority of pertussis-related deaths are in young infants. Approximately 50 out of every 10,000 children younger than 1 year of age who develop pertussis die from the disease.
- In 1997, adolescents and adults accounted for 46% of reported cases of pertussis, and they are often the ones who spread this disease to infants and children. Indeed, family members are often the source of pertussis exposure in young infants.
- In 2004, adolescents 11–18 years of age and adults 19–64 years of age accounted for 34% and 27% of the cases of pertussis in the USA, respectively. The true numbers are probably much higher in these age ranges because pertussis is often not recognized in adults. These cases are very important because teenagers and adults with pertussis can transmit the infection to other people, including infants who are at greatest risk for complications and death.

The initial pertussis vaccines were suspensions of formalin-killed whole organisms, first developed in 1914, which was shown to be effective in controlling epidemic pertussis in the early 1930s. It was combined with diphtheria and tetanus toxoids and recommended for routine administration to children in 1948. Despite the clear benefits of these vaccines at reducing pertussis, widespread parental concerns about vaccine safety arose, resulting in reduced immunization coverage. For example, in England and Wales the immunization levels dropped precipitously from 80% to 30% leading to a widespread epidemic involving more than 102,000 cases (see Figure 1.4). Although still used for control of pertussis in some countries, the whole cell pertussis vaccine is no longer used in many countries having been replaced by the acellular pertussis vaccine.

In 1991, the Food and Drug Administration licensed the acellular pertussis vaccines (diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine for use in young children [abbreviated DTaP]). These acellular pertussis vaccines consist of various components of the B. pertussis bacteria and cause much fewer side effects than the previous whole cell pertussis vaccines. Some of the newer DTaP vaccines have also included other vaccines, which allowed for a reduction in the number
of injections. In 2005, new acellular pertussis vaccines were licensed for use in adolescents and adults (abbreviated Tdap because they contain less diphtheria toxoid and the pertussis components than the DTaP) in an attempt to reduce the number of pertussis infections in very young infants.

Testing the new acellular vaccines in the 1990s presented an ethical dilemma: As the USA had a licensed vaccine—the inactivated whole cell vaccine—that was known to be relatively safe and effective, how could the new vaccine be best tested for safety and effectiveness? This was solved by testing in countries that had stopped immunizing against pertussis because of parental concerns and that were then experiencing a resurgence of cases of pertussis.

Half of those vaccinated with DTaP will experience no side effects at all. About half of those vaccinated will experience mild reactions such as soreness where the shot was given, fever, fussiness, reduced appetite, tiredness, or vomiting. Some children may experience a temporary swelling of the entire arm or leg where DTaP was given; this reaction is more common after the fourth or fifth dose of DTaP but does not indicate that it will happen again after the next dose. Unfortunately, vaccines, particularly pertussis-containing vaccines, have been incorrectly blamed for many things in the past. For example, the evidence does not support DTaP vaccines as a cause of asthma, autism, type 1 diabetes, brain damage, or sudden infant death syndrome. In addition, severe encephalopathy within 7 days after DTaP vaccination is usually explainable by another cause.

In 2004, one of the two manufacturers of tetanus toxoid-containing vaccines in the USA unexpectedly left the market because the cost of manufacturing limited the financial incentive to continue its manufacture. This caused a serious shortage of all tetanus toxoid-containing vaccines because about 9 months is needed to manufacture the vaccine.

**Vaccines prepared by trial and error attenuation**

**Yellow fever**

“From the second part of our study of yellow fever, we draw the following conclusion: The mosquito serves as the intermediate host for the parasite of yellow fever, and it is highly probable that the disease is only propagated through the bite of this insect.”


Until the 20th century, epidemics of yellow fever repeatedly devastated seaports in North America and Europe. For example, 10% of Philadelphia, the new US capital city, succumbed in 1793 as graphically described by Longfellow in his poem about the travels of Evangeline in search of Gabriel, from whom she had been separated on their wedding day by the British forces who evicted Acadian men from Nova Scotia.

Until the hypothesis by Carlos Findlay and the experiments in 1900 by the Yellow Fever Commission in Cuba led by Walter Reed, the prevailing belief was that yellow fever was spread by filth, sewage, and decaying organic matter. In their experiments, Reed and his team showed that yellow fever was not a
bacterial infection but was transmitted by the bite of the *Aedes aegypti* mosquito.

Yellow fever infection causes a wide spectrum of disease. Most cases of yellow fever are mild and similar to influenza, and consist of fever, headache, nausea, muscle pain, and prominent backache. After 3 to 4 days, most patients improve, and their symptoms disappear. However, in about 15% of patients, fever reappears after 24 hours with the onset of hepatitis and hemorrhagic fever. The “yellow” in the name is explained by the jaundice that occurs with hepatitis. Bleeding can occur from the mouth, nose, eyes, and/or stomach. Once this happens, blood appears in the vomit and feces. Kidney function also deteriorates. Up to half of those who develop the severe illness die within 10–14 days. The remainder recovers without significant organ damage.

In 1930, the regulatory function for biologics products (such as vaccines) was renamed the National Institute of Health (the forerunner of the National Institute of Allergy and Infectious Diseases). In 1934, because of a proliferation of potential new products, regulatory rules required that new biologics licensure would require the proof of both effectiveness and safety.

Only humans and monkeys can be naturally infected with yellow fever virus. Initial strains of yellow fever virus were established in 1927 in monkeys at the Rockefeller Institute in New York and the Institut Pasteur in Paris. Attempts at developing a vaccine were unsuccessful until Theiler and Smith at the Rockefeller Institute were able to attenuate the virus by subculture in mice—selecting for less virulent strains—followed by serial cultivation of the virus in chick embryo cell cultures. They used the lack of viscerotropism or encephalopathic effect in monkeys as “proof of principle” in 1936. Testing in humans quickly was begun in New York and then large field trials in Brazil in 1937.

Several important lessons were learned from yellow fever vaccine development in addition to the ability to attenuate its pathogenicity. Additional subculture of the vaccine virus in tissue cultures was found to lead to loss of vaccine immunogenicity, which led in turn to the recognition of the importance of using seed and vaccine pools in order to standardize passage level (discussed in detail in Chapter 11). Testing in monkeys became a regulatory requirement for new batches of vaccine. In addition, the vaccine virus proved to be unstable unless serum was added to the vaccine. However, the use of human serum caused more than 10,000 cases of hepatitis B in the military in 1943.

Although the vaccine has been available for more than 70 years, the number of people infected over the past 2 decades has increased, and yellow fever is now once again a serious public health issue in a number of countries. Although epidemic yellow fever used to occur in the USA, the disease now occurs only in sub-Saharan Africa and tropical South America, occurring with increased risk during the rainy seasons (July to October in West Africa and January to May in South America). In those regions, it is endemic and becomes intermittently epidemic. It is estimated globally that there are 200,000 cases of yellow fever (with 30,000 deaths) per year. However, due to underreporting, probably only a small percentage of cases are identified. Small numbers of imported cases also occur in countries free of yellow fever; in the USA and Europe, these are usually in unimmunized travelers returning from endemic areas.

The risk to life from yellow fever is far greater than the risk from the vaccine, so people who may be exposed to yellow fever should be protected by immunization. However, if there is no risk of exposure—for example, if a person will not be visiting an endemic area—there is no need to receive the vaccine. The vaccine should only be given to pregnant and breastfeeding women during vaccination campaigns in the midst of an epidemic. Yellow fever vaccine should not be given to infants under 6 months of age due to an increased risk of viral encephalitis developing in the child and, in most cases, children 6–8 months of age should have travel and immunization deferred until the child is 9 months of age or older.

Yellow fever vaccine generally has few side effects; 10–30% of vaccinees develop mild headache, muscle pain, or other minor symptoms 5 to 10 days after vaccination. However, approximately 1% of vaccinees find it necessary to curtail their regular activities. Immediate hypersensitivity reactions, characterized by rash, urticaria, or asthma or a combination of these, are uncommon (incidence 1.8 cases per 100,000 vaccinees) and occur principally in persons with histories of egg allergy.

Rarely, yellow fever vaccine can cause serious adverse side effects. Encephalitis is estimated to occur
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in 0.8 per 100,000 vaccinees in the USA. Multiple organ system failure—which is a similar illness to yellow fever—following immunization (termed yellow fever associated viscerotropic disease [YEL-AVD]) has been reported from around the world since 2001, particularly among people with certain immune deficiencies; in the USA the rate has been estimated to be 0.4 per 100,000 individuals. Both of these risks from yellow fever vaccine appear to occur more commonly in those who are over 60 years of age, and all cases have been seen in those being immunized for the first time; i.e., the risk of serious adverse events following yellow fever immunization is seen only in primary vaccinees and not in individuals who receive booster immunizations.

Poliomyelitis

Poliomyelitis was observed in antiquity, but the modern history of polio is the history of the rise of evidence-based medicine in the 19th and 20th centuries. Early in the 19th century, during the period when it was recognized that a physician could deduce a patient’s pathologic findings from the physical examination, patients with “infantile paralysis” were recognized to have lesions in the anterior horn cells of the spinal cord detected on postmortem examination. In 1840, a German orthopedist, Jacob von Heine, provided a meticulous description of the clinical features of infantile paralysis, and in 1887, Karl Oscar Medin, a pediatrician in Stockholm, observed 44 cases and is credited for assembling the first comprehensive description of the disease (giving Sweden an unenviable reputation at that time as being a disreputable place). Figure 1.5 shows a clinical case of poliomyelitis. However, it would only be a few years until other countries had similar epidemics. Indeed, in 1893, two Boston area physicians published a letter titled “Is acute poliomyelitis unusually prevalent this season?” noting that most of the cases came from the suburban communities but not from the city of Boston.

In 1905, Sweden experienced 1,031 cases of polio that were closely studied by Medin’s student Ivar Wickman. Wickman made the extraordinary observations that there were many asymptomatic and milder nonparalytic infections and that the disease was—in contrast to other infectious illnesses—not increased by crowding as a risk factor. This was confirmed by Wade Hampton Frost in the 1920s in the USA; Frost is credited as being the first US epidemiologist.

In 1912, the identification of a filterable virus, the establishment of the monkey as an animal model, and that the spinal cords showed the identical pathologic findings as humans by American scientist Karl Landsteiner opened up new vistas for research. Landsteiner ultimately received the Nobel award for his description of blood groups in 1930. In the 1940s, anatomist David Bodian at Johns Hopkins, using serologic methods and many poliovirus isolates, demonstrated that there were three polioviruses.

Treatment of poliomyelitis was a therapeutic attitude of “do nothing to aggravate the disease” until the 1920s, when Phillip Drinker at Harvard invented the iron lung respirator followed by Sister Kenny—who is considered the originator of physical therapy—popularized her ideas about “orthopedic methods” after the acute illness had subsided.

But the rise of modern virology was ushered in by John Enders with two trainees in his laboratory at Children’s Hospital in Boston in 1948 when they were able to cultivate each of the three polioviruses in monkey kidney tissue cultures, describing the histological changes they saw in culture as “cytopathogenic effects.” Enders and his trainees, Tom Weller and Frederick Robbins, received the Nobel award in 1954.

By the early 1950s, the natural history of poliovirus infection had been shown to involve replication in the
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gastrointestinal tract, occasionally followed by viremia, which on occasion infected the spinal cord anterior horn cells. The formalin-inactivated polio vaccine developed by Jonas Salk was licensed in 1954 after large field trials (400,000 immunized) demonstrated effectiveness and safety of the vaccine.

Unfortunately, little was known about the complexities of scale-up or the kinetics of poliovirus inactivation by formalin. When the first inactivated vaccines were licensed, all the manufacturers experienced production and quality control problems, culminating in the “Cutter Incident” of cases of paralytic poliomyelitis in 1955, which were caused by residual infectious virus in some of the new vaccine lots, particularly those produced by Cutter Laboratories. This led to the temporary suspension of the polio vaccine programs in the USA and elsewhere. Inactivated vaccine was subsequently rereleased after additional safety tests demonstrated consistency in production and viral inactivation. As a consequence of the problems with the Salk vaccine, the regulatory functions at the US National Institute of Allergy and Infectious Diseases (part of the National Institutes of Health) were moved to a separate institute, the Division of Biologics Standards, ultimately becoming the modern Center for Biologics Evaluation and Research of the Food and Drug Administration.

In the 1950s, Albert Sabin in Cincinnati and investigators at a number of other laboratories took the three strains of polioviruses (one each for the three serotypes of poliovirus) and passaged them repeatedly in monkey tissue cultures, testing them for attenuation by inoculating monkeys. The least neurovirulent of these, the Sabin vaccine candidate, was ultimately selected. Sabin field tested his oral vaccine in 75 million people in the former Soviet Union.

Immunologically, the inactivated vaccine differs substantially from the attenuated vaccine in that inactivated vaccine only induces humoral immunity whereas the live virus vaccine induces both humoral and duodenal antibodies (see Figure 1.6).

In the 1960s, an adventitious virus, simian virus 40 (SV40), which has been shown to cause tumors in rodents and can transform human tissue culture cells, was recognized in primary monkey kidney tissue cultures used to prepare some vaccines. It is estimated that up to 100 million Americans may have been exposed to SV40, which contaminated the inactivated polio vaccine when it was first introduced. In addition, SV40 also contaminated the first oral polio vaccine, but that contaminated vaccine was only given to people during the original clinical trials. Furthermore, SV40 has been found as a contaminant of some of the adenovirus vaccines given to military recruits during that same period of time. Once the contamination was recognized, steps were taken to eliminate it from future vaccines; no vaccines licensed for use in the USA or other countries currently are contaminated with SV40.

The oral polio vaccine was inexpensive to produce, did not require trained health providers to administer with needle and syringe (as it was given to children on a lump of sugar), and protected a higher proportion of those immunized, as well as protecting those around them by community (or herd) immunity (see Chapter 18 for details on herd immunity). When used in outbreak settings, the live vaccine also stops the transmission of polioviruses (and other related enteroviruses) when a high proportion of individuals have been immunized, because this vaccine replicates in the human gastrointestinal tract blocking enteroviral replication.

![Figure 1.6](image-url)
Because SV40 causes tumors in rodents and can transform human cell cultures, it has been intensively studied, both in the laboratory and epidemiologically as a possible cause of human malignancies. This concern appears to have now been excluded:

- Newborn babies who received SV40 in polio vaccine were followed for 35 years and had no excess risk of cancer. This is particularly important because newborn animals are much more susceptible to SV40 tumors than older animals.
- A case-control study of cancers among Army veterans found no risk of brain tumor, mesothelioma, or non-Hodgkin's lymphoma associated with receipt of adenovirus vaccine that contained large amounts of SV40.
- People infected with human immunodeficiency virus (HIV) are at increased risk of developing non-Hodgkin's lymphoma. This risk was not increased if they had received SV40-contaminated polio vaccine compared to those who had not received it.
- Earlier studies reported that many people had antibodies against SV40, but those studies now appear to have detected cross-reacting antibodies to similar but different human viruses. Using new methods to test for SV40 antibody, recent studies have demonstrated a lack of SV40 antibody response in humans—in contrast to animals.
- Molecular tools frequently used to detect SV40 in cancerous tissues may have commonly detected SV40 contaminants in the laboratory when, in fact, it was not present in the cancer.
- Finally, if SV40 caused cancer in humans, the proteins it produces in animal tumor cells should be measurable in human cancers, which they have not.

Adapted from Myers MG and Pineda DI. Do Vaccines Cause That?! I4PH Press, 2008, with permission.

Unfortunately, while replicating in the gastrointestinal tract, viral strains are excreted and can be recovered in feces. Often these strains have reverted to a neurovirulent phenotype (that is, they are capable of causing paralytic disease) due to reversion of attenuating mutations found in the live vaccine strain to those found in wild-type poliovirus. This is a rare but important complication of the oral vaccine, called vaccine-associated paralytic poliomyelitis (VAPP). This can occur among those unimmunized persons in contact with immunized children due to the excretion of viruses in feces. In addition, persons with certain immunodeficiencies also may continue to shed vaccine virus in their feces for very long periods of time (years), severely complicating efforts to eradicate poliomyelitis.

Because of continuing cases of VAPP in the USA after the elimination of wild-type polioviruses, the USA and other countries began once again to employ the safer but less effective inactivated vaccine for routine use in 2000.

**Measles**

Measles is no longer an endemic disease in the USA. However, measles often arrives via infected travelers by airplane from other areas of the world, often spreading to susceptible persons before the classic symptoms become apparent. Due to its high transmissibility by aerosol, it is frequently transmitted in emergency rooms and medical offices from people who are seeking care during the early manifestations of measles infection.

Despite an effective live virus vaccine that was licensed in 1963, measles remains one of the leading causes of death in children younger than 5 years of age and kills approximately 400 children per day worldwide. Measles is a serious disease, which spreads rapidly to others in respiratory droplets from sneezing and coughing. It is one of the most contagious diseases known.

The global measles initiative to reduce measles mortality worldwide has had remarkable success at reducing deaths from measles from 733,000 in 2000 to 164,000 in 2008. Measles in the developing world has a much higher mortality rate than in developed countries because of complex interactions between malnutrition, age at infection, type and outcome of complications, crowding or intensity of exposure, and the availability of care.

Measles in the USA prior to the measles vaccine was estimated to cause 4,000,000 cases per year (equivalent to the entire birth cohort in the USA); virtually every person had measles virus infection by age 20. There were 150,000 cases with lower respiratory
complications (such as bacterial or viral pneumonia, bronchitis, and croup); 150,000 cases of otitis media; 48,000 hospitalizations; and 4000 cases of encephalitis annually. Between 1989 and 1991, when the USA experienced renewed measles activity—prior to introducing a second dose of measles vaccine—there were 55,000 cases and more than 130 deaths.

Uncomplicated measles in developed countries begins 1 to 2 weeks after exposure. The illness begins with fever followed by cough, coryza (runny nose), and conjunctivitis, similar to many other respiratory infections; the infection is very contagious at this stage.

After several days the fever increases and the pathognomonic enanthem, Koplik spots appear (a rash on the inside of the cheek, which is often not observed). One to 2 days later (usually about day 14 after exposure) the characteristic erythematous maculopapular rash (see Figure 1.7) appears first on the face and then spreads down the body. Early on, the rash usually blanches on pressure, but as it begins to fade 3–5 days later it becomes brownish, also clearing first on the face and spreading down.

Infections of the middle ears, pneumonia, croup, and diarrhea are common complications of measles. Approximately 5% of children (500 out of 10,000) with measles will develop pneumonia. Measles encephalitis occurs in 1 per 1,000 cases of natural measles, and when it occurs it has a mortality of almost 50%; many of the survivors have permanent brain damage. This translates to 1 to 3 of every 1,000 children who get measles in the USA will die from the disease. Death occurs more commonly in infants, especially malnourished children, and among immunocompromised persons, including those with HIV infection and leukemia. These latter persons—who often cannot be immunized—can be protected by herd immunity if those around them are immune.

Subacute sclerosing panencephalitis (SSPE) is a rare fatal illness caused by ongoing measles virus infection of the brain. Symptoms of brain damage usually begin 7 to 10 years after infection. Death occurs 1 to 3 years after the onset of symptoms. Risk factors for developing SSPE include developing measles infection at a young age. The incidence of SSPE is estimated to be between 7 and 11 cases per 100,000 cases of measles. The measles vaccine virus has not been associated with SSPE.

The measles virus was first isolated in tissue culture in 1954, just as the polioviruses in the laboratory of John Enders. Vaccine development followed rapidly with licensure in the USA in 1963. The virus was passed multiple times, first in human kidney cells and then in human amnion cells. It was then adapted to chick embryos and finally passaged in chick embryo cells. The initial live virus vaccine that was licensed prevented measles complications but was associated with high rates of fever and rash, leading to further attenuation of the vaccine.

The vaccine virus was found to be both temperature and light unstable, and required the addition of stabilizers. Even in the lyophilized form with the addition of stabilizers, it must be stored in the dark at 2–8°C. After reconstitution, the virus loses about 50% of its potency in 1 hour at room temperature.

The further attenuated live virus vaccine was combined in 1971 with mumps and rubella live virus vaccines into a single injection, the measles, mumps, and rubella vaccine (abbreviated MMR), and subsequently with varicella vaccine (MMRV) in 2005. Two doses of vaccine are recommended for all the vaccine components to ensure that more than 95% of the population be immune to measles, which is the threshold for maintaining community (herd) immunity.

A formalin-inactivated vaccine was also developed and licensed at the same time as the live virus vaccine.
but is no longer utilized because those who received that vaccine developed a new disease called “atypical measles,” which resembled Rocky Mountain Spotted Fever (a tick-borne disease caused by the bacterium Rickettsia rickettsia), when they encountered live measles virus (either wild type or vaccine virus).

Following licensure of measles vaccine, rates of the disease in the USA fell dramatically. However, 95% or more of individuals must be immune to measles to prevent its transmission in communities. Because of this, most states in the 1970s instituted mandatory immunization of children as a condition of school entry. In 1991, a two-dose immunization strategy was instituted. This has resulted in elimination of endemic measles in the USA (see Figure 1.8).

Because of misinformation about measles vaccine safety in the United Kingdom, beginning in 1998, MMR vaccine coverage declined across Europe, resulting in outbreaks of measles and mumps in Europe, the USA, and Canada.

![Figure 1.8](image-url) Measles in (A) the USA (Centers for Disease Control and Prevention, 1995) and (B) Iowa (Iowa Department of Health, 2007, www.idph.state.is.us/adper/pdf/cade/decades/pdf) 1960–1989. Measles vaccine was licensed in 1963, and mandatory immunization laws were enacted widely by states in the late 1960s and 1970s. Iowa enacted its immunization law in 1977 (Iowa Administrative Code, 1977). From chapter 17 in Myers & Pineda in Barrett & Stanberry (Elsevier).
There were 140 cases of measles in the USA in 2008; more than three quarters of these cases were linked to imported measles from another country, and most of the imported cases occurred among unimmunized American travelers.

**Rubella**

Rubella is caused by a virus that is transmitted from person to person in respiratory secretions. Rubella is a mild illness; indeed, it is often asymptomatic. When symptoms occur, they include low-grade fever and swollen lymph nodes in the back of the neck followed by a generalized erythematous rash. Conjunctivitis does not occur. Self-limited complications may include joint pain, a temporary decrease in platelet count, and, uncommonly, postinfectious encephalitis. Temporary arthritis may also occur not uncommonly, particularly in adolescent and adult women; although chronic arthritis has been reported to occur in adult women, the data are inconclusive.

In contrast, rubella in pregnant expectant women—who are often asymptomatic—frequently leads to congenital rubella syndrome (CRS) in the fetus (see Figure 1.9). This is a devastating disease characterized by microcephaly, small birth size for gestational age, deafness, mental retardation, cataracts and other eye defects, heart defects, and diseases of the liver and spleen that may result in a low platelet count with bleeding under the skin. The incidence and severity of congenital defects are greater if infection occurs during early gestation; as many as 85% of expectant mothers infected in the first trimester will have a miscarriage or deliver a baby with CRS. Once fetal infection is established, viral infection occurs in multiple organs with potential progressive damage.

In 1963–1964, before vaccine was available, there was a rubella outbreak in the USA during which 12 million people were infected. Because some who were infected were pregnant women, 11,000 fetuses died and 20,000 babies were born with permanent disabilities.

Several live attenuated virus vaccines were licensed in the USA and elsewhere in 1969–1971, but the RA27/3 strain—isolated from an infected fetus and propagated in human fetal cells—was adopted in the USA and most other countries because it induced consistent and persistent immunity, had a low rate of side effects, and because recipients developed resistance to reinfection with rubella virus. As stated in the measles vaccine section, rubella vaccine in the USA is given in combination with MMR and also sometimes with the addition of varicella vaccine (MMRV).

The number of cases of rubella fell very sharply once the rubella vaccine was licensed, and became widely used in the USA in 1969; in 2009 there were only two cases of CRS reported in the USA.

Since the introduction of rubella live virus vaccine, most CRS cases occur in developing countries, although it also continues to occur in developed countries among infants born to unimmunized mothers (see Table 1.4).

**Mumps**

Mumps is also a viral respiratory infection. Before widespread vaccination, there were about 200,000 cases of mumps and 20 to 30 deaths reported each year in the USA. In 2009, there were fewer than 2000 cases.

Mumps usually begins with swelling and tenderness of one or more of the salivary glands. This lasts for about a week. In children, the infection is usually fairly mild although permanent hearing loss occurs in 1 out of 2000 cases, and aseptic meningitis occurs in about 15% of cases, but this is usually self-limited. Pancreatitis may occur in as many as 4% of cases but an association with diabetes mellitus has not been
Varicella

Varicella is highly contagious caused by varicella zoster virus (VZV), although somewhat less so than measles. In households, most individuals who are susceptible will acquire infection, as will about one in six of those exposed in school. It is spread by the airborne route primarily from the skin vesicles. Viral replication initially occurs in the oropharynx, followed by a brief viremia. After an incubation period of 10–21 days (usually 14–16 days), the normal child may have malaise and fever for a day or two, but usually all symptoms start at about the same time with the typical rash (see Figure 1.10), which appears in crops starting as macules and papules. These quickly become vesicles and then pustules followed by crust formation. In the unimmunized child, the number of lesions usually numbers between 250 and 500.

The most common complication of varicella is bacterial skin infection in about 5%. These are usually self-limited when treated with antibiotics. However, some cases of secondary infection can be invasive and
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Immunoglobulin (VZIG) given shortly after exposure of high risk individuals to VZV can prevent progressive varicella.

Multiple attempts to produce an attenuated varicella vaccine were initially unsuccessful at identifying a vaccine candidate of low reactogenicity that retained immunogenicity. However, the Japanese licensed Oka strain varicella vaccine in 1987, and it was licensed in the USA in 1995. It was prepared from an isolate of VZV obtained from a normal child with varicella. It was serially propagated in human embryo fibroblasts, fetal guinea pig cells (one of the few nonprimate cell lines that support the growth of VZV), and then in human fibroblast cultures. The Oka strain has proven to be safe and effective although it does establish latency in recipients (i.e., the virus remains dormant in dorsal root ganglia) with the potential to produce shingles (but at a reduced rate) later in life. In recent years molecular differences between the Oka strain and wild-type strains of VZV have been used to distinguish clinical isolates of VZV from vaccine strain.

In the USA, varicella vaccine is available as a monovalent vaccine and as a quadrivalent vaccine (MMRV). Because the varicella component was found to be inferior in initial studies of the early combination vaccine, the licensed MMRV vaccine contains a greater dose of VZV than the monovalent vaccine so as to be “noninferior,” a regulatory requirement.

Prior to the introduction of varicella vaccine, there were 3 to 4 million cases of varicella in the USA each year. About 10,000 people were hospitalized with complications, and approximately 100 died. While only 5% of reported cases of varicella are in adults, adults accounted for 35% of the deaths from the disease. The varicella vaccine is 85% to 90% effective for the prevention of varicella and 100% effective for prevention of moderate or severe disease (defined as many skin lesions).

Children receiving varicella vaccine in pre-licensure trials in the USA were protected for 11 years. However, “breakthrough infection” (cases of chickenpox after vaccination) can occur in some who have been immunized; more recent studies have demonstrated waning immunity over time. Breakthrough varicella usually results in mild rather than full-blown varicella, although some school outbreaks have resulted in...
some vaccinated children having more lesions that were communicable. For these reasons, a second dose of a varicella vaccine is now recommended.

A majority of people who get varicella vaccine have no side effects. Of those who do have side effects, most will have only a mild reaction such as soreness and swelling where the shot was administered, and a mild rash. Pain and redness at the injection site occurs in about one in five children (and about one in three teenagers). About one in five may also have a few chickenpox-like lesions at the injection site. One to three weeks after vaccination, some may develop a few chickenpox-like lesions elsewhere on their bodies.

Although fever occurs in as many as 15% of children following administration of the varicella vaccine, it also occurred in children who had received the placebo in comparative trials. MMRV combination vaccine has comparable rates of reactions to children who received MMR and varicella vaccine at different sites on the same day—except that those that received MMRV vaccine more commonly experienced fever, a measles-like rash, and rash at the injection site. It has also been observed that children who received MMRV for the first dose of these vaccines had an increased risk of febrile seizures of about 1 child per 1000 when compared to children who received MMR and the varicella vaccine at different sites. For these reasons, many health care professionals prefer to administer MMR and varicella vaccines as two injections at different sites for the first dose but prefer MMRV for the second dose to reduce injections.

**Herpes zoster vaccine**

Zoster (shingles) is an infection caused by the same virus that causes chickenpox. The VZV virus—which remains in the nerve cells for life after chickenpox or after the chickenpox vaccine—may reappear as shingles in later life (Figure 1.12), particularly in the elderly and those who are immunocompromised. This is because of declining cell mediated immunity to VZV (Figure 1.13). Thus, anyone who has had chickenpox or the chickenpox live virus vaccine can develop shingles. Although shingles can occur at any age, the risk increases dramatically as people get older.

When shingles develop, people often experience discomfort in a region that is followed by a rash with blisters, generally in the distribution of a dermatome (Figure 1.14). Because the rash contains virus, VZV can be transmitted to others who are susceptible to chickenpox, although the virus is much less communicable from shingles than varicella lesions.

 Reactivation of VZV in sensory neurons can destroy the cell, causing debilitating pain, which sometimes lasts for months after the rash has healed. Like the occurrence of shingles, this postherpetic neuralgia

![Figure 1.12](image-url)
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Herpes zoster and, in those who develop shingles, reduces the frequency and severity of PHN.

Vaccines for polysaccharide encapsulated bacteria

The virulence of some bacterial pathogens is greatly enhanced by the elaboration of a polysaccharide that evades opsonization. B-cell receptors recognize polysaccharide antigens; however, because they are not presented to T cells in association with major histocompatibility complex class II molecules, the immune response is T-cell independent, immunologic memory is not established, and an anamnestic response is not induced upon reexposure. Some polysaccharide vaccines for infants have proven effective in certain situations; however, because the immune systems of young infants are immature, they only respond with low titers of antibody after exposure to polysaccharide antigens. However, chemically conjugating polysaccharides to proteins was found to create a vaccine against the polysaccharide moiety that recruits T-cells, making the polysaccharide antigen immunogenic in infants younger than 6 months of age and inducing a booster response on reexposure. Indeed, the T-cell dependent B-cell immune response was initially recognized during the development of vaccines for *Haemophilus influenzae*, Type b (Hib) infections in young infants.

People with certain health problems—such as certain immune deficiencies and those who lack a
functioning spleen—are also at increased risk for acquiring invasive disease due to the encapsulated bacteria.

**Haemophilus influenzae, Type b (Hib)**

Hib causes severe bacterial infections, especially among infants 3 months to 3 years of age. In fact, before the vaccine, almost all Hib infections occurred in children younger than 5 years of age. There were more than 20,000 invasive Hib infections in children in the USA per year, about half of whom developed bacterial meningitis. Hib meningitis was essentially always fatal prior to antibiotics. With antibiotic and other treatment, the mortality of Hib meningitis dropped to about 2% but then antibiotic resistance emerged. As many as 25–50% of the children who survived Hib meningitis had permanent brain damage.

In the 1930s, Hib was recognized to be encapsulated and that the lack of a bactericidal antibody appeared to explain why this age group was at increased risk (Figure 1.15). Infants are born with an antibody directed at the capsule of Hib, which is acquired from their mother, but this is lost at about 3 months of age. They begin to reacquire the bactericidal antibody at about 2 years of age. Children with invasive Hib infections, including those with Hib meningitis, were also observed to not respond immunologically to Hib.

In the 1970s, the capsule of Hib was recognized to be polyribosylribitol phosphate (PRP), antibody to which was bactericidal. In addition, PRP was shown to be immunogenic and safe in children over 2 years of age but was not immunogenic in younger children. In 1985, a PRP vaccine was licensed for children older than 18–24 months of age as a means to reduce Hib disease burden in children 2–5 years of age, but this only represented a small proportion of the children who were at risk.

These observations led to the recognition of the T-cell dependent B-cell immune response mechanism and that that pathway in young infants and children did not develop until they reached 18–24 months of age. After PRP was chemically conjugated to carrier proteins, the conjugated PRP was shown to also be immunogenic in young infants. Field trials quickly demonstrated the safety and efficacy of candidate conjugate vaccines leading to licensure in 1987.

The impact of Hib vaccines on Hib has been remarkable both because of its effectiveness at protecting infants and young children but also because of community (herd) immunity (Figure 1.16), which occurs because these vaccines also decrease the nasal carriage of Hib.

Unfortunately, misinformation about the safety of Hib vaccine in recent years has caused some parents to withhold vaccine from their children with serious consequences for their children and their communities. In Minnesota in 2008, for example, there were five cases of invasive Hib in young children, three of whom were unimmunized, and one of whom died. One other child was too young to have been fully immunized while the other had been immunized but had a previously unrecognized immunodeficiency;
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**Streptococcus pneumoniae**

The *S. pneumoniae* are a large group of bacteria consisting of many serotypes that, like Hib, inhabit the nasopharynx of people of all ages. These bacteria (also collectively known as “pneumococci”) are capable of causing infections of the middle ear and sinuses, bacterial pneumonia and meningitis, and bacteremia. They became the chief cause of bacterial pneumonia and bacterial meningitis once there was a vaccine against Hib.

Serious pneumococcal infections are most common in infants, toddlers, smokers, and the elderly, in addition to those with certain immunodeficiencies and those who lack a functioning spleen. African-American and Native American children also have higher rates of invasive pneumococcal disease than do white children.

A multivalent pneumococcal polysaccharide vaccine was licensed in 1977 based on the distribution of strains causing invasive pneumococcal infections in adults. This 23-valent pneumococcal polysaccharide vaccine (PPS23) induces a serotype-specific capsular antibody in individuals over 2 years of age and has been employed to immunize older adults who are at increased risk of invasive pneumococcal disease (IPD) and those with chronic medical conditions (such as those with immunodeiciencies, chronic lung disease, diabetes, chronic heart disease, following a splenectomy, or after renal transplantation). The antibody response wanes rapidly following primary immunization, and although revaccination does reinstate antibody, there is no “booster response” and antibody titers are lower than primary immunization due to immune tolerance. For these reasons, and because PPS23 is not effective at protecting young infants from IPD, a heptavalent pneumococcal conjugate vaccine (PCV7 vaccine), containing the seven most common pneumococcal serotypes that cause invasive infections in children in North America, was licensed in the USA and recommended for routine use in infants in 2000.

PCV7 given to young children dramatically reduced the rates of IPD, otitis media, and nasal carriage of the vaccine serotypes among all age groups, including the immunocompromised and older individuals (Figure 1.16). Both of these latter two children should have been protected by community (herd) immunity.

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PCV7 proved to be a cost-effective vaccine because of the disease it prevents in young children but also because it provided herd immunity protection to their family members and the communities in which they lived (Table 1.5). However, while the PCV7 vaccine reduced IPD caused by the seven most common types causing infection in children, there are additional pneumococcal types that can also cause serious infections in children. Indeed, surveillance suggested that there was starting to be an increase in disease among children aged younger than 5 years due to these nonvaccine serotypes, some of which were antibiotic resistant.

Because PCV7 immunization of children also protected their family members from those serotypes in the vaccine, broadening the coverage of serotypes in the vaccine became even more desirable.

In 2010, the FDA licensed a 13-valent pneumococcal conjugate vaccine (PCV13), and that vaccine was recommended as a replacement for PCV7 in young children. However, the PPS23 vaccine also continues to be used in adults and older children because it prevents infection from additional pneumococcal serotypes.

**Neisseria meningitidis**

*Neisseria meningitidis*, or the meningococcus, is a group of encapsulated bacteria that can cause life-threatening
infections of the bloodstream, bacterial meningitis, or both. \textit{N. meningitidis} can kill children, adolescents, and young adults within hours despite early diagnosis and the use of effective antibiotics. Serious complications occur in 11–19\% of survivors, including deafness and other neurologic impairment as well as purpura and shock that may lead to gangrene and amputation of limbs (Figure 1.18). Because these bacteria are also communicable, the occurrence of a case of disease in schools is very upsetting to communities.

At least 13 serogroups of \textit{N. meningitidis} have been identified, but almost all invasive disease is caused by 1 of 5 serogroups: A, B, C, Y, and W-135. The relative importance of each serogroup depends on the geographic location, as well as other factors, such as age and crowding. For example, serogroup A is a major cause of disease in sub-Saharan Africa but is rarely isolated in the USA, whereas serogroup C has been dominant in the UK and serogroup B in New Zealand.

Large outbreaks of meningococcal disease occur in sub-Saharan Africa during the dry season (December through June) and among travelers to Mecca during hajj. However, epidemics have not occurred in the USA since the 1940s, although outbreaks continue to occur sporadically. With major reductions in the frequency of Hib and pneumococcal infections, \textit{N. meningitidis} has now become a major cause of invasive bacterial infections in the USA. Approximately 2,600 cases of meningococcal meningitis occur in children younger than 5 years old.

Meningococcal disease in the USA occurs most frequently among children younger than 2 years of age; another disease peak occurs between 15 and 24 years of age. In addition, military recruits and first-year college students, especially those living in dormitories, also have an elevated risk for meningococcal disease. Finally, close contacts of a person with meningococcal infection have a higher risk of infection, sufficient to warrant that some of these persons may be given antibiotics to prevent infection, depending on the type of exposure.

The first monovalent (group C) polysaccharide vaccine was licensed in the USA in 1974, and a quadrivalent polysaccharide vaccine against serogroups A, C, Y, and W-135 (MPS4) was licensed in 1978, which was used for individuals who were at increased risk from invasive meningococcal disease.

A quadrivalent conjugate vaccine (MCV4) was licensed in the USA in 2005 and recommended for routine use among adolescents at 11–12 years of age with a booster dose at 16. The vaccine is also recommended for others at increased risk from meningococcal disease, including those who work with the organisms (such as clinical microbiologists), travelers to hyperendemic or epidemic areas, adolescents with HIV infection, and those with complement immunodeficiencies or functional or anatomic asplenia.

Prior to US licensure of the MCV4 vaccine for children ages 11 to 12, older adolescents, and young adults, the incidence of meningococcal disease was at its nadir of 0.35 per 100,000 in the USA, although it varied from 0.5 to 1.5 cases per 100,000 population over the preceding decades.

Unfortunately, there is no serogroup B vaccine in the USA, which is the most frequent etiology of meningococcal disease in young infants and children, because the structure of the polysaccharide is similar to that of human tissue. With the complete genome of multiple serogroup organisms now available, it is hoped that a vaccine may be feasible by identifying other unrecognized surface proteins that are highly conserved. Currently, one vaccine has been licensed in Europe and another is in phase III trials.

**Vaccines for hepatitis viruses**

Hepatitis is a generic term for liver inflammation. In the late 19th century, it was recognized that a form of hepatitis was transmissible in human lymph used in a smallpox campaign in Germany and blood products were recognized as a source of hepatitis during World
War II after yellow fever vaccine containing human serum as a stabilizer was given to US soldiers. These observations were confirmed by direct inoculation of volunteers. In the 1960s and 1970s two types of hepatitis were distinguished. One was transmissible by the fecal–oral route and had a shorter incubation period (“infectious hepatitis” or hepatitis A) and the other by the percutaneous route with a longer incubation period (“serum hepatitis” or hepatitis B). Presently, five viruses (hepatitis A to E) are recognized as causing hepatitis. There are vaccines available to prevent two in the USA and Europe, and a hepatitis E vaccine has recently been licensed in China.

**Hepatitis B virus vaccine**

Hepatitis B virus (HBV) infection causes subclinical infection, acute hepatitis, fulminant hepatitis, and chronic hepatitis. The age of the individual at acquisition of HBV infection is the single most important factor in determining the clinical manifestation of infection as well as the development of chronic infection. Younger individuals are the least likely to have clinical illness but have the greatest likelihood of chronic hepatitis B infection.

Persons with chronic HBV infection (also called “chronic carriers”) are usually asymptomatic and often unaware that they are infected. About 5% of adults and 90% of newborns who are infected will develop chronic HBV infection. Approximately 25% of chronic HBV carriers die prematurely from chronic liver disease or hepatocellular carcinoma. Annually in the USA, 3000–4000 persons die from cirrhosis and another 1000–1500 from liver cancer due to HBV.

In the USA, HBV is transmitted most frequently by perinatal transmission from infected mothers to their newborns at birth, by sexual contact, by percutaneous exposure to body fluids (such as serum, saliva, semen, and vaginal fluid), or by nonsexual person-to-person contact.

The detection of an antigen in the blood of Australian aborigines in 1965—now known to have been a marker for hepatitis B surface antigen (HBsAg)—quickly led to initial trials of boiled serum as a potential vaccine. Initial plasma-derived vaccines, licensed in the USA in 1981, were quickly supplanted after the elucidation of the genomic sequence of HBV, including sequencing of the HBsAg. Recombinant HBsAg vaccine, manufactured in yeast, was licensed in the USA in 1986.

Initial HBV vaccine interventions in the USA between 1981 and 1991 targeted the highest risk groups of acquiring HBV infection by screening mothers for HBsAg (in order to begin immunization of their infants in the nursery and to give them hepatitis B immunoglobulin [HBIG]) and by attempting to identify those with risk factors. Unfortunately, many with risk factors (such as heterosexuals with contact with infected persons; those who have had multiple sexual partners or whose partner has had multiple sexual partners; intravenous drug users; and men who have sex with men) either did not know that they had a risk factor, were hard to reach, or denied having a risk factor.

In 1991, the vaccination recommendation was expanded to include immunization of all newborn infants for the following reasons:

- Universal immunization of children has proven to be the most effective immunization strategy
- Approximately 30% of people who get HBV infection do not have any identifiable risk factors, including children
- HBV infection of children of all ages leads to an increased risk to develop chronic HBV infection

In 2005, HBV vaccine recommendations were expanded further to include the following:

- Routine infant hepatitis B vaccination to begin at birth, before hospital discharge
- Implementation of enhanced programs to detect perinatal HBV infection
- Routine immunization of all previously unvaccinated children and adolescents
- Identification and vaccination of previously unvaccinated adults who were at increased risk for infection by virtue of being in settings where a high proportion of adults are likely to have a risk factor for HBV (such as incarcerated persons)

Many countries that have instituted routine HBV immunization of infants, children, and adolescents have begun reporting declines in HBV infections and declines in HBV-related liver disease. In the USA, a number of states have also begun to report similar outcomes.
Hepatitis A vaccine

Hepatitis A is caused by hepatitis A virus (HAV), a picornavirus that causes infection that is spread primarily by the fecal–oral route, particularly in regions with poor sanitary conditions. Children are the major sources of infection, being infected at an early age in developing countries. They usually have asymptomatic infection but they can shed the virus in their stool for long periods of time. Older children and adults usually develop symptoms that include fever, weakness, nausea, abdominal pain, dark urine, and yellow eyes and skin that lasts less than 2 months in most individuals, although as many as 10–15% will have illness lasting up to 6 months.

In the pre-vaccine era in the USA, there were 125,000–200,000 symptomatic cases and 70–100 died, most over the age of 40 years. About one third of the hepatitis A cases in the USA occurred in children 5 to 14 years of age. The lowest rate of infection was in adults older than 40 years of age.

In developed countries, outbreaks sometimes occur when many people have eaten from the same HAV-infected food source. In recent years, international travel has become a major source of HAV outbreaks. However, almost half of people who acquire HAV infection have no identifiable risk factor.

In the USA, hepatitis A disease occurs in community-wide outbreaks, with infection being transmitted from person to person in households and extended family settings. Infected individuals are most likely to spread HAV during the 2-week period before they know they are infected. Since most infected preschool children show no symptoms of HAV infection, they often unknowingly spread the virus to others.

Before vaccine, an interesting observation was that the rates of HAV infection and disease were much greater in some areas of the country than others. As a consequence, the hepatitis A vaccine was introduced incrementally first for children living in communities with the highest rates of disease (1996) and then for children living in states or communities with consistently elevated rates of infection (1999). The impact of immunization with hepatitis A vaccine was a dramatic decline in the rates of disease and a sharp reduction in the groups with the highest risk of infection: American Indians and Alaska Natives. Rates of hepatitis A infection are now similar in most areas of the USA (Figure 1.19). As a consequence, hepatitis A vaccine

![Figure 1.19](image_url)

has now been recommended for all children in the USA who are 12–23 months of age in order to eliminate HAV transmission nationally.

Because international travel represents such an important source of infection in the USA, families should be immunized against HAV 4 weeks before an internationally adopted child enters the household or before they embark on international travel, although travelers to Australia, Canada, western Europe, Japan, and New Zealand are at no increased risk than individuals residing in the USA. If there is insufficient time to assure immunity to HAV (at least 4 weeks), prospective parents should discuss with their health professional whether they and other family members should receive immunoglobulin prophylaxis.

Vaccines for human papillomaviruses

Human papillomaviruses (HPVs) are a group of more than 120 serologically different viruses (termed “types”). Some HPV types are spread by casual skin-to-skin contact with another person; for example, type 1 causes plantar warts on the feet and types 2 and 3 cause warts on the fingers. Others are acquired by intimate sexual contact. Approximately 40 HPV types are primarily sexually transmitted from person to person (for example, genital–genital contact, oral–genital contact, and sexual intercourse), infecting the oral, anal, or genital areas of both men and women. Genital HPV infections are very common: 25% of females have been infected with genital HPVs by 15–19 years of age, 45% by 20–24 years of age, and 70–80% by 50 years of age.

The US Centers for Disease Control and Prevention (CDC) estimates that 6.2 million Americans get a new genital HPV infection each year. Sexually active adolescents and young adults are most likely to acquire genital HPV infection. Genital HPV infections are often acquired within a few months after beginning sexual activity. The prevalence declines with age after 25 years, but increases again in women about the time of menopause. Genital infection with more than one type of HPV is common.

The vast majority of people recover from genital HPV infections uneventfully. Most genital HPV infections cause no symptoms and are cleared by the immune system within a few weeks or months. However, some people develop persistent genital HPV infection. Persistent infection with nononcogenic types of genital HPV can lead to genital warts in some people. Thus, types 6 and 11 are responsible for more than 90% of the 250,000 cases of genital warts in the USA. While it is rare, these types may also spread from mother to infant during delivery and can cause warts in the upper respiratory tract (throat, larynx) of the child. Persistent infection with “high-risk,” oncogenic genital types of HPV can lead to precancerous changes that, in turn, can lead to carcinoma in situ, which may progress to invasive cancer. Types 16 and 18 and other high-risk types may cause abnormal Pap tests and cervical cancer in women, as well as a number of other cancers in both men and women. Although there are a number of other risk factors for cervical cancer, being infected with a high-risk type HPV appears to be a necessary factor for cervical cancer development. High-risk HPV infections are also thought to cause 85% of anal cancers, 50% of other anogenital cancers, 20% of cancers of the throat and mouth, and 10% of cancers of the larynx and esophagus. Cancer registry data have shown an annual 1% increase in oropharyngel and a 3% increase in anal cancers that are genital HPV associated.

A quadrivalent HPV recombinant vaccine (HPV4) containing vaccine-like particles consisting of the L1 external protein from HPV types 6, 11, 16, 18 was licensed for use in females in 2006, and a similar bivalent vaccine containing HPV types 16 and 18 (HPV2) was licensed in 2009. In 2009, HPV4 was also licensed for the prevention of warts in males and, in 2010, for the prevention of anal cancers in both males and females. Both vaccines have proven effective at preventing HPV infections of the specific HPV types contained in the vaccines and, therefore, prevent precancers and cancers due to HPV types 16 and 18. HPV4 has also been shown to prevent genital warts due to HPV 6 and 11 in both males and females.

In 2011, routine vaccination with HPV4 was recommended for all children 11–12 years of age as a three-dose series, although the vaccination series can be started in children as young as 9 years of age. Catch-up HPV4 vaccination has also been recommended for males 13 through 21 years of age and for females 13–26 years of age. Men who have sex with men should be immunized through 26 years of age. The vaccine is also licensed for use in males through 26 years of age and women through 45 years of age.
The history of vaccine development and the diseases vaccines prevent

Influenza

Widespread epidemics of respiratory disease—presumably influenza—have been documented for hundreds of years. In the 19th century it was mistakenly thought that influenza was caused by *Haemophilus influenzae* because of its detection in lungs of people who had died with pneumonia associated with these epidemics. However, when influenza viruses were isolated in the 1930s, it was correctly proven that these were the causative agents.

Influenza viruses are classified by the types of nucleoprotein and matrix protein. There are three major types of influenza virus, termed A, B, and C. Human infections are largely caused by influenza A and B viruses. Sporadic cases of influenza C, a pathogen largely of swine, occur but have not been associated with epidemics.

Influenza viruses replicate in ciliated columnar epithelial cells with destruction of the cells. Viremia is rarely demonstrable. Infection leads to both humoral and cellular immunity, but antibody titers to the surface glycoprotein, hemagglutinin (H), correlate with protection.

Most persons infected with influenza virus shed virus in their respiratory secretions for 4 or 5 days, although children—who shed more virus than adults—usually shed virus for up to 2 weeks; immunocompromised individuals may shed virus for months. Influenza virus is spread by coughing and sneezing but the hands are also an effective means of transmission person to person.

Seasonal Influenza

- Causes annual epidemics
- Is highly infectious with a 1–5 day incubation period
- Severity of illness depends on prior influenza virus immune experience, health, and age
- May cause no symptoms in 30–50% of those infected by the virus
- Symptomatic disease: abrupt onset of fever muscle aches, sore throat, cough and headache
- Many school days (and caregiver work days) lost
- Can trigger life-threatening complications:
  - In an average year, 114,000 hospitalizations and approximately 20,000 deaths in the USA
- The most common vaccine preventable disease in the USA

Influenza Virus Infections

<table>
<thead>
<tr>
<th>Influenza A</th>
</tr>
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<tbody>
<tr>
<td>• Moderate to severe illness</td>
</tr>
<tr>
<td>• Affects all age groups</td>
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<tr>
<td>• Infects animals and humans</td>
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<tr>
<td>• Associated with seasonal epidemics</td>
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<tr>
<td>• Associated with pandemics</td>
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<tr>
<th>Influenza B</th>
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<tr>
<td>• Similar illness</td>
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<tr>
<td>• Primarily affects children</td>
</tr>
<tr>
<td>• Infects humans only</td>
</tr>
<tr>
<td>• Aspirin-associated Reye’s Syndrome*</td>
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<th>Influenza C</th>
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<tr>
<td>• Similar illness</td>
</tr>
<tr>
<td>• Infects primarily pigs</td>
</tr>
<tr>
<td>• Humans infected sporadically</td>
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*An illness in children of encephalopathy and fatty degeneration of the liver, often fatal.

Influenza Complications

Most common among
- Older adults
- Those with chronic health problems such as asthma, lung disease (including smoking), obesity
- Children younger than 5 years of age (especially younger than 2)
- Pregnant women

Complications
- Bacterial pneumonia, sinusitis, otitis media
- Encephalitis in children
- Rhabdomyelitis in adults (rare)
Children spread the virus rapidly both within families and among themselves. Because many people (30–50%) are asymptomatic—or because they work while ill—health providers also frequently transmit virus to the most vulnerable persons in society.

Influenza illness onset is abrupt with fever, myalgias, which often causes prostration; chills; anorexia; and cough; it usually lasts about 7 days. In very young children the degree of fever and the child’s irritability will often lead to hospitalization. In people with medical problems and in those over 65 years of age serious complications—mostly bacterial pneumonia—occur more frequently and may be fatal. In the USA, influenza is the most common cause of vaccine-preventable deaths, accounting for an average of approximately 24,000 deaths per year, mostly among those greater than 65 years of age.

Influenza A viruses are further subtyped according to the antigenic properties of the surface proteins—there are 18 types of hemagglutinin (H) and 11 types of neuraminidase (N). Fortunately, not all types of H and N are capable of infecting humans. Presently, influenza A types H1N1, H1N2, H3N2, and influenza B viruses are circulating in the population. Human influenza viruses are customarily identified by region of isolation, the year of isolation and the isolate number as well—such as A/Perth/16/2009 (H3N2) and B/Brisbane/60/2008.

Influenza viruses, especially influenza A viruses, cause annual epidemics, which in temperate climates occur in the autumn and winter. They are “promiscuous” viruses in the sense that during mixed infection of the same cell by two different influenza viruses the segmented single-stranded RNA (8 segments) can rapidly reassort and—without DNA and an associated repair mechanism—the H, a very plastic molecule, can mutate, or “drift,” in response to immunologic pressure. However, the virus is said to have “shifted” when the H of the viruses circulating in the community changes dramatically, for example, from A (H2N2) to (H3N2) as it did in 1967–1968.

Wild waterfowl, which usually do not become ill, are the natural reservoirs of influenza A, transmitting viruses to other animals, including domestic poultry (which may be rapidly killed) and mammals where they may recombine with mammalian influenza viruses to create new strains that may lead to antigenic shift.

When there has been a shift, most of the population is susceptible to infection and a pandemic may ensue, often involving different risk groups and which may occur at different times of the year. Many new strains emerge but pandemics only occur from time to time, usually three or four times a century. The occurrence of a pandemic requires the emergence of a strain to which most everyone is susceptible and a virus that transmits easily person to person. The severity of a pandemic is dependent on the virulence of the pathogen.

In 2009, a new influenza A strain emerged causing the best-studied pandemic in 2009–2010. Due to advances in molecular biology scientists were able to monitor the pandemic in “real-time.” The novel virus contains gene segments from viruses circulating in swine, including the H derived from the 1918 pandemic as shown in Figure 1.20.

The ensuing pandemic caused a higher rate of hospitalizations and deaths among children, pregnant women, and young adults. Of the 99.6% of influenza isolates that year that were influenza A, 99.8% were the pandemic strain, whereas previously circulating seasonal strains accounted for the remainder.

**Influenza vaccines**

To prepare candidate virus strains for vaccine manufacture, various reassortant methods are utilized to rapidly create strains that contain the desirable H and N surface proteins while rendering the strain suitable for multiplication in embryonated chicken eggs to high titer.

Ideally, in the Northern hemisphere, people should receive their annual influenza vaccine from the beginning of October through November each year, prior to the influenza season, which generally peaks during
The history of vaccine development and the diseases vaccines prevent have been prepared in cell cultures, either chick embryo fibroblasts or Madin–Darby canine kidney (MDCK) cells (depending on the country). Cell culture-derived vaccines will reduce the supply limitations imposed by the need for specific pathogen-free embryonated eggs.

Currently in the USA, following viral inactivation with either formalin or β-propriolactone, the virus particles are disrupted by a solvent in order to separate the H and N proteins from the matrix and nucleoproteins, greatly reducing the numbers of febrile and local vaccine reactions that occurred with inactivated whole cell vaccines.

Inactivated influenza vaccines
Influenza vaccines were first licensed in the USA in 1945 as formalin-inactivated virus grown in the allantoic fluid of embryonated chicken eggs. Currently, all influenza vaccine candidate seed strains must be isolated in specific pathogen-free eggs under conditions of documented good laboratory practices. Although most inactivated influenza vaccines in the USA are still grown in eggs, there are several vaccines licensed that have been prepared in cell cultures, either chick embryo fibroblasts or Madin–Darby canine kidney (MDCK) cells (depending on the country). Cell culture-derived vaccines will reduce the supply limitations imposed by the need for specific pathogen-free embryonated eggs.

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Because of the rapid drifting of the H, a new vaccine must be formulated annually. Usually, the vaccines have been formulated to contain three virus strains (H1, H3, and B; trivalent) that are selected as those expected to be the most likely to affect the USA in the upcoming winter. For the 2009–2010 season, there was also a monovalent vaccine prepared that was deployed separately from the seasonal vaccine because the newly recognized pandemic strain appeared after late December through March. However, vaccination later in the season is still considered worthwhile.

The effectiveness of influenza vaccines varies by how good the match is between the H contained in the vaccine and the strains that actually circulate in the population.

In 2010, in an attempt to reduce disease morbidity and mortality, the USA instituted a universal annual immunization policy for everyone older than 6 months of age. Because influenza vaccines are not effective in children younger than 6 months of age, immunization of their caregivers is particularly encouraged.

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Indeed, efficacy trials have demonstrated somewhat broader protection than TIV for influenza virus drift. Because of presumed viral interference, two doses of LAIV are required in children younger than 8 years of age to ensure serologic protection in 96% of recipients.

Because LAIV was associated with an increased risk among asthmatic children and has not been studied in others with medical problems or in older persons, LAIV is only administered to healthy persons 2–49 years of age, depending on the country.

In 2013, a quadrivalent live attenuated vaccine was licensed that contains two A viruses and two B viruses.

**Rotavirus vaccines**

Rotaviruses cause intestinal infection in many species of mammals, including humans, cows, and monkeys. The animal strains are antigenically distinct from those that cause human infection, and they rarely cause infection in humans.

Human rotaviruses infect virtually all children by 3 years of age. The incidence of clinical illness is highest among children 3 to 35 months of age, suggesting that maternal antibodies may initially be protective. Breast-fed infants also generally have less diarrheal disease than non-breast-fed infants.

Rotaviruses are the most common cause of severe diarrhea and dehydration in children. The illness also causes fever and vomiting, which may persist for a week or longer; it can cause persistent infection in immunocompromised people. The immune correlates of protection from rotavirus are poorly understood. However, recovery from rotavirus infection usually does not lead to permanent immunity, although the first infection is usually the most severe. After a single natural infection, most are protected against severe rotavirus diarrhea. Subsequent infections appear to confer progressively greater protection, although recurrent rotavirus infections affect persons of all ages, resulting in either asymptomatic infection or mild diarrhea that may be accompanied by vomiting and low-grade fever.

Most rotavirus infections are mild, but in about 1 in 50 cases, patients develop severe dehydration. Each year in the USA before vaccine, rotavirus infections resulted in 22.5 hospitalizations and 301 emergency
The history of vaccine development and the diseases vaccines prevent... suspensions. In 2010 DNA fragments of porcine circovirus (a single-stranded DNA virus that naturally infects pigs) were detected in one vaccine and then the second vaccine. After extensive review, the FDA determined that it was safe to use both vaccines. Both vaccines are effective against rotavirus gastroenteritis of any severity and both have high efficacy against severe rotavirus gastroenteritis. The vaccines have impacted cases of rotavirus both in the USA (Figure 1.21) and in the developing world (Figure 1.22).

room visits per 10,000 children younger than 3 years of age. That translates to 1 in 150 children being hospitalized and another 1 in 11 who required medical attention in an emergency room or an outpatient clinic for rotavirus infection. Of those with severe rotavirus infection, loss of intestinal disaccharidases often causes secondary milk intolerance. Before vaccine, it was the cause of 20 to 40 deaths in the USA annually; in developing countries, rotavirus leads to an estimated 480,000 to 640,000 deaths each year.

An initial rotavirus vaccine, a tetravalent, reassortant rhesus–human rotavirus vaccine was licensed in 1998. However, after approximately 1 million children had been immunized with that vaccine, the CDC detected an unexpected increase in the number of children who developed intussusceptions—a potentially lethal bowel disease—at a rate of approximately 1 case per 10,000 infants vaccinated (which is about three times more frequently than among unvaccinated children). That vaccine was withdrawn in 1999.

Two additional rotavirus vaccines, a pentavalent human–bovine reassortant vaccine and a monovalent naturally occurring less virulent human strain, were each extensively tested in more than 60,000 children before their licensure in 2006 and 2008, respectively, to be certain that they were not associated with intussusceptions. In 2010 DNA fragments of porcine circovirus (a single-stranded DNA virus that naturally infects pigs) were detected in one vaccine and then the second vaccine. After extensive review, the FDA determined that it was safe to use both vaccines. Both vaccines are effective against rotavirus gastroenteritis of any severity and both have high efficacy against severe rotavirus gastroenteritis. The vaccines have impacted cases of rotavirus both in the USA (Figure 1.21) and in the developing world (Figure 1.22).
Summary

- The history of vaccine development is intimately linked to the evolution of the biologic and medical sciences. Initial vaccines were developed empirically, but as science has progressed so have the technologies used to develop vaccines.
- There have been great successes at the development of vaccines for childhood diseases, which have resulted in huge decreases in the number of cases, such that many of these diseases are rarely seen today.
- New understandings of diseases pathogenesis, modern technologies, and strategies for developing pathogenic insights suggest that the future of vaccinology will lead to new ways to prevent and treat diseases with vaccines.

Further reading