# VACCINOLOGY

## AN ESSENTIAL GUIDE

EDITED BY

Gregg N. Milligan and Alan D.T. Barrett


WILEY Blackwell

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This edition first published 2015 © 2015 by John Wiley & Sons, Ltd.

*Registered office:* John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

*Editorial offices:* 9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

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*Library of Congress Cataloging-in-Publication Data*
Vaccinology : an essential guide / edited by Gregg N. Milligan, Alan D.T. Barrett.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-470-65616-7 (pbk.)
I. Milligan, Gregg N., editor. II. Barrett, A. D. T. (Alan D. T.), editor.
[DNLM: 1. Vaccines–pharmacology. 2. Vaccines–therapeutic use. 3. Drug Discovery. 4. Vaccination. QW 805]
RM281
615.3'72–dc23
2014011447

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Cover images: Vial image: courtesy of Diane F. Barrett. Syringe image: Stock Photo File #5255912. © JurgaR.
Cover design by Andy Meaden

Set in 8.75/12 pt MeridienLTStd-Roman by Toppan Best-set Premedia Limited

1 2015

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# Preface

I remember my grandmother pointing out a large cedar tree near an abandoned homestead that served as a marker for the graves of two young girls that had died of diphtheria sometime in the early 1900s. I've often thought of her story and how different the world was for her when childhood mortality from infectious diseases was so common. Thankfully, the development and utilization of safe and effective vaccines against a number of important pathogens has made a tremendous impact on public health. However, much remains to be done, and vaccines are unavailable against a number of important pathogens that directly or indirectly impact the health and welfare of humanity.

The purpose of this textbook is to serve as a framework for educating the next generation of vaccinologists and is primarily aimed at advanced undergraduate, graduate, veterinary, and medical students. However, anyone with an interest in or desire to become involved in the vaccine development pathway would find this book beneficial. This book comprises 20 chapters that cover all aspects of vaccinology. The book content includes a complete introduction to the history and practice of vaccinology, including basic science issues dealing with the host immune response to pathogens, vaccine delivery strategies, novel vaccine platforms, antigen selection, as well as the important facets of clinical testing and vaccine manufacture. Importantly, determinants of vaccine development including safety, regulatory, ethical, and economic issues that drive or preclude development of a candidate vaccine are also discussed. The book also describes vaccine regulation and clinical testing from a global perspective and examines vaccine development against both human and veterinary pathogens.

Each chapter contains a section of abbreviations used in the text as well as definitions of important terms. Where possible, we have included relevant figures and tables to enhance the chapter text. We have also included textboxes that provide examples or further explanation of important concepts, and a list of "key points" can be found at the end of the chapter as a summary of the important issues covered. Each chapter ends with a "Further Reading" section in which the reader is directed to related published material to provide further details. The index facilitates quick location of topics of interest.

We'd like to thank the many contributors who made this book possible. The book is based on lectures given in a vaccine development pathway course at the University of Texas Medical Branch, and many of the UTMB faculty who participate in the course graciously consented to render their lectures into text. We'd like to especially thank Dr. Martin Myers, Professor Emeritus in the Sealy Center for Vaccine Development, for providing a historical perspective on infectious diseases; Dr. Dirk Teuwen for taking time from his incredibly busy schedule to contribute to the manufacturing and safety monitoring content; and Drs. Caroline Poland, Robert M. Jacobson, Douglas J. Opel, Edgar K. Marcuse, and Gregory A. Poland for their discussion of the political, ethical, social, and psychological considerations involved in vaccine development. We are also deeply indebted to Ms. Sandra Rivas for help with figure preparation, and we express our deepest thanks to Diane Barrett for her artwork on the front cover.

While we have tried to be as inclusive as possible of the most important aspects of vaccine development, we realize that it would take a book many times this size to provide all the pertinent information necessary for this task. We hope to refine as well as update vaccine development information in future editions of this book for the next generation of vaccinologists.

G.N.M.
A.D.T.B.

# 1 The history of vaccine development and the diseases vaccines prevent

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## Abbreviations

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

## 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.

*Vaccinology: An Essential Guide*, First Edition. Edited by Gregg N. Milligan and Alan D.T. Barrett.

**Diseases caused by bacteria and viruses where the name of the organism and the disease is not the same**

**Chickenpox (varicella):** Varicella zoster virus
**Diphtheria:** *Corynebacterium diphtheriae*
**Intestinal tuberculosis:** *Mycobacterium bovis*
**Pertussis ("whooping cough"):** *Bordetella pertussis*
**Q fever:** *Coxiella burnetii*
**Shingles:** Varicella zoster virus
**Syphilis:** *Treponema pallidum*
**Tetanus** ("lockjaw"): *Clostridium tetani*
**Typhoid fever:** *Salmonella typhi*

The vaccine era, however, really began in 1774 with the observation by a farmer named Benjamin Jesty that milkmaids who had had cowpox seemed to be immune to smallpox. He inoculated his wife and two sons about 22 years before Edward Jenner's first inoculation and publication in 1798. At some point in the 19th century, vaccinia virus (a mouse poxvirus) replaced cowpox in the vaccine.

Many lessons were learned from the smallpox vaccine: Initially, the vaccine was pus spread from a person who had been recently immunized to an unimmunized person, but syphilis also was passed this way. It was also recognized that loss of vaccine potency occurred after serial human passage (i.e., the virus changed when it was passed from human to human so that it was no longer immunogenic) so the vaccine began to be prepared in other animals; ultimately cattle were predominantly utilized. An imported batch of vaccine from Japan in the early 1900s caused an epizootic of Q fever (caused by *Coxiella burnetii*) among US cattle, which resulted in new quarantine laws and the creation of the US Department of Agriculture. In the 1920s, the need for standardization of vaccine production led to the designation of "strains" of vaccine viruses, such as the New York Board of Health strain in the USA and the Lister strain in Europe; both so-called strains, however, were a mix of viruses with different phenotypes, including many plaque variants with differing virulence. In 1903, the mandatory immunization of Massachusetts school children with smallpox vaccine in an attempt to protect the public 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

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

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

Adapted from Myers MG and Pineda D (2008). Do Vaccines Cause That?!. I4PH Press, Galveston (with permission).
[a]Centers for Disease Control and Prevention (2011). Summary of Notifiable Diseases—United States, 2009. MMWR: 58(53).
[b]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.
[c]Vaccine-associated in an immunodeficient person.
[d]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.
[e]Children younger than 5 years of age.
[f]Introduced incrementally after licensure in 1995.
[g]Introduced incrementally after licensure in1986.

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.

**Table 1.2** Properties of Infectious Disease Preventive Vaccines

The following are properties of preventive infectious disease vaccines:

- An antigenic stimulus that elicits a specific adaptive immune response that can be recalled upon exposure to a specific agent
- Intentionally delivered
- Usually given to healthy individuals

This classic definition of a vaccine now needs to be enlarged to include therapeutic vaccines, such as:

- Herpes zoster vaccine, which restimulates immunity to varicella zoster virus in order to prevent reactivation of latent virus as shingles
- Cancer vaccines
- Vaccines for addiction

### 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

**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."

Davis, Leroy G (1934). A diphtheria epidemic in the early eighties. *MN History* 15:434–8.
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.

**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.

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

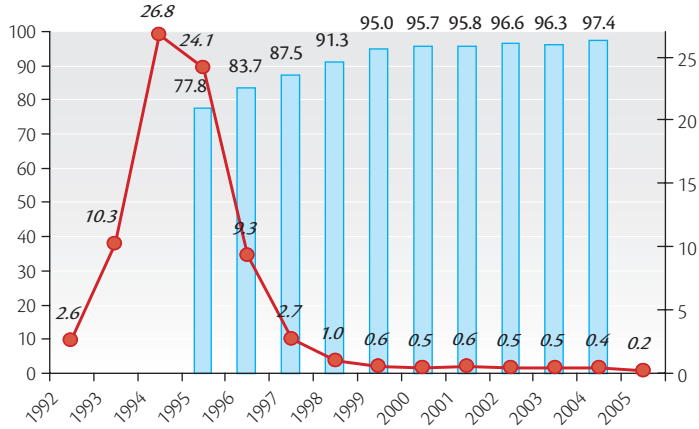


**Figure 1.2** Cases of diphtheria in the Russian Federation per 100,000 population 1992–2006. The bars demonstrate the immunization coverage rate for children as measured by the Department of Sanitation, Russian Federation. Data provided by Dr. Olga Shamshava, 2007.

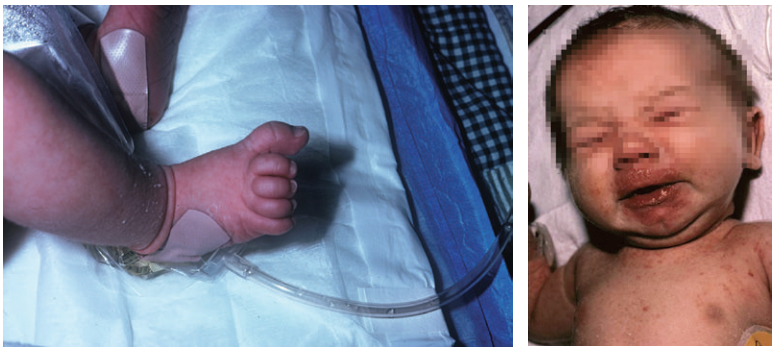

**Figure 1.3** A 7-day-old infant with neonatal tetanus. Intense spasmodic muscle contractions shown as clenching of the feet (left) and of the facial muscles causing risus sardonicus, literally a "sardonic grin" (right). The child's mother had not previously been immunized. © Martin G. Myers

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 early1920s 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).

**Table 1.3** The Impact of Tetanus Toxoid Among US Soldiers

| | Admission for Wounds | Cases of Tetanus | Cases per 100,000 Wounds |
|---|---|---|---|
| World War I | 523,158 | 70 | 13.4 |
| World War II | 2,734,819 | 12[a] | 0.4 |

Adapted from Long AP, Sartwell PE (1947). Tetanus in the U.S. Army in World War II. Bull U.S. Army Med Dept 7:371–385.
[a]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

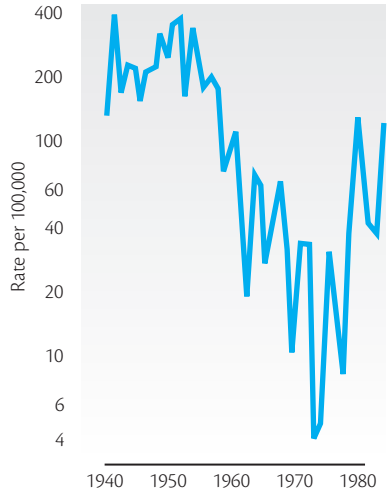


**Figure 1.4** Pertussis attack rate in England and Wales (1940–1982). Reprinted from Cherry JD. (1984). The epidemiology of pertussis and pertussis immunization in the United Kingdom and the United States: a comparative study. Current Probl Pediatr 14(2), 80.

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."
>
> Walter Reed, James Carroll, and Jesse Lazear. 1900. *The Etiology of Yellow Fever. A preliminary note.* Med Rec vi, 796. Quoted by RH Major. Classic Description of Disease, 3rd edition, 5th printing, 1959. Charles C. Thomas, Springfield, Ill.

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

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 viscerotopic 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.

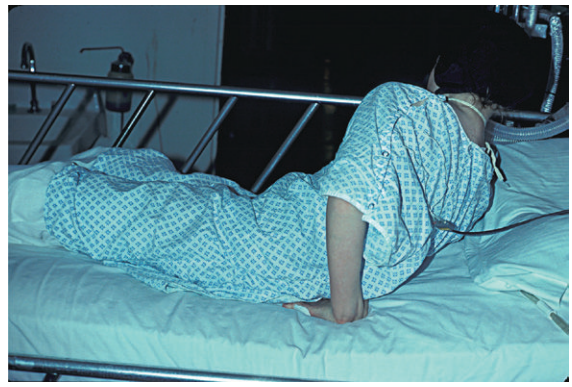

**Figure 1.5** One of the last wild-type poliomyelitis cases in the USA, a 12-year-old girl in 1979, shown here with paralysis of her right leg and arm, the "tripod sign" when trying to sit up, and the epidemiologic link, her Amish cap. Poliovirus, type 1, was recovered from her. © Martin G. Myers

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

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 adventious 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

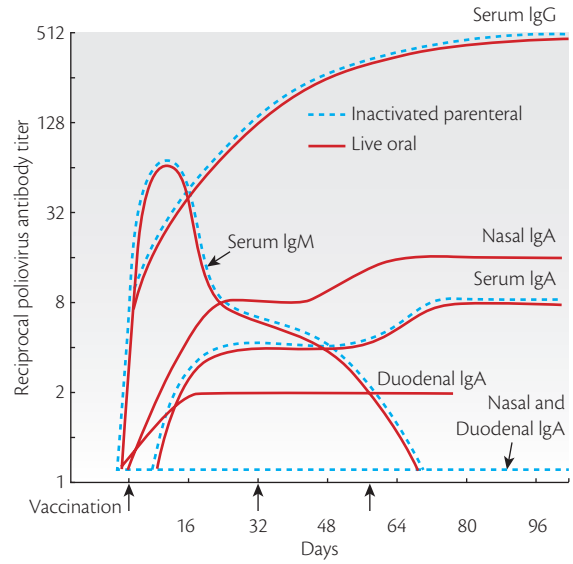


**Figure 1.6** Serum and secretory antibody responses to orally administered, live attenuated polio vaccine and to intramuscular inoculation of inactivated polio vaccine. From Ogra PL, Fishant M, Gallagher MR (1980). Viral vaccination via mucosal routes. Review of Infectious Diseases 2(3); 352–369.

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.

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.

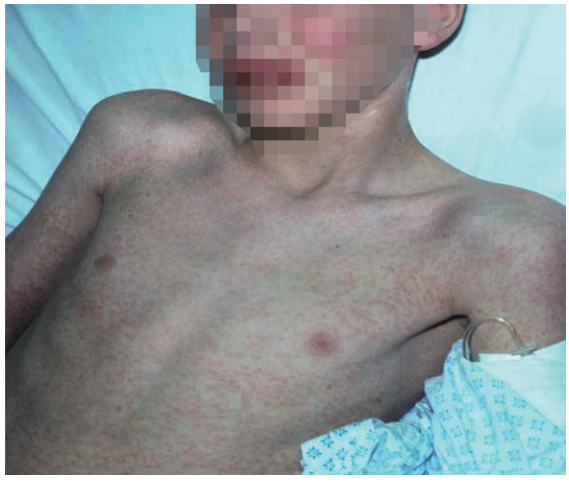

**Figure 1.7** Measles in a boy demonstrating the typical rash of measles. © Martin G. Myers

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 passaged 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