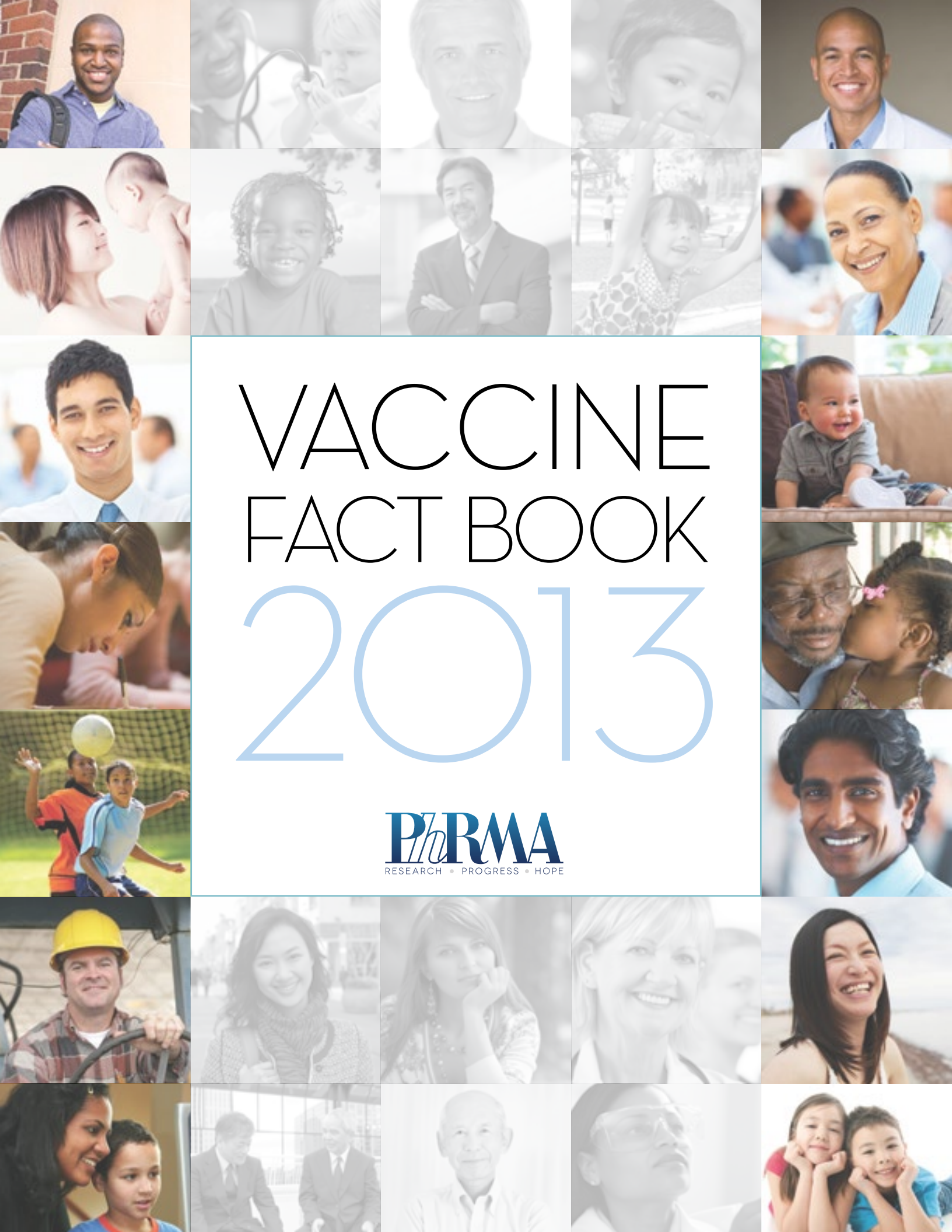


VACCINE FACT BOOK 2013

PhRMA

RESEARCH • PROGRESS • HOPE

Preface

A proverb in many languages is that prevention is better than cure. This idea is central to the development of vaccines, which have transformed human health since the time of Jenner in the late 18th Century. Smallpox has been eradicated, polio largely controlled and measles and rubella have been targeted for elimination. Bacterial meningitis is becoming rare in countries that vaccinate their children. Acquisition of hepatitis A and B can now be prevented, and vaccination against the main viral cause of death due to infantile diarrhea and dehydration is now being disseminated. Reduction of pneumonia is now possible both in infants and in the elderly. Several forms of cancer caused by viruses can now be prevented. All of this and more has been accomplished through the deployment of vaccines, particularly in the last 50 years.

Governments have reasons to promote vaccination: aside from humanitarian concerns, better health of a population lowers medical costs and is associated with broad economic benefits. Therefore, the vaccine industry has been growing in importance and new companies are springing up in developing countries, often in association with western manufacturers. Many governments consider vaccine production to be a precious resource to control epidemics of new types of influenza and other emerging infections. Industrialized as well as poor countries will want their people to have access to preventive measures that make life better and safer.

However, many infectious diseases remain uncontrolled and vaccines for them are needed. Unfortunately, some of these diseases are complex and vaccine development will not be easy. However, new techniques and strategies of vaccine development are being constantly developed and those tools, such as molecular, systems and structural biology are likely to allow progress against the difficult targets. Indeed, basic research is the foundation on which vaccinology is built.

This book seeks to explain to non-specialists what vaccines do, how they are developed, how they are given and what results have been obtained when they are routinely used. It is a dramatic and impressive story, but not well understood by the general public. Yet this story has been unfolding over the last 200 years. Those interested in history may also consult the website historyofvaccines.org.

A book about vaccines for non-scientists is particularly important for developed countries like the United States, in which many diseases have been controlled and therefore their seriousness underestimated when decisions about vaccination are made. If eternal vigilance is the price of liberty, then constant protection by vaccination is the price of good health.

Stanley A. Plotkin, MD
Emeritus Professor of Pediatrics
University of Pennsylvania

Contents

1.1 Definition of Vaccines

What is a Vaccine?

The word "vaccine" originates from the Latin term *Variolae vaccinae* (cow pox) which Edward Jenner demonstrated in 1798 could prevent smallpox in humans. Today the term vaccine applies to all biological preparations, produced from living microorganisms, that enhance immunity against disease and either prevent (prophylactic vaccines) or, in some cases, treat (therapeutic vaccines) disease. Vaccines are administered in liquid form, either by injection, by oral, or by intranasal routes.

Vaccines are composed of either the entire disease-causing micromicroorganism or some of its components. They may be constructed in several ways (See **Figure 1**):

- From living microorganisms that have been weakened, usually from cultivation under sub-optimal conditions (also called attenuation), or from genetic modification, which has the effect of reducing their ability to cause disease;
- From whole microorganisms that have been inactivated by chemical, thermal, or other means;
- From components of the disease-causing microorganism, such as specific proteins and polysaccharides, or nucleic acids;
- From inactivated toxins of toxin-producing bacteria;
- From the linkage (conjugation) of polysaccharides to proteins (this increases the effectiveness of polysaccharide vaccines in young children) (See **Figure 2**).

Examples of each type of vaccine are shown in **Table 1**.

Type of vaccine	Examples
Live-attenuated	Measles, Mumps, Rubella, Varicella zoster
Inactivated	Hepatitis A, Influenza, Pneumococcal polysaccharide
Recombinant sub-unit	Hepatitis B
Toxoid	Tetanus, Diphtheria
Conjugate polysaccharide-protein	Pneumococcal, meningococcal, *Haemophilus influenzae* type b (Hib)

TABLE 1. EXAMPLES OF VACCINES BY TYPE

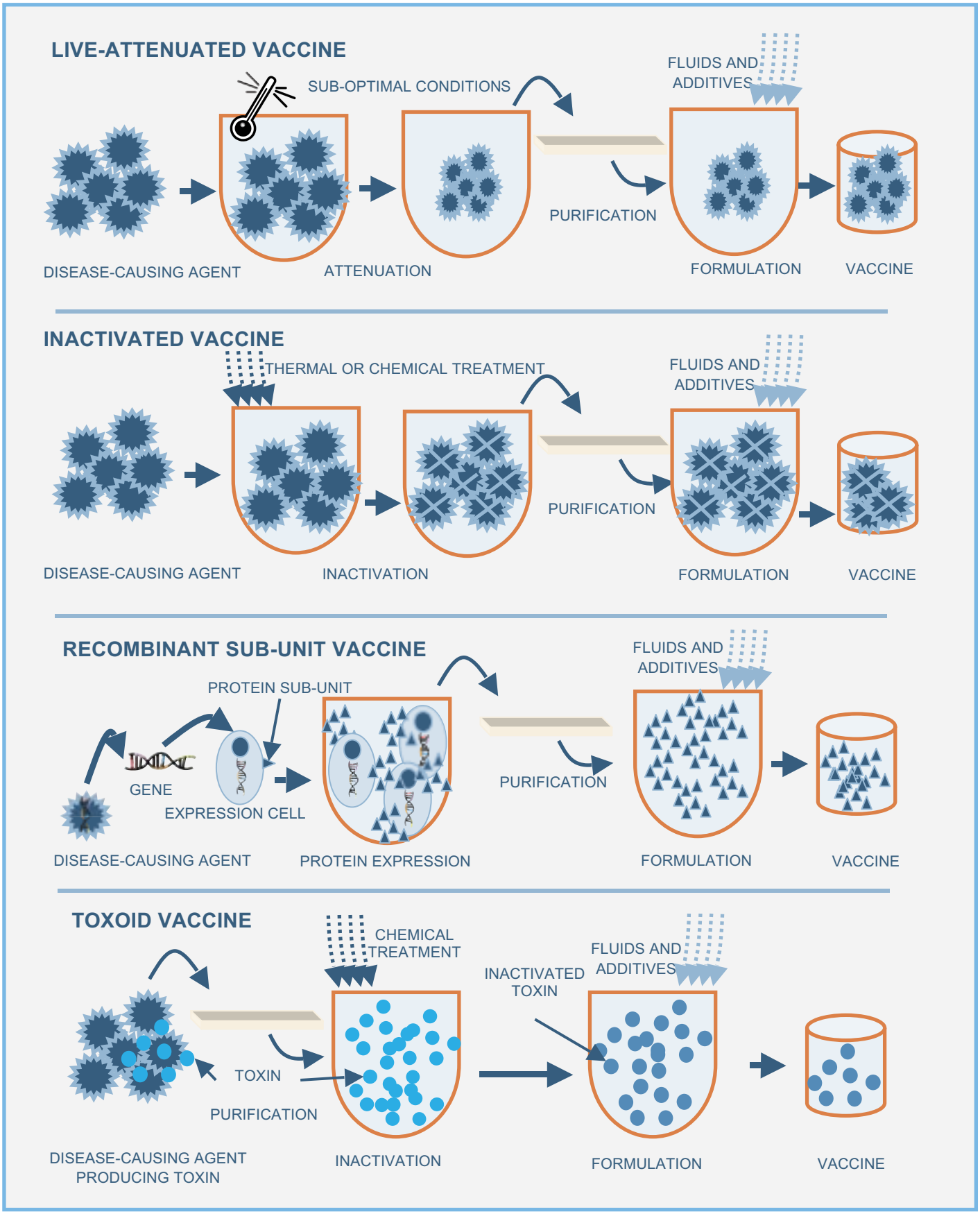


FIGURE 1: TYPES OF VACCINE CONSTRUCTS

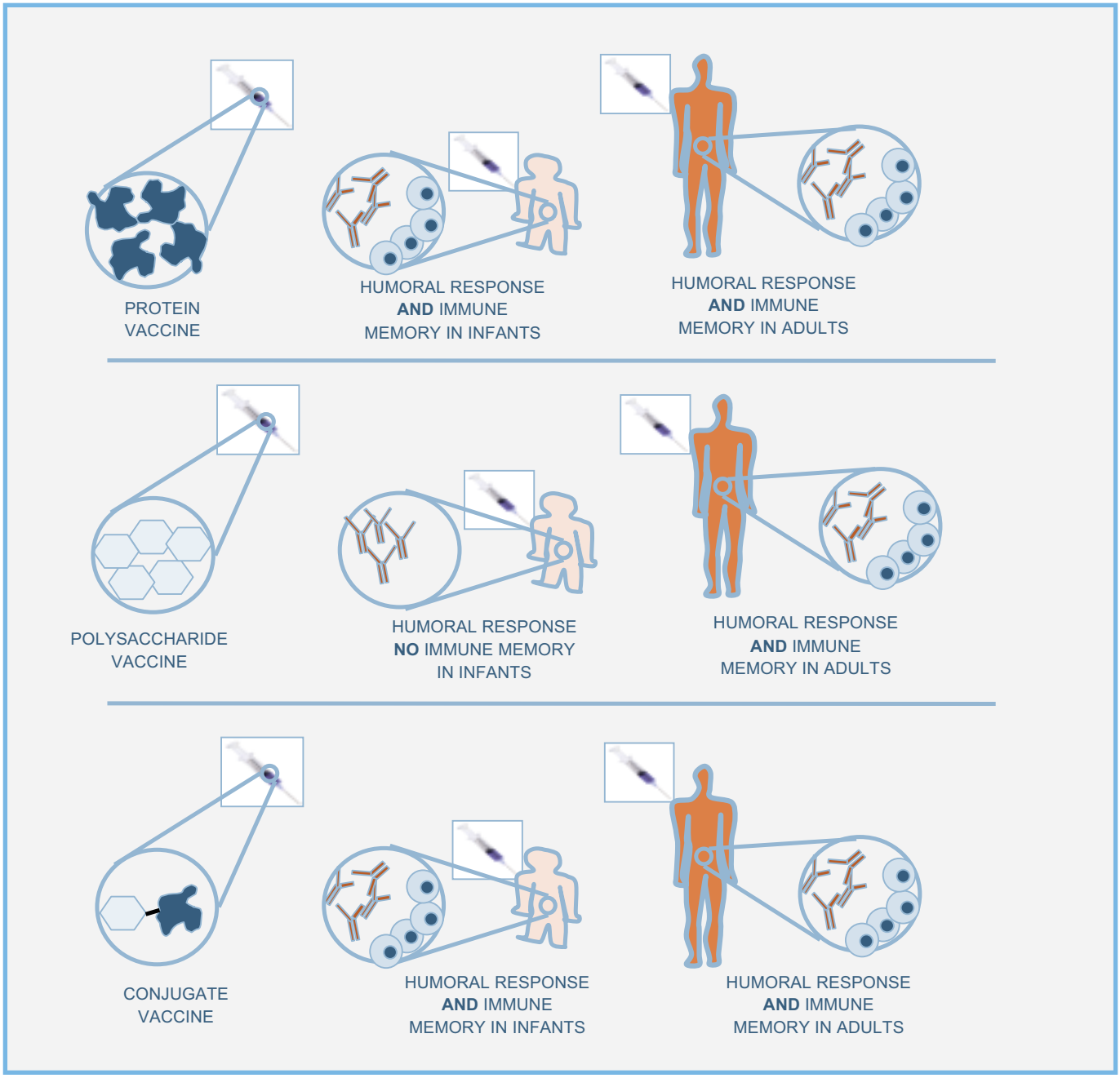


FIGURE 2: CONJUGATION OF POLYSACCHARIDES TO PROTEINS INCREASES THE EFFECTIVENESS OF POLYSACCHARIDE VACCINES IN YOUNG CHILDREN

In addition to combining several serotypes of a disease-causing microorganism in a single vaccine (e.g. 13-valent pneumococcal conjugate vaccine), vaccines against different disease-causing microorganisms can be combined to provide protection against several different diseases. These combination vaccines may contain different types of vaccines. Combination vaccines against different diseases such as diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), Hepatitis B, and polio, are commonly used in childhood immunization schedules. These vaccines incorporate both viral and bacterial vaccines and contain toxoids, purified protein sub-unit vaccine, conjugated polysaccharide vaccine, recombinant protein vaccine, and inactivated viral vaccine respectively (See **Figure 3**).

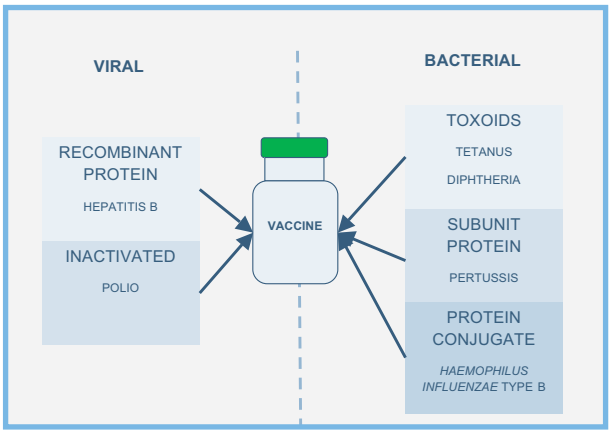


FIGURE 3. COMMON COMBINATION PEDIATRIC VACCINE CONTAINING MULTIPLE ANTIGENS OF MULTIPLE VACCINE TYPES

Vaccines may also contain antigens against several types (or serotypes) of the same disease-causing microorganism, providing protection against each type. Polio and influenza vaccines each protect against three types of virus, and some bacterial vaccines like pneumococcal vaccine protect against up to 23 different serotypes of *Streptococcus pneumoniae.*

A full list of vaccines according to their type can be seen in **Table 4**, Section 1.2.

What Does a Vaccine Contain?

In addition to the bulk antigen that goes into a vaccine, vaccines are formulated (mixed) with other fluids (such as water or saline), additives or preservatives, and sometimes adjuvants. Collectively, these ingredients are known as the excipients. These ensure the quality and potency of the vaccine over its shelf-life. Vaccines are always formulated to be both safe and immunogenic when injected into humans. Vaccines are usually formulated as liquids, but may be freeze-dried (lyophilized) for reconstitution immediately prior to the time of injection.

Preservatives ensure the sterility of the vaccine over the period of its shelf-life. Preservatives may be used to prevent contamination of multi-dose containers: when a first dose of vaccine is extracted from a multi-dose container, a preservative will protect the remaining product from any bacteria that may be introduced into the container. Or, in some cases, preservatives may be added during manufacture to prevent microbial contamination. Preservatives used in vaccines are non-toxic in the amounts used and do not diminish the potency of vaccines. But not all preservatives can be used in all vaccines. Some preservatives will alter the nature of some vaccine antigens. Preservatives commonly used in vaccine formulation are shown in **Table 2.** And some newer vaccines may not contain any preservatives.

Preservative	Vaccines
phenol	Typhoid, pneumococcal polysaccharide
benzethonium chloride	Anthrax
2-phenoxyethanol	Inactivated polio
thimerosal	Multi-dose influenza

TABLE 2. EXAMPLES OF VACCINES WITH PRESERVATIVES[1]

In addition to preservatives, some vaccines contain adjuvants. Adjuvants enhance the immune effect of the vaccine antigen, but do not themselves act as antigens. Aluminum salts are the most commonly used adjuvant for vaccines. A list of commonly adjuvanted childhood vaccines is shown in **Table 3.**

Adjuvanted Vaccine	Type of Adjuvant
Hepatitis A	Aluminum salt
Hepatitis B	Aluminum salt
Diphtheria, Tetanus, acellular Pertussis combinations (DTaP or Tdap)	Aluminum salt
Haemophilus influenzae type b (Hib)	Aluminum salt
Human Papillomavirus (HPV)	Aluminum salt *or* AS04 (aluminum salt and monophospholipid A)
Pneumococcal conjugate	Aluminum salt
Japanese encephalitis	Aluminum salt
H1N1 influenza	MF59 (oil in water emulsion) [one vaccine]

TABLE 3. EXAMPLES OF ADJUVANTED VACCINES[2]

[1] US Department of Health and Human Services (HHS). US Food and Drug Administration (FDA). Thimerosal in vaccines. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM096228#t2

[2] US Centers for Disease Control and Prevention (CDC). Vaccine safety. Frequently asked questions about adjuvants. http://www.cdc.gov/vaccinesafety/Concerns/adjuvants.html. [Accessed on June 7, 2011]

How do Vaccines Work?

When inactivated or weakened disease-causing micromicroorganisms enter the body, they initiate an immune response. This response mimics the body's natural response to infection. But unlike disease-causing microorganisms, vaccines are made of components that have limited ability, or are completely unable, to cause disease (See **Figure 4**).

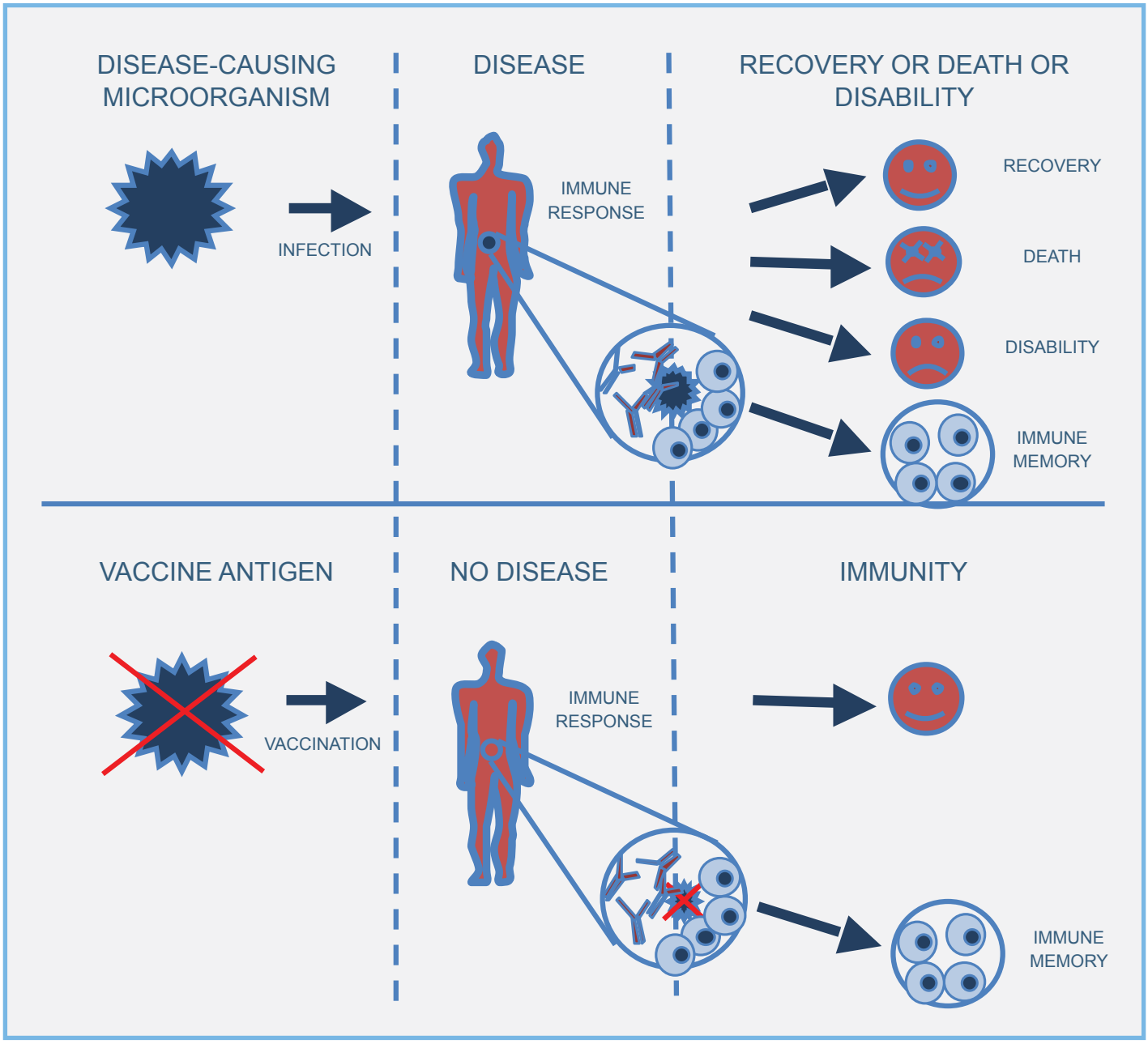


FIGURE 4. COMPARISON OF THE IMMUNE RESPONSE TO A DISEASE-CAUSING MICROORGANISM AND TO A VACCINE

The components of the disease-causing microorganisms or the vaccine components that trigger the immune response are known as “antigens”. These antigens trigger the production of “antibodies” by the immune system. Antibodies bind to corresponding antigens and induce their destruction by other immune cells (See **Figure 5**).

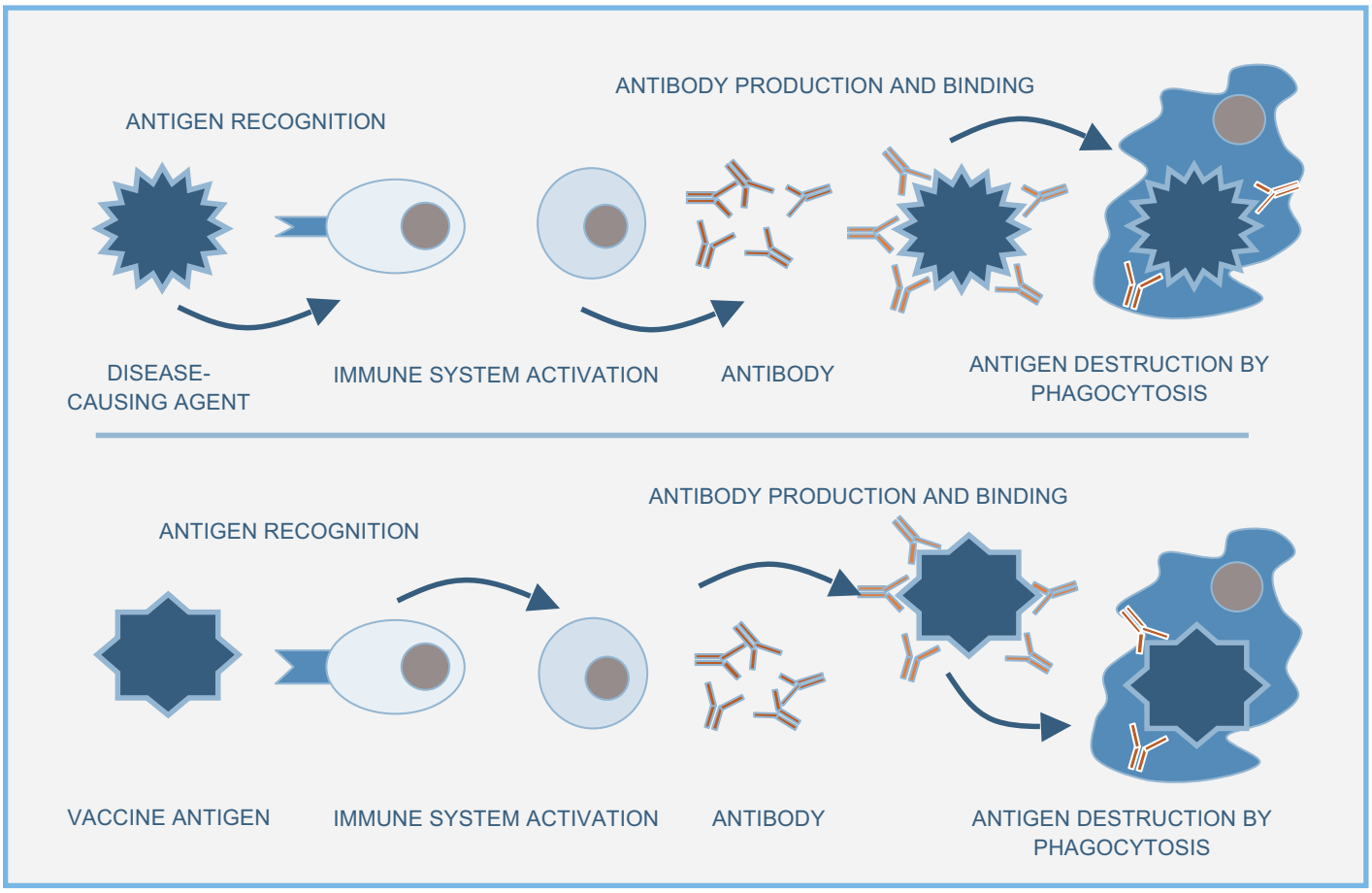


FIGURE 5. ANTIBODY DESTRUCTION OF ANTIGEN

The induced immune response to either a disease-causing microorganism or to a vaccine configures the body's immune cells to be capable of quickly recognizing, reacting to, and subduing the relevant disease-causing microorganism. When the body's immune system is subsequently exposed to a same disease-causing microorganism, the immune system will contain and eliminate the infection before it can cause harm to the body (See **Figure 6**).

The effectiveness and the duration of the protective effect of a vaccine depends both on the nature of the vaccine constituents and on the manner in which they are processed by the immune system (See Section 1.3). Some disease-causing microorganisms, like influenza, change from year to year, requiring annual immunization against new circulating strains.

In very young children, the immune system is immature and less capable of developing memory. In this age group, duration of protection can be very short-lived for some antigens.

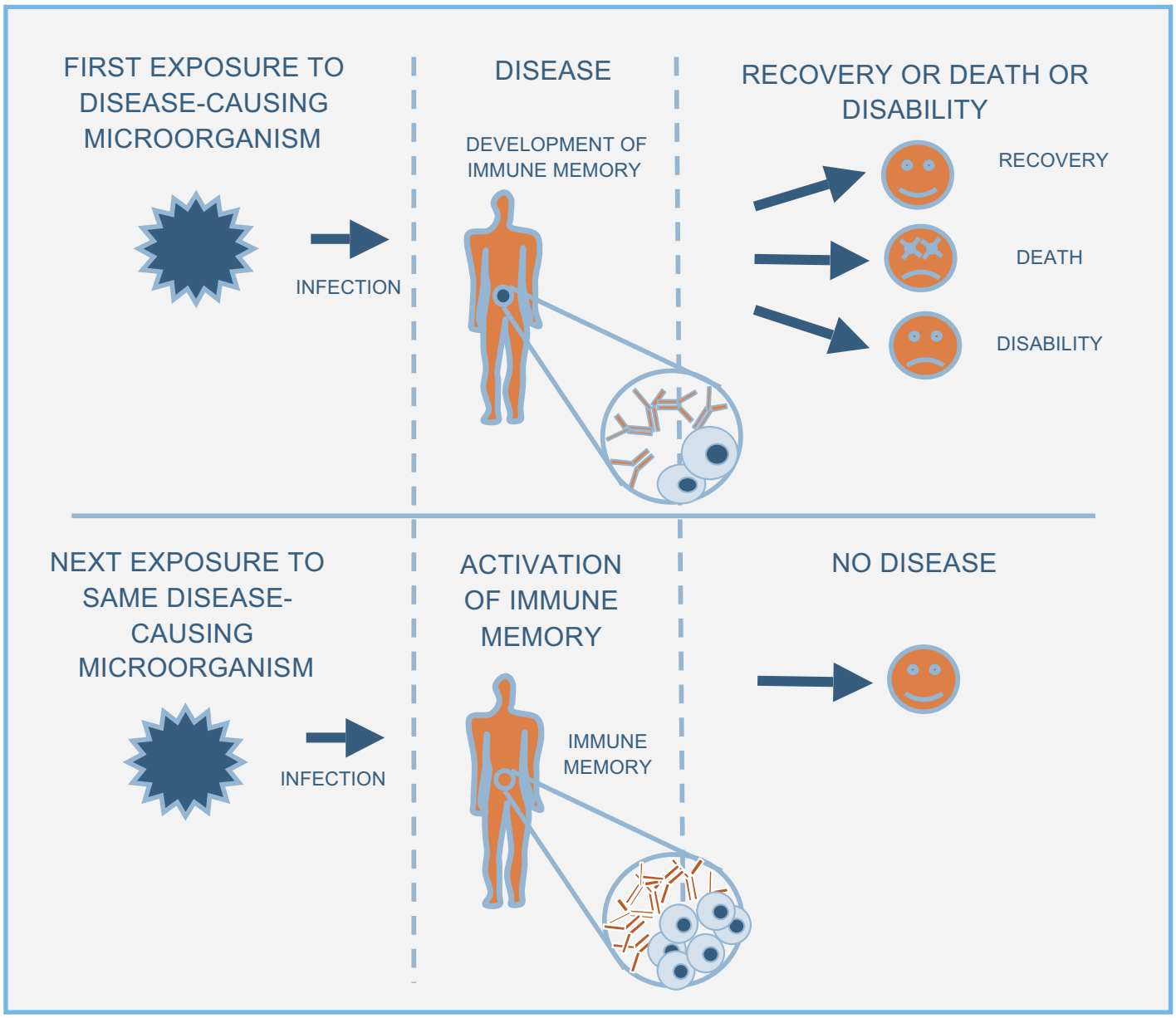


FIGURE 6. COMPARISON OF THE IMMUNE RESPONSE TO A DISEASE-CAUSING MICROORGANISM AND TO A VACCINE

THE HISTORY OF VACCINATION[3]

The first attempts to prevent disease by using the disease-causing toxin itself are reported from 7th century India where Buddhist monks drank snake venom in order to develop immunity against snake bites.

Variolation, the practice of inoculating the dried pustules of smallpox (caused by the Variolae virus) from a sick individual into a healthy individual, to prevent the healthy individual from developing the disease, developed in Central Asia in the second millennium. The practice then spread east to China and West to Turkey, Africa, and Europe.

In 1798, in England, Edward Jenner published the results of his experiments on "vaccination", the practice of inoculating the cowpox virus (closely related to the human smallpox virus), Variolae vaccinae, to prevent smallpox in humans. The term vaccination was derived from vaccinae virus. The practice became widely popularized.

Image 1: Sculpture of Edward Jenner

At the end of the 19th century Louis Pasteur began to apply the concept of vaccination to other diseases. He demonstrated that the harmful nature of disease-causing microorganisms could be weakened (or attenuated) in the laboratory. He first demonstrated the effectiveness of vaccines against chicken cholera and anthrax in animals, before developing his vaccine against rabies for use in humans in 1885.

Image 2: Painting of Louis Pasteur

At almost the same time, in the US, Daniel Elmer Salmon and Theobald Smith, in 1886, demonstrated that vaccines could be produced not just from live microorganisms, but also from killed disease-causing microorganisms. Their discovery would lead to the subsequent development of inactivated vaccines against several human diseases.

In the early 20th century it was discovered that some diseases were caused not by bacteria themselves, but by the toxins that they produced. Inactivated toxins acted like vaccines by providing protection against these toxin-induced diseases. These vaccines are known as toxoids.

By the end of the 20th century, a spurt of innovation led to the development of several new methods of producing vaccines including by recombinant microorganisms, by conjugation of polysaccharides to carrier proteins, and by the assembly of virus-like particles (VLPs).

Photos:
Source L Cranswick http://en.wikipedia.org/wiki/File:Jenner-statue-by-lachlan-mvc-006f.jpg; and http://en.wikipedia.org/wiki/File:Tableau_Louis_Pasteur.jpg

[3] Plotkin SL and Plotkin SA. A short history of vaccination. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.

1.2 Survey of Vaccine-Preventable Diseases

Which Diseases are Vaccine Preventable?

Smallpox was the first vaccine-preventable disease. After Edward Jenner's publication on the use of cowpox to protect against smallpox, the practice of smallpox vaccination became increasingly widespread. But about 100 years would elapse until the development of a second human vaccine, Louis Pasteur's rabies vaccine.

The development of new vaccines then grew exponentially, with several new human vaccines being introduced in the first half of the 20th century, but even more becoming available in the latter half and in the early 21st century. An intense period of innovation at the end of the 20th century led to the development of several new methods of producing vaccines, including the expression of proteins in recombinant microorganisms, the conjugation of polysaccharides to carrier proteins, and the construction of viral-like particles (See **Figure 7**). The rapid growth in vaccine development is expected to result in more new vaccines becoming available within the next decade.

In theory, any infectious disease might be preventable with a vaccine. But a limited understanding of the immune mechanisms involved, and the highly variable nature of the immune response to each specific disease-causing microorganism, have meant that the development of vaccines has so far been limited to a number of viral and bacterial diseases. For some diseases, like AIDS, vaccine development is particularly challenging because the HIV virus escapes the body's natural immune response. Parasitic disease, complex life cycles, or relatively large size, may limit the ability of vaccines to work effectively.

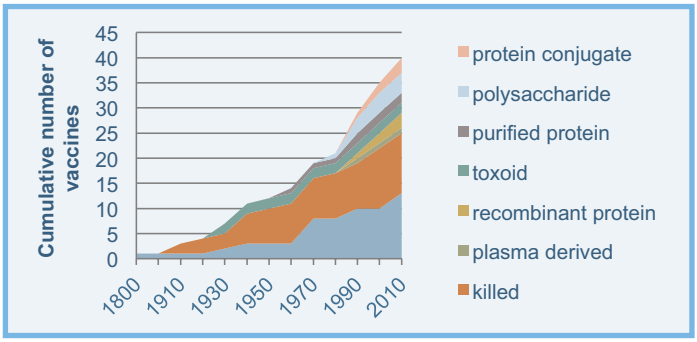


FIGURE 7. CUMULATIVE NUMBER OF VACCINES DEVELOPED SINCE THE FIRST VACCINE IN 1798, BY TYPE

Even when immune mechanisms for specific diseases are understood, there is no guarantee that the same vaccine design strategy can be successfully applied to other similar disease agents. For many years, scientists have been unable to develop safe and effective vaccines against diseases like respiratory syncytial virus (RSV)—a very common childhood respiratory infection—or dengue fever (a mosquito-borne disease that about 2.5 billion people are at risk of catching[4]).

Despite these scientific challenges, safe and effective vaccines have been developed against many diseases over the past 120 years. These are shown in **Table 4.**

Which Diseases are Routinely Prevented in Industrialized Countries?

Over 35 vaccines have been developed, many of which protect against fatal or permanently disabling diseases. Over a dozen diseases are routinely targeted by industrialized countries in pediatric immunization schedules. Additional diseases are targeted in routine adolescent and adult immunization schedules or in schedules for high-risk groups such as the chronically ill. Diseases commonly targeted by immunization programs in industrialized countries are shown in **Table 5**. Other vaccines specific to travelers, or to a geographic region, may also be recommended.

Because of the societal and financial costs of treating and managing vaccine-preventable diseases, the delay in taking up new vaccines may have important social and economic consequences.

[4] WHO. Media center. Dengue and dengue haemorrhagic fever. Fact sheet no. 117. March 2009. http://www.who.int/mediacentre/factsheets/fs117/en/

For some diseases, such as AIDS, vaccine development is particularly challenging because the HIV virus escapes the body's natural immune response.

Vaccine-preventable disease	Type of disease	Type of vaccine	Year developed	Most common severe disease outcomes
Smallpox	viral	live attenuated	1798	disfiguring, sometimes fatal
Rabies	viral	inactivated	1885	always fatal
		inactivated (cell culture)	1976	
Typhoid	bacterial	inactivated	1886	intestinal hemorrhage and perforations, encephalitis, psychosis, abscesses of internal organs, sometimes fatal
		live attenuated	1983	
		polysaccharide	1994	
		protein conjugate	2008	
Cholera	bacterial	inactivated (injectable)	1896	life-threatening dehydration, electrolyte imbalance, sometimes fatal
		inactivated and recombinant protein (oral)	1991	
		inactivated (oral)	1997	
Plague	bacterial	inactivated	1897	seizures, coma, internal bleeding, fatal within four days if not treated
Pertussis	bacterial	inactivated	1914	choking in young infants, rib fractures, hernias, incontinence, ruptured blood vessels, sometimes fatal
		purified protein	1981	
Tuberculosis	bacterial	live attenuated	1921	coughing blood, abscesses of internal organs or bone, meningitis, sometimes fatal
Diphtheria	bacterial	toxoid	1923	choking, heart and kidney failure, facial or swallowing or respiratory paralysis, sometimes fatal
Tetanus	bacterial	toxoid	1926	severe muscle spasms and bone fractures, lock-jaw, respiratory distress, sometimes fatal
Yellow fever	viral	live attenuated	1932	liver damage, internal bleeding, sometimes fatal
Japanese encephalitis	viral	Inactivated	1935	coma, deafness, loss of feeling, emotional disturbances, sometimes fatal
		live attenuated	1988	
Influenza	viral	inactivated	1936	life-threatening pneumonia, worsening of coronary heart disease, extreme muscular fatigue or aches, high fever, sometimes fatal
		live attenuated	2003	
Tick-borne encephalitis	viral	inactivated	1937	permanent neuropsychiatric effects, sometimes fatal
Mumps	viral	inactivated	1948	loss of male fertility, loss of pregnancy, meningitis, pancreatitis, brain infection, deafness
		live attenuated	1967	

TABLE 4. VACCINE-PREVENTABLE DISEASES, VACCINE TYPE, AND YEAR OF VACCINE DEVELOPMENT

Vaccine-preventable disease	Type of disease	Type of vaccine	Year developed	Most common severe disease outcomes
Anthrax	bacterial	protein	1954	blood poisoning, vomiting blood, sometimes fatal
Polio	viral	inactivated	1955	respiratory paralysis, life-long paralysis of limb(s), skeletal deformity, sometimes fatal
		live attenuated	1962	
Measles	viral	live attenuated	1963	diarrhea and severe weight loss in infants, convulsions, pneumonia, ear and brain infections, ulcerations of the eye, sometimes fatal
Rubella	viral	live attenuated	1969	incurable congenital malformations, arthritis
Meningococcal	bacterial	polysaccharide	1971 (US Army) (1981 tetravalent US)	permanent brain damage, seizures, blood poisoning, deafness, respiratory distress, organ failure, sometimes fatal
		protein conjugate	1999 (conj C); 2005 (tetravalent)	
Varicella (chickenpox)	viral	live attenuated	1974	stroke in children, skin infections, pneumonia, liver damage, kidney and heart diseases, brain infections, incurable congenital malformations
Hepatitis B	viral	plasma derived	1981	liver failure, cirrhosis, liver cancer, sometimes fatal
		recombinant protein	1986	
Pneumococcal	bacterial	23-valent polysaccharide	1983	pneumonia, meningitis, ear infections, infections of bone and heart muscle, sometimes fatal
		protein conjugate 7 valent	2000	
		protein conjugate 13 valent	2010	
Haemophilus influenzae type b	bacterial	polysaccharide	1985	meningitis, pneumonia, skin, bone and throat infections, arthritis, sometimes fatal
		protein conjugate	1987	
Hepatitis A	viral	inactivated	1995	protracted illness and loss of productivity, liver failure, sometimes fatal
Herpes Zoster	viral	live attenuated	2005	persistent pain, eye diseases and paralysis and blindness, hearing loss, vertigo, meningitis or brain infections
Rotavirus	viral	live attenuated	2006	severe dehydration, sometimes fatal
Human Papillomavirus	viral	recombinant protein	2006	genital and cervical and oral cancers, genital warts, sometimes fatal
Adenovirus types 4 and 7	viral	live attenuated, oral	2011	febrile acute respiratory disease, pneumonia and death

Bacterial diseases	Viral diseases
Diphtheria	Measles
Pertussis	Mumps
Tetanus	Rubella
Pneumococcal diseases (pneumonia, meningitis, otitis media, and others)	Polio
Haemophilus influenzae type b diseases (pneumonia, meningitis and others)	Influenza A and B
Meningococcal diseases (meningitis and others)	Hepatitis B
Tuberculosis	Chickenpox
	Herpes zoster
	Rotavirus
	Hepatitis A
	Human Papillomavirus diseases (genital/cervical/oral warts and cancers)
	Japanese encephalitis (regional importance)
	Rabies (in at-risk groups)

TABLE 5. DISEASES COMMONLY TARGETED BY ROUTINE IMMUNIZATION IN INDUSTRIALIZED COUNTRIES EXCLUDING DISEASES TARGETED BY TRAVEL VACCINES

Year	Vaccines (all origins) licensed in the US	Vaccines (all origins) licensed in Japan
1971	Measles, Mumps, Rubella	
1976		Japanese encephalitis
1977	Pneumococcal polysaccharide	
1981		acellular Pertussis
1982	Hepatitis B	
1985		Hepatitis B
1986	recombinant Hepatitis B	
1987	conjugate *Haemophilus influenzae* type b; inactivated Polio	Varicella
1988		recombinant Hepatitis B; Measles, Mumps, Rubella; Pneumococcal polysaccharide
1991	acellular Pertussis	
1992	Diphtheria, Tetanus, acellular Pertussis; Japanese encephalitis	
1993	Diphtheria, Tetanus, acellular Pertussis, *Haemophilus influenzae* type b	
1994	Plague	
1995	Varicella; Hepatitis A	Hepatitis A
1996	Combination *Haemophilus influenzae* type b, Hepatitis B (Hib-HepB)	
2000	conjugate Pneumococcal (7 valent)	
2001	Hepatitis A, Hepatitis B	
2002	Diphtheria, Tetanus, Pertussis, Hepatitis B, inactivated polio	
2003	live attenuated Influenza; adult formulation of diphtheria, tetanus, pertussis	
2005	Measles, Mumps, Rubella, Varicella (MMRV); conjugate Meningococcal	Measles, Rubella (MR)
2006	Rotavirus; Human Papillomavirus	
2007		conjugate *Haemophilus influenzae* type b
2010		conjugate pneumococcal; Human Papillomavirus
2011		Rotavirus; inactivated polio
2012		conjugate meningococcal; DTaP-IPV
TOTAL	23	16

TABLE 6. VACCINES LICENSED IN THE US AND JAPAN 1971–2012

1.3 Vaccine Efficacy and Safety

What Impact do Vaccines Have on Diseases?

Vaccines have one of the greatest impacts on public health. Their impact on reducing human mortality is second only to the provision of safe drinking water[5]. Vaccines are provided to individuals to protect them from disease, but they play an even greater role in protecting entire populations from exposure to infectious diseases. Vaccine-preventable diseases that were once prevalent in industrialized countries have virtually disappeared where vaccination has been implemented. In the 20th century, vaccines have reduced the morbidity from vaccine-preventable diseases by as much as 89–100% (See **Figure 8**).

The prevention of disease has had an enormous impact on economic development by limiting the costs of curative care and saving billions of dollars in countries where diseases have been well controlled or eliminated.

Two factors contribute to the ability of a vaccine to control or eliminate a disease

- the effectiveness and the durability of the effect of the vaccine; and,
- the level of vaccination coverage achieved in a given population.

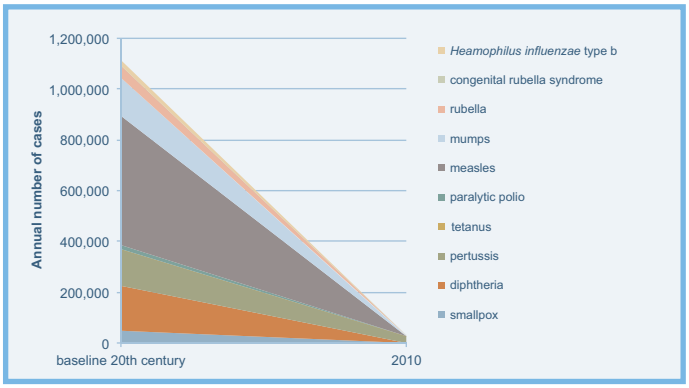


FIGURE 8. IMPACT OF IMMUNIZATION ON THE NUMBER OF ANNUAL CASES OF DISEASE IN THE USA[6,7]

These vary slightly from one country to another, but everywhere they are used licensed vaccines are considered highly effective at preventing disease (See **Figure 9** and **Figure 10**).

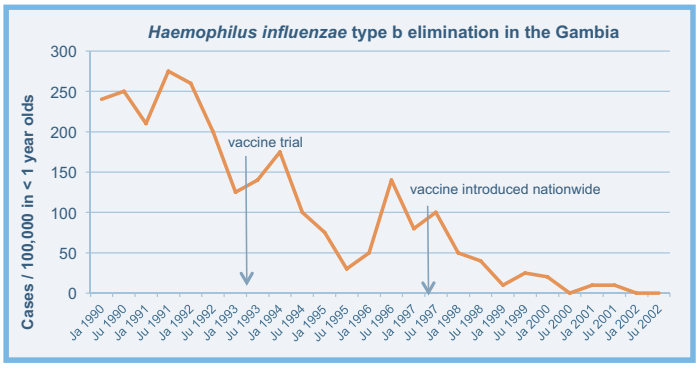


FIGURE 9. IMPACT OF IMMUNIZATION ON HIB DISEASE IN THE GAMBIA (ADAPTED—DATA ARE APPROXIMATE)[8]

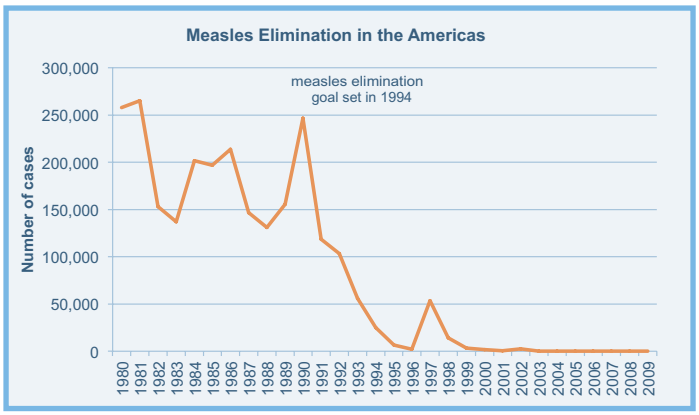


FIGURE 10. MEASLES ELIMINATION IN THE AMERICAS FROM EFFORTS IN IMMUNIZATION[9,10]

[5] Plotkin SL and Plotkin SA. A short history of vaccination. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008

[6] US CDC. Achievement in public health, 1900–1999 impact of vaccines universally recommended for children—United States 1990–1998. MMWR 48:243–248, 1999. http://www.cdc.gov/mmwr/preview/mmwrhtml/000503.htm

[7] US CDC. Summary of notifiable diseases—United States, 2009. MMWR 58 (53): 85–87, May 13, 2011. http://www.cdc.gov/mmwr/pdf/wk/mm5853.pdf

[8] Adegbola RA, Secka O, Lahai G, et al. Elimination of *Haemophilus influenzae* type b (Hib) disease from The Gambia after the introduction of routine immunisation with a Hib conjugate vaccine: a prospective study. *Lancet*. 2005;366:144–50.

[9] Andrus JK and Castillo-Solorzano C. Achieving and sustaining measles and rubella elimination. Partners for measles advocacy annual meeting. Washington DC, July 27, 2010.

[10] Pan American Health Organization. Number of measles confirmed cases in the Americas 1996–2008. http://www.paho.org/English/ad/fch/im/Measles_NumberCases.pdf

What is Vaccine Effectiveness?

Vaccine effectiveness is the reduction in incidence of a disease amongst those who have been vaccinated relative to the incidence in the unvaccinated. Because biologicals are inherently variable, individuals do not respond identically to vaccines. Vaccines may fail to induce immunity in a few individuals. But the most effective vaccines induce a protective immune response in > 95% of individuals.

If a high level of vaccination coverage is achieved with an effective vaccine, disease transmission can be interrupted. When disease transmission is interrupted, even those individuals who were not vaccinated, or who were vaccinated and did not develop immunity, will be protected from disease. This effect is known as herd immunity (See **Figure 11**). Smallpox was eradicated by achieving sufficient immunization coverage to prevent transmission of disease to unvaccinated non-immunes (susceptible).

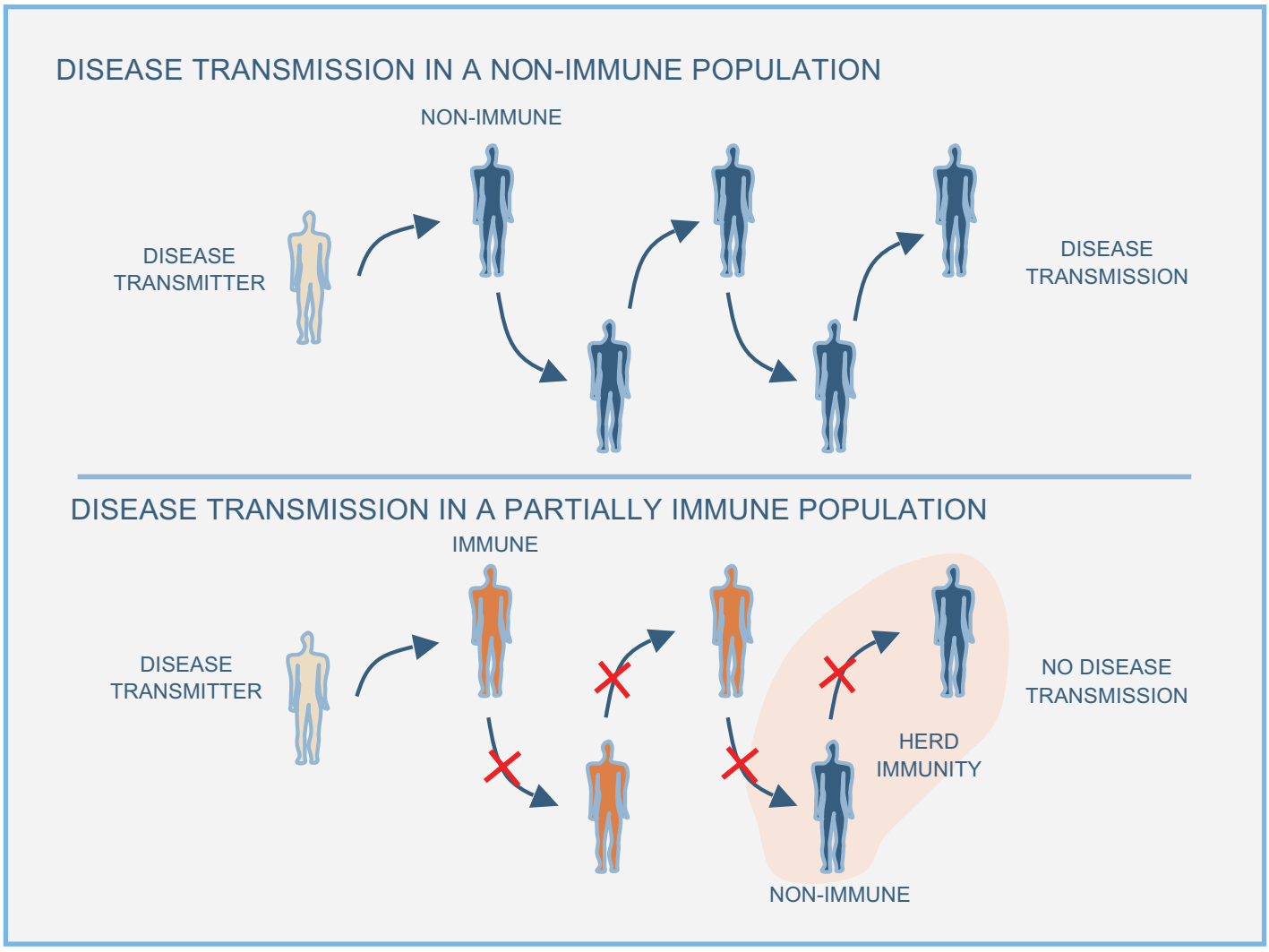


FIGURE 11. HERD IMMUNITY

The level of vaccination coverage required to interrupt disease transmission will depend on:

- the ease with which a disease is transmitted; and,
- the effectiveness of the vaccine at stimulating immunity.

The proportion of immune individuals in a population that will prevent disease from spreading is known as the herd immunity threshold. Each disease has its own herd immunity threshold. The more easily transmitted the disease, the higher the threshold (See **Table 7**). The higher the threshold, the greater the vaccination coverage and vaccine effectiveness required to interrupt disease transmission. Very easily transmissible diseases, like pertusis/whooping cough, can continue to transmit in a community even when vaccination coverage and vaccine effectiveness are very high.

Disease	Herd immunity threshold
Diphtheria	85%
Measles	83–94%
Mumps	75–86%
Pertussis	92–94%
Polio	80–86%
Rubella	80–85%
Smallpox	83–85%

TABLE 7. HERD IMMUNITY THRESHOLD FOR SOME DISEASES[11*]

* When the proportion of immune individuals in a population reaches threshold, the spread of the disease to the non-immune population can be interrupted.

Strategies to interrupt highly transmissible diseases, like measles, may require mass vaccination campaigns or re-immunization strategies to achieve disease elimination goals.

To monitor the impact of immunization programs and to set realistic disease control targets, vaccine policy makers assess how effective vaccines are at preventing diseases in their communities. The commonly used measure of impact is vaccine efficacy (or vaccine effectiveness, when measured under real operational conditions).

Vaccine Efficacy measures the decrease in incidence of a disease in the vaccinated population compared to the incidence of the disease in the unvaccinated population. In epidemiological terms, it is defined as the difference between the Attack Rate of the disease in the Unvaccinated and the Vaccinated relative to the Attack Rate in the Unvaccinated.

The **Attack Rate** is defined as the number of individuals who become infected out of the total number who are exposed to a disease. When categorized into Unvaccinated and Vaccinated groups, vaccine efficacy is calculated as[12]:

$$\text{Vaccine Efficiency} = \frac{(\text{Attack Rate in the Unvaccinated} - \text{Attack Rate in the Vaccinated})}{\text{Attack Rate in the Unvaccinated}} \times 100$$

and where Vaccine Efficiency (VE) is expressed as a percentage (See **Figure 12**).

[11] The US CDC and the WHO. History and Epidemiology of Global Smallpox Eradication. http://www.bt.cdc.gov/agent/smallpox/training/overview/pdf/eradicationhistory.pdf

[12] http://en.wikipedia.org/wiki/Vaccine_efficacy

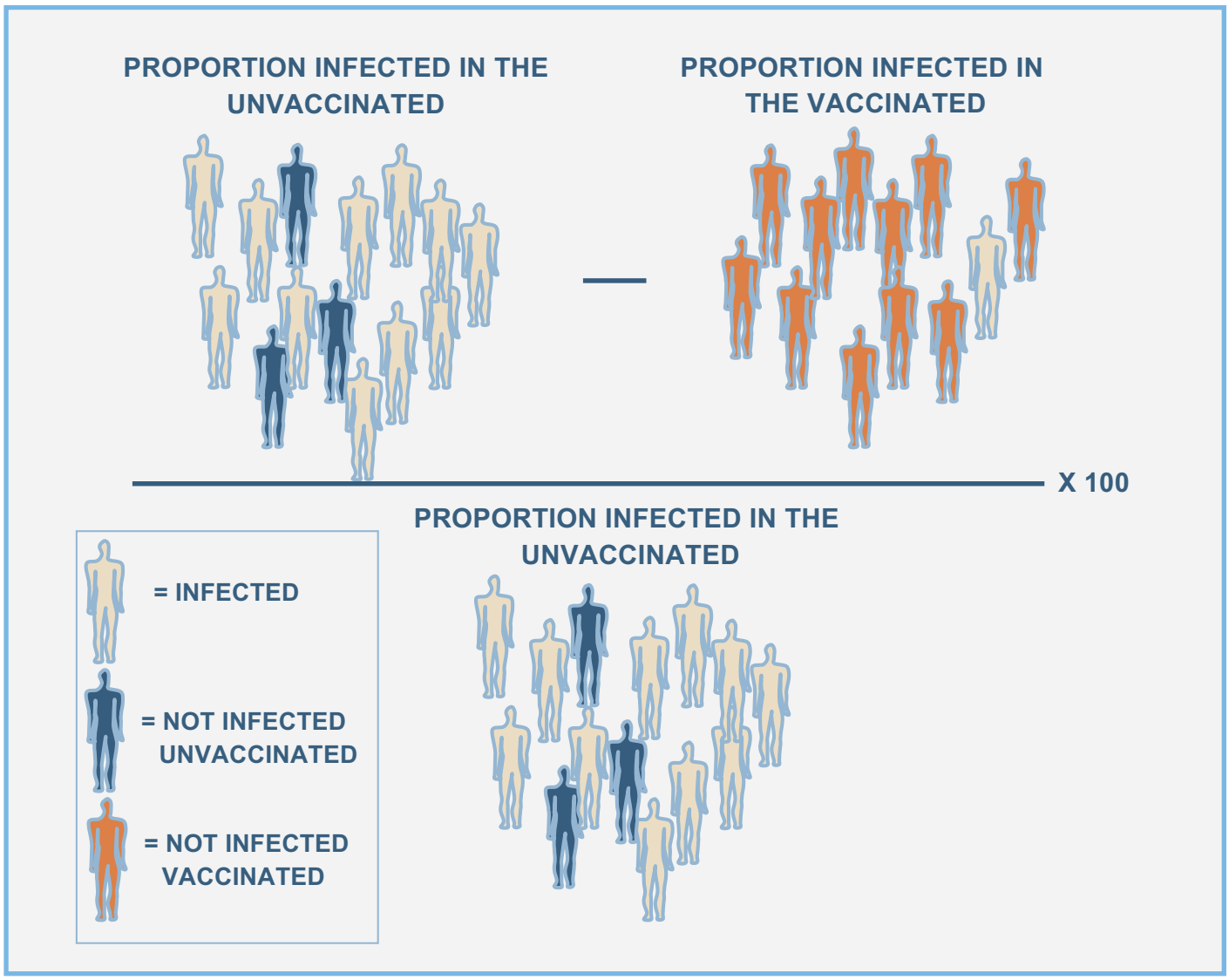


FIGURE 12. METHOD OF CALCULATION OF VACCINE EFFICACY

Vaccine Effectiveness is often distinguished from vaccine efficacy. Vaccine effectiveness measures the performance of a vaccine under field conditions (usually retrospectively), whereas vaccine efficacy measures the performance of a vaccine under study conditions (usually prospectively). Therefore vaccine effectiveness will depend not only on the performance of the vaccine, but also on the performance of the vaccine delivery program. Furthermore, whereas vaccine efficacy typically measures the prevention of a disease, vaccine effectiveness can assess the ability of a vaccine to prevent a specific outcome—for example: hospitalization or death from a specific disease.

How Efficacious are Vaccines?

Vaccine efficacy varies according to the type of vaccine and the manner in which the vaccine antigen is processed by the immune system. Vaccine efficacy may also vary between different populations. However, in general, the efficacy of licensed vaccines ranges from above 70% to almost 100% (See **Figure 13**). In other words, vaccines could be expected to reduce the attack rates in the vaccinated population by 70–100% compared to the attack rates in the unvaccinated population.

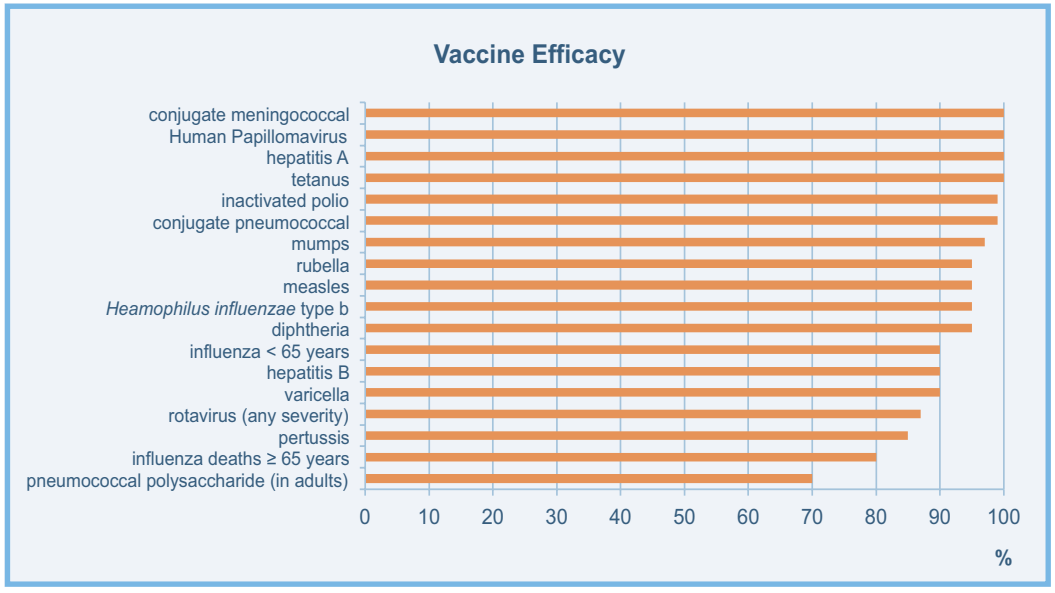


FIGURE 13. OBSERVED EFFICACIES OF SOME VACCINES (MAXIMUM VALUES ARE SHOWN FOR RANGES)[13]

[13] US CDC. Vaccines & Immunizations http://www.cdc.gov/vaccines/vpdvac/diphtheria/default.htm#clinical, and Immunization Action Coalition. Vaccine information for the public and health professionals. http://www.vaccineinformation.org/. [Accessed on June 7, 2011]

How Safe are Vaccines?

The benefits of vaccination are indisputable. Immunization has had one of the greatest impacts on health, second only to clean drinking water[14]. Vaccines prevent death, illness and/or disability. But because of the immune reactions that they induce, vaccines can cause some discomfort.

The vast majority of adverse events associated with vaccines are minor and transient. These are typically pain at the injection site, or mild fever. More serious adverse events occur rarely. Some serious adverse events may be so rare that they occur only once in millions of vaccine doses delivered[15], and some serious adverse events may occur so rarely that their risk cannot be accurately assessed[16]. Some individuals may be sensitive to some components or trace elements in some vaccines, such as eggs, antibiotics, or gelatin. Otherwise, the cause of rare or very rare adverse events is usually unknown. It is believed that rare and very rare adverse events are associated with individual differences in immune responses.

Adverse events following immunization (AEFI) are often categorized according to their frequency (See **Table 8**).

Classification	Frequency
very common	> 1/10
common	> 1/100 and < 1/10
uncommon	> 1/1,000 and < 1/100
rare	> 1/10,000 and < 1/1,000
very rare	< 1/10,000

TABLE 8. CLASSIFICATION OF AEFI[17]

The benefits of vaccination are indisputable.

[14] Plotkin SL and Plotkin SA. A short history of vaccination. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008
[15] Australian government. The Australian immunisation handbook 9th edition. 1.5. post-vaccination procedures. http://www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-adverse
[16] Public Health Agency of Canada. Canadian Immunization Guide. Part 2 Vaccine safety and AEFI. http://www.phac-aspc.gc.ca/publicat/cig-gci/p02-01-eng.php
[17] Public Health Agency of Canada. Canadian Immunization Guide. Part 2 Vaccine safety and AEFI. http://www.phac-aspc.gc.ca/publicat/cig-gci/p02-01-eng.php

All governments regulate the clinical development of vaccines. A thorough evaluation of vaccine safety must be performed before a government will grant a license to allow its use. After a vaccine license has been granted, almost all national immunization programs will continue to monitor the nature and frequency of AEFI. In the US, for example, the Vaccine Adverse Event Reporting System (VAERS) allows all stakeholders in immunization from the public and private sectors to report on the safety of licensed vaccines.

Vaccine policy-makers use the information from adverse event reporting systems to guide vaccine policies, including policies to assess the benefits and risks of immunization.

1.4 Vaccine Safety Surveillance and Evaluation

How is Vaccine Safety Surveillance Conducted?

For severe illnesses, like cancers, adverse events from therapeutic pharmaceuticals may be tolerated. But since vaccines are typically administered to healthy individuals, tolerance for adverse events is much lower. Most governments mandate the investigation of possible AEFIs. Those investigations are conducted in a comprehensive and systematic way.

Before a vaccine is licensed it is carefully studied for all possible harmful effects. Testing proceeds in a stepwise approach. Safety is first evaluated in animals. If there is no evidence of harm in animals, testing can begin in a small number of humans. If there is no evidence of harm in humans, testing proceeds to increasing numbers of human subjects.

In humans, testing proceeds in three phases:

- Phase I clinical trials involve a few dozen subjects;
- Phase II involves 50–hundreds of subjects; and,
- Phase III involves thousands or tens of thousands of subjects.

A safety concern that arises at one phase will stop the clinical study from advancing to the next phase (See **Figure 14**). The effects of the tested vaccine are compared to the effects of a placebo to determine the cause of any adverse events. Standardized case definitions of adverse events, set through the Brighton Collaboration, allow data from different clinical trials to be compared[18].

A license to allow use of the tested vaccine may be applied for when clinical testing of the vaccine is completed. All safety data from clinical testing must be submitted to a regulator for review. The regulator will carefully consider the data from all phases of clinical testing to determine if the vaccine is safe and meets the requirements for licensure. Only a vaccine which meets all of the regulator's safety requirements will be considered. The regulator may grant a conditional license if there is a possibility that a rare adverse event is associated with the vaccine. The conditions of the license may include conducting post-marketing (Phase IV) studies over a large sample size over a long period of time.

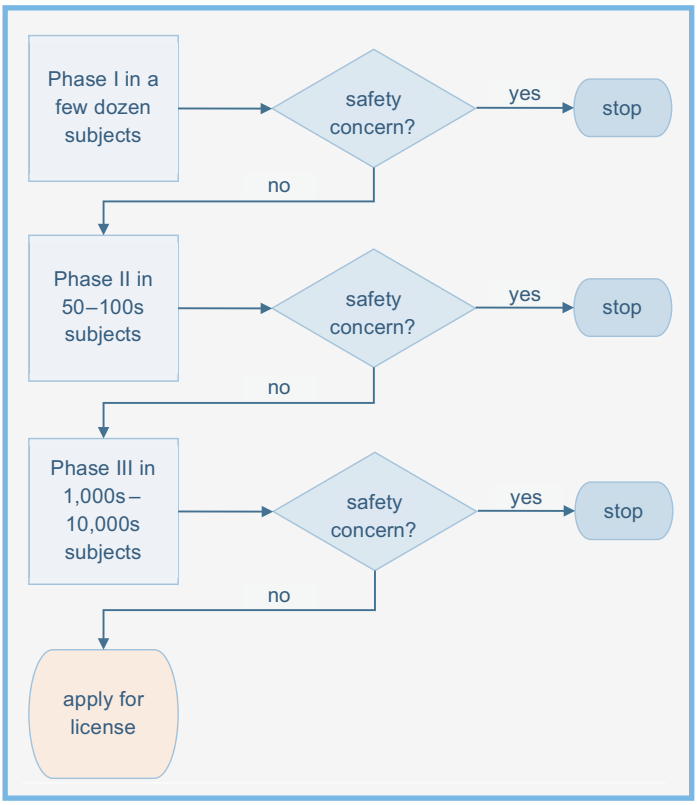


FIGURE 14. SAFETY TESTING OF VACCINES IN THREE PHASES OF CLINICAL TRIALS

[18] Offit PA, Davis RL, Gust D. Vaccine safety. pp 1630. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.

> Only a vaccine which meets all of the regulator's safety requirements will be considered. The regulator may grant a conditional license if there is a possibility that a rare adverse event is associated with the vaccine.

After a vaccine is licensed, many governments mandate the reporting of vaccine-related adverse events. In the US, this is mandated by the National Childhood Vaccine Injury Act (NCVIA). The VAERS allows the US government to evaluate the incidence of specific adverse events, or to detect variations in the rates of vaccine-related adverse events.

Governments may use a variety of methods to monitor vaccine safety. Most countries use spontaneous (or passive) safety monitoring systems. These have a relatively low cost of operation.

Some countries have a combined adverse event reporting system for both vaccines and drugs. Other countries report adverse events from vaccines and drugs through separate reporting systems (See **Table 9**).

Countries that use the same system for the reporting of adverse events from drugs and vaccines	Countries that have separate systems for the reporting of adverse events from drugs and vaccines
Sweden	Canada
New Zealand	Australia
France	Denmark
United Kingdom	USA

TABLE 9. SELECT COUNTRIES' ADVERSE EVENT REPORTING SYSTEMS FOR DRUGS AND VACCINES[19]

Many countries also monitor immunization coverage rates. In the US, the National Immunization Survey is conducted annually by telephone. The survey provides an estimate of coverage with a 95% confidence interval within 1% of the estimate.

How the US VAERS works

VAERS has been implemented jointly by the US Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) since 1990. VAERS collects reports of vaccine adverse events from anyone: from the general public, from patients or parents, from vaccine manufacturers, or from health care providers. These are collected without time restrictions. Since 2002, reports of vaccine-related adverse events can also be submitted on the VAERS website (http://vaers.hhs.gov/index), and 24-hour toll-free phone assistance is available.

[19] Offit PA, Davis RL, Gust D. Vaccine safety. pp 1631. In *Guidelines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.

Once they are received, all reported adverse events are coded and entered into the VAERS database. Reports of serious adverse events initiate a follow-up of the events 60 days and 1 year later to collect supplemental information, such as information about patient recovery (See **Figure 15**). The data on AEFIs from VAERS is made available to the public (without personal identifiers).

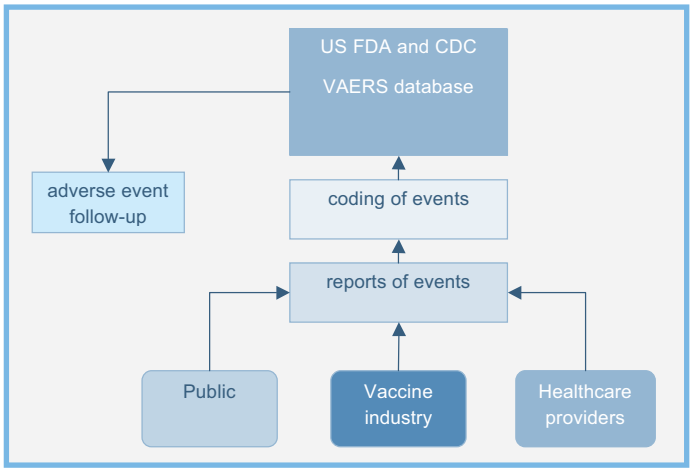


FIGURE 15. US VAERS (EXAMPLE OF A SPONTANEOUS SURVEILLANCE SYSTEM)

One of the limitations of spontaneous (or passive) surveillance is that more serious events are more likely to be reported than less serious ones. Therefore, some less serious events may be under-represented, or not detected. Or, reporting may be influenced by stories covered by the media, leading to an increase in reporting of events that may be relatively minor.

Passive surveillance systems, like VAERS, do not collect data on the total number of individuals vaccinated, so the rate of AEFIs cannot be calculated. However, by linking immunization registries with medical files, an estimate of the frequency of events can be made. The Vaccine Safety DataLink Project (VSD), in the US, is a database that collects data on vaccination histories and health outcomes from Health Management Organizations (HMOs). The data are used to study vaccine safety concerns.

Clinical centers for the study of adverse events may add to the surveillance capabilities of a country. Phase IV (post marketing) studies may also be used to evaluate specific events or risks.

How Vaccine Safety Surveillance is Conducted in Countries Other than the US

Just like in the US, many countries mandate the reporting of AEFIs. Most countries conduct spontaneous surveillance of vaccine safety. Commonwealth countries attach an adverse event reporting form to officially issued prescription pads to facilitate the collection of AEFI reports.

In addition to spontaneous surveillance systems, many countries have supplemental active surveillance systems. Canada, for example, in addition to a spontaneous reporting system, has an active surveillance system: the Immunization Monitoring Program Active (IMPACT). This involves 12 pediatric centers representing over 90% of tertiary pediatric admissions in the country[20]. A nurse-monitor and clinical investigator from each center perform active case-finding of AEFIs. They investigate and report adverse events from immunization to the Vaccine Safety Unit of the Center for Immunization and Respiratory Infectious Diseases (See **Figure 16**).

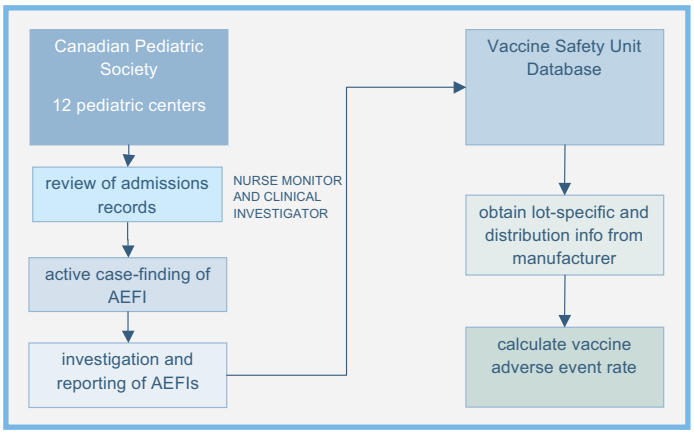


FIGURE 16. CANADIAN IMPACT SURVEILLANCE SYSTEM (EXAMPLE OF AN ACTIVE SURVEILLANCE SYSTEM)

Australia also supplements passive surveillance with an active surveillance system of sentinel units to investigate severe AEFIs[21].

Most European countries have spontaneous surveillance systems, supplemented by active surveillance activities. The structure of each national AEFI surveillance system relates to the organization of immunization in each country. In some countries, immunization and safety surveillance programs are the responsibility of the central government; in other countries they are the

[20] Public Health Agency of Canada. Vaccine safety. http://www.phac-aspc.gc.ca/im/vs-sv/caefiss-eng.php
[21] Waldman EA, Luhm KR, Monteiro SAM, de Freitas FRM. 2011. Surveillance of adverse effects following vaccination and safety of immunization programs. Rev Saude Publica. http://www.scielo.br/pdf/rsp/v45n1/en_1884.pdf

responsibility of the states or provinces. In Germany, individual physicians recommend vaccines to their patients, but reportable AEFIs are made to the local health authority who then reports them to a national safety surveillance center[22]. In some countries, reporting of AEFIs is mandatory. In others it is voluntary.

In addition to national safety surveillance, some European institutions conduct safety surveillance on a supra-national level (See **Figure 17**).

The European Medicines Agency (EMA) has a database for the reporting of adverse events from medicinal products (including vaccines) from the European Economic Area. And the World Health Organization Collaborating Center in Uppsala, Sweden, collects data of reports of AEFIs from about 40 countries. The World Health Organization (WHO) also has a Global Advisory Committee on Vaccine Safety (GACVS) that responds promptly to potential issues of vaccine safety.

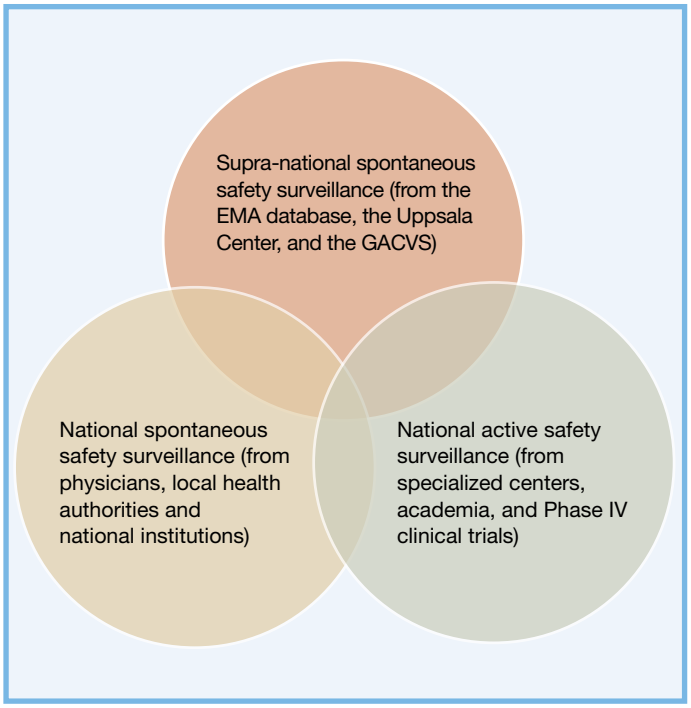


FIGURE 17. NATIONAL AND SUPRA-NATIONAL VACCINE SAFETY SURVEILLANCE IN EUROPE

Providing Information on the Benefits and Risks of Immunization

The public is increasingly demanding of information on the benefits and risks of immunization. As such, health care providers and vaccine policymakers need to provide patients and parents with up to date information from their own communities. In the US, the government provides the public with written information on the risks and benefits of immunization, through the CDC, and a vaccine information sheet (VIS) is required to be provided with each vaccination.

Many national immunization guides, and WHO guidelines, provide advice to health care providers on how to communicate the risks and benefits of immunization. This includes communications on AEFIs.

> The public is increasingly demanding of information on the benefits and risks of immunization.

[22] Waldman EA, Luhm KR, Monteiro SAM, de Freitas FRM. 2011. Surveillance of adverse effects following vaccination and safety of immunization programs. Rev Saude Publica. http://www.scielo.br/pdf/rsp/v45n1/en_1884.pdf

1.5 Cost-Effectiveness Analyses and Evaluation

Cost analyses are often used in health care. They enable rational decision-making, and enable policy-makers to evaluate cost-efficient program options. The costs and benefits of several program options can be compared to determine which provides the greatest value (either monetary or effect) (See **Figure 18**).

Several methods can be used to quantify the value of immunization programs (See **Figure 19)**. The most commonly used analyses are:

Cost: the additive costs, direct and indirect, of an intervention;

Cost-Benefit: the ratio of the costs to the quantified benefits in monetary value, i.e. costs of hospitalization prevented because of immunization;

Cost-Effectiveness: the relative costs and effects of one intervention compared to another with a same objective where the effect is typically a health gain, i.e. deaths averted, or life-years saved; and,

Cost-Utility: the ratio of the costs to the quantified effect measured in years of full health, i.e. disability- or quality-adjusted life-years.

Costs (and benefits) can be both direct and indirect (See **Table 10**)[23]:

- Direct costs are the costs of immunizing and the costs of medical treatment for the disease;
- Indirect costs include loss of productivity, lost wages, etc., of the ill and their caregivers.

Assessments of immunization programs can be made from several perspectives. They can benefit:

- the individual;
- the health system; and,
- society as a whole.

Types of costs	Examples
Direct medical	Medical personnel
	Vaccines
	Syringes
Direct non-medical	Administration
	Clinic utilities
Indirect	Time off from work due to illness (loss of wages, loss of productivity)
	Time off from work to care for the ill (loss of wages, loss of productivity)

TABLE 10. TYPES OF COSTS INCLUDED IN COST ANALYSES

Mathematical modeling is often used to estimate the costs and benefits of vaccines in a given context and from a given perspective.

Assessments of immunization programs may also take into consideration the amount of time required to observe the desired effect. Some diseases occur several years after infection (e.g. liver cancer after infection with Hepatitis B virus). Health economists typically discount future costs and benefits at a rate of 3–10% per year. This favors short-term effects over longer-term effects.

In the US, most of the economic burden from influenza ($71.3–166 billion) is attributable to the indirect costs, the result of loss of productivity[24].

[23] National Network for Immunization Information. Vaccine Economics. http://www.immunizationinfo.org/issues/immunization-policy/vaccine-economics
[24] Lynd LD, Goeree R, O'Brien BJ. Antiviral agents for influenza: a comparison of cost-effectiveness data. *Pharmacoeconomics* 2005; 23(11): 1083–1106.

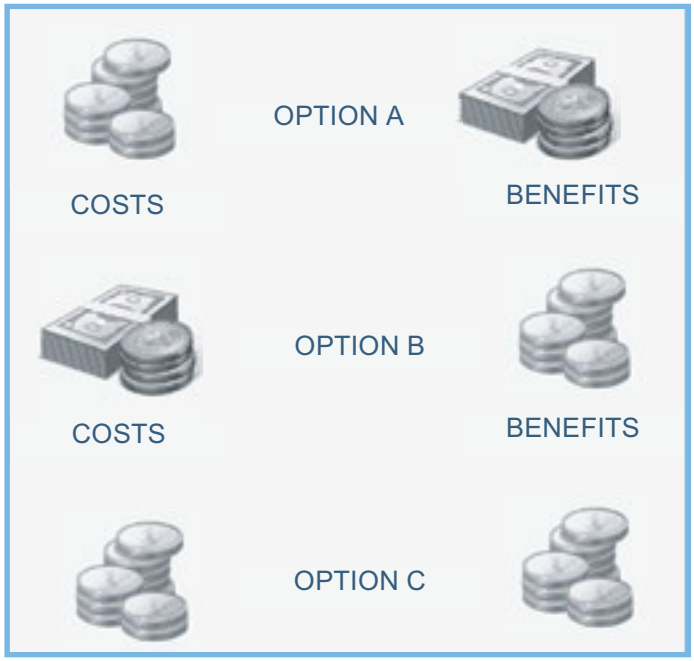


FIGURE 18. COST BENEFIT ANALYSES ASSIST IN DETERMINING WHICH PROGRAM OPTIONS PROVIDE THE GREATEST VALUE

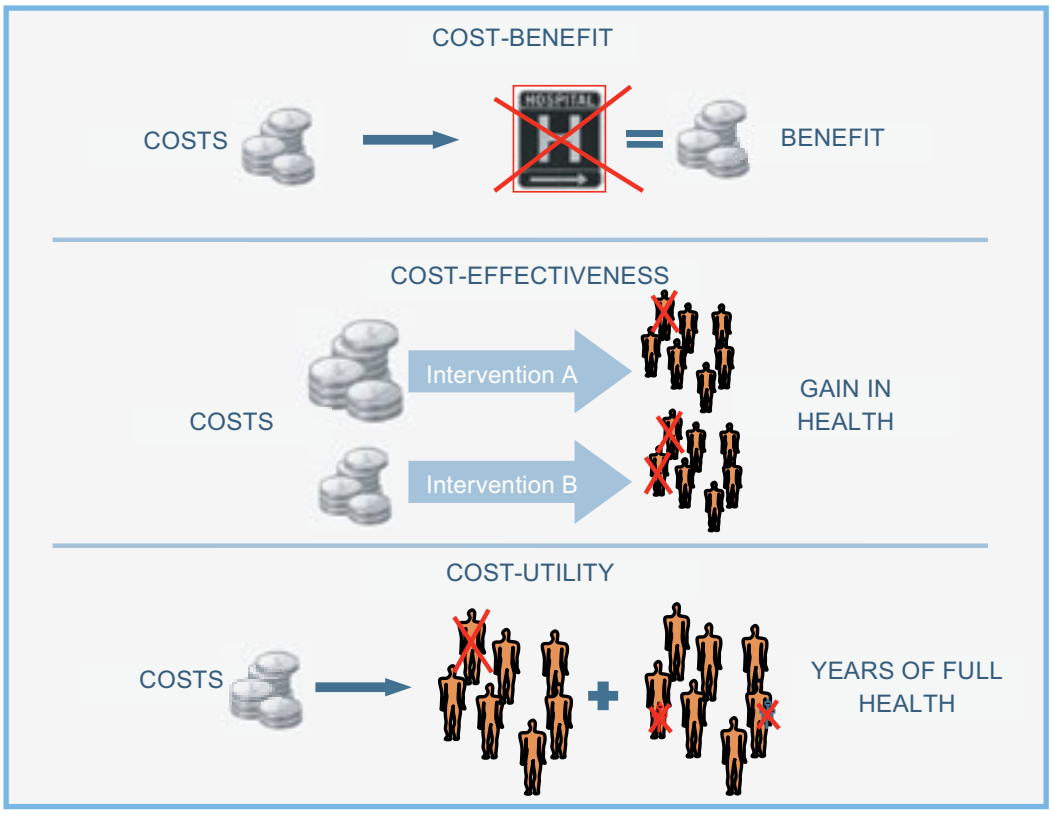


FIGURE 19. TYPES OF ECONOMIC ANALYSES COMMONLY USED TO ASSESS IMMUNIZATION PROGRAMS

The Benefit : Cost Ratio of Immunization (Cost-Benefit Analyses)

The value of immunization is most commonly assessed in terms of its ability to reduce the burden of a disease and its consequences. Reducing disease has an economic impact on the individual, on society, and on national health systems. Some economic impacts can be quantified. Others, like the value of averted deaths, may be more difficult to quantify. The quantified impacts of immunization are often reported in terms of benefit : cost ratio. A ratio of > 1.0 is cost-saving. Compared to other interventions in health, vaccines have one of the highest cost : benefit ratios.

Because of their high value, vaccines are a core component of all primary health care programs. Immunization can avert high expenditures for curative care, particularly in very young and elderly populations. In fact, unlike many other interventions in health, because vaccines prevent diseases that are costly to treat, vaccination often imparts an overall savings to the health system. In the US, seven pediatric immunizations are cost-saving, imparting a direct and societal benefit : cost ratio of 5.3 to 16.5 respectively (See **Figure 20**)[25].

Benefit : cost ratios vary according to the health care costs of each country. The less a country expends to treat diseases, the lower the benefit : cost ratio. But immunization is universally considered to be cost-effective.

The WHO recommends immunization as a fundamental component of primary health care[26].

The Cost-Effectiveness of Immunization

A benefit : cost ratio assigns a monetary value to an effect. "Cost-effectiveness" measures the costs and effects (measured as a gain in health), usually of two or more interventions with the same objective.

Cost-effectiveness analyses are used to inform program choices by determining the relative value of one strategy over another. For example, cost-effectiveness analyses in the US showed that $90–150 million/year could be saved by administering combined DTP and Hib vaccines or DTP, Hib, and Hep B vaccines, instead of administering separate injections[27].

Compared to other government interventions, including other interventions in health, the cost-effectiveness of most vaccines is exceptionally high (See **Figure 21**)[28]. Interventions are generally considered highly cost-effective if they are ≤ Gross National Income (GNI)/capita, and cost-effective if they are < 3 x GNI/capita[29].

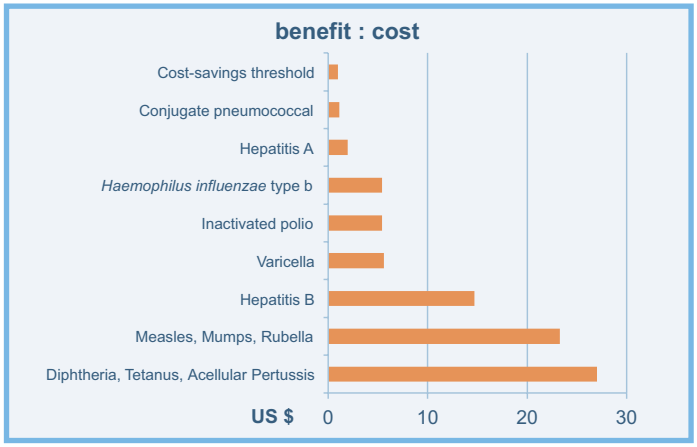


FIGURE 20. COST-SAVING BENEFIT : COST RATIOS FOR SOME VACCINES IN THE US

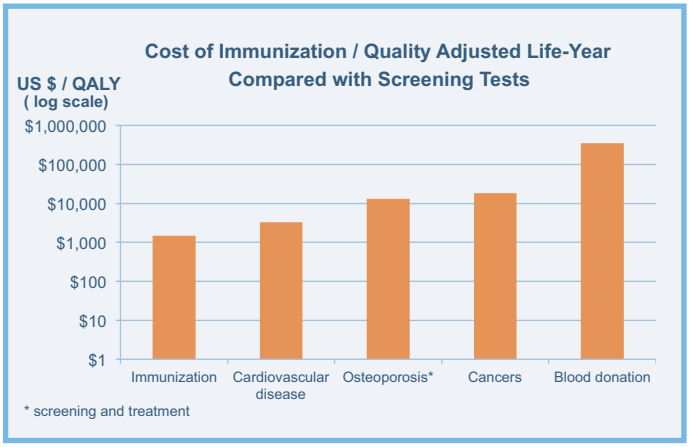


FIGURE 21. COST-EFFECTIVENESS OF IMMUNIZATION COMPARED TO COMMONLY USED SCREENING TESTS IN THE US

[25] Committee on the Evaluation of Vaccine Purchase Financing in the United States, Board on Health Care Services. Institute of Medicine. Financing Vaccines in the 21st Century: Assuring Access and Availability. National Academies Press, Washington DC, 2004.
[26] WHO. Immunization. http://www.who.int/topics/immunization/en/
[27] Miller MA, and Hinman AR. Economic analyses of vaccine policies. pp 1597. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[28] Zhou F, Santoli J, Messonnier ML et al. Economic evaluation of the 7-vaccine routine childhood immunization schedule in the United States, 2001. *Arch Pediatr Adolesc Med* 159: 1136–1144, 2005
[29] WHO. Choosing interventions that are cost effective (WHO-CHOICE). Cost-effectiveness thresholds. http://www.who.int/choice/costs/CER_thresholds/en/index.html

When cost-effectiveness analyses are quantified in years of full health, they are termed “cost-utility” analyses (See **Figure 19**).

Disability-adjusted-life-years (DALYs) or quality-adjusted-life-years (QALYs) attribute different values to morbidity and mortality relative to full health.

DALY: number of healthy life years lost;

QALY: number of healthy life years lived.

DALYs and QALYs integrate a number of subjective assumptions. But cost-utility analyses allow for the value of immunization to be compared across diseases, since some diseases have more immediate impacts than others.

Figure 22 shows the relative cost utility of some vaccines in the US[30,31,32].

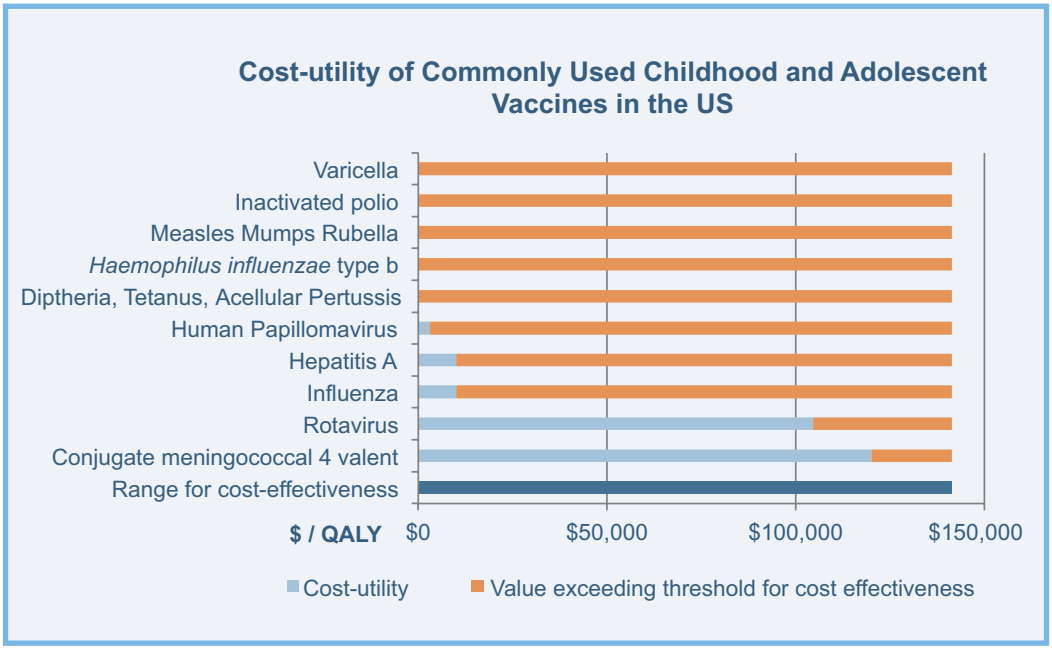


FIGURE 22. COST-EFFECTIVENESS OF CHILDHOOD AND ADOLESCENT VACCINES IN THE US. VACCINES < $0/QALY ARE COST-SAVING. ALL VACCINES SHOWN EXCEED THE THRESHOLD FOR COST-EFFECTIVENESS. (LOWEST COSTS WERE USED IF FROM A RANGE; COST FOR HPV VACCINE IS FOR IMMUNIZATION OF 12 YEAR-OLD GIRLS)

[30] Chesson H. HPV vaccine cost-effectiveness: update and review. Advisory Committee on Immunization Practices (ACIP), Feb 24, 2011.
[31] Shim E and Galvani AP. Impact of transmission dynamics on the cost-effectiveness of rotavirus vaccination. *Vaccine* 2009; 27:4025–4030.
[32] World Bank. World development indicators database, July 1, 2011. http://siteresources.worldbank.org/DATASTATISTICS/Resources/GNIPC.pdf

1.6 Vaccine Implementation Options

Vaccines are provided to the public upon the recommendations of the medical profession. The recommendations for the use of certain vaccines are endorsed by national governments who set policies with public health objectives for the control and prevention of diseases.

The implementation of immunization programs varies from country to country. All countries provide basic immunization services through the public sector. The private sector plays an important role in offering many of the same vaccines, and several others, to segments of population that access health care outside of the public sector.

Implementation of Immunization in the US

In the US, the Institute of Medicine has defined five key roles for the government in immunization. To fulfill these roles, adequate financing policies and practices for immunization are necessary (**Figure 23**)[33]:

Vaccine purchase: the US CDC Vaccine for Children (VFC) program purchases about 55% of childhood vaccines directly from vaccine manufacturers. Funding for the program is provided by Medicaid.

Vaccine delivery: VFC vaccines are provided to both public and private sector health care providers. VFC vaccines are made available, at no cost, to children eligible for Medicaid. The remaining 45% of childhood vaccines (non-VFC vaccines) are delivered through the private sector, in doctors' offices and health clinics.

Disease surveillance: in the US, most childhood vaccine-preventable diseases are notifiable. Notifiable vaccine-preventable disease data, including vaccination status, is collected by the National Notifiable Disease Surveillance System, at the US CDC, on a weekly basis.

Surveillance of vaccination coverage: there are several systems used to monitor immunization performance:

- The annual National Immunization Survey provides an estimate of vaccine coverage by collecting information over the telephone from a representative population sample (a variety of methods are used to ensure that the information is validated and is representative of ethnic and income groups, e.g. by cross-checking records from health providers);

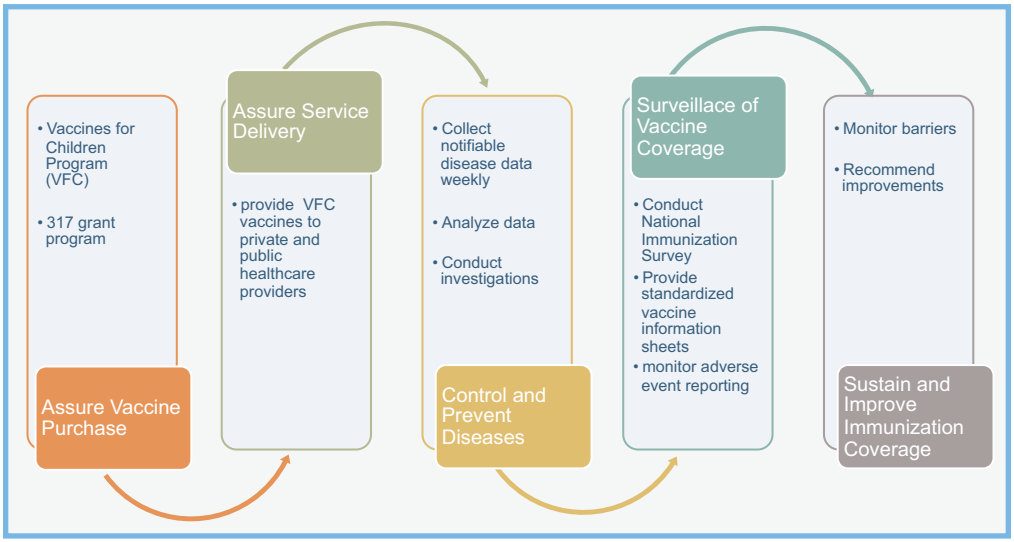


FIGURE 23. KEY GOVERNMENT ROLES IN IMMUNIZATION SUPPORTED BY IMMUNIZATION FINANCE POLICIES AND PRACTICES

[33] Committee on Immunization Financing Policies and Practices, Division of Health Care Services and Division of Health Promotion and Disease Prevention. Calling the Shots. National Academy Press, Washington DC, 2000.

- The VFC providers and HMOs also assess immunization coverage using a standardized program through the Health Plan Employer Data Information Set (HEDIS);

- Immunization Information Systems (IIS) (previously called immunization registries) are confidential computerized databases that record vaccine doses administered by participating health care providers.

Sustaining and Improving Immunization Coverage

All 50 US states have laws requiring immunization before school entry, but parents can file a request for their children to opt out, and immunization is never coercive. Governments link immunization reminders to other government services, like the supplemental food program for woman, infants, and children, to ensure that immunization coverage is maintained. Standing orders in nursing homes and hospitals are also used to improve coverage in adults and the elderly.

Implementation of Immunization in Europe

The European region is very diverse and immunization policies vary considerably from country to country. Some countries, like Germany, have a decentralized public health system, where the states are responsible for the implementation of immunization (as is the case in the US). In Germany, the costs of immunization are covered mostly by statutory insurance provided by employers.

Other European countries, like the UK, have a strong centralized, comprehensive, health system which includes responsibility for immunization. In the UK, the national government provides all recommended vaccines to the public at no cost. The national government is also responsible for disease surveillance and monitoring and encouraging vaccination coverage.

In all countries, disease surveillance and surveillance of immunization coverage are a national responsibility. Supra-national institutions like the European Center for Disease Prevention and Control (ECDC) strengthen surveillance within the European Union (EU) through a network of laboratories. And the EU also funds other networks that support the surveillance activities of member states. The WHO's European Regional Office (EURO), in coordination with the ECDC, also conducts surveillance for vaccine-preventable diseases and monitors the performances of countries' immunization coverage (See **Figure 24**).

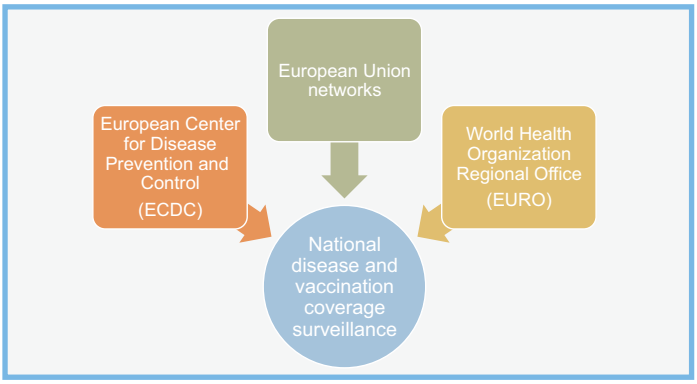


FIGURE 24. SUPPORT MECHANISMS IN EUROPE FOR NATIONAL SURVEILLANCE OF VACCINE-PREVENTABLE DISEASES AND VACCINATION COVERAGE

Immunization policies and implementation are determined within each country. They are not subject to EU legislation. But vaccines can be licensed in other EU countries through a centralized procedure. This procedure grants marketing authorization in all EU member states.

Implementation of Immunization in the Asia-Pacific Region

The Asia-Pacific region is very heterogeneous. Countries in the region span all classes of economic development. As a result, approaches to immunization are widely varied. Unlike Europe, the region does not have a centralized regulatory body to license vaccines. But the Japan Pharmaceuticals and Medical Devices Agency (PMDA) and the Ministry of Health, Labor, and Welfare is a signatory to the International Conference on Harmonization (ICH) with the US and Europe. This is intended to encourage the standardization of the requirements for vaccine licensing between Japan, the US, and Europe.

The Asia-Pacific region does not have a regional vaccination support program, like the one administered by the Pan-American Health Organization (PAHO) in Latin America. Most countries in the region rely on national expert immunization committees to recommend vaccines. Most countries then provide recommended vaccines at no cost through public sector health outlets. However, recommendations for vaccines vary considerably between countries in the region.

1.7 National Immunization Recommendation Systems

How are Immunizations Recommended?

Many countries have national immunization technical advisory groups (NITAGs) to help governments determine which vaccines should be used to achieve public health objectives[34]. The nature and composition of these committees varies by country, but the purpose and function of these committees is similar.

How Immunizations are Recommended in the US

In the US, the Advisory Committee on Immunization Practices (ACIP) is the only federal government recommending body for vaccines[35]. It issues recommendations for vaccines that are used by health care providers in both public and private systems. Other institutions, such as the American Academy of Pediatrics Committee on Infectious Disease (COID, the "Red Book" committee) and the American Academy of Family Physicians collaborate to issue a single immunization schedule in the US. A separate committee, the National Vaccine Advisory Committee (NVAC), advises the US government primarily on program policies and strategies (See **Figure 25**).

[34] WHO. Immunizations, Vaccines and Biologicals. National advisory committees on immunization. http://www.who.int/immunization/sage/national_advisory_committees/en/index.html
[35] US CDC. Vaccines & Immunizations. Recommendations and Guidelines: ACIP. http://www.cdc.gov/vaccines/acip/index.html

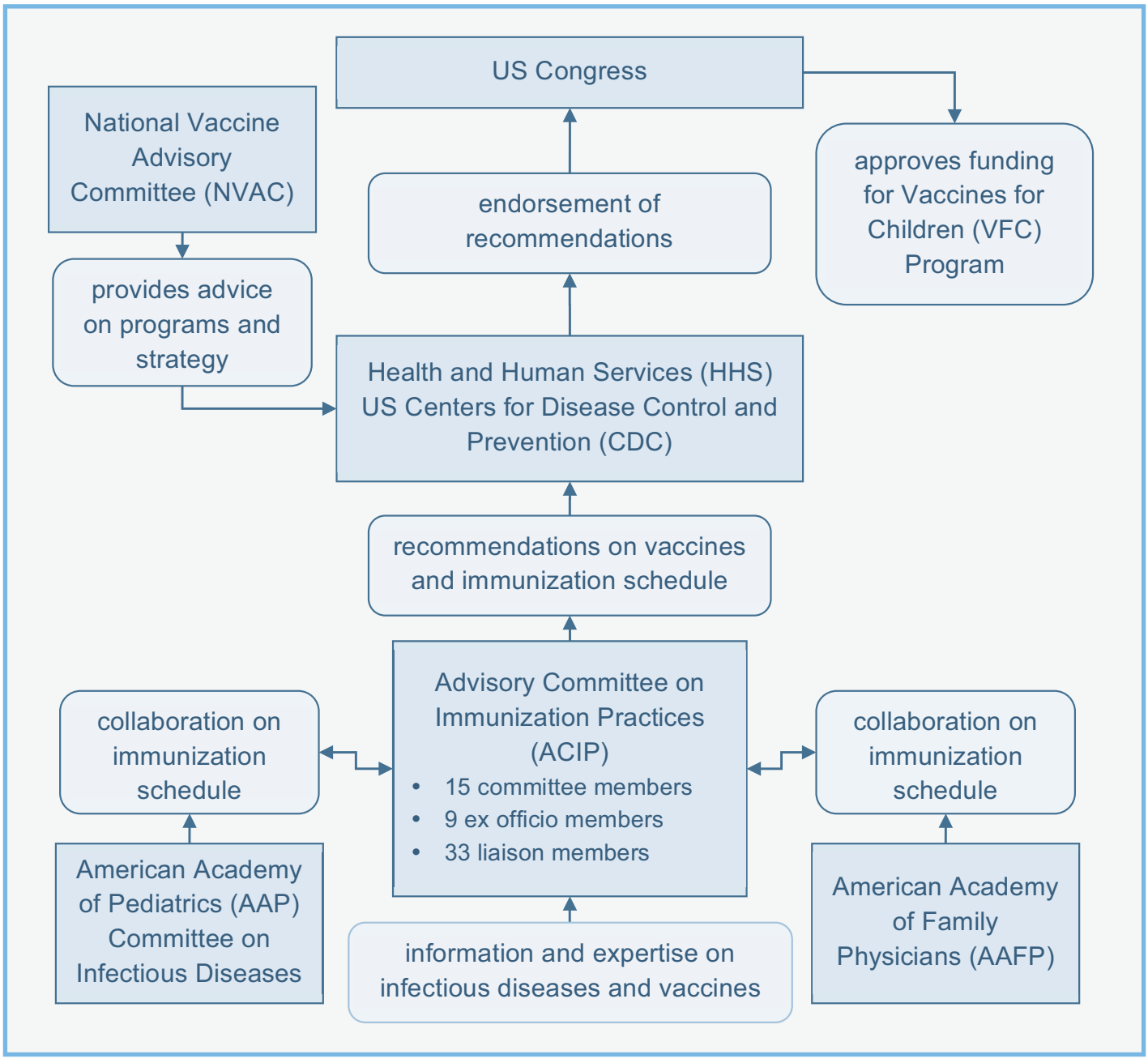


FIGURE 25. ORGANIZATION AND RECOMMENDATION PROCESS OF THE US ACIP AND ITS PARTNERS

The 15 ACIP members are appointed by the Secretary of Health and Human Services (HHS) for a term of 2 years, to provide advice to HHS and the US CDC. They come from a broad array of institutions across the country, including academia, hospitals, public health and government institutions. In addition to committee membership, the ACIP has a broad array of *ex officio* and liaison members representing a complete national spectrum of interests in immunization (See **Figure 26** and **Figure 27**).

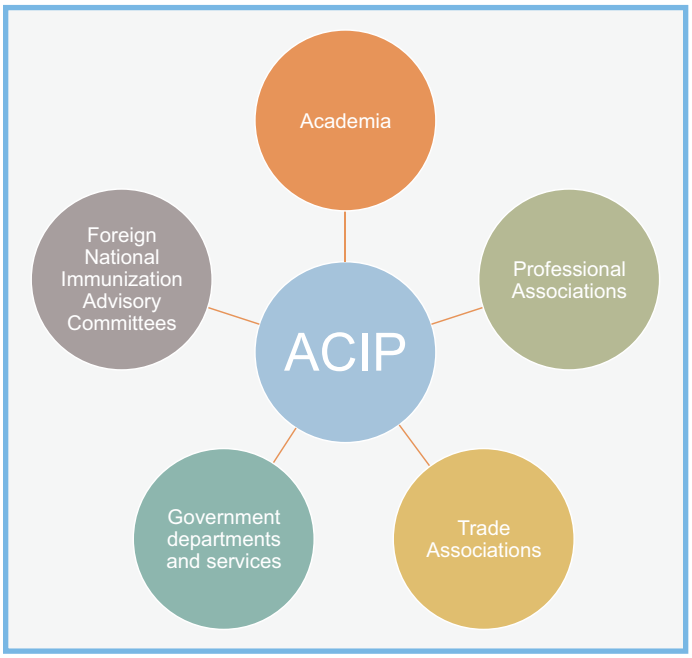


FIGURE 26. BROAD ARRAY OF REPRESENTATION IN THE ACIP

Once ACIP's recommendations have been accepted by HHS and CDC, recommended vaccines are funded by the VFC. Children under 18 years of age who qualify for Medicaid, or do not have health insurance, or whose health insurance policies do not provide for vaccines, or who are Native Americans receive vaccines at no cost through the VFC.

Likewise, under the Affordable Healthcare Act, health insurers must now provide ACIP recommended vaccines at no out-of-pocket expense to the policy holder, and insurers cannot charge premiums for vaccines.

“Under the Affordable Healthcare Act, health insurers must now provide ACIP recommended vaccines at no out-of-pocket expense to the policy holder, and insurers cannot charge premiums for vaccines.

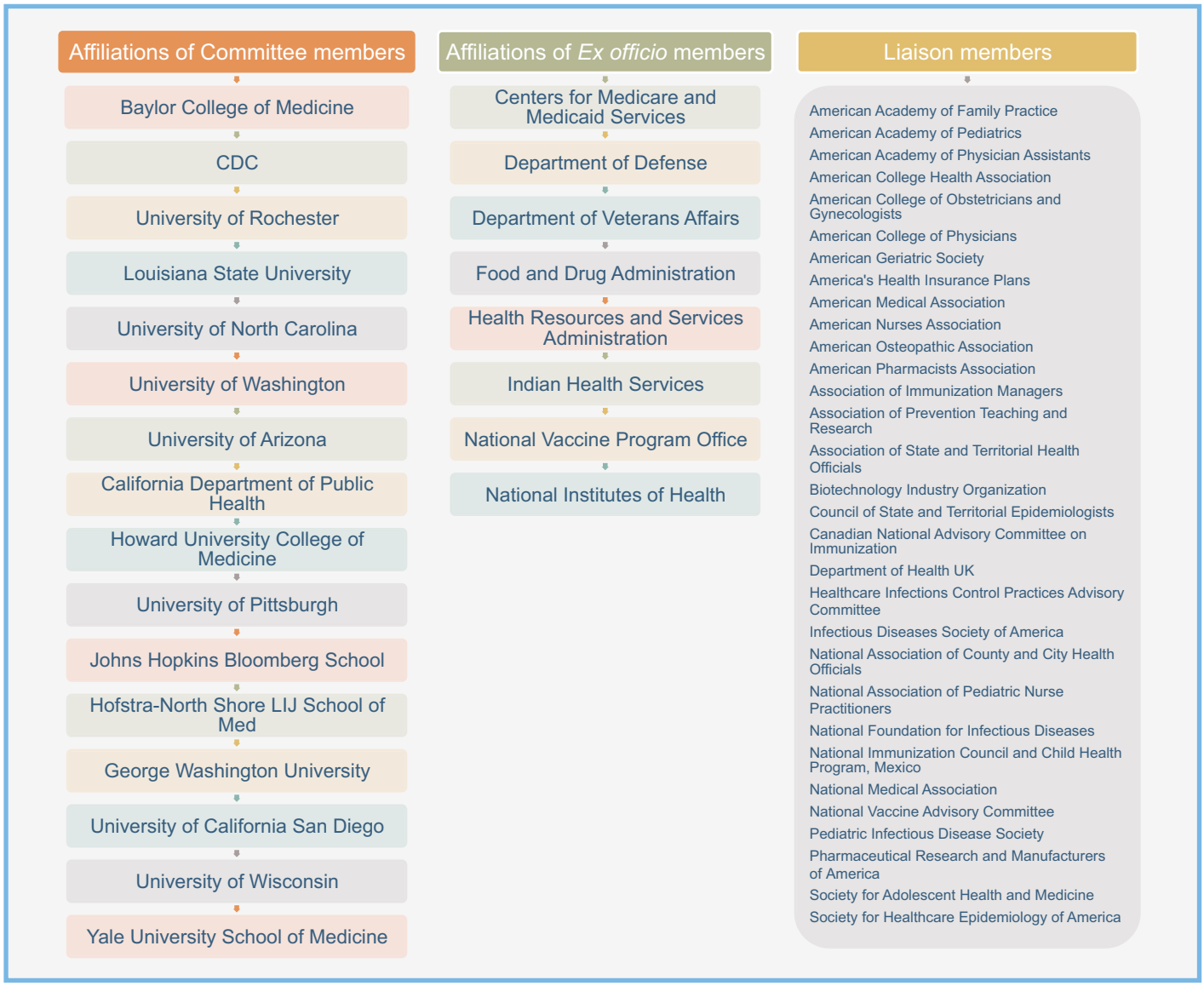


FIGURE 27. AFFILIATIONS OF MEMBERS OF THE US ACIP IN 2013 SHOWING REPRESENTATION FROM A WIDE DIVERSITY OF INSTITUTIONS AND ORGANIZATIONS

How Australia Recommends Immunizations

The Australian Technical Advisory Group on Immunization (ATAGI) is the national immunization technical advisory group for Australia[36]. ATAGI performs several functions:

- provides technical advice to the Minister for Health and Ageing on the administration of vaccines in Australia;
- advises the Pharmaceutical Benefits Advisory Committee (PBAC) on the effectiveness and use of existing, new and emerging vaccines; and,
- produces the Australian Immunisation Handbook (approved by the National Health and Medical Research Council)[37] (See **Figure 28**).

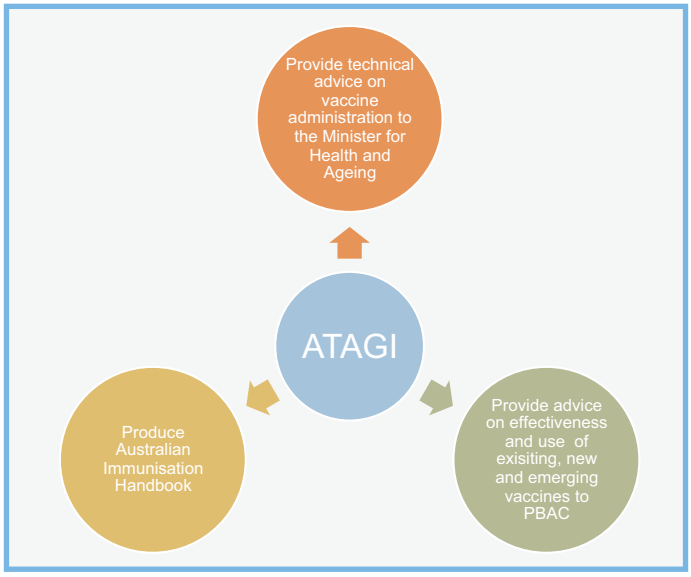


FIGURE 28. FUNCTIONS OF THE ATAGI

As part of the process of providing advice to the Minister, ATAGI submits evidence to the PBAC. The PBAC conducts an economic assessment of vaccines being considered. Once the assessment has been made, the recommendations of ATAGI are then forwarded to the Minister for Health and Ageing. The final decision to adopt a new vaccine rests with the Minister. If funding of more than AUS$ 10 million are required the decision goes to the government's cabinet.

In addition to providing the Minister for Health and Ageing with recommendations for vaccines, ATAGI produces the Australian Immunization Handbook. This provides clinical guidelines for health professionals on the safest and most effective use of vaccines in their practice. It is produced in consultation with the National Immunization Committee (NIC), with the Communicable Diseases Network Australia (CDNA), the Australian Drug Evaluation Committee (ADEC), and the Adverse Drug Reactions Advisory Committee (ADRAC).

Like the US ACIP, membership in ATAGI includes a broad array of stakeholders. In addition to the public health and infectious diseases experts on the committee, the committee includes membership from consumer groups, general practitioners, and nursing representatives[38]. Member affiliations are shown in **Figure 29**.

[36] Australian Government. Department of Health and Ageing. Immunisation Advisory Bodies. ATAGI. http://www.health.gov.au/internet/immunise/publishing.nsf/content/advisory-bodies
[37] Australian Government. Department of Health and Ageing. The Australian Immunisation Handbook 9th Edition 2008. http://www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-home
[38] Australian Government. Department of Health and Ageing. Immunisation advisers appointed. http://www.health.gov.au/internet/immunise/publishing.nsf/Content/advisory-bodies

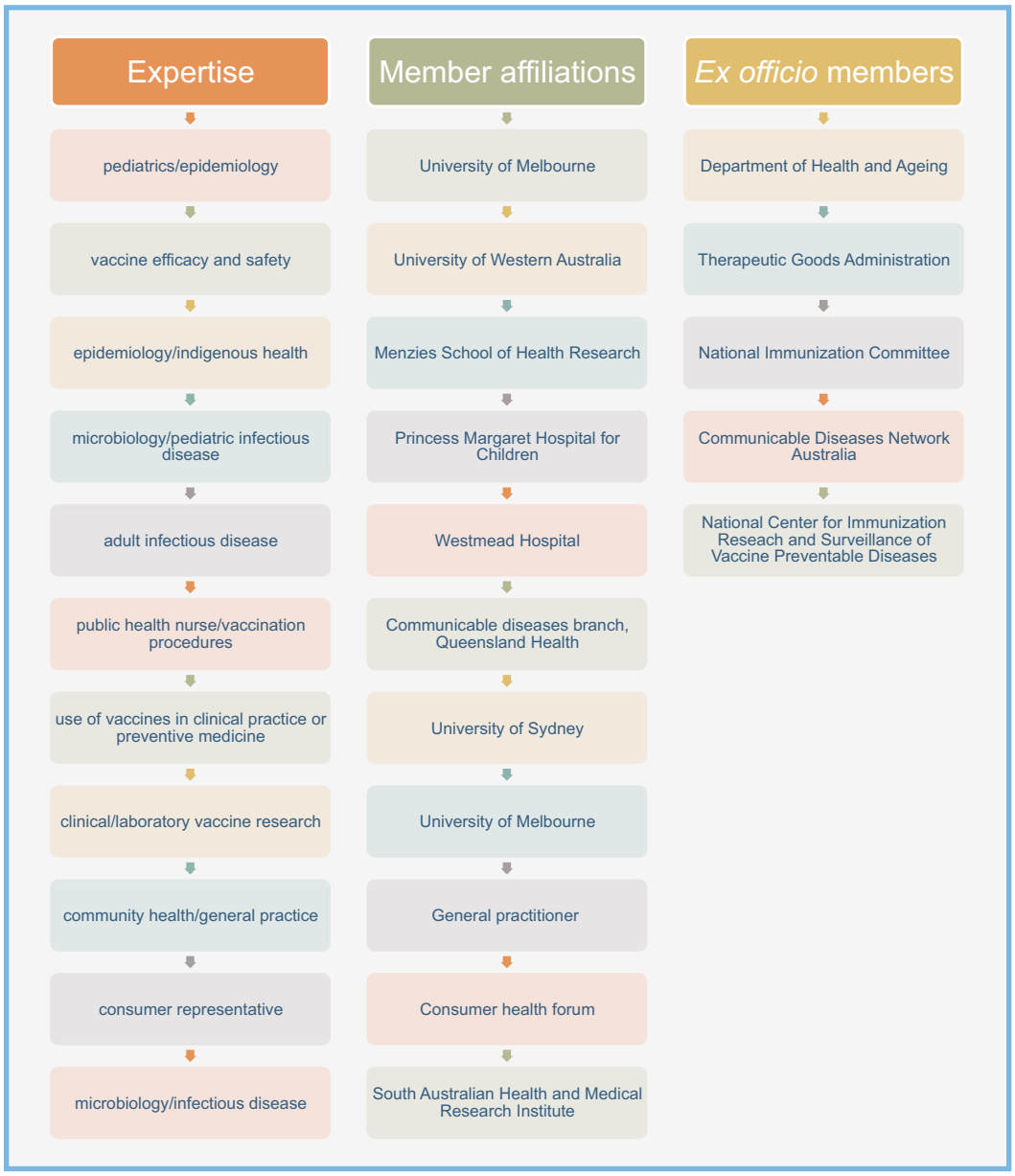


FIGURE 29. AFFILIATIONS OF MEMBERS OF THE ATAGI

How Countries, Other than Australia and the US, Recommend Immunizations

Most other countries have similar approaches to that of the US for recommending immunization. In Germany and the UK, for instance, recommendations on vaccine use are made by a national committee of experts—Ständige Impfkommission (STIKO) and the Joint Committee on Vaccines and Immunization (JCVI)—respectively (See **Table 11**). These committees provide advice to the ministry of health. In some countries, the recommendations of the national advisory committee may be adapted at the local level. In other countries, national advisory committees recommend vaccines, but local health authorities determine which specific products they wish to utilize.

Country	National Immunization Technical Advisory Group (NITAG)	Acronym
Australia	Australian Technical Advisory Group on Immunisation	ATAGI
Austria	Impfausschuss des OSR	
Canada	National Advisory Committee on Immunization	NACI
France	Comite technique de vaccin	CTV
Germany	Ständige Impfkommission	STIKO
Hong Kong	Scientific Committee on Vaccine Preventable Diseases	
Indonesia	Immunization Committee of the Indonesian Pediatric Society	
Ireland	National Immunization Advisory Committee	
Netherlands	Gezondheidsraad-Commissie RVP	
Singapore	Expert Committee on Immunization	ECI
Switzerland	Eidgenössischen Kommission für Impffragen	EKIF
Taiwan	Advisory Committee on Immunization Practices	ACIP
UK	Joint Committee on Vaccination and Immunisation	JCVI
US	Advisory Committee on Immunization Practices	ACIP

TABLE 11. SAMPLE LIST OF SOME NITAGS

In the Asia-Pacific region, many countries have expert immunization committees: the Taiwan ACIP, the Singapore Expert Committee on Immunization (ECI), the Hong Kong Scientific Committee on Vaccine Preventable Diseases. Other countries may rely on Pediatric Societies or other academic-type bodies to act as the recommending body to governments. These bodies may also recommend additional or optional vaccines not included in a basic national schedule. Thai recommendations include additional and optional vaccines in addition to the basic pediatric schedule.

Countries that do not have a national advisory committee of experts, or that are not advised by national medical associations, typically follow WHO recommendations for an Expanded Program on Immunization (EPI) schedule.

A sample list of NITAGs is shown in **Table 11**[39].

How Supra-National Organizations Recommend Immunizations

The WHO provides leadership on global health matters for the members of the United Nations (UN). This includes articulating evidence-based policies for health. In 1999, the WHO established the Strategic Advisory Group of Experts (SAGE) to provide guidance on immunization to the department of Immunization, Vaccines and Biologicals (IVB). The SAGE advises the IVB on policies and strategies for all immunizations[40].

For countries that do not have their own NITAGs, the recommendations of the SAGE often guide their policies and practices.

Like the US ACIP, the SAGE is composed of 15 members who are experts in epidemiology, public health, vaccinology, pediatrics, internal medicine, infectious diseases, immunology, drug regulation, programme management, immunization delivery, health-care administration, health economics, and vaccine safety. And like ACIP, the SAGE has affiliate members who participate as observers—e.g. Unicef, Global Alliance for Vaccines and Immunization (GAVI), WHO Regional Offices, vaccine companies. Affiliations of members are shown in **Figure 30**.

The SAGE meets twice annually to review immunization progress and policy issues and formulate recommendations for the Director General of the WHO which are published in the Weekly Epidemiological Record (WER, www.who.int/wer). For specific issues, SAGE may constitute time-limited working groups.

[39] WHO. Immunizations, Vaccines and Biologicals.National Advisory Committees. http://www.who.int/immunization/sage/national_advisory_committees/en/index1.html
[40] WHO. SAGE—Terms of Reference. March 29, 2011. http://www.who.int/immunization/sage/SAGE_TOR_part_1_Annex_3_29_Mar_2011.pdf

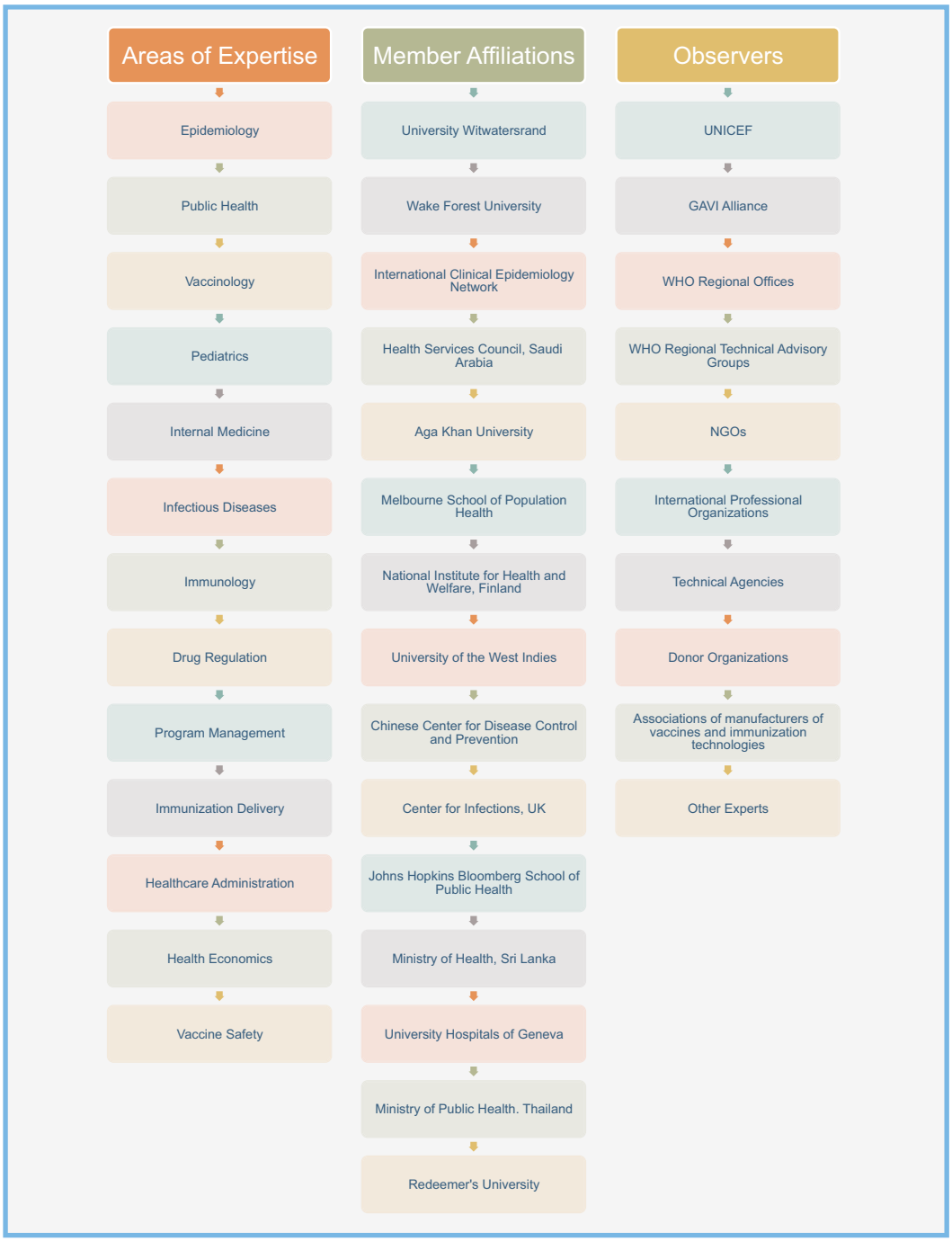


FIGURE 30. AFFILIATIONS OF CURRENT MEMBERS OF WHO'S SAGE[41]

[41] WHO. Immunizations, Vaccines and Biologicals. Current SAGE members. http://www.who.int/immunization/sage/members/en/index.html

The WHO issues position papers on the use of vaccines on the basis of the SAGE recommendations[42]. However, unlike ACIP, the recommendations of the SAGE have no legal bearing on the UN member states and do not result in appropriations of funding for vaccines. As such, in drafting its recommendations, the SAGE often accounts for the difference in wealth between nations and formulates its recommendations on the basis of greatest priority so that the lowest-income countries can apply their scarce resources to the areas of greatest public health need.

The WHO position papers on the use of vaccines can be found at: http://www.who.int/immunization/position_papers/en/.

“In drafting its recommendations, the SAGE often accounts for the difference in wealth between nations and formulates its recommendations on the basis of greatest priority so that the lowest-income countries can apply their scarce resources to the areas of greatest public health need.

[42] WHO. IVB. WHO vaccine position papers. http://www.who.int/immunization/position_papers/en/

Vaccine implementation varies between countries, but generally countries with similar levels of income have comparable immunization systems. One exception is Japan. Japan has a level of wealth similar to countries in Western European, Australia and the US, but has an immunization program that is considerably less progressive. Most industrialized countries strongly value immunization as a cost-effective means to prevent disease and save on treatment costs, and as a means to preserve economic development. Immunization is also valued by some industrialized countries as an asset against bioterrorism.

Like many other complex and capital intensive industries, the vaccine industry in highly consolidated. The vaccine market is dominated by a few large vaccine suppliers in industrialized countries. The costs associated with developing new vaccines require that vaccines be sold on the global market in order to be able to recoup R&D investments. Furthermore, almost all countries import at least some vaccines because not all national suppliers produce every antigen available.

Vaccine research and development has largely been restricted to the few vaccine producing countries. More than two thirds of new vaccines developed in the last 25 years have been developed in the US[43].

[43] Douglas RG, Sadoff J, Samant V. The vaccine industry. pp 37. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.

2.1 The Global Vaccine Market

The global vaccine market represented about 3% of the pharmaceutical market, at about $27.3 billion in 2012[44,45]. Six manufacturers (Merck & Co, GlaxoSmithKline, Sanofi Pasteur, Sanofi Pasteur MSD, Pfizer, and Novartis) account for the majority of the market (80% in 2012) (See **Figure 31**)[46,47,48,49,50].

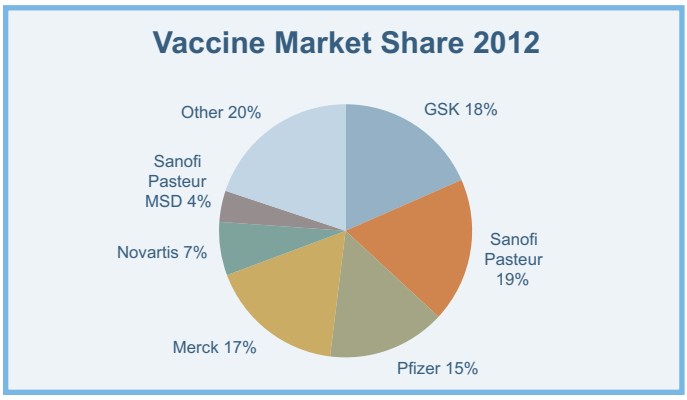


FIGURE 31. THE DOMINANT SUPPLIERS IN THE GLOBAL VACCINE MARKET 2012

Growth in the global vaccine market is expected to continue at around 12% compound annual growth rate (CAGR) over the next 5 years[44].

The US vaccine market was estimated at $12.8 billion in 2012, or about $10.2 billion for human vaccines[51]. The US vaccine market is projected to reach $17.4 by 2018, at a CAGR of 5.3%.

The growth in the vaccine market is driven by the sales of recently developed vaccines and by new vaccine markets. The fastest rate of growth is anticipated in the Asia-Pacific region, and in Latin America[52].

Several vaccines now generate over $1 billion in annual sales (See **Figure 32**)[53] and GAVI is expected to expend more than $1 billion/year on vaccines.

New vaccines under development are projected to add to the growth of the current market.

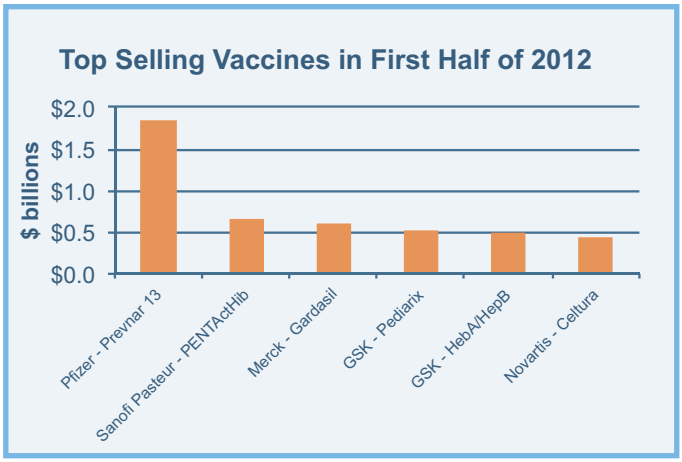


FIGURE 32. BRAND NAME VACCINES THAT GENERATED MORE THAN $1 BILLION IN SALES IN 2010

[44] Research and Markets: Global vaccine market forecast to 2017.Yahoo finance. May 20, 2013. http://finance.yahoo.com/news/research-markets-global-vaccine-market-134100384.html
[45] IMS Health Market Prognosis, May 2012. http://www.imshealth.com/deployedfiles/ims/Global/Content/Corporate/Press%20Room/Top-Line%20Market%20Data%20&%20Trends/2011%20Top-line%20Market%20Data/Regional_Pharma_Market_by_Spending_2011-2016.pdf
[46] Merck 2012 Form 10-K.Feb 28, 2013. http://www.merck.com/investors/financials/annual-reports/
[47] Sanofi 2012 Annual report. Feb 7, 2013. http://en.sanofi.com/investors/events/corporate/2013/2013-02-07_Results_2012.aspx
[48] GSK 2012 Annual report. Mar 6, 2013. http://www.gsk.com/investors/annual-reports/annual-report.html
[49] Pfizer 2012 Annual report. Apr 25, 2013. http://www.pfizer.com/investors/financial_reports/financial_reports.jsp
[50] Novartis 2012 Annual report. http://www.novartis.com/newsroom/corporate-publications/annual-report-2012.shtml
[51] Transparency Market Research. U.S. Vaccine Market-Industry Analysis, Size, Share, Growth, And Forecast, 2012–2018. Sept 13, 2012. http://www.prnewswire.com/news-releases/us-vaccine-market-is-expected-to-reach-usd-174-billion-by-2018-transparency-market-research-169594456.html
[52] Global Industry Analysts Inc. Human Vaccines—A Global Strategic Business Report. March 13, 2012. http://www.prweb.com/releases/prophylactic_vaccines/therapeutic_vaccines/prweb9278427.htm
[53] Fierce Vaccines. 20 top-selling vaccines—H1 2012. http://www.fiercevaccines.com/special-report/20-top-selling-vaccines/2012-09-25

2.2 Vaccine Development

The development process for vaccines is unique. Vaccine development is highly capital intensive and risky. Given the importance of safety with biologics, the vaccine industry is highly regulated. Vaccine development proceeds in an iterative fashion. Less than one in 10 vaccine candidates achieve licensure. The high failure rate is due to the unpredictability of the biological microorganisms needed to produce vaccines, and to the uncertainty of how the human immune system will process and react to the vaccine antigen. Some vaccine candidates may produce appropriate levels of immune response, but induce important adverse reactions. Other vaccine candidates may be safe, but ineffective at preventing diseases. With the current tendency to combine several antigens into a single vaccine, the challenges associated with developing safe and effective vaccines are even greater.

Research to discover new vaccine antigens and novel approaches to immunization usually takes several years, and costs tens of millions of dollars. Once a discovery is made, several developments must be undertaken to reach the licensing stage. Those developments include (See **Figure 33**):

Process development: to produce an economically viable vaccine, consistently, in a manner that satisfies regulators;

Clinical development: to demonstrate the safety and measure the protective effect of the vaccine in humans; and,

Assay development: to develop the appropriate tests to ascertain the purity, potency and stability of the vaccine under development.

Process development is further divided into bulk manufacturing and product finishing. Bulk manufacturing involves the culture of live microorganisms, followed by separation and purification of the desired antigen. Finishing involves the formulation with either adjuvant and/or stabilizer and the filling of vials or syringes.

Clinical development, as described earlier, involves the iterative process of testing a vaccine candidate in a progressively larger number of human subjects.

Assay development is required because the vaccine candidate will be novel and will therefore require specific tests to identify it and characterize the product to the satisfaction of the regulators.

The development of each of these processes is very lengthy, requiring on average 10–15 years. The total development costs can reach close to $US1 billion (See **Figure 34**)[54].

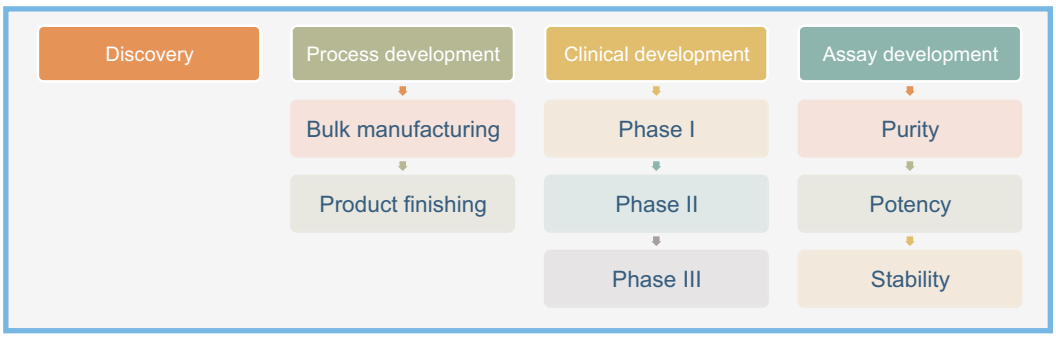


FIGURE 33. DIFFERENT TYPES OF DEVELOPMENT NECESSARY TO REACH THE VACCINE LICENSING STAGE

[54]Bentley W. Research and the University of Maryland. Center for Bioprocess Innovation. http://www.umresearch.umd.edu/VPRPubfiles/Center%20for%20Bioprocess%20Innovation%201.29.08.pdf

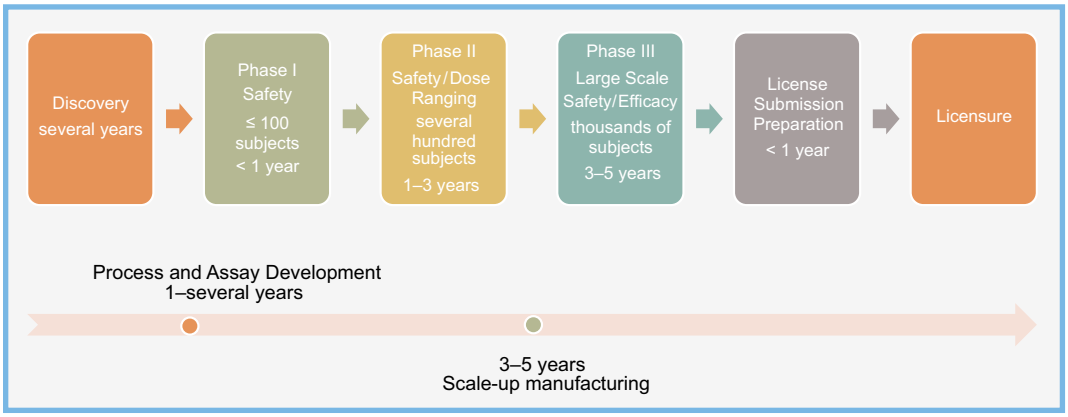


FIGURE 34. VACCINE DEVELOPMENT PROCESS OVER A PERIOD OF UP TO 15 YEARS AT A COST OF UP TO $1 BILLION

2.2.1 Clinical Development

After being thoroughly tested in an animal model, vaccine candidates that are found to be safe and induce immunity can advance to testing in humans. To license a vaccine, three phases of clinical testing must be completed in healthy subjects (See **Figure 35**)[55]:

Phase I: early safety and immunogenicity trials that involve < 20 subjects and can be completed in under 1 year;

Phase II: safety, dose ranging, and immunogenicity trials that involve about 50–hundreds of subjects and that take 1–3 years to complete; and,

Phase III: large-scale safety and efficacy trials involving thousands of subjects and requiring 3–5 years to complete.

Image 3. Vaccine manufacturing in an aseptic environment

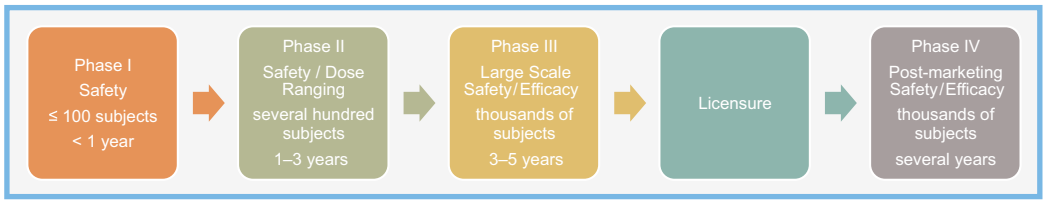


FIGURE 35. THE FOUR PHASES OF CLINICAL DEVELOPMENT OF VACCINES

[55] Douglas RG, Sadoff J, Samant V. The vaccine industry. pp 37. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.

Clinical testing costs hundreds of millions of dollars to complete. In the first three phases of clinical testing regulators may require data from 90,000 subjects or more to affirm safety and efficacy.

These phases proceed in a stepwise fashion. Only vaccine candidates that are determined to be safe and capable of inducing an immune response advance to a next phase (See **Figure 15**, Section 1.4). Vaccines under development are compared to a placebo control group to ensure that their observed effectiveness and safety are not random.

A regulator may also require further clinical testing after a vaccine license has been granted. Clinical studies after licensure are Phase IV post-marketing studies. These typically assess safety and or efficacy in very large populations. Because of their size, these studies may detect very rare vaccine-associated events that may have gone undetected in Phase III testing.

Clinical testing costs hundreds of millions of dollars to complete. In the first three phases of clinical testing regulators may require data from 90,000 subjects or more to affirm safety and efficacy[56]. These subjects may be recruited from multiple trial centers on all continents.

All clinical data collected from clinical testing must be thoroughly analyzed and submitted to regulators for their review.

[56] GlaxoSmithKline. EMA maintains position on the continued use of Rotarix™ (rotavirus vaccine). Media Center, May 21, 2010.

2.3 Vaccine Manufacturing

The manufacture of vaccines is achieved from the propagation of living microorganisms. Some of these may be dangerous human pathogens. Therefore, the manufacture of vaccines is conducted in a highly regulated and controlled environment. All vaccine manufacturers are subject to national and international regulatory control and must comply with specifications for Good Manufacturing Practices (GMP). These requirements vary between countries, but the fundamentals are common:

- ensure that products are safe for use in humans; and,
- ensure that the identity, strength, quality and purity of products consistently meet regulatory specifications.

Manufacturing is conducted in an aseptic environment and closely monitored by quality control measures. Vaccines also require a strict cold chain to maintain their stability. Under most circumstances vaccines are shipped and stored under refrigeration.

The actual production processes vary somewhat for different types of vaccines. Some components of the manufacturing process are specific to either viral or bacterial vaccine production. In all cases, biologicals are inherently variable. Manufacturers must, therefore, carefully characterize and store the master seed viruses or bacteria used to start each production run. This helps to ensure the consistency of the end-product.

In general, the production of vaccines entails four basic steps (See **Figure 36**):

Propagation entails the multiplication (or amplification) of the living microorganism used in the vaccine;

Isolation entails the separation of the living microorganism from the cells or growth media used in the propagation step;

Purification removes all materials that may be adhering to the isolated microorganisms, or selectively separates the portion of the living microorganism to be used in the vaccine; and,

Formulation involves the mixing of the purified product in solutions to obtain a desired concentration. It may also include the addition of preservatives to some vaccines, to ensure the sterility of the product over a longer period of time, or to prevent cross-contamination during dose extraction from vials.

At the end of the manufacturing process, vaccines are typically filled in vials or syringes and packaged for shipping to health care providers. (See **Figure 37**).

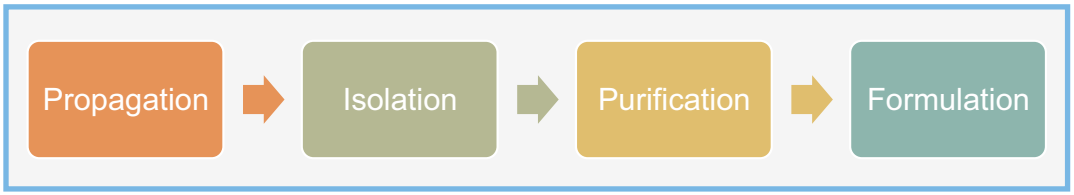


FIGURE 36. THE FOUR STEPS IN THE PRODUCTION OF VACCINES

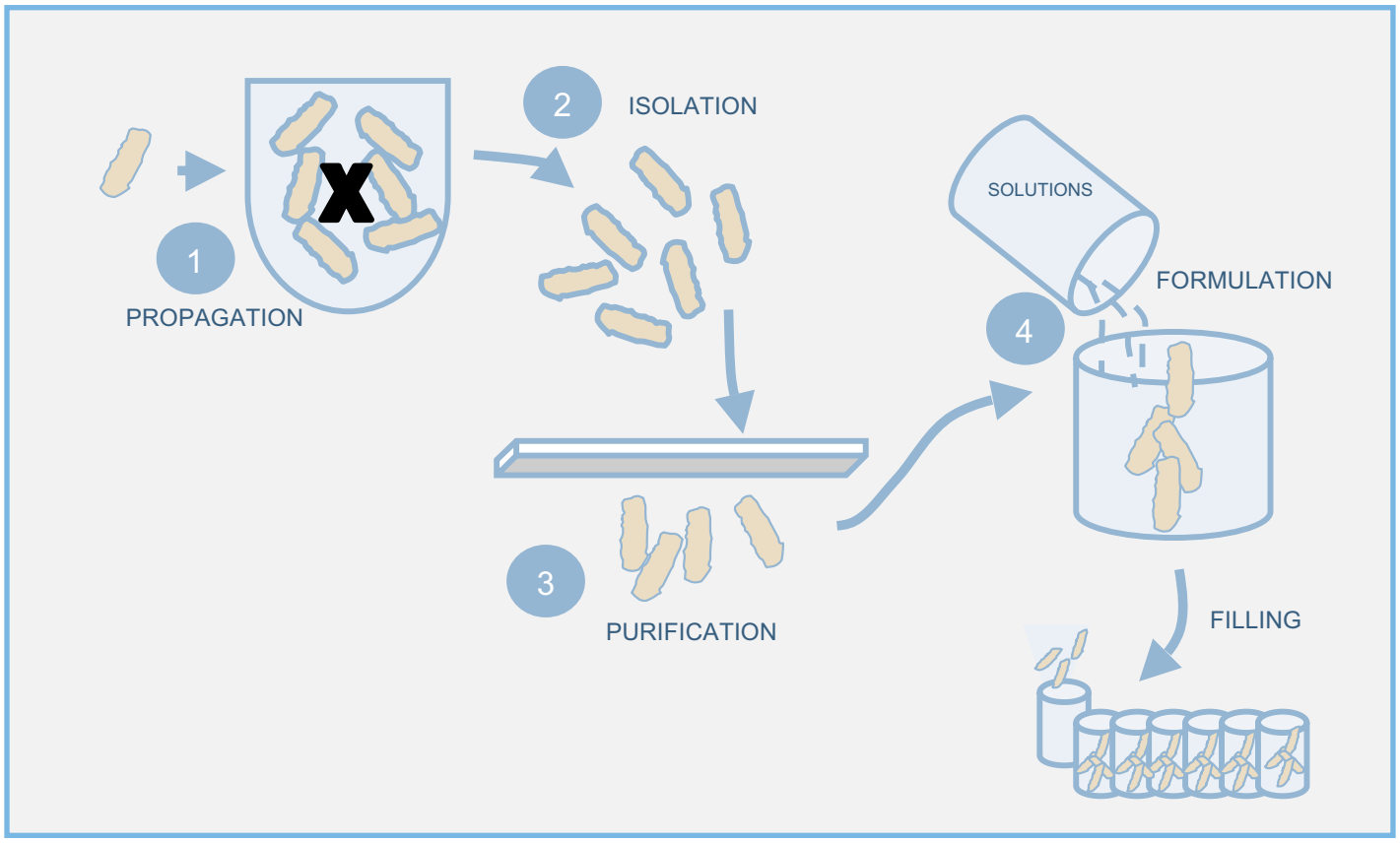


FIGURE 37. PROCESSES INVOLVED AT EACH OF THE FOUR STEPS OF VACCINE MANUFACTURING

Viral Vaccines: Because viruses only grow within living cells, viruses for vaccines are propagated in cells (e.g. in chicken eggs) or in continuous cell lines (e.g. Vero cells). Once the virus has been propagated, it must then be isolated from the cells and the cell-culture medium. This may be achieved by several techniques including chemical lyses of the cell, centrifugation and filtration, or homogenization.

The next step, purifying the virus, may likewise involve multiple techniques of centrifugation, ultra-filtration or chromatography, or chemical purification. At this stage, viruses may also be chemically inactivated for killed vaccine preparations.

Then the viral preparation is formulated by mixing it with the constituents that allow each dose to be safely delivered in the right concentration. This is the point where the product may also be combined with other antigens (e.g. measles–mumps-rubella vaccine). The formulated product is filled in vials or syringes. Some vaccines are freeze-dried (lyophilized) at this stage, to prolong their shelf-life.

Bacterial Vaccines: Bacteria do not require living cells to propagate and are instead grown in bioreactors containing specific culture media. After propagation, isolation may be conducted by centrifugation or specific polysaccharide extraction techniques. Purification is specific to the antigen, but may include chemical precipitation or fractionation, or ultra-filtration and chromatography steps. At this stage, carrier proteins may be conjugated to some polysaccharide vaccines and the conjugate vaccine is then purified by various filtration or chromatography techniques. The purified products are then formulated and at this stage may be combined with several other antigens. Some polysaccharide vaccines contain several types of polysaccharide (e.g. pneumococcal polysaccharide vaccine contains 23 different types of polysaccharide), and some bacterial vaccines are combined with other bacterial and/or viral antigens (e.g. diphtheria-tetanus-pertussis-Hib-Hepatitis B or DTP-Hib-HepB).

2.3.1 Cost Trends in Vaccine Development and Manufacturing

Vaccine manufacturing has evolved dramatically over the last half century (See **Image 4, Image 5, Image 6**)[57]. New techniques for the manufacture and testing of vaccines have transformed the manufacturing environment. New vaccines, like multivalent conjugate vaccines, are considerably more complex to manufacture than traditional inactivated whole-cell vaccines. The increased sophistication of the manufacturing process means that the cost of manufacturing has significantly increased in the last few decades.

Image 4. Vaccine manufacturing in the 1950s

In addition, the regulatory environment has evolved to a point where as many as 500 quality control tests may be conducted in the manufacture of a single vaccine[58].

Vaccine manufacture is highly capital intensive. A manufacturing facility alone will cost up to $500 million[59]. Because manufacturing costs are largely fixed, large manufacturers may produce vaccines in massive amounts (e.g. hundreds of millions of doses every year) to achieve economies of scale in production.

Image 5. Vaccine manufacturing in the 1970s

But scaling vaccine production requires a significant investment in time. Even for relatively simple processes, like vaccine packaging, up to 2 years may be required to install and validate new packaging machinery. Building a new manufacturing facility takes on average 5 years to complete and validate with regulatory authorities (See **Figure 38**).

Image 6. Vaccine manufacturing in the 2000s

[57] Rutty CJ, Barreto L, Van Exan R, Gilchrist S. Conquering the Crippler, Canada and the Eradication of Polio. *Can J Pub Health* 2005; 96 (2) : 12–24.
[58] GlaxoSmithKline. Global Vaccines Public Policy Issues. Addressing developing world production—technology transfer. December 2009. http://www.gsk.com/policies/Technology-Transfer-Vaccines.pdf
[59] Pharmaceutical Networking. GlaxoSmithKline—New vaccine manufacturing plant—St-Amand-les-Eaux, France. 2010. http://www.pharmaceutical-networking.com/glaxosmithkline-new-vaccine-manufacturing-plant-st-amand-les-eaux-france/

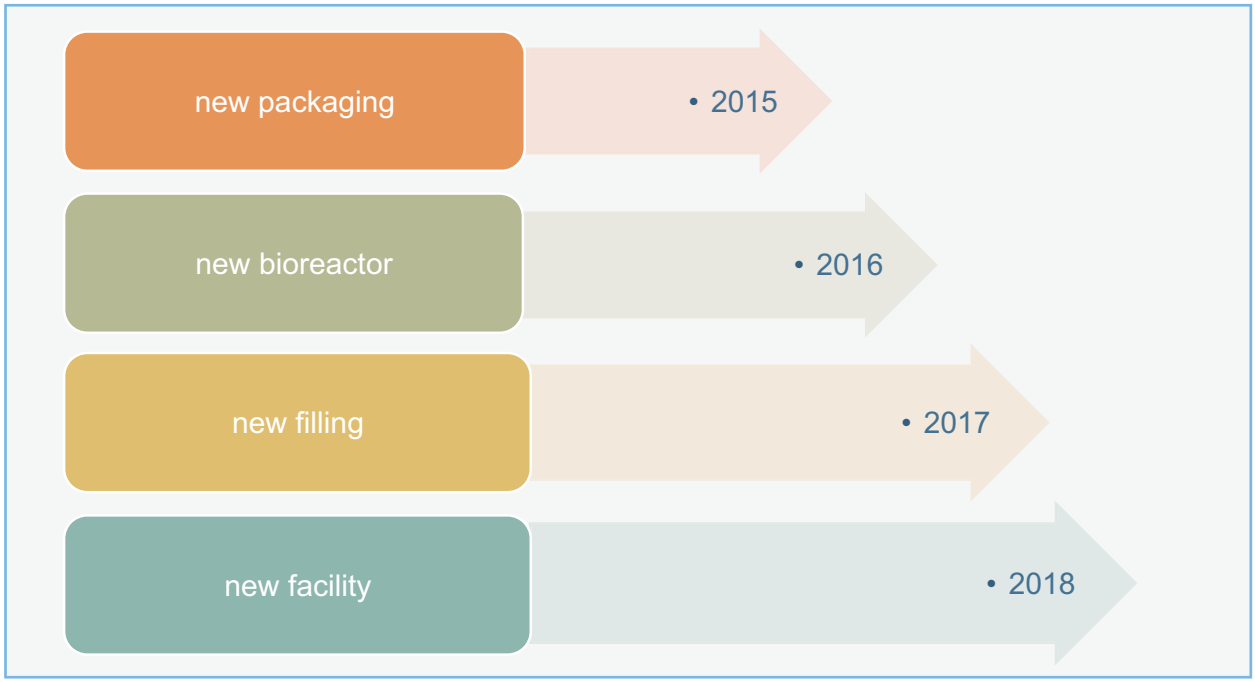


FIGURE 38. TYPICAL TIMELINES TO INSTALL AND VALIDATE NEW INDUSTRIAL CAPACITY FOR DECISIONS MADE IN 2013

2.4 Vaccine Registration and Approval

Because of their biological nature and because they are largely administered to healthy individuals, the entire vaccine development and manufacturing process is regulated. Before vaccines are licensed, the three successive phases of clinical development must be approved by a national regulatory authority and may only proceed from one phase to the next upon approval of the national regulator. When a phase III trial has been completed, the manufacturer must apply for a license to sell the vaccine. The license application review is so thorough and complete that it takes between 1 to 2 years to complete (See **Figure 39**). The regulator has the authority to refuse or withdraw a product license if the manufacturer is not compliant with current regulations.

After vaccines are licensed, manufacturing is strictly controlled by regulators who test and have authority over the release of each production batch of vaccine.

Regulators and sponsors also monitor the consistency of product from one production batch to the next (See **Figure 40**). Inactivation and attenuation are also checked to ensure that the product does not expose individuals to risk. Regulators and sponsors will subject the product to multiple tests, with redundant checks, to ensure that the testing itself is yielding correct results.

General **safety testing** is performed by injection of the final container product in the abdomen (intraperitoneal) of an appropriate animal model.

Identity testing is specific to the nature of the vaccine, but can include neutralization of a live-attenuated viral vaccine with an antiserum.

Purity testing must demonstrate that the vaccine is free of extraneous materials including moisture and pyrogenic substances. The products used in the manufacture of the vaccine must also meet standards of purity.

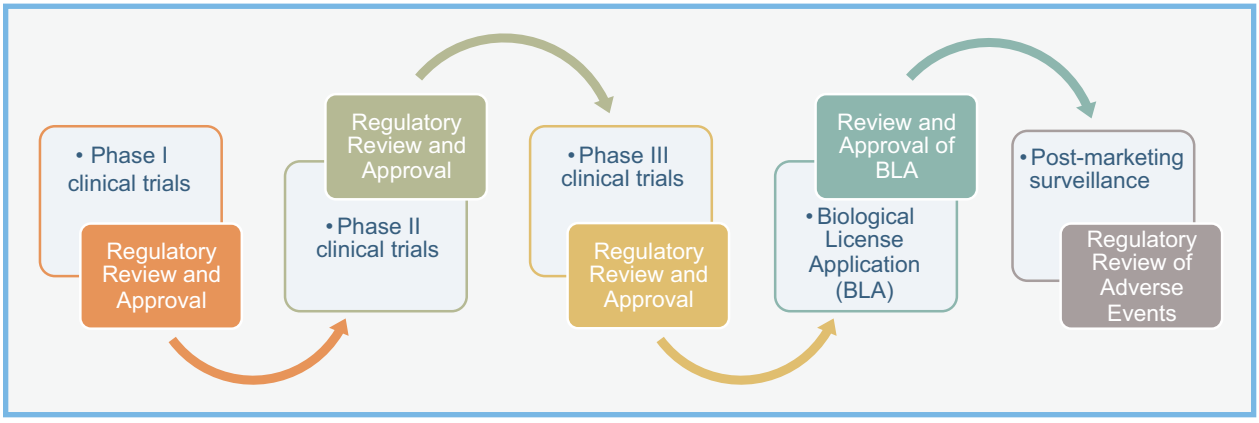


FIGURE 39. REGULATORY PROCESS FOR VACCINES UNDER DEVELOPMENT

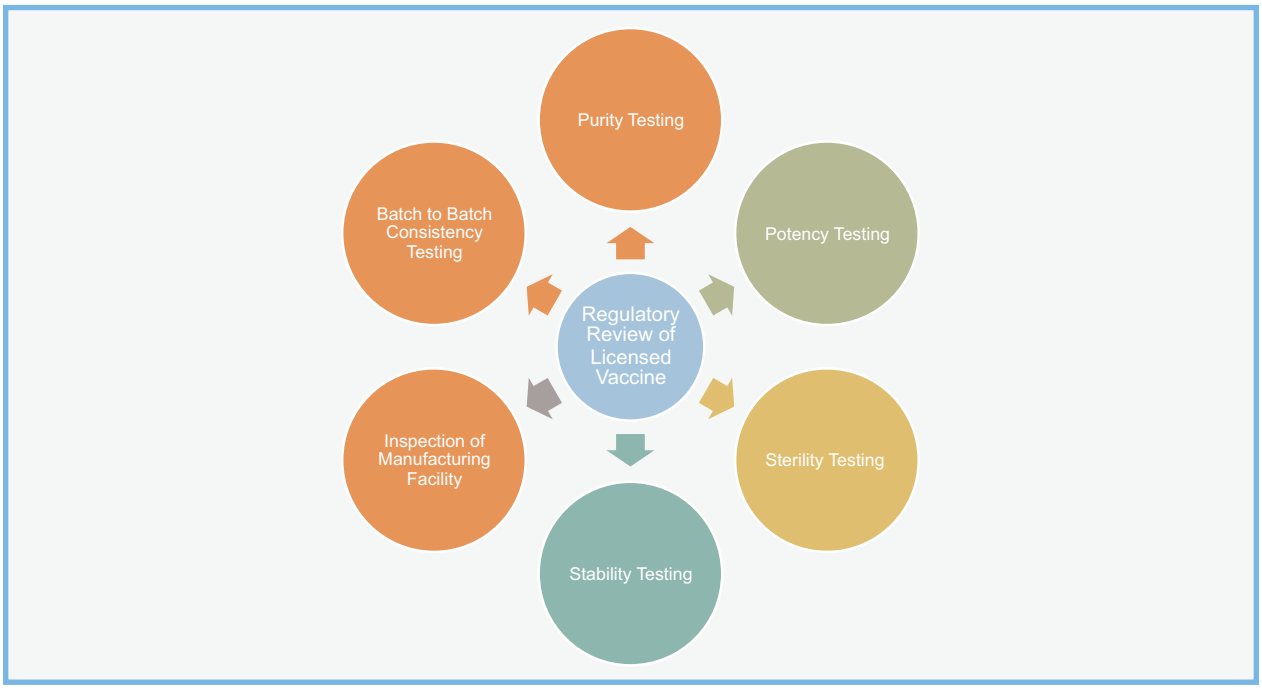


FIGURE 40. REGULATORY TESTING OF LICENSED VACCINES

Potency testing involves demonstrating that the vaccine confers protective immunity. The tests are specific to the vaccines being tested, but often involve virulent challenge in an animal model, or virus titration, or other quantification of an antigen. It is also necessary to demonstrate that the potency of the individual components of a combination vaccine are preserved when combined (because some antigens can reduce the immune response to others).

Sterility is tested on both bulk and finished vaccines.

Regulators also regularly inspect manufacturing facilities to ensure compliance with current GMPs. GMPs are a set of guidelines that ensure consistency of quality of production.

Regulators control the labels on final containers and accompanying product inserts. Labeling and package inserts must be supported by scientific data and the regulator reviews the language to ensure that it is not misleading, or false. Any changes will usually require the regulator's approval first. Regulators may

also regulate the advertising of products and monitor advertising for misleading claims. Claims for products must be balanced with information about their safety.

In order to produce safe and efficacious vaccines and to comply with regulations, vaccine manufacturers carry out extensive quality assurance and quality testing during the manufacture of vaccines. Up to 500 quality control tests may be conducted in the manufacture of a single vaccine[60]. Quality testing may account for as much as 70% of the time to manufacture[61].

How Vaccines are Regulated in the US

The US Biologics Control Act, enacted in 1902, noted that testing the purity of a final product was insufficient to ensure quality. It required that manufacturing facilities be inspected. In 1944, the Public Health Services Act empowered the US government to license both biologicals and biological manufacturing facilities. It became illegal for biologicals to be sold without a license.

Vaccines are regulated by the FDA's Center for Biologics Evaluation and Research (CBER). Vaccine developers must apply to CBER for permission to both develop and sell vaccines (See **Figure 41**).

Prior to licensure, vaccines are regulated by the Investigational New Drug (IND) Regulations. The vaccine developer (sponsor) must apply for permission to conduct a clinical study. The application must include information about:

- the composition of the investigational new product;
- the source of the investigational new product;
- the method of manufacture of the investigational new product; and,
- the methods used to determine the safety, purity, and potency of the investigational new product.

The sponsor must also provide a summary of all laboratory and animal pre-clinical testing. A description of the proposed clinical trial and the qualifications of the investigators are also required (See **Figure 42**). The endpoints for vaccine licensure include vaccine safety and efficacy, but safety must be demonstrated at each phase of the study.

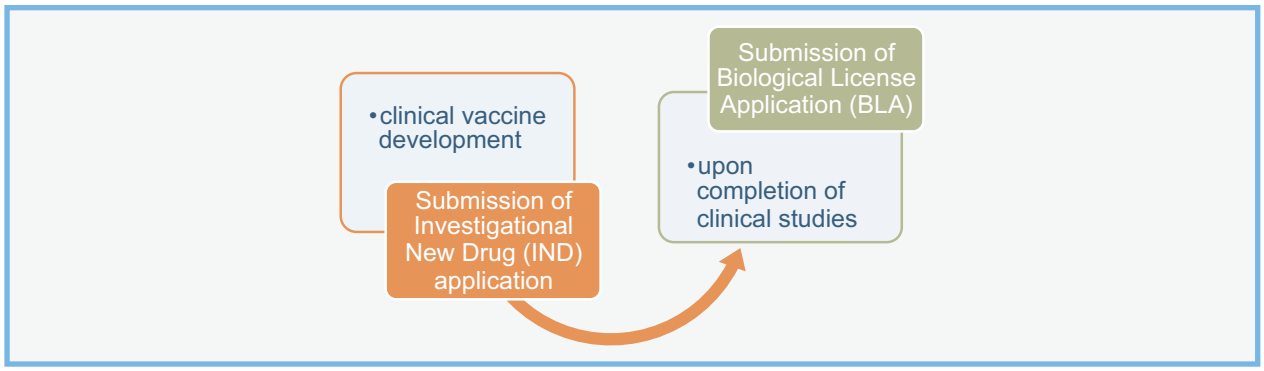


FIGURE 41. PERMISSIONS THAT MUST BE SOUGHT FROM THE FDA'S CBER FOR THE DEVELOPMENT AND SALE OF VACCINES

[60] GlaxoSmithKline. Global Vaccines Public Policy Issues. Addressing developing world production—technology transfer. December 2009. http://www.gsk.com/policies/Technology-Transfer-Vaccines.pdf

[61] Cutliffe N. 2010. Pathway to access: Manufacturing, supply, and procurement systems. In: Building on the legacy of vaccines in Canada: value, opportunities, and challenges. BIOTECH Canada. http://www.biotech.ca/uploads/vic/vaccines_7_2010.pdf

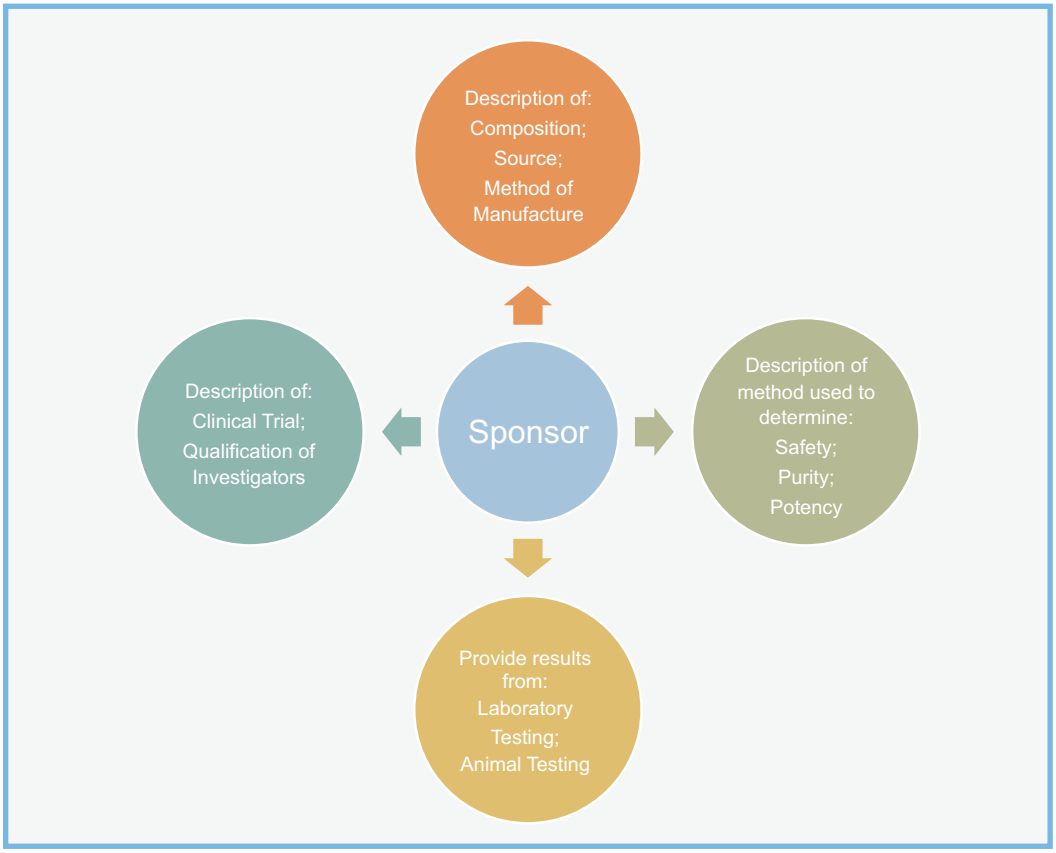


FIGURE 42. REQUIREMENTS FOR AN IND APPLICATION

When studies are near completion and show promise of safety and efficacy, the sponsor may submit a Biologics License Application (BLA) to the CBER Office of Vaccines Research and Review (OVRR). The application must submit evidence of compliance with standards for all of the requirements shown in **Table 12**. In addition, the application must include a description of:

- the manufacturing process;
- data on stability;
- product samples and lot test results;
- samples labels, enclosures and containers;
- address of locations of manufacture; and,
- an environmental assessment.

Evidence of Compliance	Required submissions
Organization and personnel	Manufacturing process
Buildings and facilities	Stability data
Equipment	Lot testing results
Control of components, containers and closures	Product samples
Production and process controls	Sample labels
Packaging and labeling controls	Enclosures and containers
Holding and distribution	Environmental assessment of manufacture
Laboratory controls	
Records to be maintained	

TABLE 12. REQUIREMENTS FOR A BLA SUBMISSION

The BLA also includes a site inspection. This involves an in-depth review of:

- facilities;
- records;
- production processes;
- equipment;
- quality control methods; and,
- personnel.

Once a vaccine has been licensed, post-marketing regulation requires manufacturers to submit test samples and test results from each production lot. CBER must "release" or reject the lot based on the results submitted and/or its own testing. Manufacturers are inspected at least every 2 years (every year for influenza vaccine producers, since there is a new influenza formulation every year) for:

- process related issue (documentation of processes);
- quality related issues (reporting of out-of-specs, product release, training of personnel); and,
- facility and production related issues (heating, ventilation, air conditioning).

(See **Figure 43**)

How Vaccines are Regulated in Countries Other than the US

Industrialized countries have similar regulatory agencies to the US FDA's CBER. But each country's requirements of vaccine manufacturers are slightly different. In addition, supra-national regulators, like the EU's Committee for Medicinal Products for Human Use (CHMP) at the EMA, may also regulate vaccines.

In Europe, manufacturers can license vaccines either through a centralized procedure of the EMA, which allows for a single market authorization within EU member states, or they can alternately license through their national regulatory authority. If they license through their national regulatory agency, licenses will be limited to the country where the license was issued.

Regulatory Harmonization

Europe, the US and Japan, have sought to increase regulatory harmonization between countries through the ICH of drugs. Increasingly, national regulatory agencies are exchanging information. The EMA and US FDA, for instance, have confidentiality agreements that allow for the exchange of information on legal and regulatory issues, inspection reports, and post-marketing surveillance. The US FDA also has similar confidentiality agreements with the NRAs of Australia, Canada, France, Germany, Israel, Japan, Mexico, New Zealand, Ireland, Singapore, South Africa, Switzerland and the UK.

FIGURE 43. AREAS INSPECTED BY CBER AT VACCINE MANUFACTURING SITES

2.5 Vaccine Funding

Routine immunization of children is considered one of the most cost-effective interventions in health. Governments have a vested interest in immunization because, in addition to protecting the individual, immunizations also protect the community from disease. Therefore, all governments recommend vaccines for public use as a cost-effective means to reduce the occurrence of diseases and their associated treatment or management costs.

Which vaccines a government recommends depends on several factors. For example:

- the epidemiology of a vaccine-preventable disease (i.e. how frequently it occurs, how many people it affects when it does occur);
- the severity of a disease (i.e. whether it can be fatal); and,
- the public's concern over for the disease (e.g. meningitis).

How governments select which vaccines to use is also variable from country to country. Usually, governments rely on their NITAGs to review the balance of benefits and risks associated with available (or soon to be available) vaccines. Their recommendations may be periodically reviewed and modified, if epidemiology changes (e.g. the eradication of smallpox) or safety issues arise.

Many countries are also mandated by their national laws to fund recommended vaccines, to ensure that the target population has sufficient access to recommended vaccines.

2.5.1 US Advisory Committee on Immunization Practices (ACIP)

The goals of the ACIP are to provide advice that will reduce incidence of disease and increase safe use of vaccines. The committee members are appointed by the Secretary of HHS to provide guidance to HHS and the CDC on the control of vaccine-preventable diseases. The committee develops written recommendations on age of vaccination, number of doses, and contraindications. HHS and the CDC must endorse ACIP's recommendations for them to be enacted.

ACIP's recommendations are the basis for the annual CDC "childhood and adolescent" and "adult" immunization schedules. Vaccines recommended for routine administration in children are covered by the VFC. The VFC covers children up to 18 years of age who are eligible for Medicaid, uninsured, native American, or underinsured. These vaccines are provided to private sector providers for vaccination of eligible children (about 45% of birth cohort) (See **Figure 44**). Historically, HHS and the CDC have endorsed all ACIP recommendations.

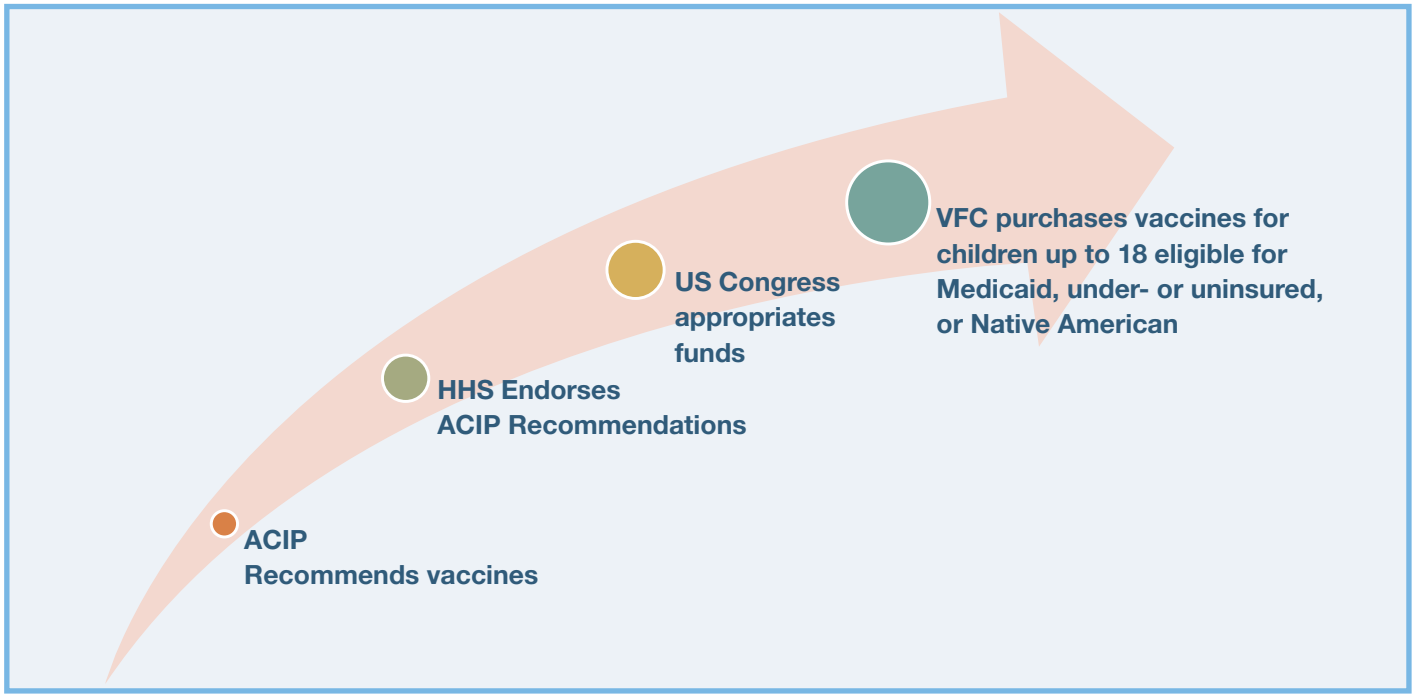


FIGURE 44. FUNDING FOR THE VFC PROGRAM IN THE US

> The goals of the ACIP are to provide advice that will reduce the incidence of disease and increase safe use of vaccines.

2.5.2 Australia

The decision to adopt a vaccine into the national immunization schedule includes advice from the ATAGI and an economic assessment of the candidate vaccine by the PBAC. A decision to adopt a vaccine incurs an obligation to fund the new vaccine. The decision is made by the Minister for Health and Ageing, or the government's cabinet, if funding of more than AUS$ 10 million are required (See **Figure 45**).

The NIC, in turn, is responsible for the implementation of the Immunize Australia Program. The Immunize Australia Program provides vaccines at no charge through the National Immunization Program (NIP) Schedule which currently includes 16 vaccines[62].

Funding is provided by the Australian government through a number of channels, including governments of States and Territories for the NIP, Medicare (the universal health insurance in Australia), the subsidy of immunization provided through private care, and to the Victorian Cytology Service for the administration of HPV (See **Figure 46**).

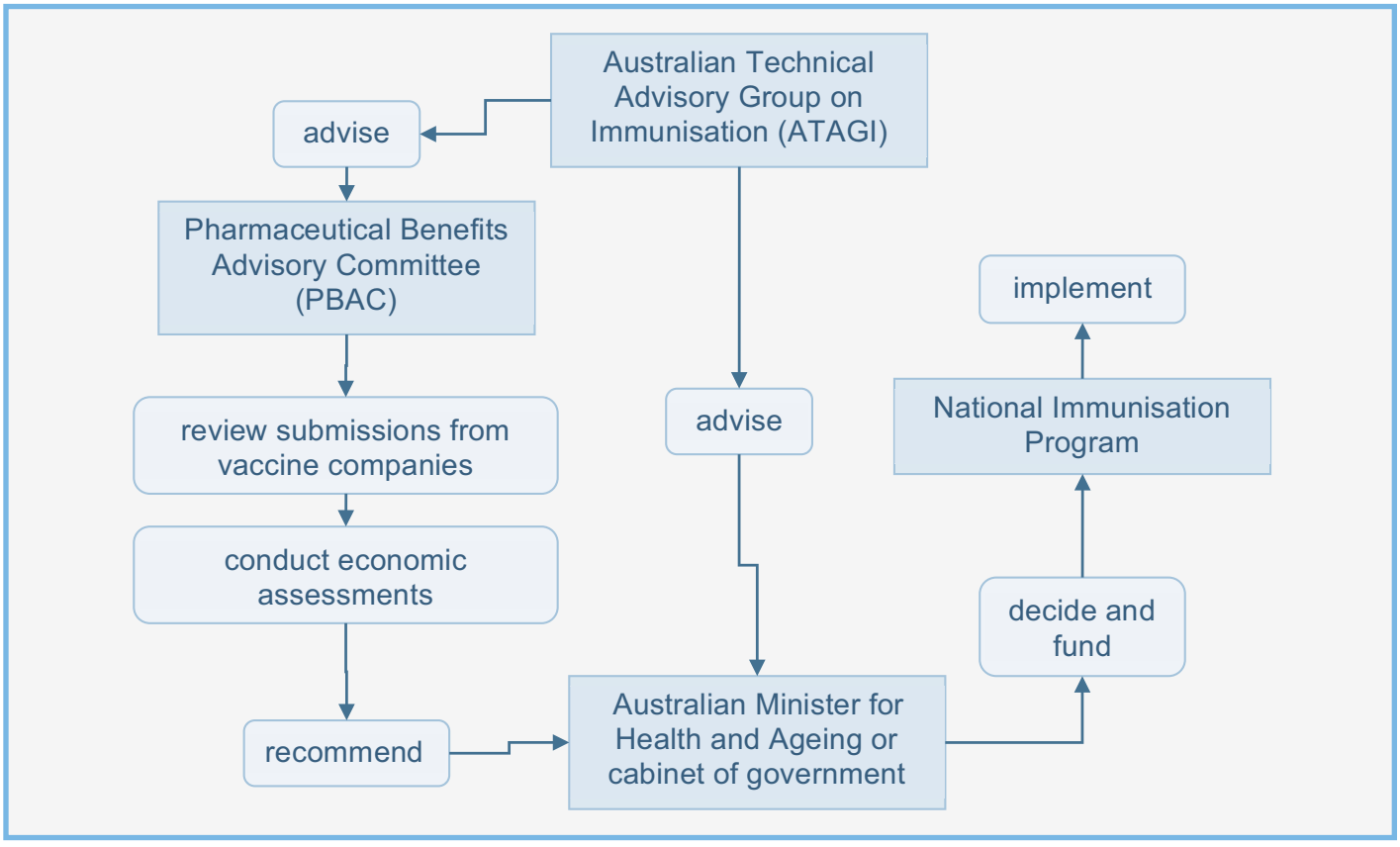


FIGURE 45. DECISION-MAKING PROCESS FOR VACCINE FUNDING IN AUSTRALIA

[62] Australian Government. Department of Health and Ageing. Immunise Australia Program. About the Program. http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/about-the-program

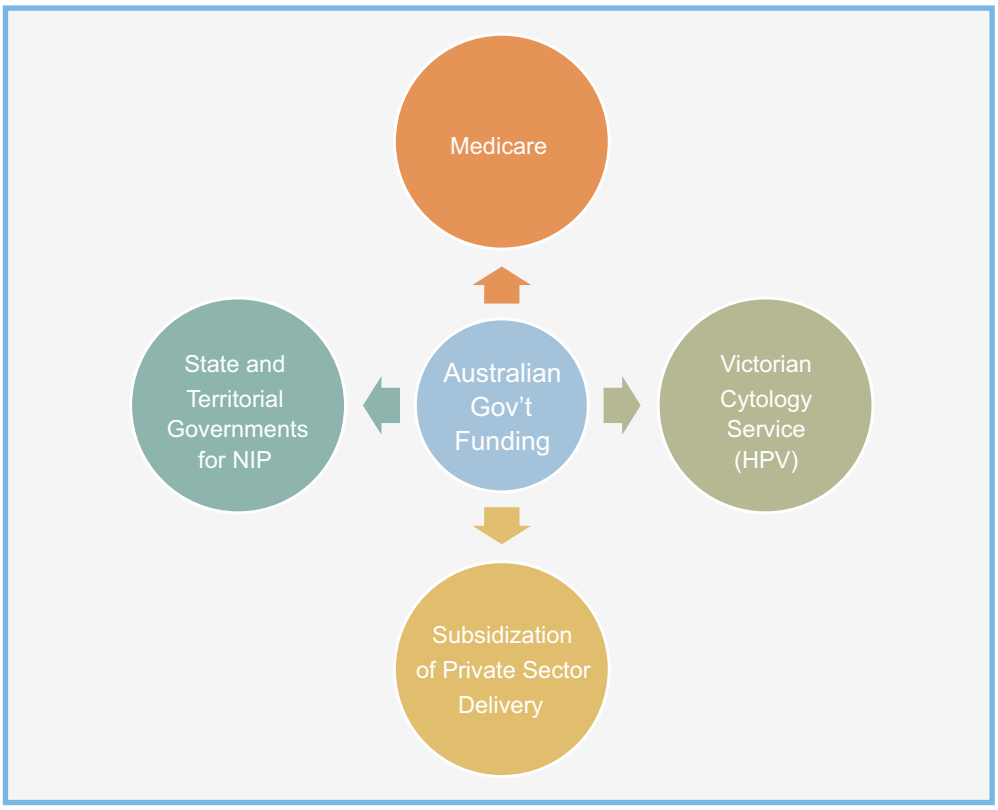


FIGURE 46. CHANNELS OF GOVERNMENT FUNDING FOR IMMUNIZATION IN AUSTRALIA

2.5.3 Other

Most industrialized countries have similar advisory groups (see **Table 11**, Section 1.8, page 41) and formal funding processes for immunization. In Europe, the source of funding varies between countries. In Germany, the costs of immunization are covered mostly by statutory insurance provided by employers. In other European countries, like the UK, the national government provides for all recommended vaccines to the public at no cost.

Most countries in the Asia-Pacific region rely on national expert immunization committees to recommend vaccines and most countries then provide recommended vaccines at no cost through public sector health outlets.

Many developing countries do not have functioning NITAGs and may rely heavily on WHO for immunization policy and on donor funding for immunization. A full review of NITAGs is available in *Vaccine* at: http://www.sivacinitiative.org/download/Vaccine_Supplement_NITAGs_19042010.pdf.

3.1 Polio Eradication, Global

The Cause[63]

Poliomyelitis is a paralyzing, sometimes fatal, viral disease that dates back more than 3,000 years (See **Image 7** and **Image 8**). But the disease was not described in the medical literature until 1789. It remained relatively uncommon until the 19th century when small outbreaks began occurring in Europe. By the end of the 19th century, polio was occurring in epidemics in Europe and North America. Karl Landsteiner and Eric Popper identified the causative virus in 1908. Their discovery paved the way for the development of a vaccine.

Image 7. Egyptian stele portraying priest with polio
SOURCE: HTTP://UPLOAD.WIKIMEDIA.ORG/WIKIPEDIA/COMMONS/5/5C/POLIO_EGYPTIAN_STELE.JPG

Image 8. Bilateral polio of the legs
SOURCE: HTTP://WWW.POLIOERADICATION.ORG/POLIOAND PREVENTION.ASPX

In 1931, Burnet Mcnamara discovered that polio was caused by more than one strain of the virus and by 1951 it was understood that there were 3 types of polio virus: types 1, 2, and 3. This was critical for the development of a protective vaccine. In 1949, Enders, Weller and Robbins won a Nobel Prize for demonstrating how virus could be cultured in order to produce a vaccine.

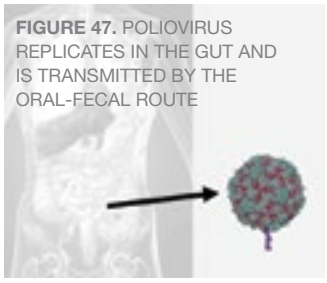


FIGURE 47. POLIOVIRUS REPLICATES IN THE GUT AND IS TRANSMITTED BY THE ORAL-FECAL ROUTE

The disease is spread by the oral-fecal route (See **Figure 47**).

The Impact of the Disease

Prior to a vaccine, the US experienced an average of 20,000 cases of polio annually. By 1988, an estimated 350,000 cases were occurring annually in 127 countries. Because effective vaccines were already available and being widely used, the World Health Assembly (WHA), the decision making body of the WHO, resolved to eradicate polio from the planet by the year 2000. At that time, polio had already been virtually eliminated from North America, Western Europe and Japan. The goal has not been achieved, but the number of cases of polio is at an all time low and intense efforts are underway to achieve the goal as soon as possible.

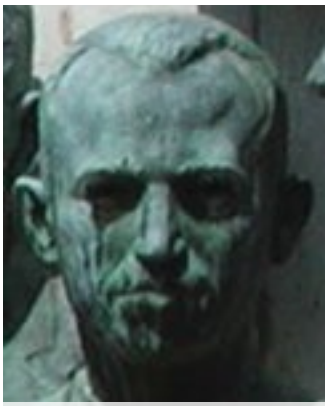


Image 9. Bust of Jonas Salk

Image 10. Albert Sabin
SOURCE: HTTP://UPLOAD.WIKIMEDIA.ORG/WIKIPEDIA/COMMONS/B/B9/ALBERT_SABIN.JPG

The Vaccine

The first polio vaccine was developed by Jonas Salk (See **Image 9**) in 1955. His vaccine was produced from inactivated virus. A live-attenuated oral polio vaccine was later developed by Albert Sabin (See **Image 10**) in 1963. Both vaccines were trivalent vaccines incorporating all three types. The development of safe and effective vaccines allowed for mass immunization on a national scale. Vaccines made the goal of polio eradication possible, given that polio is strictly a disease of humans, transmitted directly from one person to another.

Both vaccines are still in use today. The inactivated vaccine is widely used in industrialized countries. The live-attenuated vaccine is primarily used in developing countries.

The impact of the Vaccine

The introduction of a vaccine in 1955 had an almost immediate effect. Cases of indigenous polio began disappearing altogether

[63] Sutter RW, Kew OM, Cochi SL. Polio vaccine-live. pp 632. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.

within a few years. Sweden introduced a vaccine in 1957 and by 1962 had stopped wild polio transmission. Iceland introduced vaccine in 1956 and by 1960 had no more wild polio. Likewise, in the US, the incidence of polio fell by 95% between the introduction of a vaccine in 1955 and 1961, in spite of incomplete vaccination coverage[64] (See **Figure 48**)[65].

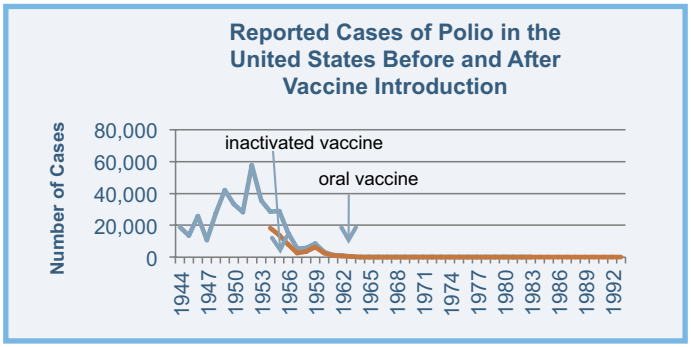


FIGURE 48. IMPACT OF IMMUNIZATION ON CASES OF POLIO IN THE UNITED STATES

In 1988, a global polio eradication initiative was launched. The state of polio before the launch is shown in **Figure 49.** Over 350,000 cases of paralytic polio were estimated to occur annually. Under the eradication initiative, children received polio immunization either through a routine pediatric schedule or in mass campaigns, or both. By 1994, 2000, and 2002, wild polio transmission was certified eliminated in all of the Americas, the Western Pacific, and Europe respectively[66]. And by 2010, polio was endemic in only 4 countries: Afghanistan, India, Nigeria and Pakistan[67].

Wild polio type 2 virus was globally eradicated in 1999, but wild type 1 and 3 polioviruses continue to be transmitted in three endemic countries (Afghanistan, Pakistan, and Nigeria) and cases have been imported into Somalia and Kenya in 2013. By mid-2013, the number of cases reported globally were down to 34[68].

The current state of polio is shown in **Figure 50**. Countries reporting cases in 2013 are shown in **Figure 51**[69].

Stopping immunization after the spread of polio has been interrupted exposes countries to risk. Live-attenuated vaccine viruses can survive in the environment for a period of time, and they can spread from human to human. Under these conditions, live-attenuated vaccine viruses can revert to their wild form. After immunization ceases, a reverted live-attenuated poliovirus could accidentally be reintroduced into a population. As a consequence, even after polio has been globally eradicated, many countries will opt to continue to immunize indefinitely with an inactivated vaccine.

All countries are now required to introduce at least one dose of IPV in infant immunization schedules by end of 2015[70].

The economic impact of polio immunization: In the absence of polio control, the cost of treating polio cases, in the US alone, has been estimated to approach $1 billion annually[71]. Globally, polio eradication is estimated to have incremental net benefits of $40–50 billion between 1988 and 2035[72].

> Prior to a vaccine, the US experienced an average of 20,000 cases of polio annually. By 1988, an estimated 350,000 cases were occurring annually in 127 countries.

[64] Plotkin SA, Vidor E. Polio vaccine-inactivated. pp 620–623. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[65] US CDC. MMWR Summary of notifiable diseases, United States, 1993. http://www.cdc.gov/mmwr/preview/mmwrhtml/00035381.htm
[66] Global Polio Eradication. History of Polio. http://www.polioeradication.org/Polioandprevention/Historyofpolio.aspx
[67] Global Polio Eradication. Infected countries. http://www.polioeradication.org/Infectedcountries.aspx
[68] Global Polio Eradication. Data and monitoring. http://www.polioeradication.org/Dataandmonitoring.aspx
[69] Global Polio Eradication. Data and monitoring. Polio this week. http://www.polioeradication.org/Dataandmonitoring/Poliothisweek.aspx
[70] Global Polio Eradication Initiative Strategic Plan. Dec 7, 2012. http://www.polioeradication.org/Portals/0/Document/Resources/StrategyWork/GPEIStrategicPlan_DRAFTMonitoringFramework07Dec2012.pdf
[71] Sutter RW, Kew OM, Cochi SL. Polio vaccine-live. pp 643. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[72] Duintjer Debbens RJ, Pallansch MA, Cochi SL, et al. Economic analysis of the global polio eradication initiative. Vaccine 2010; 29: 334–343.

Data is projected to 2008 WHO legal template

FIGURE 49. IN 1988, 125 COUNTRIES HAD RECURRING (ENDEMIC) POLIO DISEASE (COUNTRIES IN RED)

Data at HQ as of 19 July 2011

FIGURE 50. TOTAL NUMBER OF COUNTRIES REPORTING WILD POLIO VIRUS DISEASE IN MID-2013 (RED DOTS)

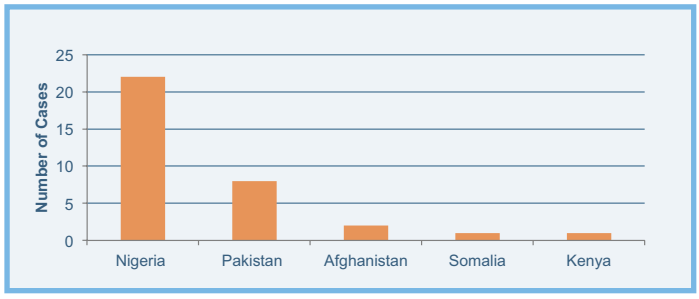


FIGURE 51. COUNTRIES REPORTING POLIO CASES IN 2013

3.2 Haemophilus Influenzae Type b (Hib)

The Cause

Haemophilus influenzae type b (Hib) is a bacteria responsible for meningitis, pneumonia, and other invasive diseases particularly in infants and children under 5 years of age (See **Image 11**).

There are six serotypes of the polysaccharide encapsulated *Haemophilus influenzae*. Type b accounts for 95% of all serious diseases caused by this microorganism. Non-encapsulated, non-typable forms of the bacteria also exist.

The microorganism is carried in the pharynx and spread by respiratory droplets (**Figure 52**).

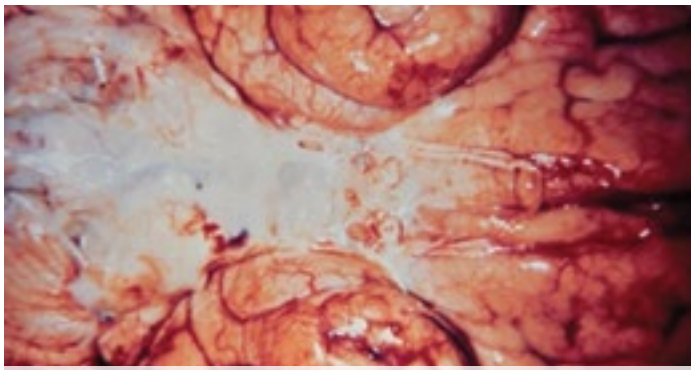


Image 11. Purulent meningitis from Hib.
SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY

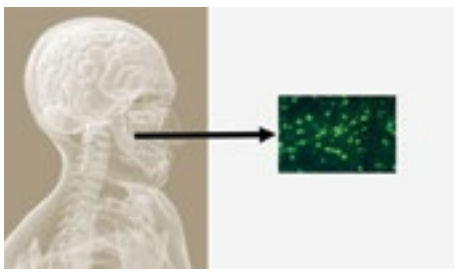


FIGURE 52. NASOPHARYNGEAL CARRIAGE AND AEROSOL SPREAD OF HIB
SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY

The Impact of the Disease[72,73,74]

Prior to immunization, about 3 million cases and 400,000 annual deaths were attributable to Hib globally. Incidence in the US was 20–88/100,000 children under 5 years of age, or about 20,000 cases annually, over half of which were cases of meningitis. Incidence was much higher in some native American populations, reaching 491/100,000 in children under 5 years.

In Europe, rates comparable to those of the US were observed. In Africa, the Pacific Islands, and the Middle East incidences were very high. Incidence in the < 1 year age group is the highest at as many as 200 cases of meningitis/100,000 in Africa. Case fatality rates from meningitis can be as high as 40%, depending on the setting.

In Asia incidence has been found to be lower than elsewhere, but some experts believe that this is likely due to masking of the disease from widespread use of antibiotics.

Figure 53 shows reported incidences of Hib disease in children under 5 years of age, prior to the introduction of a vaccine.

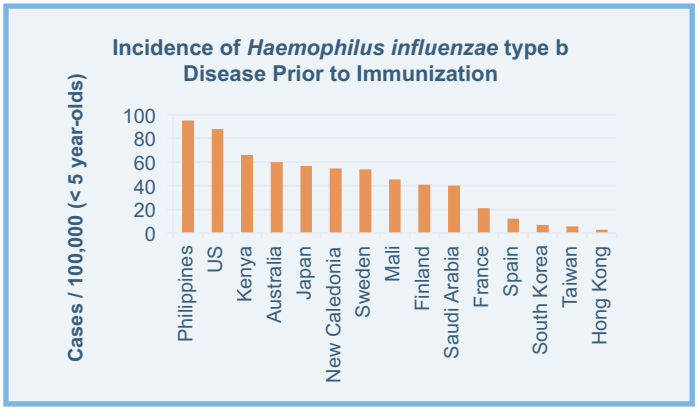


FIGURE 53. INCIDENCE OF HIB DISEASE FROM SELECT COUNTRIES, IN CHILDREN < 5 YEARS OF AGE, PRIOR TO IMMUNIZATION (WHERE RANGES OF INCIDENCE ARE REPORTED, THE HIGHEST VALUES ARE SHOWN)

[72] Chandran A, Watt JP, Santosham M. *Haemophilus influenzae* vaccines. pp 162. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[73] Hib Initiative. Research and Surveillance. http://www.hibaction.org/research.php#disease_burden
[74] Broker M. Burden of invasive disease caused by *Haemophilus influenzae* type b in Asia. Jpn J Infect Dis 2009; 62: 87–92.

The Vaccine

The first vaccine developed in the early 1980s was a polysaccharide vaccine. Polysaccharide vaccines do not stimulate lasting immunity in children less than 2 years of age.

In 1987, the first protein conjugate polysaccharide vaccine was licensed for use in infants. Unlike polysaccharide vaccines, protein conjugate vaccines stimulate lasting immunity in young children. Today there are several licensed protein conjugate Hib vaccines. One of three different carrier proteins are used to conjugate (link) with the Hib polyribosylribitol phosphate (PRP) polysaccharide:

- tetanus toxoid;
- outermembrane protein complex of *Neisseria meningitidis* strain B_{11}; or
- nontoxic variant of diphtheria toxin from Corynebacterium diphtheria C7 (CRM_{197}).

Conjugate Hib vaccine is now usually provided in combination with DTP or DTaP containing vaccines.

The Impact of the Vaccine

Everywhere the vaccine has been introduced very rapid declines of over 90% in the rate of disease have been observed. In the US, since the introduction of a conjugate Hib vaccine, the incidence of the disease has declined by 99%[75]. African countries where the vaccine has been introduced have experienced marked declines in the incidence. The Gambia has reduced the incidence to 0 from a high of > 200 cases/100,000 in < 1 year-olds (See **Figure 9**)[76].

In the UK, the incidence of disease declined immediately after the introduction of a vaccine in a 3 dose primary series (See **Figure 54**)[77]. The incidence rose slightly in the late 1990s, but has fallen again since the introduction of a fourth booster dose at 12 months of age. Most countries deliver 3 doses in a primary series. Most industrialized countries also deliver a booster dose after 12 months of age.

The vaccine has also been found to have an important herd effect (See **Figure 11**). This is because the vaccine prevents the bacteria from being carried in the nasopharynx of those individuals vaccinated. Vaccinated individuals, in addition to not getting infected, do not spread the disease in the community. For this reason, in settings where immunization coverage has been less than optimal, declines in incidence of the disease have nevertheless been observed.

Countries that have introduced conjugate Hib vaccine have eliminated Hib disease as a public health problem.

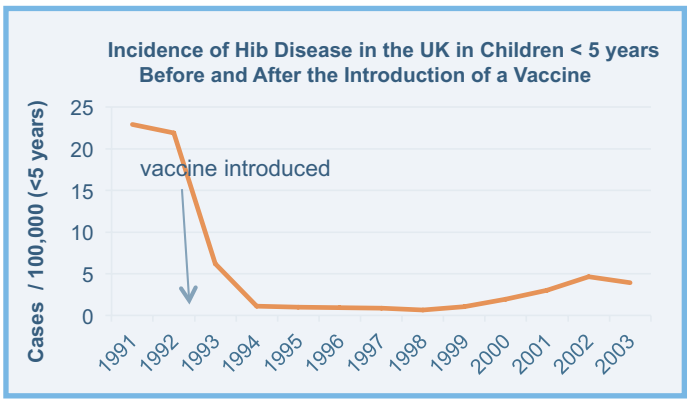


FIGURE 54. ALMOST IMMEDIATE IMPACT OF CONJUGATE HIB VACCINE ON THE INCIDENCE OF HIB IN < 5 YEAR OLDS IN THE UK

[75] Wikipedia. Hib vaccine. http://en.wikipedia.org/wiki/Hib_vaccine#Impact
[76] Adegbola RA, Secka O, Lahai G, et al. Ellimination of *Haemophilus influenzae* type b (Hib) disease from The Gambia after the introduction of routine immunisation with a Hib conjugate vaccine: a prospective study. *Lancet*. 2005;366(9480):144–50.
[77] McVernon J, Trotter CL, Slack MPE et al. Trends in *Haemophilus influenzae* type b infections in adults in England and Wales: surveillance study. BMJ 2004; 329: 655–658.

3.3 Mumps

The Cause[78]

Mumps is a viral disease first described by Hippocrates in the fifth century BC. The virus was identified by Johnson and Goodpasture in 1934. The virus most commonly invades the salivary glands causing swelling and pain (See **Image 12**). It is transmitted by respiratory droplets (See **Figure 55**).

The Impact of the Disease

Although children are often affected, outbreaks of the disease are noted to occur commonly in military personnel. In children, in addition to infection of the salivary glands (parotitis), the virus can cause lower respiratory disease. In adults, the virus causes inflammation of the testicles (orchitis) in 37% of post-pubertal men and inflammation of the breasts (mastitis) in 31% of post-pubertal women.

In the pre-vaccine era, mumps was the leading cause of viral encephalitis in the US. Neurological complications can occur from mumps encephalitis, including deafness.

In Japan, deafness from mumps has recently been found to occur at a higher incidence than previously thought. Deafness was thought to occur in about 0.5–5.0/100,000 cases of mumps. Hashimoto et al. found the incidence of deafness from mumps to be approximately 1/1,000 in Japan[79]. In 2005, Kawashima et al. found that the number of cases of deafness from mumps was steadily increasing in Japan[80]. The number of cases in 1987 was estimated at 300, but had jumped to 650 by 2001. The increase in the number of cases of deafness correlated with an increase in the incidence of mumps. Complications of mumps are summarized in **Table 13**.

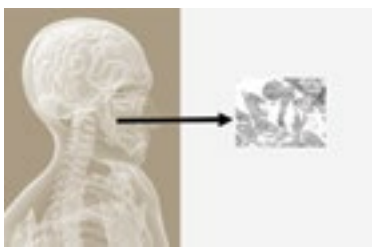


FIGURE 55. MUMPS IS TRANSMITTED BY AEROSOL ROUTE
SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY
HTTP://PHIL.CDC.GOV/PHIL/DETAILS.ASP?PID=8757

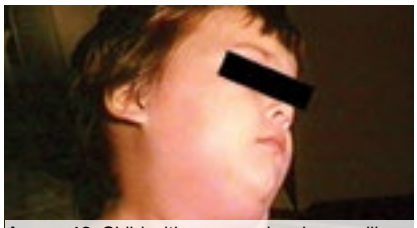


Image 12. Child with mumps showing swelling of the salivary glands.
SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY
HTTP://PHIL.CDC.GOV/PHIL/DETAILS.ASP?PID=130

The Vaccine[81]

The first vaccines from the 1950s were formalin-inactivated and did not impart lasting immunity. Instead, live-attenuated vaccines replaced inactivated vaccines in the 1960s. Thirteen different vaccine strains are produced today in several different types of cells.

Mumps vaccine is available as a monovalent or in combination with measles (MM), or measles and rubella (MMR), or measles, rubella and varicella vaccines (MMRV).

The Impact of the Vaccine

Prior to the use of mumps vaccines, the incidence of the disease was several hundred cases/100,000 population with most cases occurring in children from 5–9 years of age in industrialized countries. Countries that introduced mumps vaccine have virtually eliminated the disease. In the US, cases have declined by more than 98% since the introduction of a vaccine. Other countries that

Complication	Frequency
inflammation of the testicles (orchitis)	37% post-pubertal men
inflammation of the breasts (mastitis)	31% post-pubertal women
deafness	0.5–5.0/100,000 mumps cases; 1/1,000 mumps cases in Japan

TABLE 13. COMPLICATIONS AND FREQUENCIES OF MUMPS COMPLICATIONS

[78] Plotkin SA, Rubin SA. Mumps vaccines. pp 435–465. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[79] Hashimoto H, Fujioka M, Kinumaki H et al. An office-based prospective study of deafness in mumps. *Pediatr Infect Dis J* 2009; 28: 173-5.
[80] Kawashima Y, Ihara K, Nakamura M et al. Epidemiological study of mumps deafness in Japan. *Auris Nasus Larynx* 2005; 32: 125–128.
[81] Plotkin SA, Rubin SA. Mumps vaccines. pp 435–465. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.

have used mumps vaccine have experienced similar declines in cases (See **Figure 56**)[82].

The efficacy of mumps vaccines varies by strain, the number of doses used, and by outbreak settings. In initial clinical trials with the Jeryl Lynn strain, efficacy ranged from 92–96%. When studied in outbreaks (in the US) efficacy has ranged from 78–91%. Efficacy with other strains of vaccine in other countries has generally been within these ranges.

Mumps vaccines are associated with a very small risk of aseptic meningitis, which varies by strain and by manufacturer. But the long-term effects of post-vaccine meningitis are either very rare or absent. Furthermore, the risk of meningitis from natural mumps infection is much higher (1–10%). In Japan, mumps immunization was found to lower the risk of aseptic meningitis by 25-fold compared to natural mumps infection[83].

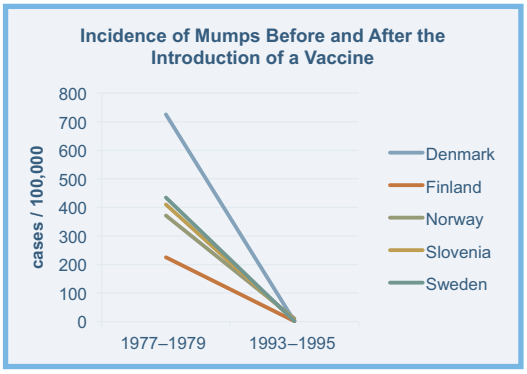


FIGURE 56. DECLINE IN INCIDENCE OF MUMPS FOLLOWING THE INTRODUCTION OF A VACCINE IN A TWO-DOSE SCHEDULE

3.4 Measles Eradication, Global

The Cause[84]

Measles is one of the most contagious viral diseases. It causes a rash, acute upper respiratory illness, and can lead to complications that can be fatal, especially in children (See **Image 13**). In ancient times, the disease was confused with other rash-causing diseases, including smallpox. It was recognized as a separate disease by the end of the 17th century. It was understood to be caused by an infectious agent by the beginning of the 20th century. The disease is spread by aerosol (See **Figure 57**).

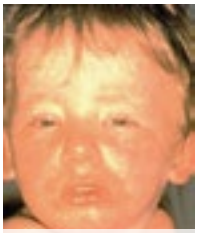


Image 13. Measles rash.
SOURCE: CDC

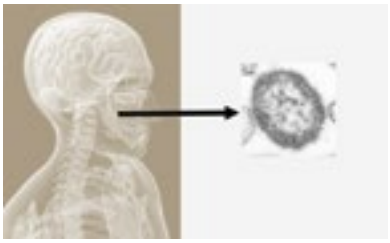


FIGURE 57. TRANSMISSION OF MEASLES VIRUS IS BY AEROSOL ROUTE
SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY
HTTP://PHIL.CDC.GOV/PHIL/DETAILS.ASP?PID=8429

The measles virus was first isolated in 1954 by Enders and Peebles and developed into a live-attenuated vaccine by 1963.

The Impact of the Disease[85]

The case-fatality rate in industrialized countries is about 1–3 deaths/1,000 cases, but is several times higher in developing countries and can reach 15%. In the pre-vaccine era, because of the highly contagious nature of the disease, virtually everyone in industrialized countries was infected with the measles virus by adolescence. In developing countries all children could be infected by as early as 4 years of age. It was a leading cause of infant deaths, blindness, and disability.

In 2000, measles remained the leading cause of death in children from a vaccine-preventable disease and the fifth most frequent cause of all deaths in children under 5 years of age, killing about 777,000 children every year.

[82] Plotkin SA, Rubin SA. Mumps vaccines. pp 440–442. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[83] Plotkin SA, Rubin SA. Mumps vaccines. pp 451–452. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[84] Strebel P, Papania MJ, Dayan GH et al. Measles vaccines. pp 353–398. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[85] Strebel P, Papania MJ, Dayan GH et al. Measles vaccines. pp 358–359. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008

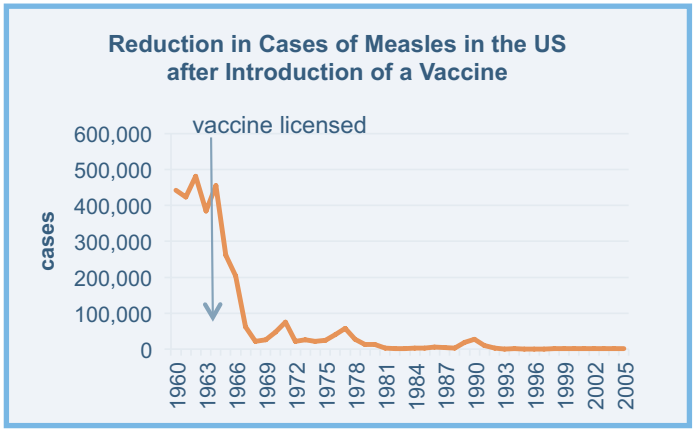


FIGURE 58. DECLINE IN CASES OF MEASLES IN THE US AFTER INTRODUCTION OF A VACCINE

The Vaccine

Measles vaccines are live-attenuated, produced on chick embryo fibroblasts. Unlike polio and some other viruses, there is a single serotype of measles virus.

Measles vaccines are highly effective (90–95%) against wild virus. Initially, a single dose in infancy or early childhood was recommended in most immunization schedules. With increasing measles control, a second dose of measles vaccine is now recommended in most immunization schedules, at varying intervals after the first dose. In the US, a first dose is recommended at 12–15 months and a second dose at 4–6 years of age.

Some countries (Canada, UK, Australia, New Zealand) have also conducted a one-time nationwide campaign among school children to reduce the number of persons at risk. Most industrialized countries also now deliver measles vaccine in combination with mumps and rubella vaccines MMR (also live-attenuated viral vaccines). Most recently, some industrialized countries have introduced a combination vaccine containing measles, mumps, rubella, and varicella (MMRV) in childhood immunization schedules. Developing countries often use measles vaccine alone.

Adverse events are mild and commonly include fever and/or rash in 5–15% of recipients (or higher rates with MMR or MMRV). Evidence does not support any causal relation to irritable bowel syndrome or childhood autism.

The Impact of the Vaccine

Prior to the introduction of the vaccine, virtually every child became infected with measles. In the US alone, this amounted to almost half a million infections every year. Today, it is estimated that 2.7 million deaths would occur worldwide, every year, in the absence of measles immunization[86]. Most industrialized countries introduced measles vaccines in the 1960s and have since experienced remarkable declines in disease incidence (See **Figure 58**)[87,88].

However, because the virus is so highly transmissible, the elimination of wild measles virus requires a 2 dose vaccination strategy. In the Americas, intense efforts in the 1980s and 1990s to eliminate measles included mass immunization campaigns to increase immunization coverage and to immunize the un-immunized or re-immunize the previously immunized.

The economic impact of measles immunization: In the US, in 2001 dollars, the benefit : cost ratio was estimated at 14.2 for direct costs and 26.0 for indirect costs[89]. Likewise, in Australia, economic analyses suggest that measles immunization results in a net benefit to the community of $9.1 billion, or $8.5 billion to the government[90].

The Goal of Eradication

Because of the high morbidity and mortality associated with measles in the absence of immunization, and because of the excellent benefit : cost ratio for measles immunization, 5 out of 6 regions of the world have set elimination targets for measles: Americas by 2000; Europe and Middle-east by 2010; western Pacific by 2012, and Africa by 2020. The Americas have achieved a 99% reduction in disease since 1990 and the transmission of virus is considered interrupted. The remaining cases that occur in the Americas are primarily from persons who have travelled to the US and spread their infection.

[86] American Academy of Pediatrics. Why Immunize? http://www.aap.org/advocacy/releases/whyimmunize.htm
[87] CDC. Summary of notifiable diseases, United States, 1994. MMWR 1995; 43:1. http://www.cdc.gov/mmwr/preview/mmwrhtml/00039679.htm
[88] CDC. Summary of notifiable diseases, United States, 2005. MMWR 2007; 54: 2-92. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5453a1.htm
[89] Strebel P, Papania MJ, Dayan GH et al. Measles vaccines. pp 359. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[90] Applied economics. Immunisation programs: measles and Hib disease. http://www.appliedeconomics.com.au/pubs/reports/health/ph05.htm

The WHO, in 2003, resolved to halve the deaths from measles by 2005, by increasing routine immunization coverage and delivering supplemental immunizations. Now a 2 dose strategy is endorsed for all countries, regardless of economic status or vaccine coverage. The eradication (global elimination) is technically feasible, but will require very high vaccination coverage to achieve.

Enormous progress toward a goal of eradication has been made in all regions of the world. Deaths from measles have declined by more than 50% (See **Figure 59**)[91].

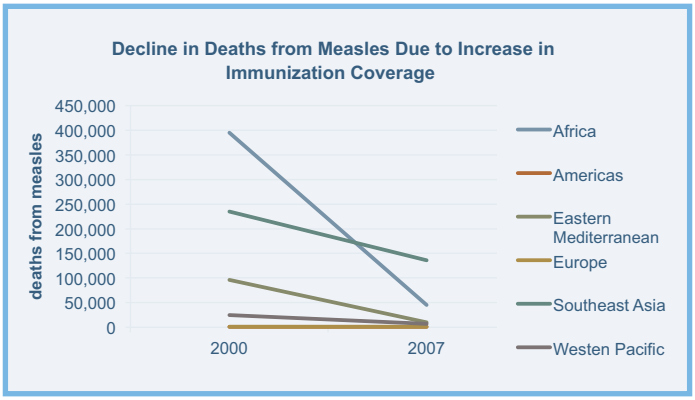


FIGURE 59. DECLINE IN THE NUMBER OF DEATHS FROM MEASLES DUE TO INCREASED IMMUNIZATION COVERAGE

3.5 Rotavirus

The Cause

Rotavirus is a highly contagious common viral disease spread by oral-fecal route (See **Figure 60**). It is the most common cause of severe diarrhea in infants and young children (See **Image 14**). There are five groups of rotaviruses: A, B, C, D and E. Group A contains animal and human serotypes (strains). Fourteen "G" serotypes and several "P" types are known to exist, but only six "G" serotypes are commonly associated with human disease: G1, G2, G3, G4, G9, and G12. Each of these "G" types is further characterized by a "P" type which is numbered. Common types of virus circulating in the US are P[8]G1, P[4]G2, P[8]G3, P[8]G4, P[8]G9, and P[6]G9[92].

These viruses multiply in the gut, and transmission of the disease is from person to person contact—not from contaminated water and food.

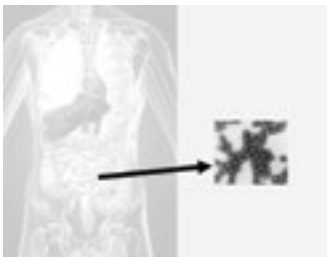


FIGURE 60. TRANSMISSION OF ROTAVIRUS BY FECAL-ORAL ROUTE
SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY
HTTP://PHIL.CDC.GOV/PHIL/DETAILS.ASP?PID=197

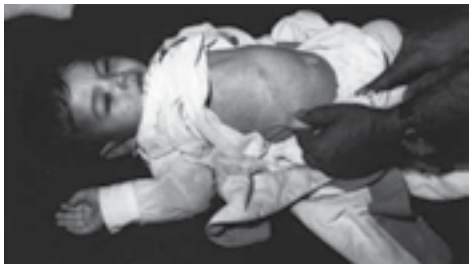


Image 14. Child dehydrated from rotavirus diarrhea.
SOURCE: WHO, D MAHALANABIS
HTTP://WWW.VACCINEINFORMATION.ORG/ROTAVIRUS/PHOTOS.ASP

The Impact of the Disease

Rotavirus is the most common cause of severe diarrhea in infants. It is responsible for 2.7 million episodes of illness per year in the US, and for about $1 billion in direct and indirect costs[93]. Globally, rotaviruses kill over 500,000 children every year and account for about 25% of deaths from all diarrheal diseases (See **Figure 61**)[94]. Rotavirus accounts for about 40% of hospitalization for diarrhea in children under 5 years of age, and approximately 100 million episodes of diarrhea every year.

[91] CDC. Progress in global measles control and mortality reduction, 2000–2007. MMWR 2008; 57: 1303–1306. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5748a3.htm?s_cid=mm5748a3_e
[92] CDC. Prevention of rotavirus gastroenteritis among infants and children recommendations of the ACIP. *MMWR* 2009; 58: 1–25. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5802a1.htm
[93] Clark HF, Offit PA, Parashar UD et al. Rotavirus vaccines. pp 715–734. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[94] Tate JE, Patel MM, Steele AD, et al. Global impact of rotavirus vaccines. *Expert Rev Vaccines* 2010; 9: 395–407

By 2–3 years of age all children have been exposed to rotavirus. In Asia, without rotavirus vaccination, an estimated 171,000 children will die of rotavirus by the age of 5 years, 1.9 million will be hospitalized, and 13.5 million will require an outpatient visit (See **Figure 62**)[95].

Because rotavirus is equally prevalent in industrialized countries, vaccines are also important for prevention in settings with good sanitation.

The Vaccine

Rotavirus vaccines are made from either a single strain (monovalent) of live-attenuated human rotavirus (GSK, Rotarix™) or from 5 (pentavalent) live-reassortant human-bovine viruses (Merck, RotaTeq™). Both are administered orally, in 2 and 3 doses, given before 24 and 32 weeks respectively.

The first rotavirus vaccine licensed for use in humans was made from simian-human reassortant rotaviruses. Careful study of AEFI showed that this vaccine was associated with a higher risk of the extremely rare event of intestinal folding (intussusception) (15 cases/1,000,000 children vaccinated). The risk was highest after a first dose of vaccine. Even though the public health benefits far exceeded the risks associated with intussusceptions, the simian-human reassortant vaccine was discontinued because of the concerns for liability.

Because of the history of the simian-human reassortant vaccine, the two currently licensed vaccines have been extensively evaluated for the risk of intestinal intussusception. Neither vaccine is associated with a higher risk of intussusceptions (See **Table 14**).

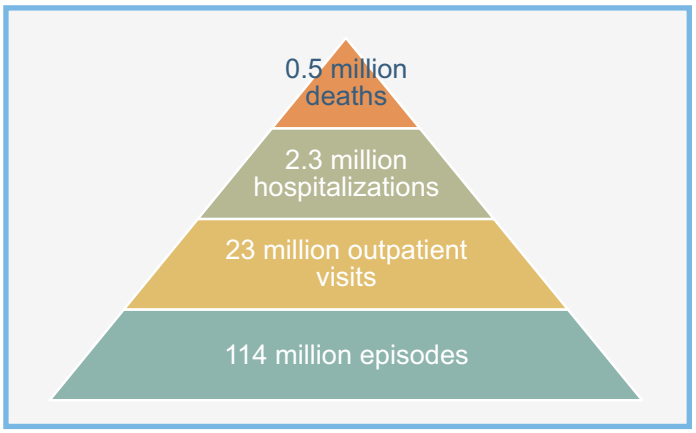


FIGURE 61. GLOBAL BURDEN OF ROTAVIRUS DISEASE

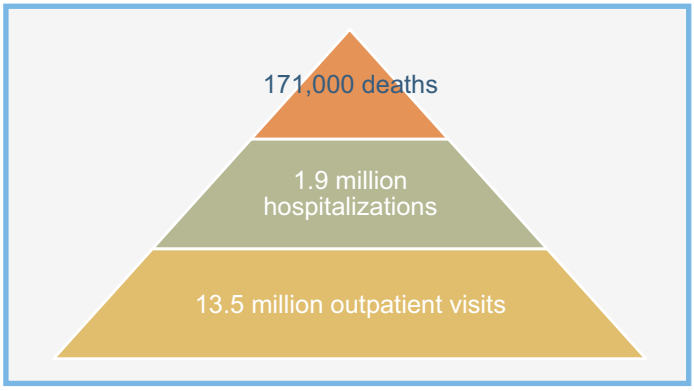


FIGURE 62. IMPACT OF ROTAVIRUS IN ASIA IN THE ABSENCE OF IMMUNIZATION

1 year after dose 1	Live Reassortant Human-Bovine Rotavirus (n = 34,837)	Placebo (n = 34,788)	Live-Attenuated Human Rotavirus (n = 10,159)	Placebo (n = 10,010)
Intussusception	13	15	4	14

TABLE 14. RISK OF INTUSSUSCEPTION IS NOT ELEVATED FOLLOWING ROTAVIRUS VACCINATION WITH LICENSED LIVE HUMAN-BOVINE REASSORTANT AND HUMAN LIVE-ATTENUATED VACCINES

[95] Podewils LJ, Antil L, Hummelman E, et al. Projected cost-effectiveness of rotavirus vaccination for children in Asia. *J Infect Dis* 2005; 192: s133-145.

Adverse events reported from both vaccines are mild and temporary and include vomiting, diarrhea, and fever. In clinical trials, these adverse events were reported at similar rates to those from the placebo groups (See **Table 15**).

Adverse Event	Live Reassortant Human-Bovine Rotavirus	Placebo	Live-Attenuated Human Rotavirus	Placebo
Vomiting	4%	3%	8%	8%
Diarrhea	6%	5%	3%	3%
Fever	18%	18%	28%	34%

TABLE 15. COMMON ADVERSE EVENTS FROM ROTAVIRUS VACCINES (SOLICITED WITHIN SEVEN DAYS AFTER THREE DOSES OF LIVE-REASSORTANT HUMAN-BOVINE ROTAVIRUS; WITHIN EIGHT DAYS AFTER TWO DOSES OF LIVE-ATTENUATED HUMAN ROTAVIRUS) [96,97]

The Impact of the Vaccine

The two currently licensed rotavirus vaccines have excellent efficacy, ranging from 85–98% against rotavirus disease. In some settings, the vaccines have reduced hospitalizations for diarrhea of any cause by 42–63% in children < 1 year of age[98] (See **Figure 63**)[99].

The impact of rotavirus vaccines has been almost immediate in countries where they have been introduced (See **Figure 64**)[100].

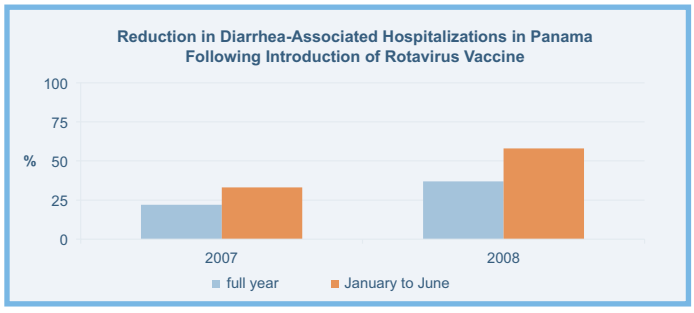


FIGURE 63. REDUCTION IN HOSPITALIZATION FOR ANY-CAUSE DIARRHEA IN CHILDREN < 5 YEARS IN PANAMA, FOLLOWING INTRODUCTION OF A ROTAVIRUS VACCINE IN 2006

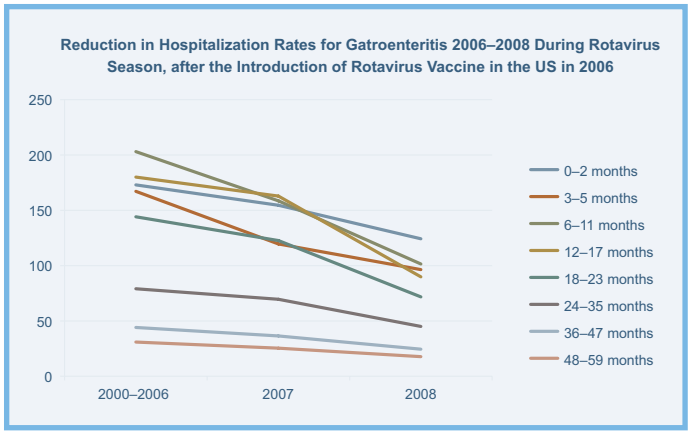


FIGURE 64. REDUCTION IN HOSPITALIZATION RATES FOR GASTROENTERITIS BY AGE GROUP DURING ROTAVIRUS SEASON IN THE US, FOLLOWING INTRODUCTION OF ROTAVIRUS VACCINE

[96] Merck. RotaTeq prescribing information. July 2011. http://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf
[97] GSK Source. Rotarix prescribing information. February 2011. https://www.gsksource.com/gskprm/en/US/adirect/gskprm?cmd=ProductDetailPage&product_id=1244173585205&featureKey=600594#nlmhighlights
[98] Sirica C and Wuethrich B. Roatvirus: interesting facts about a virus on the rise. Micobiowiki. Jan 9, 2009. http://microbiowiki.wetpaint.com/page/Rotavirus%3A+Interesting+facts+about+a+virus+on+the+rise
[99] Molto Y, Cortes JE, de Oliveira LH et al. Reduction of diarrhea-associated hospitalizations among children aged < 5 years in Panama following the introduction of rotavirus vaccine. *Pediatr Infect Dis* J 2011; 30: s16–s20.
[100] Curns AT, Steiner CA, Barrett M et al. Reduction in acute gastroenteritis hospitalizations among US children after introduction of rotavirus vaccine: analysis of hospital discharge data from 18 US states. *JID* 2010; 201(11):1617–1624.

Marked declines in the incidence of rotavirus disease have been observed in the seasons following rotavirus vaccine introduction in Latin America[101], Europe[102], Australia[103], and the US[104] (See **Table 16**).

Country	Impact	Vaccine Effectiveness
Australia	• 45% reduction in proportion of positive rotavirus tests in 2007; • 43% reduction in proportion of positive rotavirus tests in 2008; • 75% reduction in rotavirus hospitalizations in New South Wales in 2008–2009	• 85% against rotavirus infections; • 89.3% efficacy against rotavirus infections in Queensland
Austria	• 74% reduction in rotavirus-associated hospitalizations	• 61–98%
Belgium	• 65% reduction in mean hospitalization days from rotavirus gastroenteritis in 2007–2008; • 83% reduction in mean hospitalization days from rotavirus gastroenteritis in 2008–2009; • 50% reduction of rotavirus infections in 2008–2009; • 75% reduction in rotavirus positive gastroenteritis	
Mexico	• 42% reduction in any-cause diarrhea mortality; • 11% reduction in diarrhea-associated hospitalizations in 2007; • 40% reduction in diarrhea-associated hospitalizations in 2009	
El Salvador	• 79% reduction of rotavirus diarrhea; • 81% reduction in rotavirus-associated hospitalization in < 5 years in 2008; • 48% reduction in diarrhea-associated health visits during rotavirus season in 2008; • 35% reduction in diarrhea-associated health visits during rotavirus season in 2009; • 69% reduction in rotavirus-associated hospitalization in < 5 years in 2009	• 74% against severe and 88% against very severe rotavirus gastroenteritis
Nicaragua	• 23% reduction for any-cause diarrhea	• 52–63% against severe rotavirus gastroenteritis; • 73–86% against very severe rotavirus gastroenteritis
Panama	• 22% reduction in diarrhea-associated hospitalizations in < 5 years in 2007 (37% for Jan–Jun); • 37% reduction in diarrhea-associated hospitalizations in < 5 years in 2008 (58% for Jan–Jun)	
US	• 60% reduction in peak proportion of positive rotavirus tests in 2007–2008; • 42% reduction in peak proportion of positive rotavirus tests in 2008–2009; • 82% reduction in proportion of positive rotavirus tests in 2009–2010; • 16% reduction in hospitalization rates for any-cause diarrhea in < 5 years in 2007; • 46% reduction in hospitalization rates for any-cause diarrhea in < 5 years in 2008	

TABLE 16. IMPACT OF ROTAVIRUS IMMUNIZATION IN SELECT COUNTRIES[105, 99, 106, 98, 107, 98 108, 109]

[101] De Oliveira LH, Danovaro-Holliday C, Sanwogou NJ, et al. Progress in the introduction of the rotavirus vaccine in Latin America and the Caribbean—four years of accumulated experience. *Pediatr Infect Dis J* 2011; 30: s61–s66.

[102] Braeckman T, Herck KV, Raes M, et al. Rotavirus vaccines in Belgium—policy and impact. *Pediatr Infect Dis J* 2011; 30: s21–s24.

[103] Buttery JP, Lambert SB, Grimwood K, et al. Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's national childhood vaccine schedule. *Pediatr Infect Dis J* 2011; 30: s25–s29.

[104] Tate JE, Cortese MM, Payne DC, et al. Uptake, impact, and effectiveness of rotavirus vaccination in the United States—review of the first three years of postlicensure data. *Pediatr Infect Dis J* 2011; 30: s56-s60.

[105] Tate JE, Patel MM, Steele AD, et al. Global impact of rotavirus vaccines. *Expert Rev Vaccines* 2010; 9: 395–407.

[106] Tate JE, Mutuc JD, Panozzo CA, et al. Sustained decline in rotavirus detections in the United States following the introduction of rotavirus vaccine in 2006. *Pediatr Infect Dis J 2011*; 30: s30–s34.

[107] Molto Y, Cortes JE, de Oliveira LH et al. Reduction of diarrhea-associated hospitalizations among children aged < 5 years in Panama following the introduction of rotavirus vaccine. *Pediatr Infect Dis J* 2011; 30: s16–s20.

[108] Quintanar-Solares M, Yen C, Richardson V, et al. Impact of rotavirus vaccination on diarrhea-related hospitalizations among children < 5 years of age in Mexico. *Pediatr Infect Dis J* 2011; 30: s11–s15.

[109] Yen C, Armero Guardado JA, Alberto P, et al. Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccinations in El Salvador. *Pediatr Infect Dis J* 2011; 30: s6–s10.

As of 2013, 17 countries in the Americas (in addition to Canada and the Unites States) were using rotavirus vaccines[110]. Post licensure efficacy trials have confirmed efficacy in Latin American countries. When co-administered with oral polio vaccine in six Latin American countries, vaccine efficacy was found to be 81% against severe diarrhea and vomiting (gastroenteritis)[111].

Image 15. President Bolanos of Nicaragua administering a first dose of rotavirus vaccine.
SOURCE: MERCK VACCINES

Impact of Rotavirus Immunization in Nicaragua

In 2005, the health system in Nicaragua had been overwhelmed by an outbreak of rotavirus disease. The country reported over 64,000 cases of diarrhea (from any cause) and 56 deaths from diarrhea[112]. In 2006, in partnership with Merck, Unicef, and international health organizations, rotavirus vaccine was introduced for the first time in a developing country. For three years, Merck donated rotavirus vaccine for all infants in Nicaragua.

President Enrique Bolaños administered the first dose of oral vaccine on October 27, 2006[113].

The vaccine has since prevented 77% of very severe cases of rotavirus diarrhea[114] in Nicaragua and cut hospital admissions and emergency room visits by 50%[115]. In children less than 1 year of age, vaccine was 88% effective against hospitalization from rotavirus gastroenteritis[116].

3.6 Human Papillomavirus (HPV)

The Cause

HPVs were originally thought to be benign wart causing viruses. But in the 1980s, the Nobel Prize winning Harald zur Hausen hypothesized that HPVs were likely the cause of cervical cancer.

HPV commonly infects humans and can cause warts and cancers. The virus is made up of two proteins (L1 and L2) which are assembled in pentameres (See **Figure 65**).

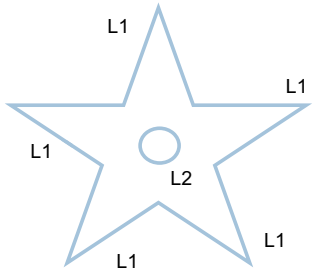


FIGURE 65. SINGLE PENTAMERE OF HPV (WHOLE VIRUS HAS 72 PENTAMETERS)

[110] PATH. Rotavirus vaccine access and delivery. Complete country rotavirus introduction list. April 27, 2013. http://sites.path.org/rotavirusvaccine/rotavirus-advocacy-and-communications-toolkit/country-introduction-maps-and-list/
[111] Tregnaghi MW, Abate HJ, Valencia A, et al. Human rotavirus vaccine is highly efficacious when coadministered with routine expanded program of immunization vaccines including oral poliovirus vaccine in Latin America. *Pediatr Infect Dis J* 2011; 30: e103–108. http://www.ncbi.nlm.nih.gov/pubmed/21378594
[112] Merck. Nicaraguan vaccination program. http://www.merck.com/responsibility/access/access-feature-nicaraguan.html
[113] PATH Rotavirus Vaccine Project—Summary Report. http://www.rotavirusvaccine.org/files/RVP_SummaryReport_Final.pdf
[114] View Change.Org. Living proof: Nicaragua—a vaccine's remarkable impact. http://www.viewchange.org/videos/living-proof-nicaragua-a-vaccines-remarkable-impact
[115] PATH. Press Room. New evidence on rotavirus vaccines in Asia demonstrate significant protection against the most common deadly form of childhood diarrhea. Press release. http://www.path.org/news/pr100805-rotavirus-vaccines-Asia.php
[116] Mast TC, Espinoza F, Palacio del Carmen L, et al. Effectiveness of the oral pentavalent rotavirus vaccine in Nicaragua. Poster presentation 28th annual meeting of the European Society for Pediatric Infectious Diseases. May 4–8, 2010. http://www.kenes.com/espid2010/posters/Abstract596.htm

About 80% of women in the US will be infected by at least one strain of HPV by 50 years of age. There are about 200 types of HPV. More than 40 types cause genital infections. Types 16 and 18 are now known to cause 70% of cervical cancers and the majority of genital cancers. Types 6 and 11 cause 90% of genital warts. These virus types are transmitted sexually (See **Figure 66**).

HPV may be cleared by the immune system quickly (weeks or months) after infection. But sometimes the virus persists for a long period of time (up to 10 years). It is in these persons that normal cells may be transformed into cancerous cells. These transformations occur because viral proteins (E6 and E7) inactivate human tumor suppressor proteins.

Based on their characteristics, HPVs are classified into four groups. Each group may include several types (See **Table 17**)[117].

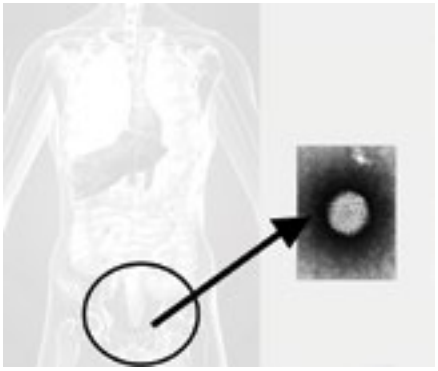


FIGURE 66. GENITAL AND HIGH-RISK GENITAL HPVs ARE TRANSMITTED SEXUALLY
SOURCE: NIH-VISUALS OLINE. LABORATORY OF TUMOR VIRUS BIOLOGY

Group	Site	Effects	Cancer-causing	Common HPV Types
Benign skin	skin	warts	no	1, 2
Epidermodysplasia verrucruciformis	skin	flat warts	yes	5, 8
Genital	genitals	warts	no (but can cause precancerous lesions)	6, 11
High-risk genital	genitals	flat warts	yes (can also cause precancerous lesions)	16, 18, 33, 45

TABLE 17. CLASSIFICATION OF HPVs (ADAPTED FROM VACCINES 5TH EDITION)

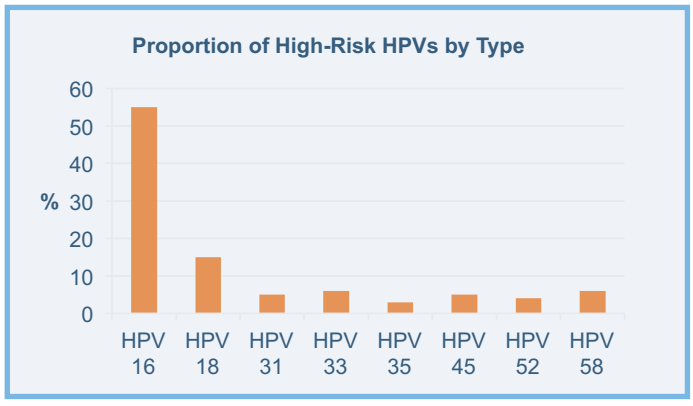


FIGURE 67. GLOBAL DISTRIBUTION OF HIGH-RISK HPVs BY TYPE (VALUES ARE APPROXIMATE)

The Impact of the Disease[118]

Globally, cervical cancer is the second or third most common cancer in women, depending on the country screening practices. It results in 273,000 deaths/year or 2.7 million years of life lost[119]. In Latin America and Eastern Europe, this represents more life years lost than from tuberculosis and AIDS.

About 70% of young women who become sexually active will become infected with one or more types of HPV within 5 years. About 52–58% of cervical cancers are caused by HPV type 16, depending on the region. Up to an additional 20% are caused by HPV type 18. The remainder are caused mostly by types 31, 33, 35, 45, 52, and 58 (See **Figure 67**)[120].

[117] Schiller JT, Frazer IH, Lowy DR, et al. Human papillomavirus vaccines. pp 246. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[118] Schiller JT, Frazer IH, Lowy DR, et al. Human papillomavirus vaccines. pp 243–257. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[119] WHO. Human papillomavirus and HPV vaccines: technical information for policy-makers and health professionals. Department of Immunizations, Vaccines and Biologicals. 2007. http://whqlibdoc.who.int/hq/2007/WHO_IVB_07.05_eng.pdf
[120] WHO. Human papillomavirus and HPV vaccines: technical information for policy-makers and health professionals. Department of Immunizations, Vaccines and Biologicals. 2007. http://whqlibdoc.who.int/hq/2007/WHO_IVB_07.05_eng.pdf

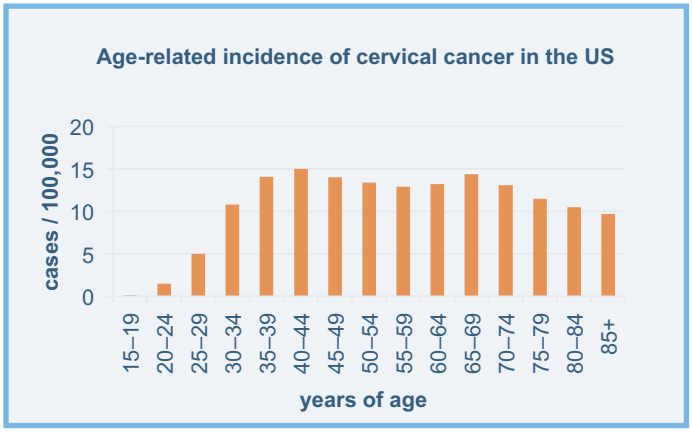


FIGURE 68. AGE-RELATED INCIDENCE OF CERVICAL CANCER IN THE US

The incidence of cervical cancer varies considerably, even within a country. Incidence tends to be higher in developing countries or in minority populations. Incidence peaks in the 40–44 year age group in the US (See **Figure 68**)[121]. In 2011, about 12,710 new cases of cervical cancer and about 4,290 deaths are expected to occur in the US[122].

The Vaccine[123]

A vaccine for use in humans was developed by using the L1 protein which makes up the shell (capsid) of the virus (See **Figure 64**). The star shaped L1 proteins (pentameres) self assemble into VLPs. The L1 protein can be produced from a number of cell lines. Currently licensed vaccines are produced in insect cells or in yeast. Since the vaccine is made from the L1 protein only (and not from the whole virus) the vaccine is not infectious and cannot cause cancer like HPVs.

The two vaccines licensed for use are:

- a bivalent vaccine (types 16 and 18, Cervarix™ from GSK); and,
- a quadrivalent vaccine (types 6, 11, 16, and 18, Gardasil™ from Merck).

Both vaccines are injectable and given in 3 doses over 6 months. Because vaccines prevent infection and the rate of infection increases rapidly within the first years of sexual activity, vaccination is focused on girls before they become sexually active. In the US, the ACIP recommends vaccination at 11–12 years of age, and up to 26 years of age for catch-up immunization. In addition to the prevention of cervical cancer, the quadrivalent vaccine, Gardasil™, is also approved for prevention of vulvar or vaginal cancers in females and for the prevention of genital warts, anal cancers, and precancerous or dysplastic lesions in females and males 9–26 years of age[124].

The Impact of the Vaccine

In clinical trials, both vaccines proved highly effective (94–96%) at preventing persistent infections against corresponding HPV types. Both vaccines were nearly 100% effective at preventing cervical intraepithelial neoplasia (CIN) (a precursor to cervical cancer)[125].

On the basis of clinical trial data, several countries introduced HPV vaccine into national immunization programs shortly after they were licensed (See **Table 18**).

Preventing persistent infection with HPV is presumed to result in an important reduction in the incidence of cervical cancer. But this effect will only be observed at some point in the future because the time required to develop cervical cancer is 10 or more years. Nevertheless, countries who have already implemented HPV immunization programs may already be observing some reductions in incidence in vaccine-eligible age groups. A study in Australia found that incidence of high-grade abnormalities in girls < 18 years had decreased by 38% 3 years after vaccine introduction[126], and the prevalence of genital warts in the vaccinated population has decreased by 59%[127].

Evidence is growing for the ability of vaccine HPV types to cross-protect against some other high-risk HPV types.

[121] National Cancer Institute. Surveillance Epidemiology and End Results. SEER Cancer Statistics Review 2004–2008. http://seer.cancer.gov/csr/1975_2008/browse_csr.php?section=5&page=sect_05_table.07.html
[122] National Cancer Institute. Cervical cancer. http://www.cancer.gov/cancertopics/types/cervical
[123] Schiller JT, Frazer IH, Lowy DR, et al. Human papillomavirus vaccines. pp 243–257. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[124] MerckVaccines.com. Gardasil indications. http://www.merckvaccines.com/Products/Gardasil/Pages/indications.aspx
[125] Schiller JT, Frazer IH, Lowy DR, et al. Human papillomavirus vaccines. pp 243–257. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[126] Wikipedia. HPV vaccine. http://en.wikipedia.org/wiki/HPV_vaccine
[127] Brotherton JML, Fridman M, May CL, et al. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. *Lancet* 2011; 377: 2085–2092.

Country	Year added to immunization schedule	Immunization schedule
Australia	2007	12–13 years; catch-up in males 14–15 years until the end of this school year
Austria	2006	9–15 years
Belgium	2007	10–13 years
Canada	2007	11–14 years (female)
Denmark	2009	12 years
France	2007	voluntary for girls and women 14–23 years not sexually active or sexually active < 1 year
Greece	2007	mandatory for girls entering grade 7; available to girls and women 12–26 years
Iceland	2011	12 years
Ireland	2008	12–13 years
Israel	2012	12 years
Latvia	2009	12 years
Luxembourg	2008	12 years
Macedonia	2009	12 years (female)
Mexico	2008	9 years (female)
Netherlands	2009	12–13 years
New Zealand	2008	girls and women born after 1990; routine for girls in grade 8 or 12 years of age
Norway	2009	routine for girls 12–13 years
Portugal	2007	13 years
Panama	2008	10 years (female)
Slovenia	2009	11–12 years
Spain	2007	11–14 years
Sweden	2010	voluntary for girls 10–12 years
Switzerland	2008	11–14 years
United Kingdom	2008	routine for girls 12–13 years; catch-up for girls up to 18 years of age
United States	2007	11–12 years; catch up 13–18 years

TABLE 18. COUNTRIES WITH HPV VACCINE IN IMMUNIZATION SCHEDULES[128]

[128] Donovan B, Franklin N, Guy R, et al. Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data. *Lancet Infect Dis* 2010; 11:39–44.

Impact of HPV Vaccination in Australia

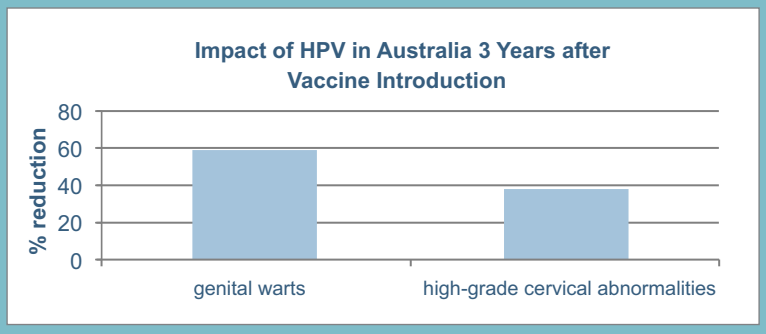
Australia introduced HPV vaccine in 2007. Between 2007 and 2009 Australia conducted a national catch-up campaign. 72% of girls aged 14 and 15, and nearly 66% of girls aged 16 and 17, were vaccinated with three doses[129].

Australia now routinely administers vaccine to 12 and 13 year-old girls in their high school vaccination program. Vaccines are provided at no cost to girls and approved for boys 9–15 years of age.

The National HPV Vaccination Program Register monitors the impact on cervical cancer rates, and vaccination coverage, and provides reminders for full immunization.

Because cervical cancer usually occurs several years after infection, the full impact on the incidence of cervical cancer cannot be measured for several years. Nevertheless, the age-adjusted incidence of HPV type 16 was expected to have decreased by 56% from pre-vaccine levels, by 2010. By 2050 a 92% reduction in incidence of HPV type 16 infections is expected[130,131].

How the reduction in infections will impact cervical cancer is difficult to assess. All infections do not result in cancer, and the measured incidence of cervical cancer depends on the quality of a screening program. But already high-grade cervical abnormalities in girls < 18 years have decreased by 38%, 3 years after vaccine introduction[132]. And the prevalence of genital warts in the vaccinated population has decreased by 59%[133].



[129] Australian Government. Department of Health and Ageing. HPV. http://www.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-hpv
[130] Cancer Council. Questions and Answers: New research on HPV: HPV infections will plummet by 2010. http://www.cancer.org.au/File/NewsMedia/MediaReleases2008/CERUresearchHPVQ&A.pdf
[131] Smith MA, Canfell K,Brotherton JML, et al. The predicted impact of vaccination on human papillomavirus infections in Australia. *Intl J Cancer* 2008; 123: 1854–1863.
[132] Brotherton JML, Fridman M, May CL, et al. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. *Lancet* 2011; 377: 2085–2092.
[133] Donovan B, Franklin N, Guy R, et al. Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data. *Lancet Infect Dis* 2010; 11:39–44.

3.7 Pneumococcal Disease

The Cause

Pneumococci are bacteria (*Streptococcus pneumoniae*) that can inhabit (colonize) the nasopharynx in humans but normally do not cause disease. Occasionally these bacteria may spread to the ears, lungs, brain, or other organs in the body (**Figure 69**). The spread of the bacteria may be localized in the respiratory tract and cause ear or sinus infections. If it spreads beyond, it causes invasive pneumococcal disease (IPD). The disease varies according to the organs that are affected. Typically IPD manifests as blood poisoning (bacteremia), pneumonia, or meningitis. The young and the elderly are most often affected.

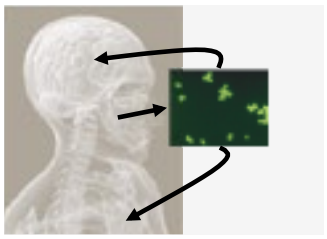


FIGURE 69. PNEUMOCOCCI COLONIZE THE BACK OF THE NOSE. WHEN THEY SPREAD TO OTHER ORGANS IN THE BODY THEY CAUSE ILLNESS
SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY
HTTP://EN.WIKIPEDIA.ORG/WIKI/FILE:PNEUMOCOCCUS_CDC_PHIL_ID1003.JPG

Pneumococci were first identified in 1881 and were recognized as the cause of lobar pneumonia (See **Image 16**). Today pneumococci have been classified in over 90 serotypes based on differences in a polysaccharide capsule that surrounds them. The polysaccharide capsule plays a role in virulence and in how the bacteria are processed by the immune system. Some serotypes account for more invasive disease than others. The top 20 serotypes account for the majority of disease cases.

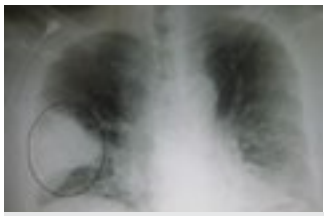


Image 16. Chest X-ray showing pneumococcal lobar pneumonia
SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY
HTTP://EN.WIKIPEDIA.ORG/WIKI/FILE:PNEUMOCOCCUS_CDC_PHIL_ID1003.JPG

Pneumococcal infections can be treated with antibiotics, but in recent years antibiotic-resistant strains of pneumococci have emerged. Because of their frequency and because of the severity of the diseases that they cause, pneumococcal infections are best prevented by immunization.

The Impact of the Disease

Pneumococcal disease is widespread throughout the world, and is the most important cause of bacterial meningitis, pneumonia, and ear infections (otitis media) in the US and in many other countries. Nearly everyone will experience a pneumococcal infection during childhood.

Pneumococcal disease can complicate viral infections such as measles or influenza[134]. Increases in pneumococcal disease are observed during influenza outbreaks.

Globally, acute respiratory infections account for almost 2 million deaths in children every year, and 1 million deaths are from pneumococcal pneumonia in children < 5 years old[135]. Most other serious cases of pneumococcal disease occur in persons 50 years and older.

Prior to childhood immunization in the US, 500,000 episodes of pneumococcal pneumonia and 63,000 cases of IPD were estimated to have occurred annually[136]. About 17,000 of these cases occurred in children under 5 years of age[137]. The US experienced about 6,100 deaths from IPD each year. About 700 cases of meningitis and 200 deaths occurred annually in children under 5 years of age (See **Table 19**).

The incidence of IPD is highest in infants and young children. **Table 21** shows the incidence rates of IPD in select countries before childhood pneumococcal vaccines were introduced. Differences in surveillance systems and diagnostics between or within countries may account for some of the variation seen.

[134] National Foundation for Infectious Diseases. Facts about pneumococcal disease. http://www.nfid.org/factsheets/pneumofacts.shtml
[135] Black S, Eskola J, Whitney C, et al. Pneumococcal conjugate and pneumococcal common protein vaccines. pp 531–567. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[136] CDC. What would happen if we stopped vaccinations? Pneumococcal. http://www.cdc.gov/vaccines/vac-gen/whatifstop.htm#pneumo
[137] CDC. Preventing pneumococcal disease among infants and young children. Recommendations of the ACIP. *MMWR* 2000; 49 (RR-9): 1–35.

Syndrome	number of cases annually
bacteremia	1,300
meningitis	700
death	200
ear infection (otitis media)	5,000,000

TABLE 19. FREQUENCY OF PNEUMOCOCCAL SYNDROMES IN THE US IN CHILDREN < 5 YEARS, PRIOR TO CHILDHOOD PNEUMOCOCCAL IMMUNIZATION[138]

In addition, some ethnic groups may be particularly vulnerable (See **Table 21**).

Next to the very young, the elderly experience the next highest incidence of IPD. In 1998–1999, incidence rates in the US were 40.8/100,000 for persons 50 years and over, 61.5/100,000 for persons 50–64 years, and 61.5/100,000 for persons > 65 years.

Country	period	incidence in < 2 years of age	incidence in < 5 years of age
Japan (Chiba Prefecture)	2003–2006	19.5–23.8	12.6–13.8
Japan (Kamikawa and Soya sub-prefectures)	2000–2010	79.2	43.1
UK	1980–1999	37.8	20
Spain	1988–2001	93.5	55.3–58.8
Mozambique	2001–2003		416
US	1998	167	100

TABLE 20. INCIDENCE OF IPD IN YOUNG CHILDREN IN SELECT COUNTRIES[139,140,141,142,143]

Age (years)	incidence (cases/100,000) US General Population	incidence (cases/100,000) US Navajo and Apache
< 2	167	2,396
2–4	36	227 (2–5 years)
5–9	6	54
10–19	3	35

TABLE 21. INCIDENCE OF INVASIVE PULMONARY DISEASE IN CHILDREN IN THE US IN 1998, PRIOR TO THE INTRODUCTION OF A CHILDHOOD PNEUMOCOCCAL VACCINE[144]

[138] CDC. Pneumococcal disease and pneumococcal vaccines. May 2009. www.cdc.gov/vaccines/pubs/pinkbook/downloads/Slides/Pneumo11.ppt
[139] Sakata H. Invasive *Streptococcus pneumoniae* infections in children in Kamikawa and Soya subprefecture, Hokkaido, Japan, 2000–2010, before the introduction of 7-valent pneumococcal conjugate vaccine. *J Infect Chemother* 2011; DOI: 10.1007/s10156-011-0264-8
[140] Bernaola Iturbe E, Aristequi Fernandez J, Herranz Aquirre M, et al. Study of the incidence of invasive pneumococcal disease in neonates and children aged less than 5 years in the Basque country and Navarre [Spain]. An Esp Pediatr 2002; 57: 301–309.
[141] Roca A, Sigauque B, Quinto LI, et al. Invasive pneumococcal disease in children < 5 years of age in rural Mozambique. Trop Med Intl Health 2006; 11: 1422–1431.
[142] Ispahani P, Slack R, Donald F, et al. Twenty year surveillance of invasive pneumococcal disease in Nottingham: serogroups responsible and implication for immunization. Arch Dis Child 2004; 89: 757–762.
[143] Ishiwada N, Kurosaki T, Terashima I, et al. Incidence of pediatric invasive pneumococcal disease in Chiba prefecture, Japan (2003–2006). *J Infect* 2008; 57: 455–458.
[144] CDC. Preventing pneumococcal disease among infants and young children. Recommendations of the ACIP. *MMWR* 2000; 49 (RR-9): 1–35.

Mortality rates from IPD in the US are approximately 7–28% for all age groups and as high as 11–44% for the elderly[145]. Case-fatality rates for pneumococcal meningitis can reach 40% and cause permanent injury in 30–50% of cases.

High-risk groups including persons with HIV, persons without a spleen, persons with chronic heart and/or lung disease and cigarette smokers are particularly vulnerable to pneumococcal infections.

In the US, there are about 15 million visits to the doctor each year for ear infections (acute otitis media) alone. The cost of these visits is estimated at about $5 billion. As many as 55% of these visits may be for pneumococcal infections.

The Vaccines

In 1977, a first pneumococcal vaccine was licensed. The first vaccine was a polysaccharide vaccine against 14 types of pneumococci. It was replaced in 1983 with a polysaccharide vaccine against 23 types (23-valent) (See **Table 22**). The 23-valent vaccine protected against > 85% of the strains that caused IPD in adults.

But polysaccharide vaccines are typically insufficiently immunogenic in infants and young children. To render polysaccharide vaccines immunogenic in this age group, a protein is coupled to the polysaccharide. This process is known as protein conjugation.

A conjugate pneumococcal vaccine was first licensed in 2000. The first conjugate vaccine protected against the seven types most frequently responsible for IPD in American infants and young children (See **Table 23**). It protected against about 90% of IPD in this age group.

In 2009, a 10-valent (decavalent) conjugate pneumococcal vaccine was licensed. It contains types 1, 5, and 7F, in addition to the types in the 7-valent vaccine. These three serotypes are more prevalent in developing countries.

In 2010, a 13-valent conjugate pneumococcal vaccine was licensed. It contains types 3, 6A, and 19A in addition to the types contained in the 10-valent vaccine.

The Impact of the Vaccine

Pneumococcal polysaccharide vaccine has been shown to significantly reduce the risk of IPD in immunocompetent adults. Some studies have shown the vaccine to have an effectiveness of about 75%, although the age of vaccination may influence the level and duration of effectiveness.

Efficacy from clinical trials for conjugate pneumococcal vaccine has ranged from over 75% to over 95% against invasive disease caused by the serotypes contained in the vaccine. Childhood pneumococcal vaccination has had an almost immediate impact on the burden of pneumococcal disease (See **Figure 70**)[146].

In addition, childhood conjugate pneumococcal immunization programs have had a herd effect, impacting the incidence of disease in unvaccinated age groups (See **Figure 71**)[147]. By 2003, there were 30,000 fewer cases of IPD in the US, including 20,000 fewer in children and adults who did not receive the vaccine[148]!

Pneumococcal serotypes contained in the 23-valent polysaccharide vaccine
1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F

TABLE 22. PNEUMOCOCCAL TYPES CONTAINED IN 23-VALENT PNEUMOCOCCAL POLYSACCHARIDE VACCINE

Pneumococcal serotypes contained in the 7-valent conjugate vaccine
4, 6B, 9V, 14, 18C, 19F, 23F

TABLE 23. PNEUMOCOCCAL TYPES CONTAINED IN 7-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

[145] Black S, Eskola J, Whitney C, et al. Pneumococcal conjugate and pneumococcal common protein vaccines. pp 531–567. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[146] CDC. Pneumococcal disease and pneumococcal vaccines. May 2009. www.cdc.gov/vaccines/pubs/pinkbook/downloads/Slides/Pneumo11.ppt
[147] Simonsen L, Taylor RJ, Young-Xu Y, et al. Impact of pneumococcal conjugate vaccination of infants on pneumonia and influenza hospitalizations and mortality in all age groups in the United States. mBio 2011; 2(1):e00309-10.

A decline in antibiotic resistant serotype invasive pneumococcal infections has also been observed in the US.

Conjugate pneumococcal vaccination has reduced incidence of vaccine-preventable serotypes by 99–100% as demonstrated in post-licensure studies. Since the first vaccine was licensed in 2000, most industrialized countries have introduced conjugate pneumococcal vaccination for infants where incidences have also declined remarkably. The use of these vaccines in developing countries, where the burden of pneumococcal disease is very high, is expected to save millions of lives.

The vaccine has been highly cost effective, costing about $7,800/life-year saved in the US when accounting for a herd effect. The herd effect and reduction of infectious pulmonary disease in adults is even greater than the direct impact on children.

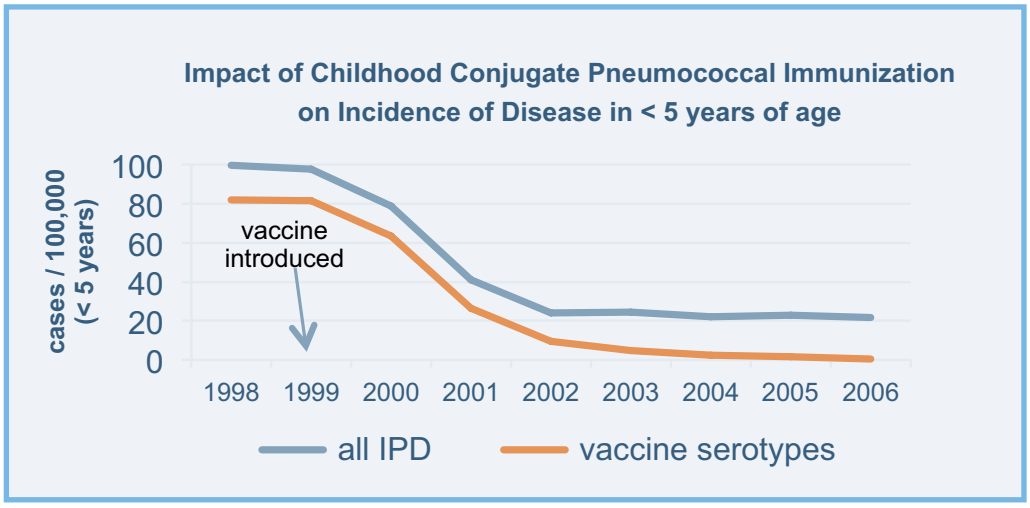


FIGURE 70. DIRECT IMPACT OF CONJUGATE PNEUMOCOCCAL IMMUNIZATION ON INCIDENCE OF PNEUMOCOCCAL DISEASE IN < 5 YEARS OF AGE

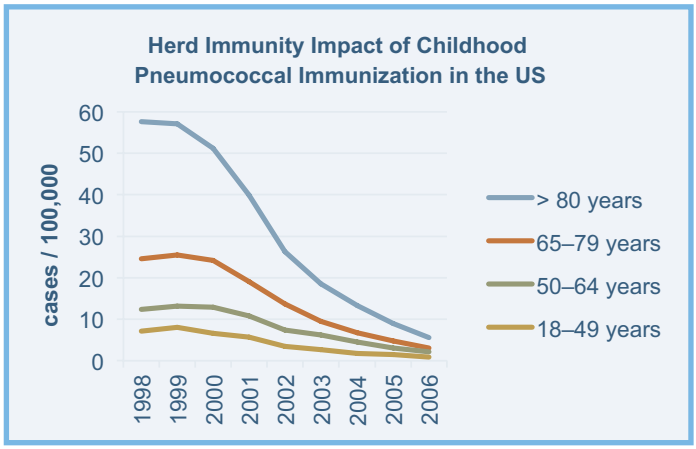


FIGURE 71. IMPACT OF CHILDHOOD PNEUMOCOCCAL IMMUNIZATION ON OTHER UN-IMMUNIZED AGE GROUPS

[148] CDC. What would happen if we stopped vaccinations? Pneumococcal. http://www.cdc.gov/vaccines/vac-gen/whatifstop.htm#pneumo

3.8 Varicella Zoster Virus (VZV)

The Cause[149]

Varicella Zoster Virus (VZV) causes two diseases: varicella (chickenpox) and herpes zoster (shingles). Varicella is a disease resembling smallpox (See **Image 17**). It wasn't until 1767 that varicella was recognized as distinct from smallpox. A century later, Steiner proved that varicella was infectious. In 1892, Bokay suggested that there was a link between varicella and herpes zoster and that these were two different diseases that result from a same virus[150].

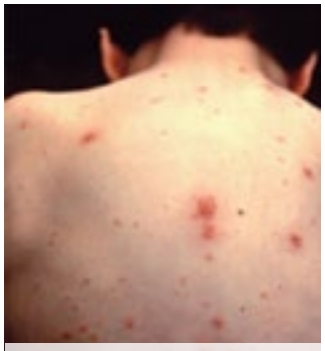


Image 17. Typical pustular lesions of varicella in a child.
SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY
HTTP://PHIL.CDC.GOV/PHIL/DETAILS.ASP

Varicella is transmitted by the viruses contained in the skin lesions, or from the upper respiratory tract through air (See **Figure 72**). There is only one serotype of varicella-zoster virus and the disease is exclusive to humans.

A first infection results in varicella. The virus then remains dormant in the body. When the body's immune system is weakened, for any number of reasons, the virus can be reactivated and cause herpes zoster.

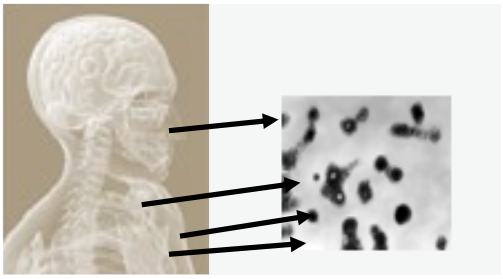


FIGURE 72. TRANSMISSION OF VARICELLA-ZOSTER VIRUS FROM VARICELLA IS AIRBORNE FROM SKIN LESIONS OR UPPER RESPIRATORY TRACT
SOURCE: E PALMER CDC PUBLIC HEALTH IMAGE LIBRARY
HTTP://PHIL.CDC.GOV/PHIL/DETAILS.ASP

Herpes zoster is a painful vesicular rash localized to a portion of the body such as around the waist (See **Image 18**).

The Impact of the Disease

Varicella

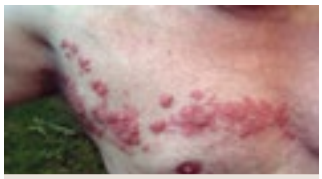


Image 18. Herpes zoster showing vesicular rash localized over the right chest.
SOURCE: FISLE
HTTP://EN.WIKIPEDIA.ORG/WIKI/FILE:HERPES_ZOSTER_CHEST.PNG

Almost all humans are infected by the fourth decade of life, but the incidence of the disease peaks in early childhood. Prior to immunization in the US, the annual incidence of disease was approximately 1,500–1,600/100,000 (See **Table 24**). There were approximately 4 million cases of varicella annually and about 11,000–13,500 hospitalizations in the US.

Varicella predisposes to group A Streptococcus infections and can lead to pneumonia in the young. The case-fatality rate in the US prior to immunization approximated 2.6 deaths per 100,000 cases. But fatality rates are 20 times higher in adults and 50 times higher in developing countries. In countries with high HIV sero-prevalence, fatality rates may be higher.

The major economic impact of the disease is from school and workdays missed due to parents caring for sick children. Hospitalization rates in industrialized countries may average 4.0–4.5/100,000 population.

Country	Cases of varicella/100,000 population
United Kingdom	240–880
Scotland	480–790
France	1,000–1,350
United States	1,500–1,600

TABLE 24. INCIDENCE OF VARICELLA IN SELECT COUNTRIES PRIOR TO THE INTRODUCTION OF VARICELLA VACCINATION

[149] Gershon AA, Takahashi M, Seward JF. Varicella vaccine. pp 915–958. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[150] Gershon AA, Takahashi M, Seward JF. Varicella vaccine. pp 915–958. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.

Herpes zoster

Prior to immunization, by 40 years of age over 99% of the population had been infected with varicella-zoster virus. The at-risk population for herpes zoster was therefore enormous. The annual incidence of herpes-zoster in the US, in the general population, was 120–480/100,000, but 720–1,180 frequency /100,000 for persons 60 years and older[151]. This represented > 1 million cases/year.

The Vaccine

All strains of varicella-zoster virus used to produce varicella vaccines are derived from the Oka strain of VZV. This strain and a corresponding vaccine were originally developed by Michiaki Takahashi in Japan, at the University of Osaka.

The vaccine was first introduced in Japan, in 1988. It was licensed in the US in 1995. It is available from several suppliers in a monovalent form, or in combination with Measles, Mumps, Rubella vaccine. The quadrivalent vaccine (MMRV) was licensed in the US in 2005.

A higher-dose VZV vaccine for the prevention of herpes zoster was licensed in the US in 2006.

VZV vaccines are believed to impart long-lasting immunity (10–20 years). They may result in mild rash and fever in about 5% of vaccine recipients.

The Impact of the Vaccine

Immunogenicity to varicella vaccine is excellent and vaccine efficacy from clinical trials has been evaluated at over 90% from a single dose and over 98% after 2 doses. Effectiveness trials of vaccines post-licensure confirm rates as high as 100% against moderate or severe disease[152].

The US was the first country to introduce a universal childhood varicella immunization program, in 1995, but close to a dozen other countries now have similar programs (See **Table 25**).

Countries using childhood varicella vaccine
Australia
Canada
Germany
Israel
Italy
Korea, Republic
Qatar
Uruguay
United States

TABLE 25. COUNTRIES THAT HAVE UNIVERSAL CHILDHOOD VARICELLA IMMUNIZATION PROGRAMS

The US ACIP recommends a 2 dose policy for varicella in children, similar to MMR vaccine. Since the introduction of varicella vaccine in the US, the incidence of varicella has declined by as much as 90% and hospitalizations have been reduced by > 90% in children (See **Figure 73**)[153]. Direct expenses for hospitalizations and care for varicella had decreased by 74% by 2005.

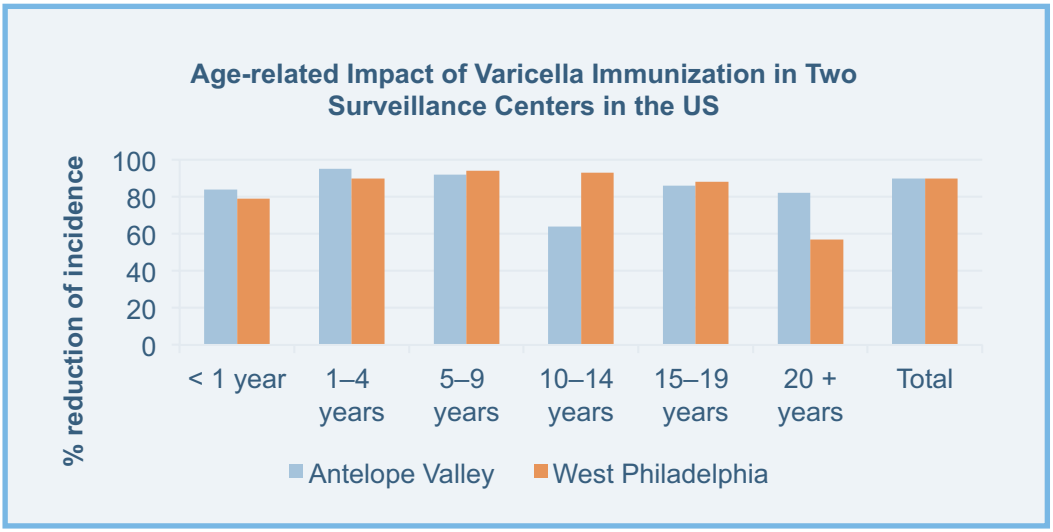


FIGURE 73. IMPACT OF VARICELLA IMMUNIZATION BY AGE IN TWO SURVEILLANCE CENTERS IN THE US.

[151] Levin MJ. Zoster vaccine. pp 1057–1068. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[152] Gershon AA, Takahashi M, Seward JF. Varicella vaccine. pp 915–958. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[153] Gershon AA, Takahashi M, Seward JF. Varicella vaccine. pp 915–958. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.

3.9 Hepatitis B

The Cause[154]

Hepatitis B virus infects the liver and alters liver function. The disease can be both acute and chronic. In acute disease, viral infection results in raised liver enzyme levels after about 60 days and causes jaundice about 90 days after infection. The liver becomes large and painful and about 40% of infections lead to hospitalization, in the US. About 0.5–1% of infections may result in a fulminant form of disease (very rapid progression) leading to liver failure. In the fulminant form, up to 33% of cases result in death.

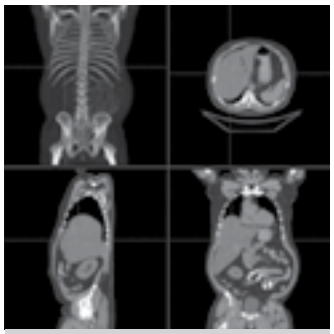


Image 19. CT scan showing enlargement of the liver as often occurs in chronic hepatitis B infections.
SOURCE: HTTP://UPLOAD.WIKIMEDIA.ORG/WIKIPEDIA/COMMONS/F/FE/SE000.JPG

In chronic infections, there is an initial period of viral replication in the liver. This is followed by a period of low (or no) viral replication and no liver disease. But hepatitis B surface antigens (HBsAg) persist in the blood for at least 6 months. Chronic hepatitis B increases the risk of hepatocellular carcinoma (cancer of the liver) and cirrhosis (See **Image 19**).

The virus spreads by transmission from mother to child at birth, close contact, sexual contact and direct contact with mucosa, blood or body fluids (See **Figure 74**). In the US, about 24,000 infants are born to Hepatitis B infected mothers. About 50% of new cases in the US are acquired by sexual contact, and 15% from injection-drug use.

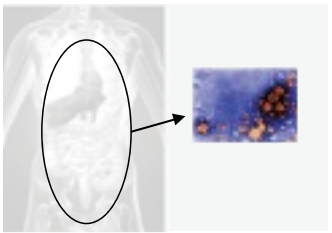


FIGURE 74. TRANSMISSION OF HEPATITIS B VIRUS IS FROM BODY FLUIDS AND SEXUAL CONTACT
SOURCE: E PALMER CDC PUBLIC HEALTH IMAGES LIBRARY
HTTP://PHIL.CDC.GOV/PHIL/DETAILS.

The risk of developing chronic infection is greatest when acquired perinatally or in early childhood. At a young age most infections are asymptomatic.

The Impact of the Disease

Globally, about 2 billion people have been infected, and 350 million are living with chronic hepatitis B infection. About 600,000 die each year from the consequences of chronic hepatitis B infection (See **Figure 75**)[155]. Twenty-five % of adults with chronic hepatitis B who became infected during childhood will die of liver cancer or liver cirrhosis.

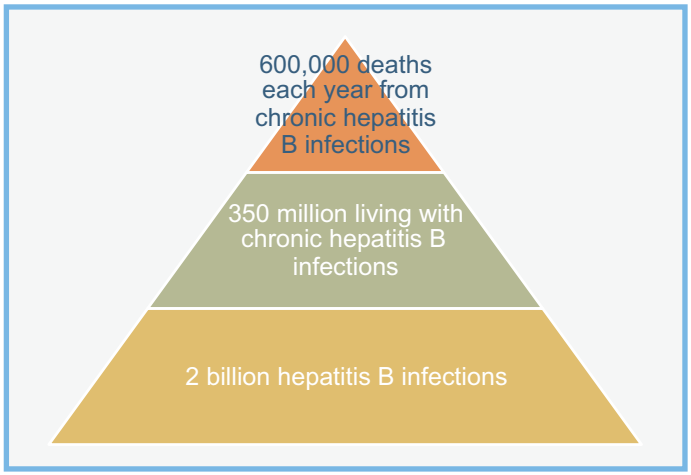


FIGURE 75. GLOBAL IMPORTANCE OF HEPATITIS B

In the US, prior to hepatitis B immunization, about 200,000–300,000 persons were infected each year. There are about 1.25 million chronic hepatitis B infections in the US, resulting in 4,000–5,000 deaths each year[156].

The prevalence of chronic infections is much higher in regions of the world: East Asia, Southeast Asia, the Middle East, the Amazon basin, the Pacific Islands and Africa. In these regions, the lifetime risk of developing hepatitis B is > 60%. Before immunization was introduced in East Asia and Southeast Asia, as many as 30–50% of chronic infections in children were the result of transmission from the mother to the child at birth.

[154] Mast EE, Ward JW. Hepatitis B vaccine. pp 205–241. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[155] WHO. Media center. Hepatitis B. Fact sheet no. 204. August 2008. http://www.who.int/mediacentre/factsheets/fs204/en/index.html
[156] Mast EE, Ward JW. Hepatitis B vaccine. pp 205–241. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.

The Vaccine

The first hepatitis B vaccine developed and licensed in 1981 was produced from the plasma of persons chronically infected with hepatitis B. Hepatitis B surface antigen was filtered from the plasma and served as the vaccine antigen. In 1986 a recombinant protein vaccine was licensed. The recombinant vaccine was manufactured from hepatitis B surface antigen produced in yeast cells.

The vaccine is given in 3 or 4 doses in a primary series by injection. Over 150 countries now recommend hepatitis B vaccination. Hepatitis B vaccine is commonly administered in combination with other childhood vaccines.

Serious adverse events are extremely rare, but local transient mild reactions occur. Pain (3–29%) and fever (1–6%) are most commonly reported.

The Impact of the Vaccine

Recombinant hepatitis B vaccines are 80–100% effective at preventing hepatitis B infections and 70–95% effective at preventing perinatal infections if the first dose is given within 12 hours of birth[157].

Everywhere they have been used, hepatitis B vaccines have significantly reduced the incidence of acute hepatitis B. In the US, reports of acute hepatitis B have continued to decline since the introduction of routine infant hepatitis B vaccination in 1991. However, because many infections are asymptomatic or go unreported, reports of acute hepatitis B may underestimate the true number of new infections (See **Figure 76**).

In addition to reducing the incidence of acute hepatitis B infections, routine infant hepatitis B immunization has also been found to be effective at reducing the incidence of chronic hepatitis B infections (See **Figure 77**).

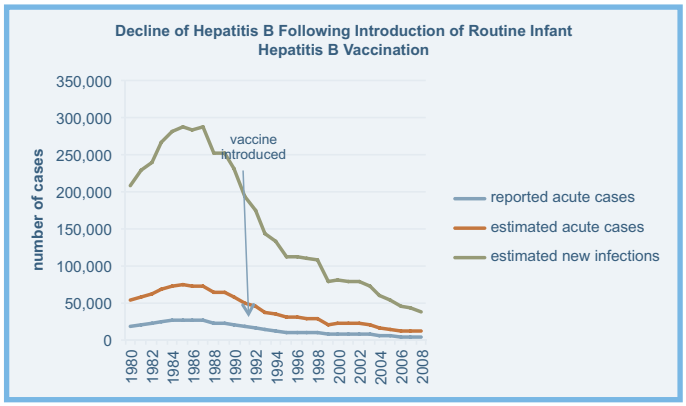


FIGURE 76. IMPACT OF ROUTINE INFANT HEPATITIS B IMMUNIZATION IN THE US[158]

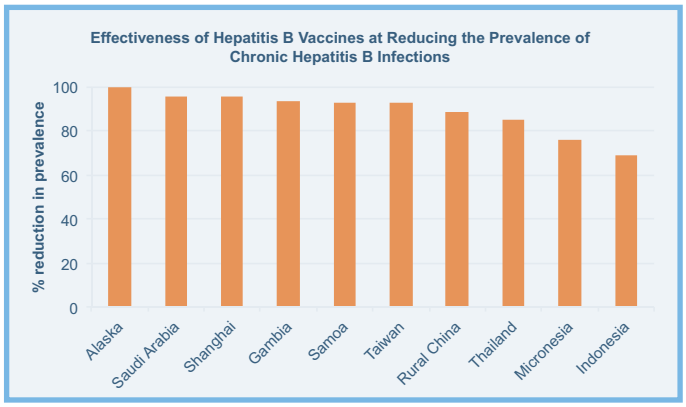


FIGURE 77. EFFECTIVENESS OF HEPATITIS B VACCINES AT REDUCING THE PREVALENCE OF CHRONIC HEPATITIS B INFECTIONS IN SELECT AREAS[159]

[157] Mast EE, Ward JW. Hepatitis B vaccine. pp 205–241. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[158] CDC. Viral hepatitis statistics and surveillance. Disease burden from viral hepatitis A, B, and C in the United States.http://www.cdc.gov/hepatitis/Statistics/index.htm
[159] Mast EE, Ward JW. Hepatitis B vaccine. pp 205–241. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.

4.1 Globally

Over 40 vaccines have been developed for the prevention of human diseases. Several vaccines protect against multiple serotypes of virus or bacteria (e.g. polio types 1, 2, and 3). Several vaccines are delivered in combination to protect against multiple diseases.

Most countries routinely use only a portion of vaccines available to them. The selection of vaccines for use in a national schedule is based on the local epidemiology and the risks associated with each specific vaccine-preventable disease.

In 1974, the WHA resolved to build on the success of the smallpox eradication program and ensure that all children benefited from the ability of vaccines to save lives. In 1977, the WHO set a goal of providing universal immunization for children by 1990, through the EPI[160].

In resource poor countries, the WHO recommended the prioritization of childhood immunization and the protection of women of child-bearing age. For more than 20 years, the EPI targeted only six diseases: tuberculosis, polio, measles, diphtheria, pertussis and tetanus. Now WHO recommendations are part of an overarching strategy and vision for immunization that promotes routine immunization of all age groups and includes several additional target diseases (See **Table 26**).

Universal recommendations			
Antigen	Children	Adolescents	Adult
BCG (tuberculosis)	√		
Hepatitis B	√	For high risk or not previously immunized	
Polio	√		
Diphtheria, Tetanus, Pertussis	√	Td booster	Td booster
Haemophilus influenzae type b (Hib)	√		
Pneumococcal conjugate	√		
Rotavirus	√		
Measles	√		
Human Papillomavirus		Girls only	

Regional recommendations			
Japanese Encephalitis Virus	√	booster	
Yellow Fever	√		
Some High-Risk recommendations			
Typhoid	Primary series and booster		
Cholera	Primary series and booster		
Meningococcal A	√		
Hepatitis A	Primary series		
Rabies	Primary series		
Recommendations for some immunization programs			
Mumps	√		
Rubella	√	Or adolescent girls and women of child-bearing age	
Influenza	√	Revaccinate annually	

TABLE 26. WHO RECOMMENDATIONS FOR IMMUNIZATION[161]

[160] WHO. Immunization service delivery and accelerated disease control. EPI. http://www.who.int/immunization_delivery/en/
[161] WHO.Table 1. Recommended Routine Immunization—Summary of WHO Position Papers. October 21, 2010. http://www.who.int/immunization/policy/Immunization_routine_table1.pdf

4.1.1 Access to Vaccines in Lower-Income Countries

At the time that the WHO's EPI was launched in 1977, all six vaccines included in the program could together be purchased for less than $1.00. Several new vaccines were developed after the launch of the EPI and were quickly introduced in higher-income countries, but not in lower-income countries. This was due in large part to the cost of new vaccines, deemed unaffordable for poor countries who were greatly dependent on donor support for the purchase of even the least expensive vaccines. Ironically, the burden of vaccine-preventable diseases was often greatest in lower-income countries.

In 2000, GAVI was launched to try to shorten the lag time between the introduction of new vaccines in higher-income countries and introductions in lower-income countries. The alliance between the Bill & Melinda Gates Foundation, the WHO, Unicef, the World Bank, and the vaccine industry originally prioritized the introduction of Hepatitis B, Hib, and Yellow fever vaccines through the creation of a dedicated fund (the Vaccine Fund) to purchase vaccines and support the delivery of vaccines in low-income countries.

GAVI has since expanded its support to low-income countries to include several other vaccines: pneumococcal conjugate, rotavirus, meningococcal A conjugate, HPV, and combined measles-rubella (MR) vaccine. As of March 2013, it had disbursed over $4.6 billion in support to 70 countries[162].

The funding for GAVI has come from traditional bilateral supporters of immunization, with the greatest contributions coming from the US and Norway[163], but also through novel fund-raising initiatives. In 2006, six governments (the UK, France, Italy, Spain, Sweden and Norway) backed the issuance of bonds to institutional investors through the International Finance Facility for Immunization (IFFIm), raising $1 billion. By 2012, four other governments had joined, raising $3.6 billion in bond proceeds[164].

In addition to differential pricing, by which a number of research-based vaccine companies have offered low prices to the poorest countries, other novel mechanisms to make purchasing of vaccines easier for poor countries have also been developed and piloted. The Advanced Market Commitment (AMC) was launched in 2009 with $1.5 billion from the UK, Italy, Canada, Russia, Norway and the Bill & Melinda Gates Foundation[165]. Under the terms of the AMC, suppliers of pneumococcal conjugate vaccine commit to supply low-income countries with the vaccine at $3.50/dose for 10 years. In return, the supplier receives an additional $3.50/dose for about 20% of the doses sold, paid from the AMC fund. This represents a 90% reduction in price compared to prices in high-income countries.

These and other initiatives have made important progress in ensuring that life-saving vaccines are accessed everywhere. Building on these successes, the Decade of Vaccines (DoV) collaboration was launched in 2010 to extend the full benefits of immunization to all people by 2020[166]. The Bill & Melinda Gates Foundation have pledge $10 billion to research, develop and deliver vaccines for the world's poorest countries, and a Global Vaccine Action Plan has been drawn up to ensure coordination and collaboration amongst all partners in the immunization community. By improving access to immunization an additional 20 million lives can be saved.

[162] GAVI Alliance. Disbursement by country. March 2013. http://www.gavialliance.org/results/disbursements/
[163] GAVI Alliance. Key figures: donor contributions and pledges. Dec 31, 2012. http://www.gavialliance.org/funding/donor-contributions-pledges/
[164] IFFIm. Origins of IFFIm. 2013. http://www.iffim.org/about/origins-of-iffim/
[165] GAVI Alliance. About the pneumococcal AMC. http://www.gavialliance.org/funding/pneumococcal-amc/about/
[166] DoV Collaboration. http://www.dovcollaboration.org/

4.2 US

In the US, immunization has been classified as one of the top 10 public health achievements of the 20th century. Vaccine-preventable diseases are now at a record low. In addition, for every dollar the US spends on immunization against 10 vaccine-preventable diseases (diphtheria, tetanus, pertussis, polio, hepatitis B, Hib, measles, mumps, rubella, and varicella), it saves $5.30 and society saves $16.50[167]. Every 26 days, the US saves the equivalent of its entire investment in the smallpox eradication program from savings on treatment of disease alone[168].

In 1977, the US launched a national immunization initiative. Its goals were to achieve national vaccination coverage of 90% by 1979 and establish a permanent system to provide immunization services to the annual US birth cohort of 3 million. At that time, an estimated 20 million children were not fully immunized.

In 1991, a new objective was set: to ensure that 90% of children had completed the full series of vaccinations by their second birthday. And in 1993, the Childhood Immunization Initiative was launched to improve the quality and quantity of vaccine delivery services, expand access to vaccines, enhance community involvement, improve the measurement of immunization coverage and surveillance of vaccine-preventable diseases, simplify the immunization schedule, and improve vaccines.

The number of vaccine-preventable diseases covered by the current childhood immunization schedule in the US has doubled, from 8 to 16 diseases, in the last 20 years (See **Table 27**).

“

In 1991, a new objective was set: to ensure that 90% of children had completed the full series of vaccinations by their second birthday.

[167] Orenstein, WA, Rodewald LE, Hinman AR, et al. Immunization in the United States. pp 1479–1510. In *Vaccines* 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[168] Brilliant LB. The management of smallpox eradication in India: a case study and analysis. Ann Arbor, University of Michigan Press, 1985.

	Age of administration													
Antigen	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years	7–10 years	11–12 years	13–18 years
Influenza					Annually									
Inactivated Polio			√	√		√					√			
Pneumococcal conjugate			√	√	√	√				Pneumococcal polysaccharide high-risk				
Haemophilus influenzae type b			√	√	√	√								
Diphtheria, Tetanus, acellular Pertussis			√	√	√		√				√		Tetanus, diphtheria, acellular pertussis	
Rotavirus			√	√	√									
Hepatitis B	√	√				√								
Measles, Mumps, Rubella						√					√			
Varicella						√					√			
Hepatitis A							√			high-risk				
Meningoccal conjugate										high-risk			√	booster at 16 years
Human Papillomavirus													√	

TABLE 27. CHILDHOOD IMMUNIZATION SCHEDULE IN THE US (EXCLUDING CATCH-UP SCHEDULE)[169]

[169] CDC. Immunizations schedules. Birth–18 years & "catch-up" immunization schedules. United States 2013. http://www.cdc.gov/vaccines/schedules/index.html

The Adult immunization schedule, in addition to providing for boosters of childhood vaccines, also provides for immunization against varicella zoster, an excruciatingly painful and potentially neurologically damaging condition (See **Table 28**).

Antigen	19–21 years	22–26 years	27–49 years	50–59 years	60–64 years	≥ 65 years
Influenza	1 dose annually					
Tetanus, Diphtheria, Acellular Pertusis/ Tetanus, Diphtheria	1 dose of Tdap then Td every 10 years					Td every 10 years
Varicella	2 doses					
Human Papillomavirus	3 doses (females) if not yet received					
	3 doses (males) if not yet received	or other risk				
Herpes zoster					1 dose	
Measles, Mumps, Rubella	1 or 2 doses					
Pneumococcal polysaccharide	1or 2 doses high-risk					1 dose
Meningococcal polysaccharide	1 or more doses high-risk					
Hepatitis A	2 doses high-risk					
Hepatitis B	3 doses high-risk					

TABLE 28. ADULT IMMUNIZATION SCHEDULE IN THE US[170]

[170] CDC. Immunization schedules. Adult immunization schedules. United States 2013. http://www.cdc.gov/vaccines/schedules/hcp/adult.html

4.3 European Union (EU)

European countries do not have a unified vaccination policy. The number and types of vaccines used in European countries varies from one country to the other. However, the EU's ECDC and the WHO's EURO do provide common guidance to member states on matters related to immunization. The EURO policy framework targets a number of diseases for prevention by vaccination.

Diseases typically targeted by immunization in Europe are shown by country in **Table 29** below.

Country/year last updated	BCG (tuberculosis)	Diphtheria, Tetanus, acellular Pertussis	*Haemophilus influenzae* type b	Inactivated Polio	Hepatitis B	Pneumococcal Conjugate	Measles, Mumps, Rubella	Diphtheria, Tetanus	Diphtheria, Tetanus-Inactivated Polio	Tetanus	Diphtheria, Tetanus, acellular Pertussis	Varicella	Human Papillomavirus	Rotavirus	Meningococcal C
Austria/08		√	√	√	√	√	√		√		√	√	√	√	
Belgium/11		√	√	√	√	√	√				√		√	√	√
Bulgaria/10	√	√	√	√	√	√	√	√							
Croatia/08	√	√	√	√	√		√	√							
Cyprus/09	√	√	√	√	√	√	√					√			√
Czech/10	√	√	√	√	√	√	√			√					
Denmark/09		√	√	√	√	√	√				√		√		
Estonia/09	√	√	√	√	√		√	√							
Finland/11	√	√	√	√		√	√				√			√	
France/10	√	√	√	√	√	√	√	√					√		√
Germany/10		√	√	√	√	√	√				√	√	√		√
Greece/07	√	√	√	√	√	√	√	√				√			√
Hungary/10	√	√	√	√	√	√	√				√				
Iceland/10		√	√	√			√				√				√
Ireland/10	√	√	√	√	√	√	√	√					√		√
Italy/08		√	√	√	√	√	√				√	√			√
Latvia/11	√	√	√	√	√	√	√	√				√	√		
Lithuania/08	√	√	√	√	√		√	√							
Luxemburg/08		√	√	√	√	√	√				√		√	√	√
Malta/10	√	√	√	√	√		√	√							
Netherlands/06		√	√	√	√	√	√	√							√
Norway/10	√	√	√	√	√	√	√	√					√		
Poland/07	√	√*	√	√*	√		√	√							
Portugal/09	√	√	√	√	√		√	√					√		√
Romania/10	√	√	√	√	√		√	√							
Slovakia/11	√	√	√	√	√	√	√	√							
Slovenia/09	√	√	√	√	√		√			√	√		√		
Spain/08		√	√	√	√		√	√				√	√		√
Sweden/10	√	√	√	√	√	√	√				√		√		
Switzerland/08	√	√	√	√	√	√	√	√				√	√		√
Turkey/10	√	√	√	√*	√	√	√	√							
United Kingdom/11	√	√	√	√	√	√	√	√					√		√

TABLE 29. CHILDHOOD VACCINES USED IN EUROPEAN COUNTRIES (LAST UPDATE OF SCHEDULE RANGE FROM DEC 2006–JULY 2011)[171]

[171] Euvacnet. National childhood vaccination schedules. http://www.euvac.net/graphics/euvac/vaccination/vaccination.html

4.4 Australia

The Australian childhood immunization schedule closely resembles that of the USA (See **Table 30**).

The adult Australian immunization schedule provides for pneumococcal and influenza vaccines. Influenza is not part of the routine childhood immunization schedule (See **Table 31**).

	Age of administration												
Antigen	Birth	1 month	2 months	4 months	6 months	12 months	18 months	24 months	4 years	10 years	12 years	13 years	15–17 years
Hepatitis B	√		√	√	√*	√*					√		
Rotavirus			√	√	√								
Diphtheria, Tetanus, acellular Pertussis			√	√	√				√				Tetanus diphtheria, acellular pertussis
Haemophilus influenzae type b			√	√	√	√							
Pneumococcal conjugate			√	√	√								
Pneumococcal polysaccharide							high-risk						
Inactivated Polio			√	√	√				√				
Influenza													Aboriginal high-risk
Measles, Mumps, Rubella						√			√				
Varicella							√				√		
Hepatitis A						high-risk							
Meningococcal C conjugate						√							
Human Papillomavirus											girls		

TABLE 30. AUSTRALIAN CHILDHOOD IMMUNIZATION SCHEDULE[172]

Antigen	15–49 years	50 years and over	65 years and over
Influenza	high-risk Aboriginal	Aboriginal	√
PPV23	high-risk Aboriginal	Aboriginal	√

TABLE 31. AUSTRALIAN ADULT IMMUNIZATION SCHEDULE[173]

[172] Australian government. Department of Health and Ageing. National Immunisation Program Schedule (Valid from 1 July 2007). http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/E875BA5436C6DF9BCA2575BD001C80BF/$File/nip-schedule-card-july07.pdf

[173] Australian government. Department of Health and Ageing. National Immunisation Program Schedule (Valid from 1 July 2007). http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/E875BA5436C6DF9BCA2575BD001C80BF/$File/nip-schedule-card-july07.pdf

4.5 Japan

Like in many industrialized countries, several routine vaccines are included in the Japanese childhood immunization schedule, and these are provided at no cost in public health centers. But Japan also has a voluntary schedule. The cost of these vaccines is not covered by the state and these are available only in pediatrician offices or private clinics. A table of Japan's routine and voluntary childhood immunization schedule, relative to other countries in the same region routine schedules, is shown in **Table 32** below.

	Japan	Australia	Korea, Republic	Singapore	Indonesia	Thailand	USA
GNI/capita (US$)	37,780	43,770	19,830	37,220	2,230	37,760	47,240
BCG (tuberculosis)	routine		√	√	√	√	
Diphtheria, Tetanus, Pertussis					√	√	
Diphtheris, Tetanus, acellular Pertussis	routine	√	√	√			√
Oral Polio				√	√	√	
Inactivated Polio	routine	√	√		√		√
Diphtheris, Tetanus, acellular Pertussis—IPV	routine						
Haemophilus influenzae type b	routine	√					√
Hepatitis B	voluntary	√	√	√	√	√	√
Measles					√	√	
Measles, Rubella or combination	routine						
Measles. Mumps, Rubella		√	√	√		√	√
Mumps	voluntary						
Japanese Encephalitis Virus	routine		√			√	
Tetanus					√		
Diphtheria, Tetanus	routine				√		
Tetanus, Diphtheria			√			√	
Tetanus, Diphtheria, acellular Pertussis				√			√
Pneumococcal conjugate	routine	√		√			√
Varicella	voluntary	√	√				√
Meningococcal C conjugate		√					
Meningococcal A,C,W,Y conjugate						high risk	√
Human Papillomavirus	routine	√					√
Rotavirus	voluntary	√					√
Hepatitis A	voluntary	high risk					√
Typhoid			high risk				
Influenza	voluntary	high risk	high risk	√			√

TABLE 32. JAPAN'S CHILDHOOD IMMUNIZATION SCHEDULE COMPARED TO OTHER COUNTRIES IN THE REGION AND THE US[174, 175, 176]

[174] WHO. WHO Vaccine Preventable Diseases Monitoring System. http://apps.who.int/immunization_monitoring/en/globalsummary/countryprofileselect.cfm
[175] Japan Health Care Info. Routine and voluntary vaccinations in Japan. Nov 1, 2012. http://www.nih.go.jp/niid/images/vaccine/schedule/2012/ImmEN121101.pdf
[176] Library of Congress. Japan: three vaccinations added to routine vaccination schedules. Apr 9, 2013. http://www.loc.gov/lawweb/servlet/lloc_news?disp3_l205403546_text

4.6 Global Changes in Use of Vaccines

Over the last several decades countries have had to rapidly adapt and develop immunization policies and practices to keep up with the development of new vaccines.

Initiatives, such as the Childhood Immunization Initiative of the early 1990s, helped the United States to develop systems to efficiently achieve public health objectives for disease prevention. These systems include the provision of vaccines for children who are uninsured or otherwise would not have access to immunization.

With clear objectives, solid policies, and robust implementation systems, Europe and the US have been very quick to adopt recently licensed vaccines. These investments in prevention are expected to have net advantages over curative care that would otherwise be required, particularly at a time of budgetary constraint and austerity.

But not all countries have been so quick to adapt to vaccine developments. By 2000, many developing countries had not updated their immunization programs and policies from the 1970s when they were first launched. The WHO's Vision and Immunization Strategy, launched at the start of the 2000s, was developed to assist developing countries to further develop policies and immunization objectives. The WHO's overarching strategy for immunization has evolved to include several new vaccines that have become available since the 1970s. It also includes new target groups, such as adolescents and adults, for specific immunizations.

Vaccine research and development is lengthy and risky. From discovery to license requires 10–15 years. Approximately one out of 10 vaccines that enter clinical development will reach the market. Which vaccines will be successfully developed is impossible to predict.

Over 100 vaccines are currently under development. A few of these may reach the market in the next decade.

In 2013, the global leaders in vaccine research and development reported the vaccines shown in **Table 33** to be under clinical development.

Manufacturer	Phase I	Phase II	Phase III
Merck		Pneumococcal conjugate	9-valent Human Papillomavirus
			inactivated Herpes Zoster
			6-valent pediatric combination (diphtheria, tetanus, pertussis, polio, hepatitis B, and *Haemophilus influenzae* type b)
Novartis	cytomegalovirus	*Pseudomonas aeruginosa*	cell cultured influenza in the US
	group B *Streptococcus*	meningococcal B in the US	adjuvanted influenza in the US
	HIV	cell cultured influenza	pediatric inactivated influenza in the US
	pneumococcal	conjugate meningococcal A, B, C, Y, W135	
Pfizer	smoking cessation	Alzheimer's disease	
	Clostridium difficile	4-valent *Staphylococcus aureas*	adolescent and young adult meningococcal B
	Asthma		
Sanofi Pasteur	pneumococcal	*Clostridium difficile*	4-valent pediatric combination (diphtheria, tetanus, pertussis, polio)
	Pseudomonas aeruginosa	4-valent rotavirus	6-valent pediatric combination (diphtheria, tetanus, pertussis, polio, hepatitis B, and *Haemophilus influenzae* type b)
	tuberculosis	purified vero rabies	4-valent inactivated influenza
		4-valent meningococcal A, C, Y, W135 conjugate	4-valent dengue
GlaxoSmithKline	*Staphylococcus aureus*	tuberculosis	Measles-Mumps-Rubella
	HIV	HIV immunotherapy	Malaria
	Non-typeable *Haemophilus influenzae*	pneumococcal conjugate	Herpes Zoster

TABLE 33. VACCINES UNDER DEVELOPMENT BY GLOBAL VACCINE LEADERS, BY CLINICAL PHASE OF DEVELOPMENT[177, 178 179, 180, 181]

[177] Merck. Merck pipeline. July 29, 2011. http://www.merck.com/research/pipeline/home.html
[178] Sanofi Pasteur. Sanofi Pasteur R&D portfolio. Feb 9, 2011. http://www.sanofipasteur.com/sanofi-pasteur2/front/index.jsp?siteCode=SP_CORP&codePage=PAG_22_1288245984593&lang=EN&codeRubrique=22
[179] Pfizer. Pfizer pipeline—our medicines in development. Aug 11, 2011. http://www.pfizer.com/research/product_pipeline/product_pipeline.jsp
[180] Novartis. Welcome to Novartis vaccines. Pipeline. 2011. http://www.novartisvaccines.com/products-diseases/pipeline.shtml
[181] GlaxoSmithKline. Product development pipeline. March 2013. http://www.gsk.com/research/our-product-pipeline.html

Vaccine research and development by specific disease areas is shown in **Table 34**.

Bacterial Diseases	Viral Diseases	Parasitic Diseases	Therapeutic
Buruli ulcer	Cytomegalovirus	Fascioliasis	Allergic rhinitis
Clostridium difficile	Dengue	Human African Trypanosomiasis	Alzheimer's
Chlamydia species, including trachomatis	Ebola	Hookworm	Breast cancer
Escherichia coli	Epstein-Barr	Leishmaniasis	Cervical cancer
Helicobacter pylori	Herpes simplex types 1 and 2	Lymphatic filariasis	Colorectal cancer
Leprosy	Hepatitis C	Malaria	Lung cancer
Meningococcus B	Hepatitis E	Onchocerciasis	Melanoma
Plague	HIV	Schistosomiasis	Pediatric cancers
Pseudomonas aeruginosa	Influenza		Multiple sclerosis
Shigella	Parainfluenza		Cocaine addiction
Staphylococcus	Respiratory syncytial virus		Nicotine addiction
Streptococcus group A & B	Coronaviruses		
Tuberculosis	West Nile		

TABLE 34. VACCINE RESEARCH AND DEVELOPMENT BY DISEASE AREA[182]

Vaccine research and development is lengthy and risky. From discovery to license requires 10 to 15 years. Approximately one out of 10 vaccines that enter clinical development will reach the market.

[182] Keith JA, Bigger LA, Arthur PA, et al. Delivering the promise of the DoV: Opportunities and challenges in the development of high quality new vaccines. *Vaccine* 2013. 31S: B184– B193

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Pharmaceutical Research and Manufacturers of America
950 F Street, NW, Washington, DC 20004

www.phrma.org