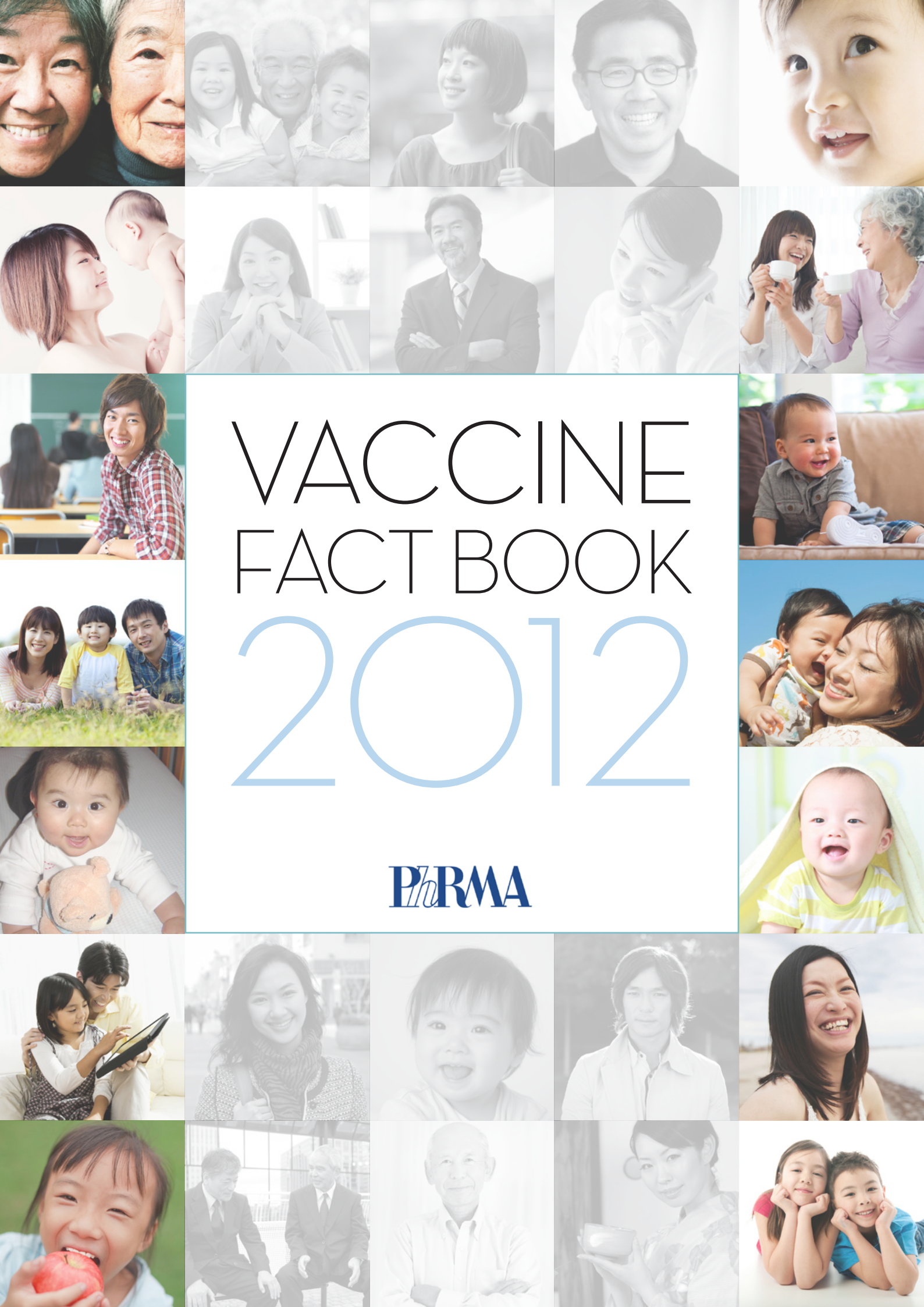


VACCINE FACT BOOK 2012

PhRMA

Preface

"Prevention is better than cure" is a proverb in many other languages as well. This idea is central to the development of vaccines, which have transformed human health since the time of Edward 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 B at birth can now be prevented. All of this and more has been accomplished by the development and deployment of vaccines. Most of these advances occurred in the last 50 years.

More and more vaccines are being developed and brought into use. Japanese scientists have contributed to the recent creation of powerful vaccines, notably against pertussis and chickenpox. These two vaccines are used throughout the world. It is, therefore, fitting that Japan also takes advantage of other new vaccines such as rotavirus, pneumococcal conjugates and human papillomavirus, which can, respectively, prevent infantile diarrhea and dehydration, invasive infections and pneumonia, and various forms of cancer, particularly cancer of the cervix in women. Japanese children and adults should share in the benefits of vaccination. Moreover, governments have a reason to promote vaccination: better health of a general population lowers medical costs and is associated with broad economic benefits. Therefore, the vaccine industry has been growing in importance and in many countries, including Japan, governments consider vaccine production as a precious resource, for example, to control epidemics of new types of influenza and other emerging infections.

New techniques and strategies of vaccine development are being constantly discovered and it is likely there will be more diseases that can be prevented. It will be challenging to educate physicians and the public about vaccines and to find the best ways to implement vaccination. Nevertheless, industrialized and poor countries will want their populations to have access to preventive measures that make life better and safer.

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 unfortunately not well understood by the general public. However, once people understand it is likely that they will demand that vaccines be made available to them in sufficient quantity and at an affordable price.

I know that my dear student and friend, the late Hitoshi Kamiya, would have agreed with me. Hitoshi studied in my laboratory at Philadelphia Children's Hospital in 1981. After his return to Japan, we kept in touch and I had the opportunity to visit him many times. I watched him become the chief exponent of vaccines in Japan through his knowledge and the force of his personality. Hitoshi Kamiya's untimely death was a tragedy and I miss him very much. I would like to dedicate this book to his memory because he was a remarkable person and did much good for his country.

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

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

- From living organisms 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 organisms that have been inactivated by chemical, thermal or other means;
- From components of the disease-causing organism, 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, *Haemophlius influenzea* type b (Hib)

TABLE 1. EXAMPLES OF VACCINES BY TYPE

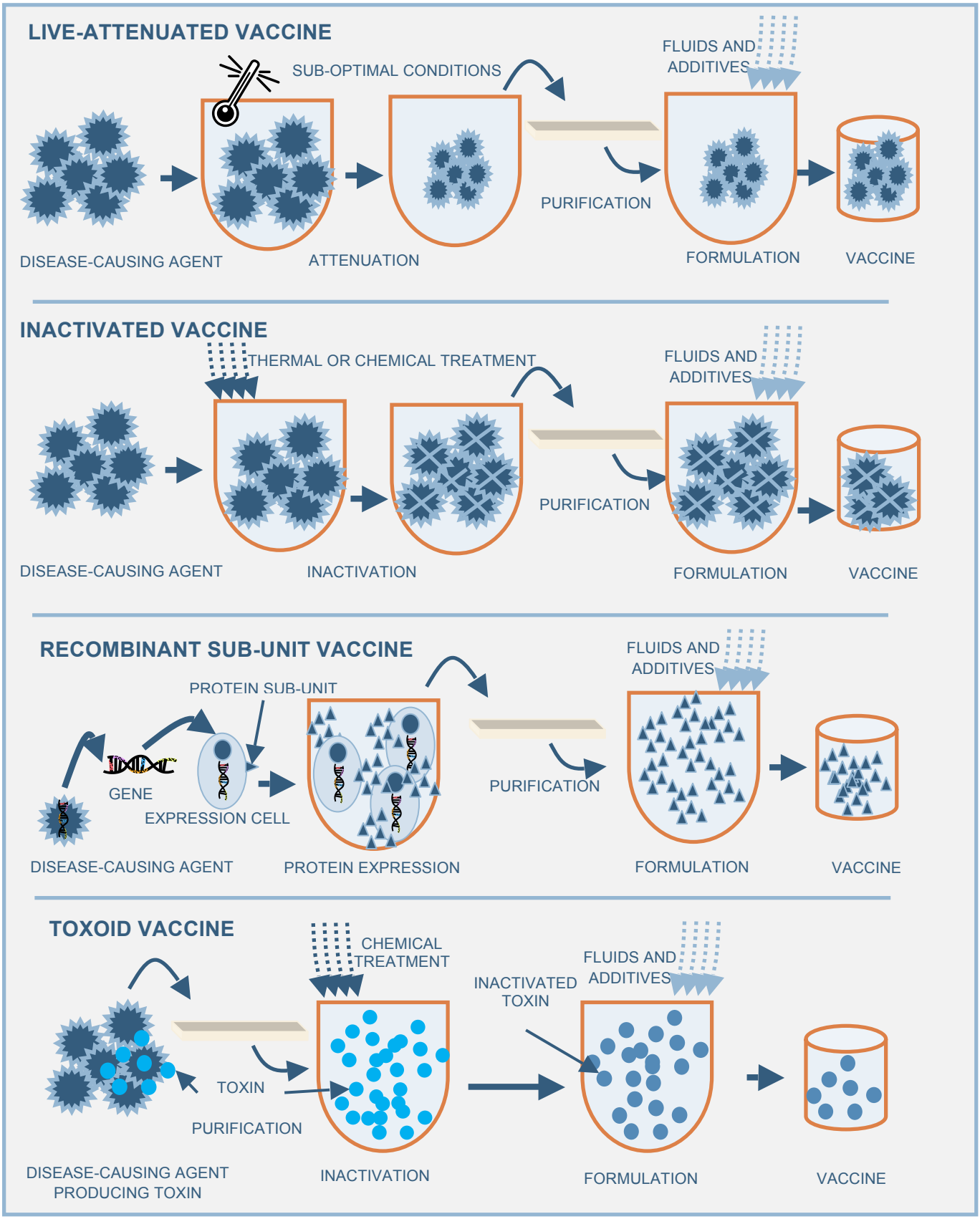

LIVE-ATTENUATED VACCINE
SUB-OPTIMAL CONDITIONS
FLUIDS AND ADDITIVES
PURIFICATION
DISEASE-CAUSING AGENT
ATTENUATION
FORMULATION
VACCINE
INACTIVATED VACCINE
THERMAL OR CHEMICAL TREATMENT
FLUIDS AND ADDITIVES
PURIFICATION
DISEASE-CAUSING AGENT
INACTIVATION
FORMULATION
VACCINE
RECOMBINANT SUB-UNIT VACCINE
PROTEIN SUB-UNIT
FLUIDS AND ADDITIVES
GENE
EXPRESSION CELL
PURIFICATION
DISEASE-CAUSING AGENT
PROTEIN EXPRESSION
FORMULATION
VACCINE
TOXOID VACCINE
CHEMICAL TREATMENT
FLUIDS AND ADDITIVES
INACTIVATED TOXIN
TOXIN
PURIFICATION
DISEASE-CAUSING AGENT PRODUCING TOXIN
INACTIVATION
FORMULATION
VACCINE

FIGURE 1

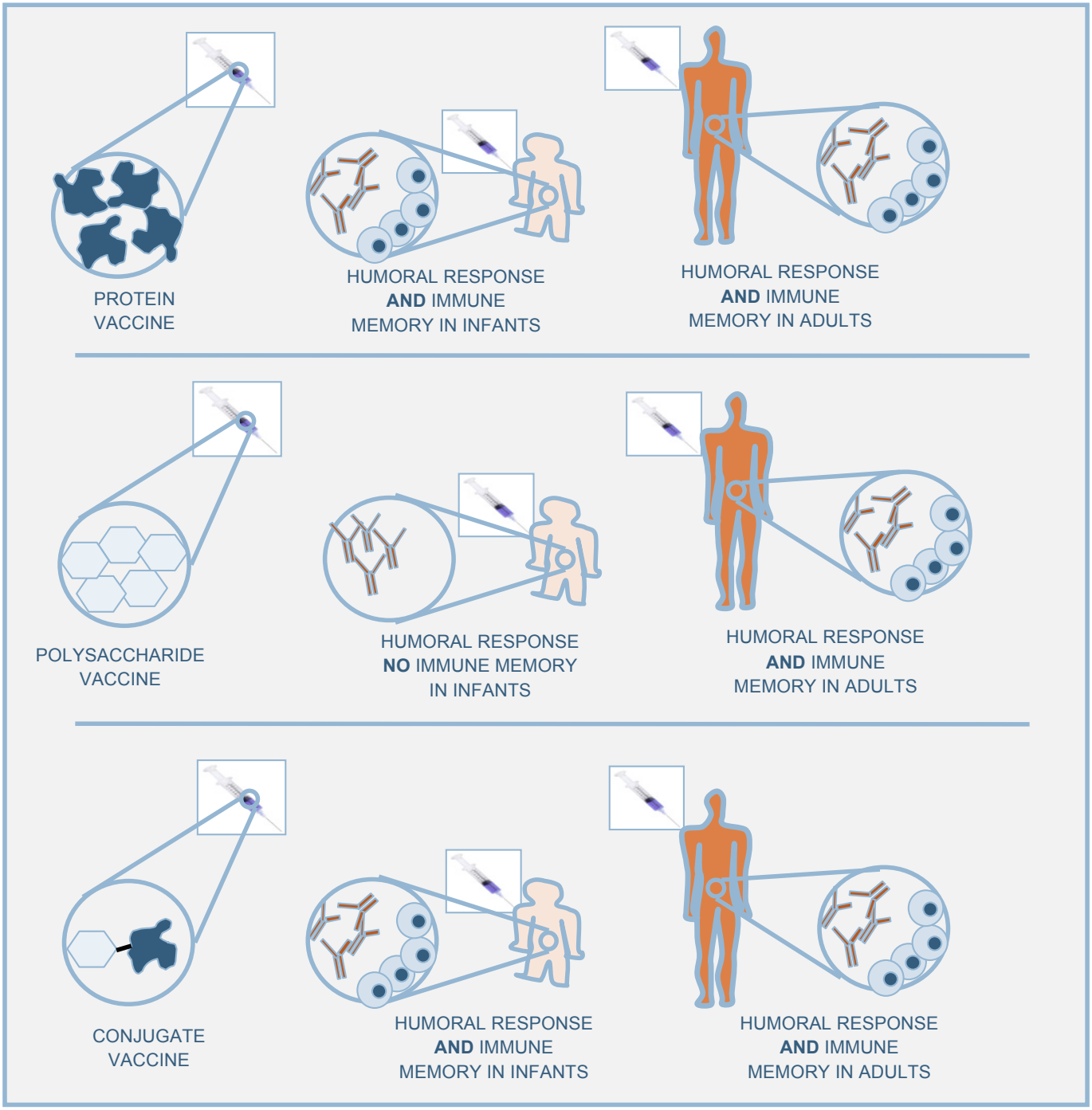


FIGURE 2

In addition to combining several serotypes of a disease-causing organism in a single vaccine (e.g. 13-valent pneumococcal conjugate vaccine), vaccines against different disease-causing organisms 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, *Heamophilus influenzae* type b, 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**).

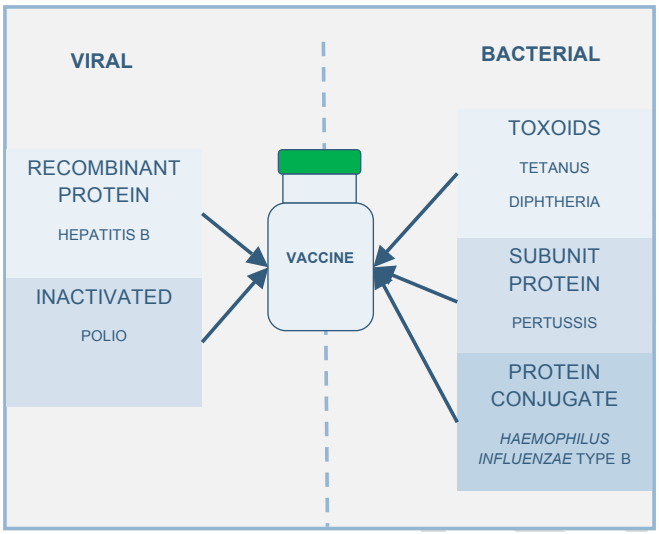


FIGURE 3. COMMON COMBINATION PEDIATRIC VACCINE CONTAINING MULTIPLE ANTIGENS OF MULTIPLE VACCINE TYPES

Vaccines may also contain antigens against several types (or serotypes) of the same disease-causing organism, providing protection against each type. Polio and influenza vaccines each protect against 3 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 so as 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**. Although there is no evidence of harm caused by any preservative, vaccines in the US and Europe have, for the most part, been free of thimerosal (or contain only trace quantities) for several years now. And some newer vaccines may not contain any preservative.

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. Adjuvanted vaccines may have a slightly higher rate of adverse reactions, including pain at the injection site, malaise and fever. 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 Papilloma Virus (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. US Food and Drug Administration. Thimerosal in vaccines. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM096228#t2

[2] US Centers for Disease Control and Prevention. 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 microorganisms enter the body, they initiate an immune response. This response mimics the body's natural response to infection. But unlike disease-causing organisms, vaccines are made of components that have limited ability, or are completely unable, to cause disease (See **Figure 4**).

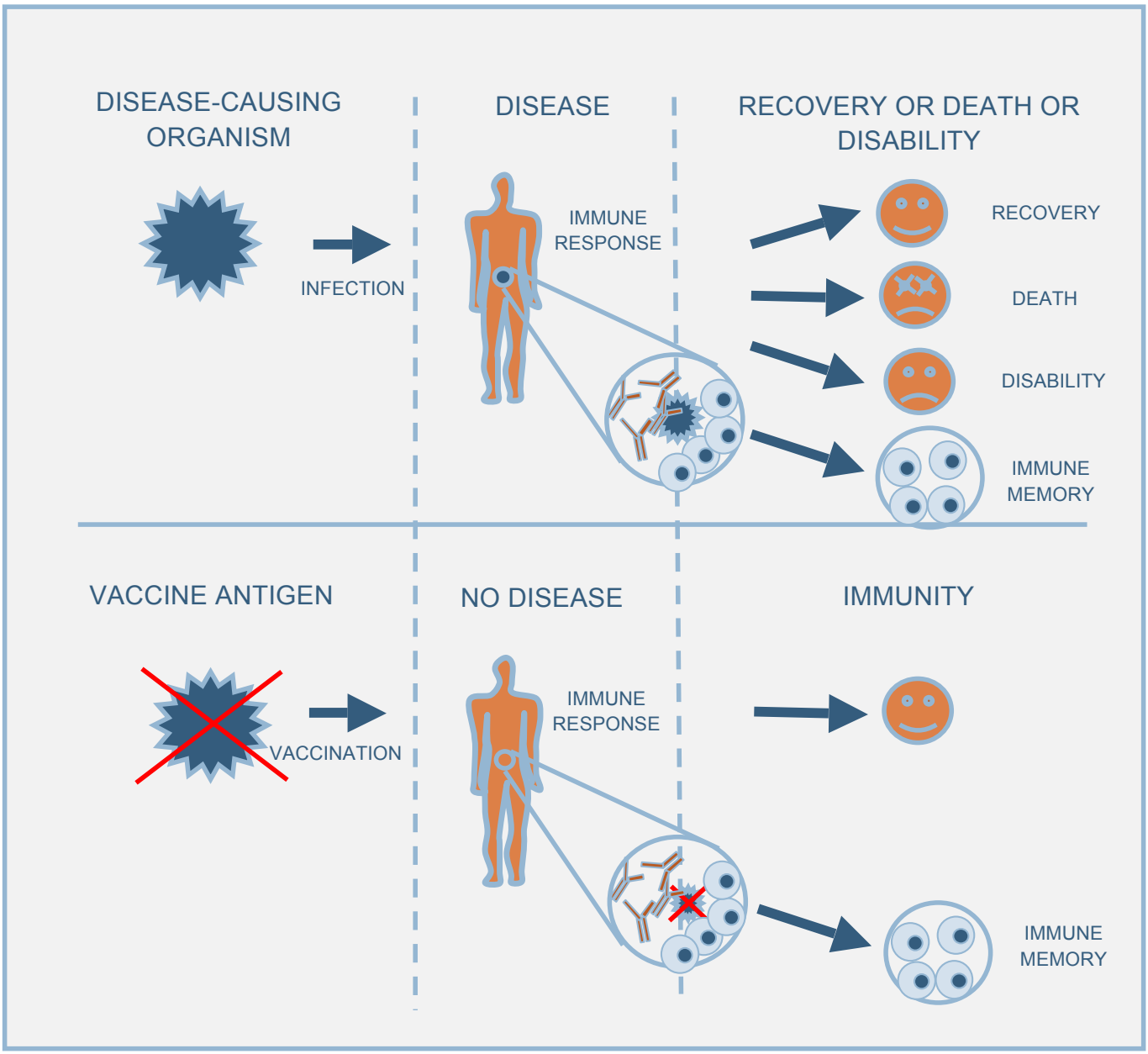


FIGURE 4. COMPARISON OF THE IMMUNE RESPONSE TO A DISEASES-CAUSING ORGANISM AND TO A VACCINE

The components of the disease-causing organisms 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**).

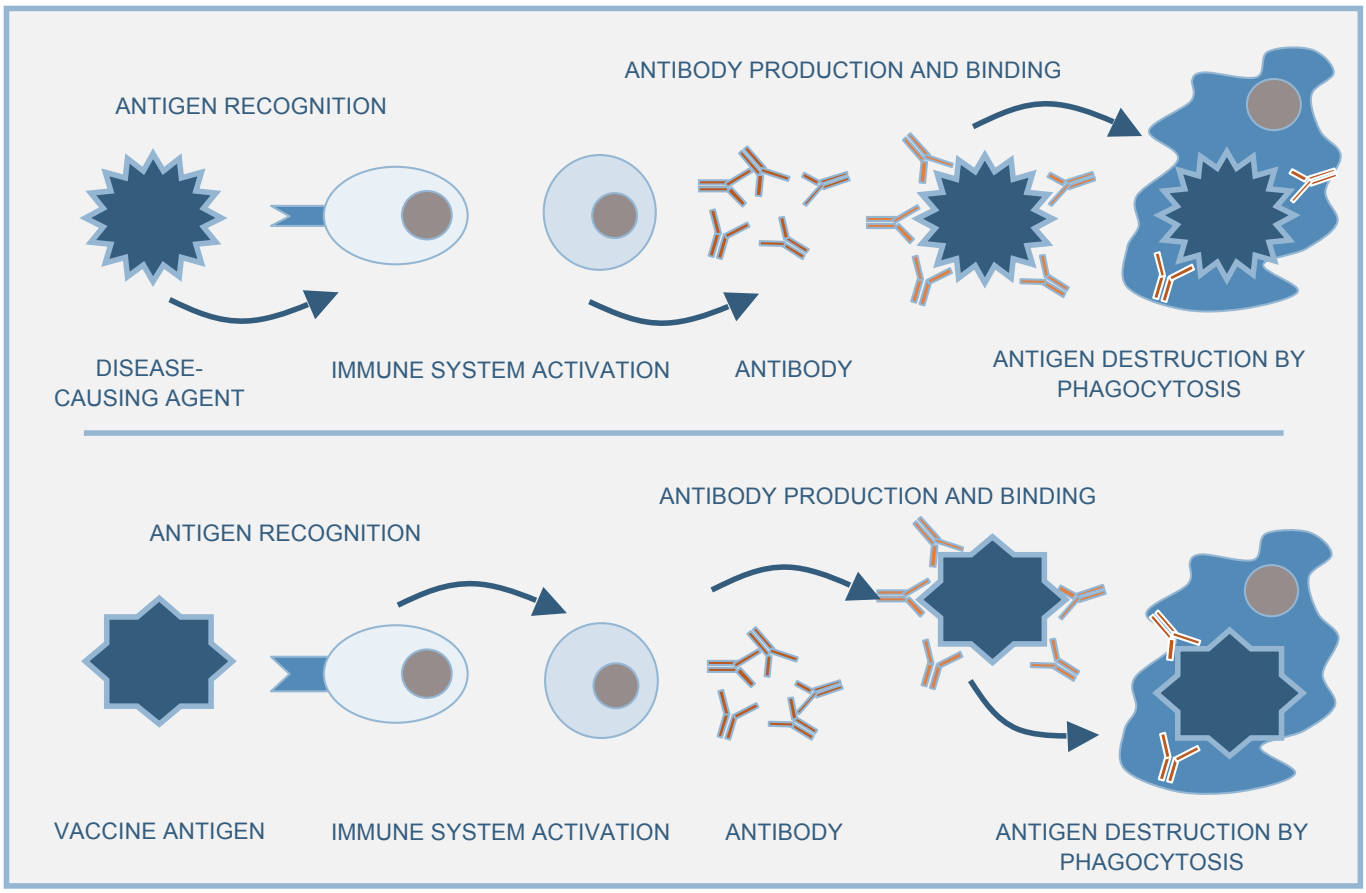


FIGURE 5. ANTIBODY DESTRUCTION OF ANTIGEN

The induced immune response to either a disease-causing organism or to a vaccine configures the body's immune cells to be capable of quickly recognizing, reacting to, and subduing the relevant disease-causing organism. When the body's immune system is subsequently exposed to a same disease-causing organism, 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 depend 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 organisms, such as 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 polysaccharide antigens.

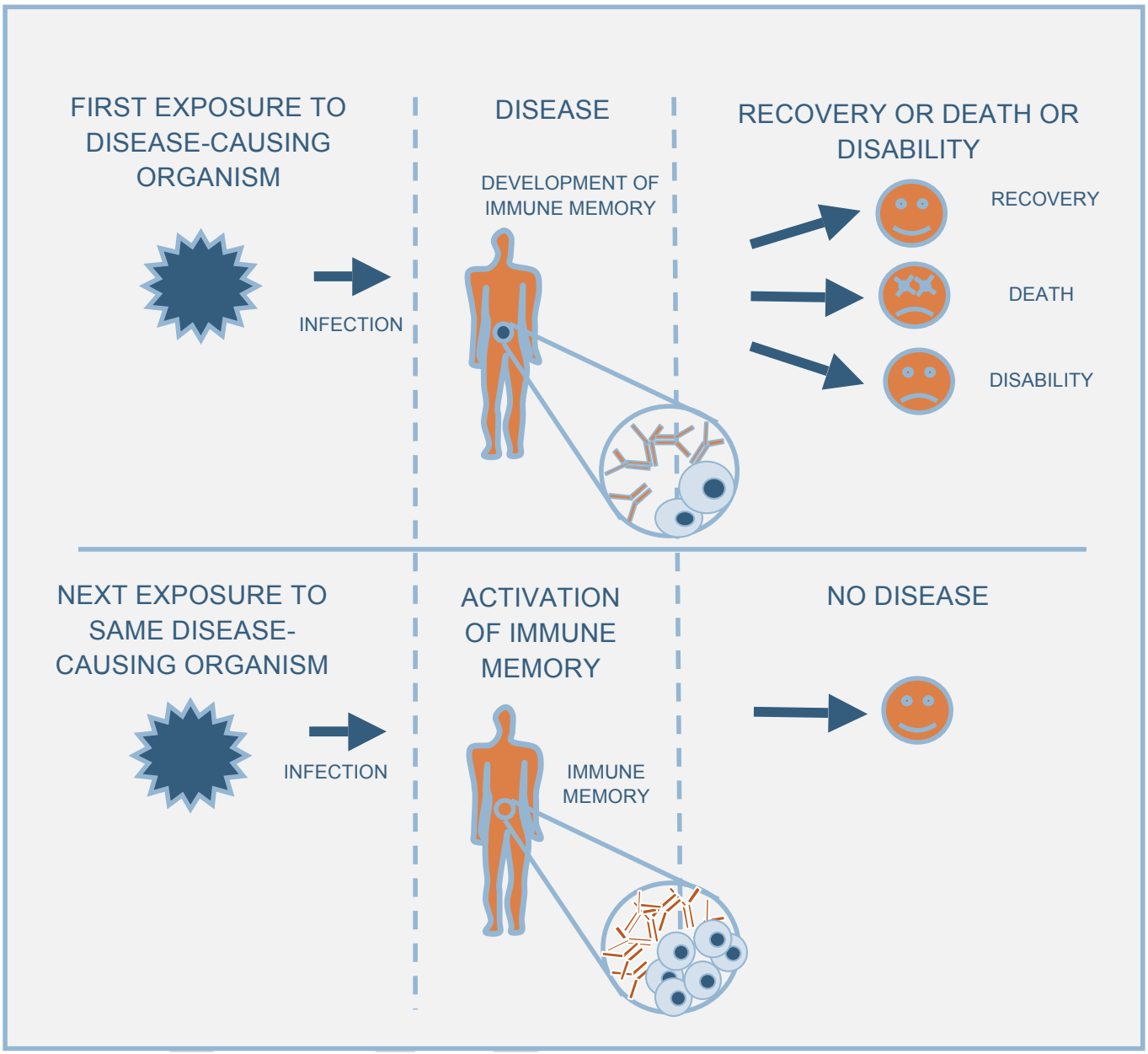


FIGURE 4. COMPARISON OF THE IMMUNE RESPONSE TO A DISEASES-CAUSING ORGANISM AND TO A VACCINE

BOX 1. THE HISTORY OF VACCINATION[3]

The first attempts to prevent disease by using the disease–causing organism against 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.

Bust 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 organisms 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.


Painting of Louis Pasteur

In 1886, in the US, Daniel Elmer Salmon and Theobald Smith demonstrated that vaccines could be produced not just from live organisms, but also from killed disease-causing organisms. 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 organisms, by conjugation of polysaccharides to carrier proteins, and by the assembly of virus-like particles.

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 organisms, 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 organism, have meant that the development of vaccines has so far been limited to a number of viral and bacterial diseases. For some diseases, such as AIDS, vaccine development is particularly challenging because the HIV virus escapes the body's natural immune response. For parasitic disease, complex life-cycles, or relatively large size, may limit the ability of vaccines to work effectively.

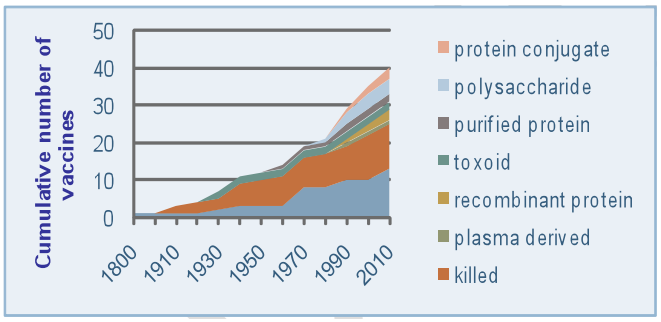


FIGURE 7. CUMULATIVE NUMBER OF VACCINES DEVELOPED SINCE THE FIRST VACCINE IN 1798, BY TYPE

Even when immune mechanisms for specific diseases are understood, there is no guarantee that a same vaccine design 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]).

But very safe and effective vaccines have been developed against several diseases over the past 120 years. These are shown in **Table 4 on page 15**.

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 on page 16**. Other vaccines specific to travelers, or to a geographic region, may also be recommended.

Some industrialized countries are particularly eager to ensure that life-saving vaccines are introduced quickly in national immunization programs when they become available. Other countries may take several years to consider new vaccine introductions. **Figure 8** shows the number of years that elapsed between the granting of vaccine licenses in the US and the granting of licenses in Japan, for some vaccines.

Table 6 on page 17 shows the difference between the number of vaccines licensed in the USA and Japan over the last 40 years. 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] World Health Organization. Media center. Dengue and dengue haemorrhagic fever. Fact sheet n° 117. March 2009. http://www.who.int/mediacentre/factsheets/fs117/en/

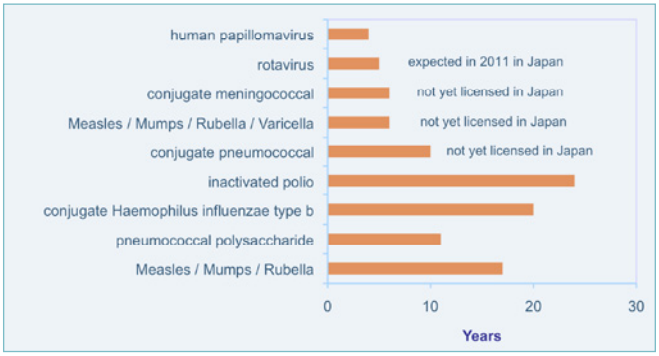


FIGURE 8. NUMBER OF YEARS BETWEEN THE GRANTING OF VACCINE LICENSES IN THE US AND THE GRANTING OF VACCINE LICENSES IN JAPAN (FOR SOME VACCINES)

“

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 vaccine 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
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
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
Yellow fever	viral	live attenuated	1932	liver damage, internal bleeding, sometimes fatal
Influenza	viral	inactivated	1936	life-threatening pneumonia, worsening of coronary heart disease, extreme muscular fatigue or aches, high fever, sometimes fatal
		live attenuated	2003	
Polio	viral	inactivated	1955	respiratory paralysis, life-long paralysis of limb(s), skeletal deformity, sometimes fatal
		live attenuated	1962	
Pneumococcal	bacterial	23-valent polysaccharide	1983	pneumonia, meningitis, ear infections, infections of bone and heart muscle, sometimes fatal
		protein conjugate	2000	

Vaccine-preventable disease	Type of disease	Type of vaccine	Year vaccine developed	Most common severe disease outcomes
Measles	viral	live attenuated	1963	diarrhea and severe weight loss in infants, convulsions, pneumonia, ear and brain infections, ulcerations of the eye, sometimes fatal
Mumps	viral	inactivated	1948	loss of male fertility, loss of pregnancy, meningitis, pancreatitis, brain infection, deafness
		live attenuated**	1967	
Rubella	viral	live attenuated***	1969	incurable congenital malformations, arthritis
Varicella (chickenpox)	viral	live attenuated*	1974	stroke in children, skin infections, pneumonia, liver damage, kidney and heart diseases, brain infections, incurable congenital malformations
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
Japanese encephalitis	viral	Inactivated*	1935	coma, deafness, loss of feeling, emotional disturbances, sometimes fatal
		live attenuated	1988	
Tick-borne encephalitis	viral	inactivated	1937	permanent neuropsychiatric effects, sometimes fatal
Hepatitis A	viral	inactivated	1995	protracted illness and loss of productivity, liver failure, sometimes fatal
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)	
Heamophilus influenzae type b	bacterial	polysaccharide	1985	meningitis, pneumonia, skin, bone and throat infections, arthritis, sometimes fatal
		protein conjugate	1987	
Hepatitis B	viral	plasma derived	1981	liver failure, cirrhosis, liver cancer, sometimes fatal
		recombinant protein	1986	
Anthrax	bacterial	protein	1954	blood poisoning, vomiting blood, sometimes fatal
Human Papillomavirus	viral	recombinant protein	2006	genital and cervical and oral cancers, genital warts, sometimes fatal

*Developed in Japan; **Urabe Am9 strain developed in Japan; ***Several Japanese vaccine strains.

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

Bacterial diseases	Viral diseases
Diphtheria	Measles
Pertussis	Mumps
Tetanus	Rubella
Pneumococcal diseases (pneumonia, meningitis, otitis media, and others)	Polio
Heamophilus 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 Papilloma Virus 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	Vacciness (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 Papilloma Virus	
2007		conjugate Haemophilus influenzae type b
2010		conjugate pneumococcal Human Papillomavirus
2011		Rotavirus (expected)
TOTAL	23	12

TABLE 6. VACCINES LICENSED IN THE US AND JAPAN 1971-2011

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 9**).

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

These vary slightly from one country to another, but everywhere they are used licensed vaccines are considered highly effective at preventing disease (See **Figure 10** and **Figure 11**).

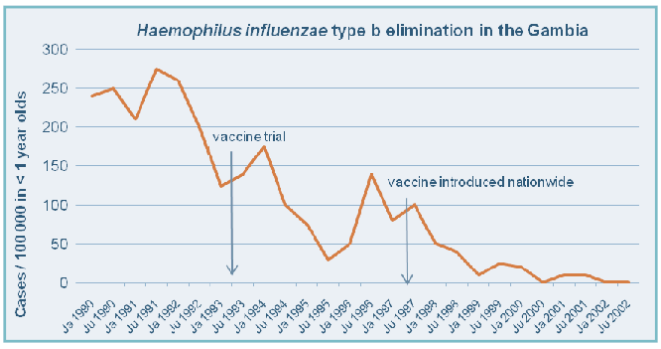


FIGURE 10. IMPACT OF IMMUNIZATION ON HIB DISEASE IN THE GAMBIA (ADAPTED – DATA ARE APPROXIMATE)[8]

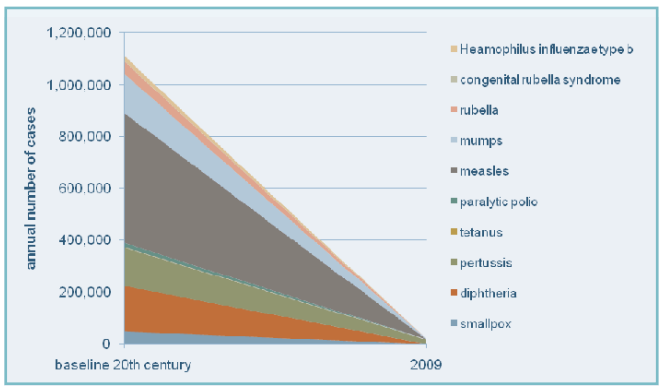


FIGURE 9. IMPACT OF IMMUNIZATION ON THE NUMBER OF ANNUAL CASES OF DISEASE IN THE USA[6,7]

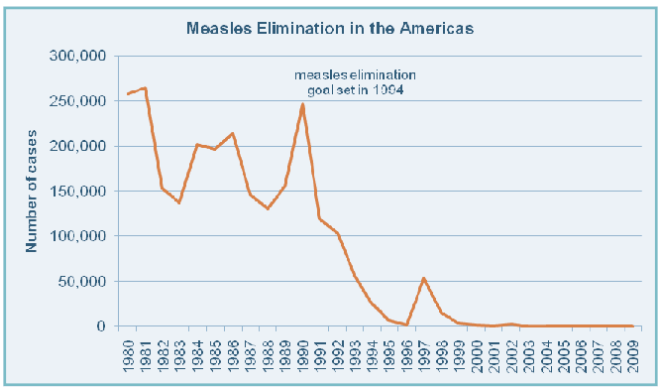


FIGURE 11. MEASLES ELIMINATION IN THE AMERICAS FROM EFFORTS IN IMMUNIZATION[9,10]

[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 Center for Disease Control and Prevention. 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/00056803.htm
[7] US Center for Disease Control and Prevention. Summary of notifiable diseases – United States, 2009. MMWR 58 (53): 85-87, May 13, 2011. http://www.cdc.gov/mmwr/pdf/wk/mm5853.pdf

What is vaccine efficacy?

Vaccine efficacy 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 12**). Smallpox was eradicated by achieving sufficient immunization coverage to prevent transmission of disease to unvaccinated non-immunes (susceptible).

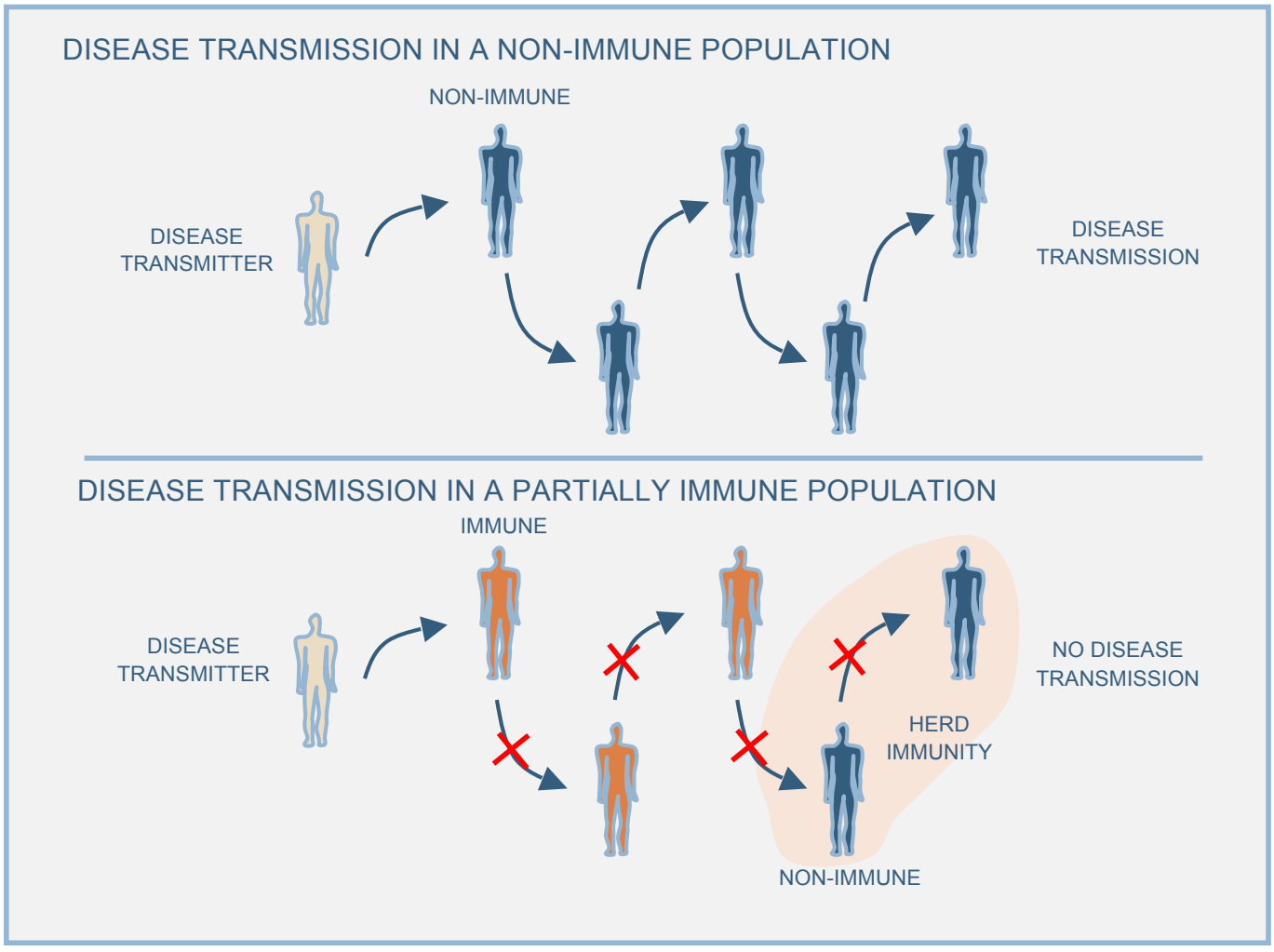


FIGURE 12. HERD IMMUNITY

[8] 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;366:144-50.
[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

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, such as measles, can continue to transmit in a community even when vaccination coverage and vaccine effectiveness are very high.

Strategies to interrupt highly transmissible diseases, such as 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 Efficiency 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]:

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

and where Vaccine Efficacy (VE) is expressed as a percentage (See **Figure 13**).

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 nonimmune population can be interrupted.

[11] The US Centers for Disease Control and Prevntion and the World Health Organization. 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

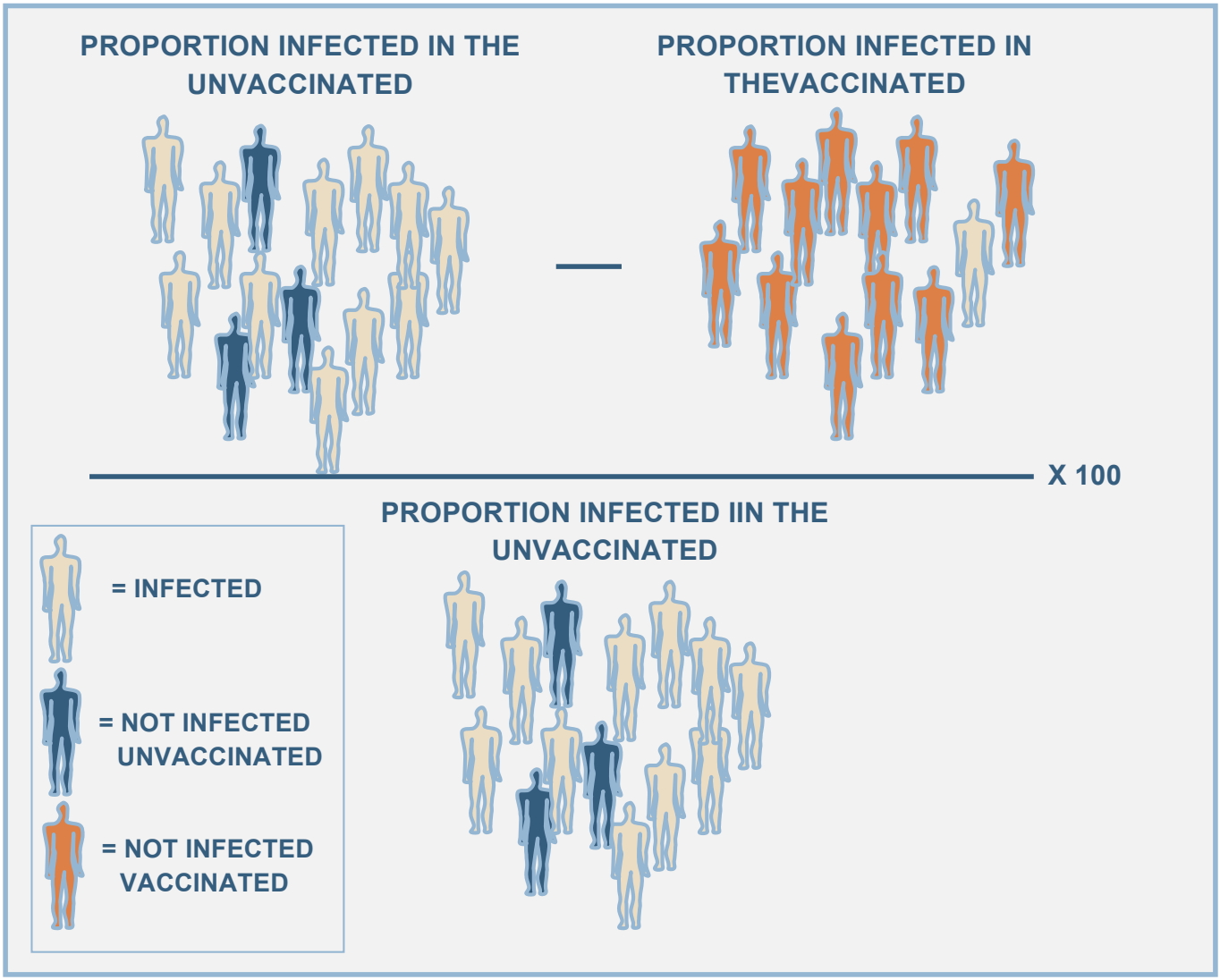

PROPORTION INFECTED IN THE UNVACCINATED
PROPORTION INFECTED IN THEVACCINATED
X 100
PROPORTION INFECTED IIN THE UNVACCINATED
= INFECTED
= NOT INFECTED UNVACCINATED
= NOT INFECTED VACCINATED

FIGURE 13.

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 14**). 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.

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 (See **Table 8**). 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 9**).

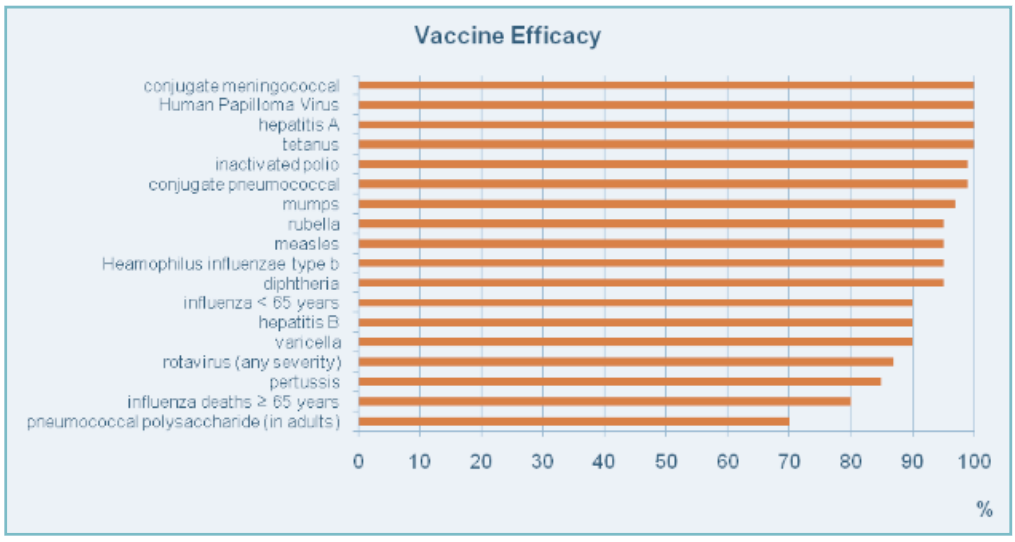


FIGURE 14. OBSERVED EFFICACIES OF SOME VACCINES (MAXIMUM VALUES ARE SHOWN FOR RANGES)[13]

[13] US Centers for Disease Control and Prevention. 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]
[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 immunization 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 Adverse Events Following Immunization. http://www.phac-aspc.gc.ca/publicat/cig-gci/p02-01-eng.php

Vaccine	Pain, swelling, redness	Fever > 38°C	Systemic symptoms
BCG (against tuberculosis)	90-95%		
Haemophilus influenzae type b	5-15%	2-10%	
Hepatitis B	adults 15% children 5%	1-6%	
Measles / Measles, Mumps, Rubella / Measles, Rubella	~10%	5-15%	5% rash
Oral polio	very rare	< 1%	<1% diarrhea, headache, muscle pains
Tetanus / Tetanus, diphtheria	~10% 50-85% booster doses	~10%	~25% irritability and malaise
Pertussis (whole cell)	up to 50%	up to 50%	up to 55% irritability and malaise

TABLE 8. COMMON REACTIONS TO VACCINES ROUTINELY USED IN SEVERAL INDUSTRIALIZED COUNTRIES[17]

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 9. CLASSIFICATION OF ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)[18]

The benefits of vaccination are indisputable.

[17] World Health Organization. Immunization Safety Surveillance: guidlimes for managers of immunization programs on reporting and investigating adverse events following immunization. Immunization Focus, World Health Organization Western Pacific Region, Manila, 1999.
http://www.who.int/immunization_safety/publications/aefi/en/AEFI_WPRO.pdf
[18] Public Health Agency of Canada. Canadian Immunization Guide. Part 2 Vaccine safety and Adverse Events Following Immunization.
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 adverse events following immunization. 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, such as 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 adverse events following immunization (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 involve 50 – hundreds of subjects; and,
- Phase III involve 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 15**).

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[19].

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 and /or over a long period of time.

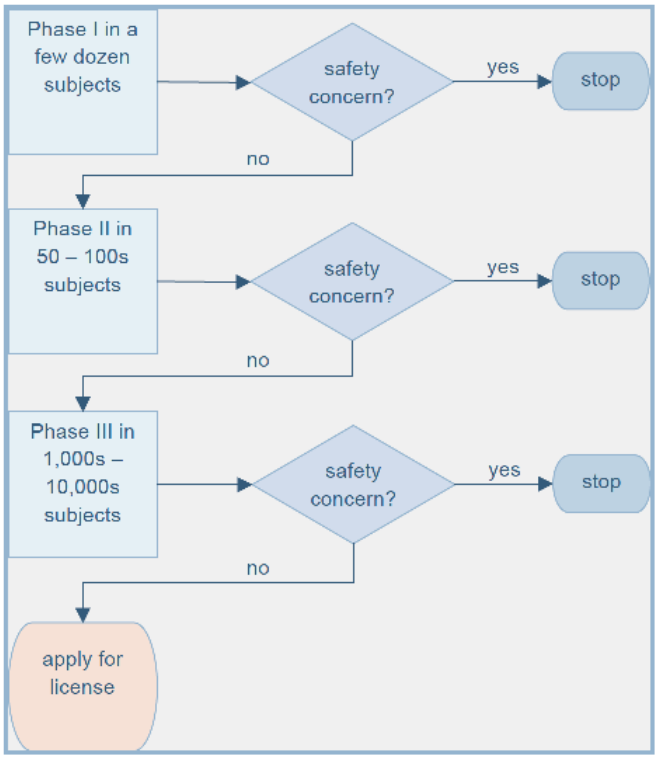


FIGURE 15. SAFETY TESTING OF VACCINES IN THREE PHASES OF CLINICAL TRIALS

[19] 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 Vaccines Adverse Event Reporting System (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 10**).

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	Japan
New Zealand	Canada
France	Denmark
United Kingdom	India
Sweden	Australia
New Zealand	Germany
Sweden	USA

TABLE 10. SELECT COUNTRIES' ADVERSE EVENT REPORTING SYSTEMS FOR DRUGS AND VACCINES[20]

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 Vaccine Adverse Event Reporting System (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 healthcare providers. These are collected without time restrictions. Since 2002 reports of vaccine-related adverse

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

events can also be submitted on the VAERS website (http://vaers.hhs.gov/index), and 24-hour toll-free phone assistance is available.

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 one year later to collect supplemental information, such as information about patient recovery (See **Figure 16**). The data on AEFIs from VAERS is made available to the public (without personal identifiers).

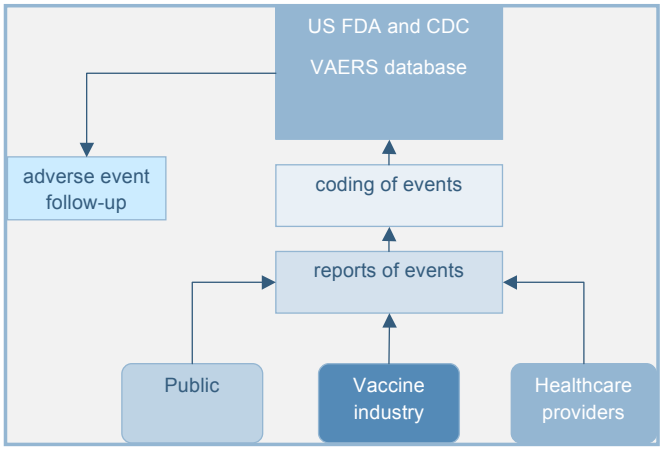


FIGURE 16. US VACCINE ADVERSE EVENT REPORTING SYSTEM (EXAMPLE OF A SPONTANEOUS SURVEILLANCE SYSTEM)

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 more than 90% of tertiary pediatric admissions in the country[21]. 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 17**).

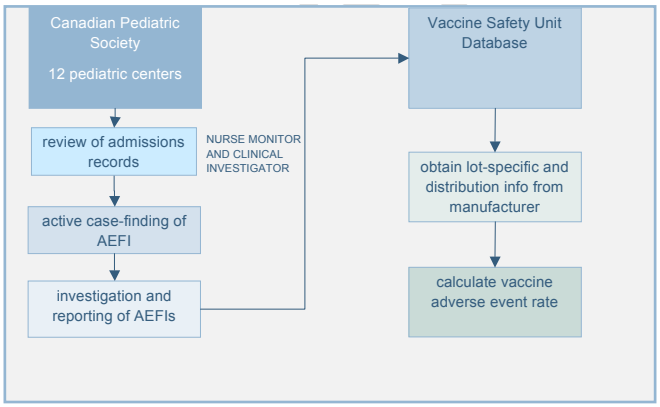


FIGURE 17. CANADIAN IMPACT SURVEILLANCE SYSTEM (EXAMPLE OF AN ACTIVE SURVEILLANCE SYSTEM)

Australia also supplements passive surveillance with an active surveillance system of sentinel units to investigate severe AEFIs[22].

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 responsibility of the states or provinces. In Germany, individual physicians recommend vaccines to

[21] Public Health Agency of Canada. Vaccine safety. http://www.phac-aspc.gc.ca/im/vs-sv/caefiss-eng.php
[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

their patients, but reportable AEFIs are made to the local health authority who then reports them to a national safety surveillance center[23]. 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 18**).

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 (WHO) Collaborating Center in Uppsala, Sweden, collects data of reports of AEFIs from about 40 countries. The WHO also has a Global Advisory Committee on Vaccine Safety (GACVS) that responds promptly to potential issues of vaccine safety.

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, healthcare 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 healthcare providers on how to communicate the risks and benefits of immunization. This includes communications on AEFIs.

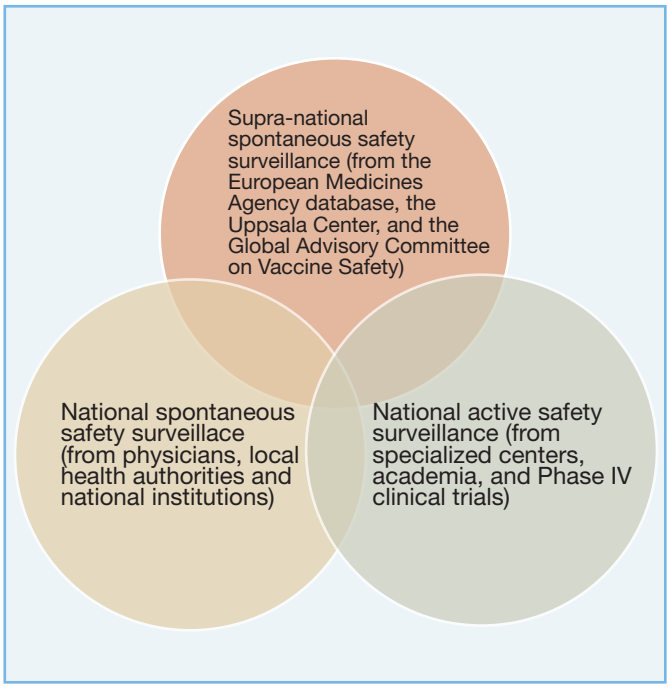


FIGURE 18. NATIONAL AND SUPRA-NATIONAL VACCINE SAFETY SURVEILLANCE IN EUROPE

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

[23] 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 Vaccine injury compensation systems

Origin of the US vaccine injury compensation system

Vaccines are produced under strict government regulations and are thoroughly studied for safety before and after they are licensed. Very rarely, severe vaccine adverse events may occur following immunization with licensed vaccines. This may occur because the incidence of an AEFI was too low to be detected during the registration process. When they do occur, severe AEFIs are thoroughly investigated. The great majority of severe AEFIs are found to be coincidental events that occur over a large number of vaccines delivered (i.e., events that occur around the time of vaccination, but are not caused by vaccination).

If governments did not protect vaccine manufacturers from liability for injury, vaccine manufacturers would be continuously exposed to the risk of liability. This in turn could reduce the willingness of manufacturers to produce and sell vaccines.

In the 1970s, precedent-setting legal actions caused several vaccine manufacturers to stop producing several vaccines. Gross sales of all vaccines, from all manufacturers in the US, amounted to $3 million in 1980. But damages awarded in a lawsuit had the potential to be far greater.[25] The negative impact of legal action on the willingness of vaccine manufacturers to produce vaccines, and the observed increase in vaccine prices to offset the increased risk of liability, compelled some governments to develop injury compensation systems. These were designed to secure the supply of needed vaccines.

In the US 'swine flu' incident of 1976 (the emergence of a new strain of H1N1 influenza in pigs that caused the death of a military recruit and was believed to be closely related to the influenza pandemic strain of 1918), a swine flu vaccine was highly demanded by the US government to prevent a human epidemic of the disease from occurring. But because of prior, precedent-setting legal actions against vaccine companies, no vaccine manufacturer was willing to produce and sell a swine flu vaccine. To get vaccine manufacturers to agree to produce a swine flu vaccine, the US government had to enact new legislation. The Swine Flu Act made the US government the defendant in any legal actions brought against swine flu vaccine manufacturers, for alleged injury. A decade later (in 1986), the US National Childhood Vaccine Injury Act (NCVIA) established the National Vaccine Injury Compensation Program (VICP).

What is an injury compensation system?

Vaccine injury compensation systems are meant to rapidly award those who inadvertently suffer injury from properly produced and administered vaccines. They are designed as no-fault systems that do not require proof of negligence on the part of the manufacturer (e.g. from improper design) or healthcare provider (e.g. from inadequate warning of risk). As such, punitive damages cannot be sought unless a manufacturer can be shown to have been grossly negligent. Instead, compensation is awarded based on the healthcare needs of the allegedly injured.

In addition to providing protection from legal action against vaccine manufacturers, vaccine injury compensation systems also provide protection for healthcare providers. In the absence of protection, healthcare providers might be unwilling to provide immunization services.

The awards in an injury compensation program are generally determined based on an established injury table which lists mandatory reportable adverse events (See **Table 11**)[25].

[25] Health Resources and Services Administration. http://www.hrsa.gov/vaccinecompensation/table.htm

Vaccine	Adverse Event	Time interval
Tetanus containing	Anaphylaxis or anaphylactic shock	0-4 hours
	Brachial neuritis	2-28 days
	Any acute complication or sequela (including death) of above events	Not applicable
Pertussis containing	Anaphylaxis or anaphylactic shock	0-4 hours
	Encephalopathy or encephalitis	0-72 hours
	Any acute complication or sequela (including death) of above events	Not applicable
Measles, mumps, and rubella containing vaccines	Anaphylaxis or anaphylactic shock	0-4 hours
	Encephalopathy or encephalitis	5-15 days
	Any acute complication or sequela (including death) of above events	Not applicable
Rubella containing	Chronic arthritis	7-42 days
	Any acute complication or sequela (including death) of above events	Not applicable
Measles containing	Thrombocytopenic purpura	7-30 days
	Vaccine-Strain Measles Viral Infection in an immunodeficient recipient	0-6 months
	Any acute complication or sequela (including death) of above events	Not applicable
Oral Polio	Paralytic polio	0-30 days (non immunodeficient); 0-6 months (immunodeficient); Not applicable (vaccine associated community case)
	Vaccine-strain polio	0-30 days (non immunodeficient); 0-6 months (immunodeficient); Not applicable (vaccine associated community case)
	Any acute complication or sequela (including death) of above events	Not applicable
Inactivated Polio	Anaphylaxis or anaphylactic shock	0-4 hours
	Any acute complication or sequela (including death) of above events	Not applicable
Hepatitis B containing	Anaphylaxis or anaphylactic shock	0-4 hours
	Any acute complication or sequela (including death) of above events	Not applicable
Haemophilus influenzae type b (Hib)	No condition specified	Not applicable
Varicella	No condition specified	Not applicable
Rotavirus	No condition specified	Not applicable
Pneumococcal conjugate	No condition specified	Not applicable
Any new vaccine recommended by the CDC for routine administration to children (includes Hepatitis A, influenza, meningococcal conjugate, and Human Papilloma Virus)	No condition specified	Not applicable

TABLE 11. US VACCINE INJURY TABLE

The detailed Injury Table can be accessed at:
http://www.hrsa.gov/vaccinecompensation/table.htm

How the US National Vaccine Injury Compensation Program (VICP) works

The US the National Childhood Vaccine Injury Act (NCVIA) mandates that vaccine manufacturers and healthcare providers report those adverse events listed in the Vaccine Injury Table. In the US, reporting of adverse events is made through the Vaccine Adverse Event Reporting System (VAERS).

Because childhood vaccination is mandatory in the US, the national Vaccine Injury Compensation Program (VICP) covers routine vaccines for children (against a total of 16 diseases).

The VICP is administered by the Department of Health and Human Services (HHS), the Department of Justice (DOJ), and the Office of Special Masters, US Court of Federal Claims.

In addition, the VICP is monitored by the Advisory Committee on Childhood Vaccines (ACCV). The ACCV is composed of physicians, parents and attorneys. The ACCV makes recommendations on operations of the VICP, including for changes to the Vaccine Injury Table, when appropriate. The National Vaccine Advisory Committee (NVAC) has broad oversight of the VICP, and makes recommendations on a broad array of issues, including vaccine research, production, delivery, safety and efficacy (See **Figure 20** on page 32).

Funding for the VICP is generated by the collection of an excise tax of $0.75 on each dose of vaccine sold for each disease prevented (i.e. $0.75 X 3 = $ 2.25 for MMR).

The process for claiming compensation for injury from a vaccine is shown in **Figure 21** on page 32[26].

The VICP Trust Fund was established in 1988. Since that time, the annual number of vaccine injury compensation claims has remained fairly constant. Spikes in claims occurred when attention-getting allegations were made for the association of encephalopathy with DTP and for the association of autism with thimerosal. The annual numbers of petitions filed since the start of the program are shown in **Figure 19**[27].

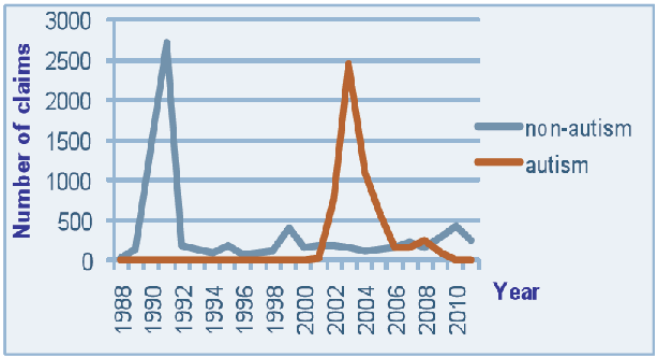


FIGURE 19.

> The national Vaccine Injury Compensation Program covers routine vaccines for children (against a total of 16 diseases).

[26] US Department of Health and Human Services. Health Resources and Services Administration. National Vaccine Injury Compensation Program. http://www.hrsa.gov/vaccinecompensation/

[27] US Department of Health and Human Services. Health Resources and Services Administration. National Vaccine Injury Compensation Program. Statistics reports. http://www.hrsa.gov/vaccinecompensation/statistics_report.htm

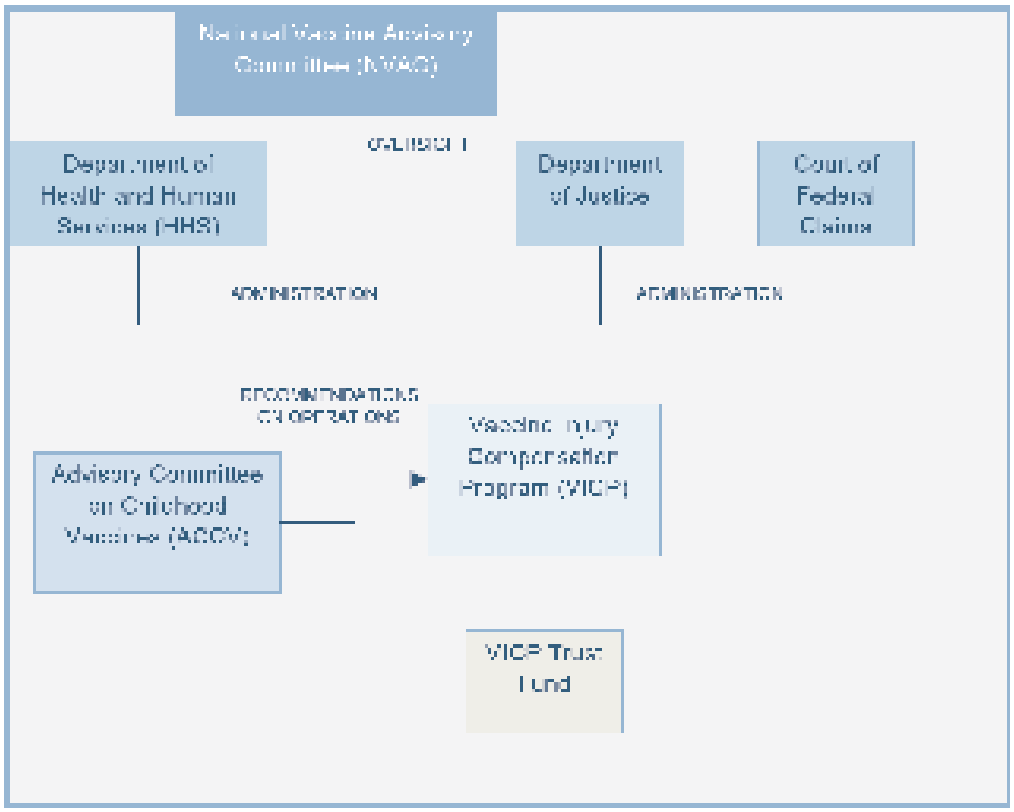


FIGURE 20. ORGANIZATION OF VACCINE INJURY COMPENSATION PROGRAM IN THE US

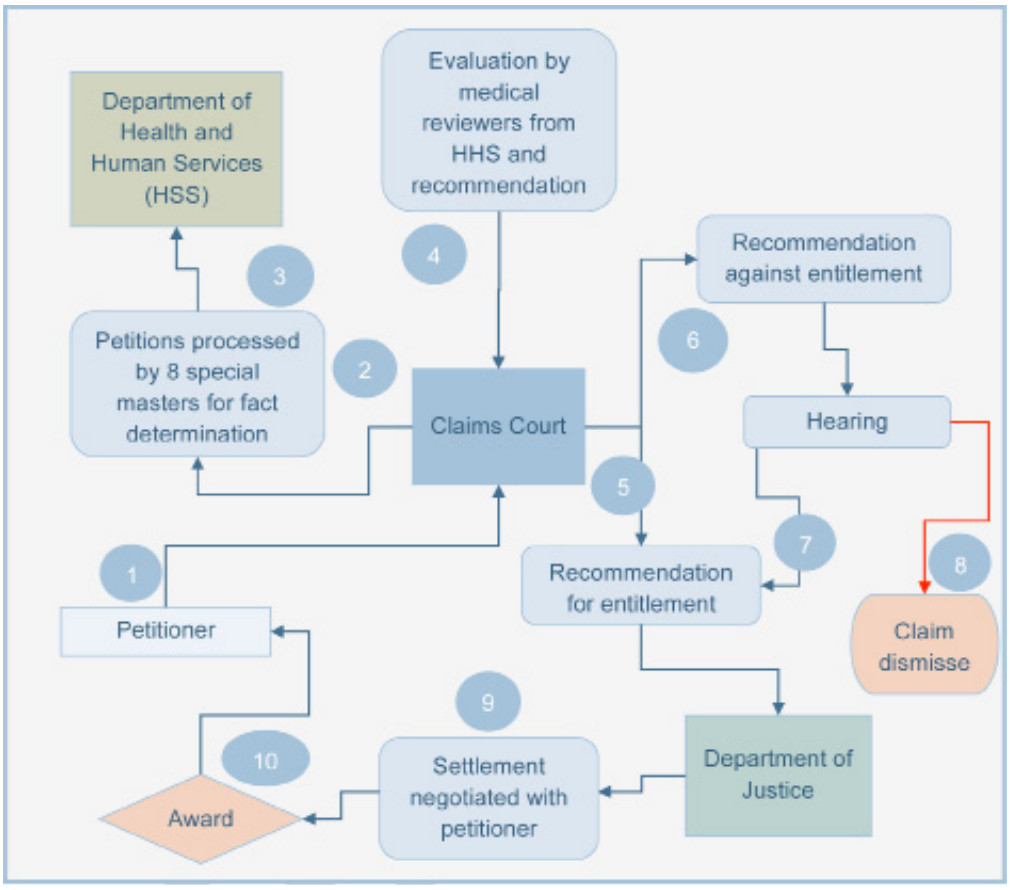


FIGURE 21. VACCINE INJURY COMPENSATION CLAIM PROCESS IN THE US

1. Patients (or their attorneys) file petitions with the Court of Claims;
2. Petitions are processed by eight dedicated special masters for fact determination;
3. Valid claims are sent to the Department of Health and Human Services (HSS) for evaluation by medical reviewers - eligibility for compensation is determined by proof of a condition listed in the Vaccine Injury Table (VIT), or by proof that an injury not listed in the VIT was caused by a vaccine. Petitioners must also prove that injury required hospitalization or lasted for more than six months;
4. Recommendations of the medical reviewers on petitioners' entitlement to compensation are forwarded to the Court of Claims;
5. Recommendations for entitlement, are almost always accepted by the Court of Claims and submitted to the Department of Justice;
6. Recommendations against entitlement proceed to a hearing;
7. Hearings may, based on the testimony presented, reject the recommendations of the medical reviewers and recommend entitlement to compensation to the petitioner;
8. Hearings that accept recommendations against entitlement result in dismissal;
9. When entitlement has been awarded, the Department of Justice will reach agreement with the petitioner on the amount to be awarded;
10. The award is evaluated based on the injured individual's future needs and paid in lump sum and an annuity. A lump sum is limited to $250,000.00 for death. Compensation ranges from $120 to $9.1 million. In addition, reasonable attorney fees are paid for both successful and unsuccessful petitioners.

Note that the petitioner may, nevertheless, pursue a claim against a vaccine manufacturer if a VICP award is denied or rejected because it is deemed to be insufficient. Details on the claims process for the VICP can be found at: http://www.hrsa.gov/vaccinecompensation/

The number of awards granted, and the amount of compensation, has varied from year to year[28]. The highest number of awards was granted in the late 1990s. The annual amount of compensation has ranged from about $50 million to $180 million (See **Figure 22**).The annual amounts paid out by the VICP Trust Fund are slightly higher than the amounts of the awards because payouts include attorney fees.

The number of petitions to the VICP by type of vaccine varies considerably[29]. The greatest number of claims was made against DTP vaccine in the 1990s. DTP has since been replaced with the less reactogenic DTaP vaccine in the US. The cumulative number of claims against DTaP vaccine is notably smaller. The numbers of claims for compensation filed with the VICP, and the number of awards, for each type of vaccine, from 1988 – 2010, are shown in **Figure 23**.

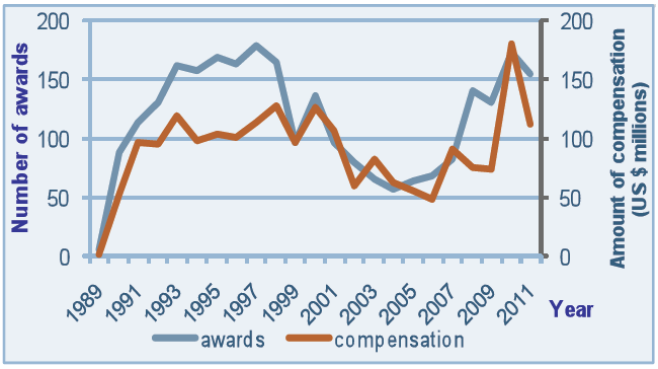


FIGURE 22. ANNUAL NUMBER OF VICP AWARDS AND ANNUAL AMOUNTS OF COMPENSATION AWARDED FROM THE VICP TRUST FUND

The number of awards granted, and the amount of compensation, has varied from year to year.

[28] US Department of Health and Human Services. Health Resources and Services Administration. National Vaccine Injury Compensation Program. Statistics reports. http://www.hrsa.gov/vaccinecompensation/statistics_report.htm
[29] US Department of Health and Human Services. Health Resources and Services Administration. National Vaccine Injury Compensation Program. Statistics reports. http://www.hrsa.gov/vaccinecompensation/statistics_report.htm

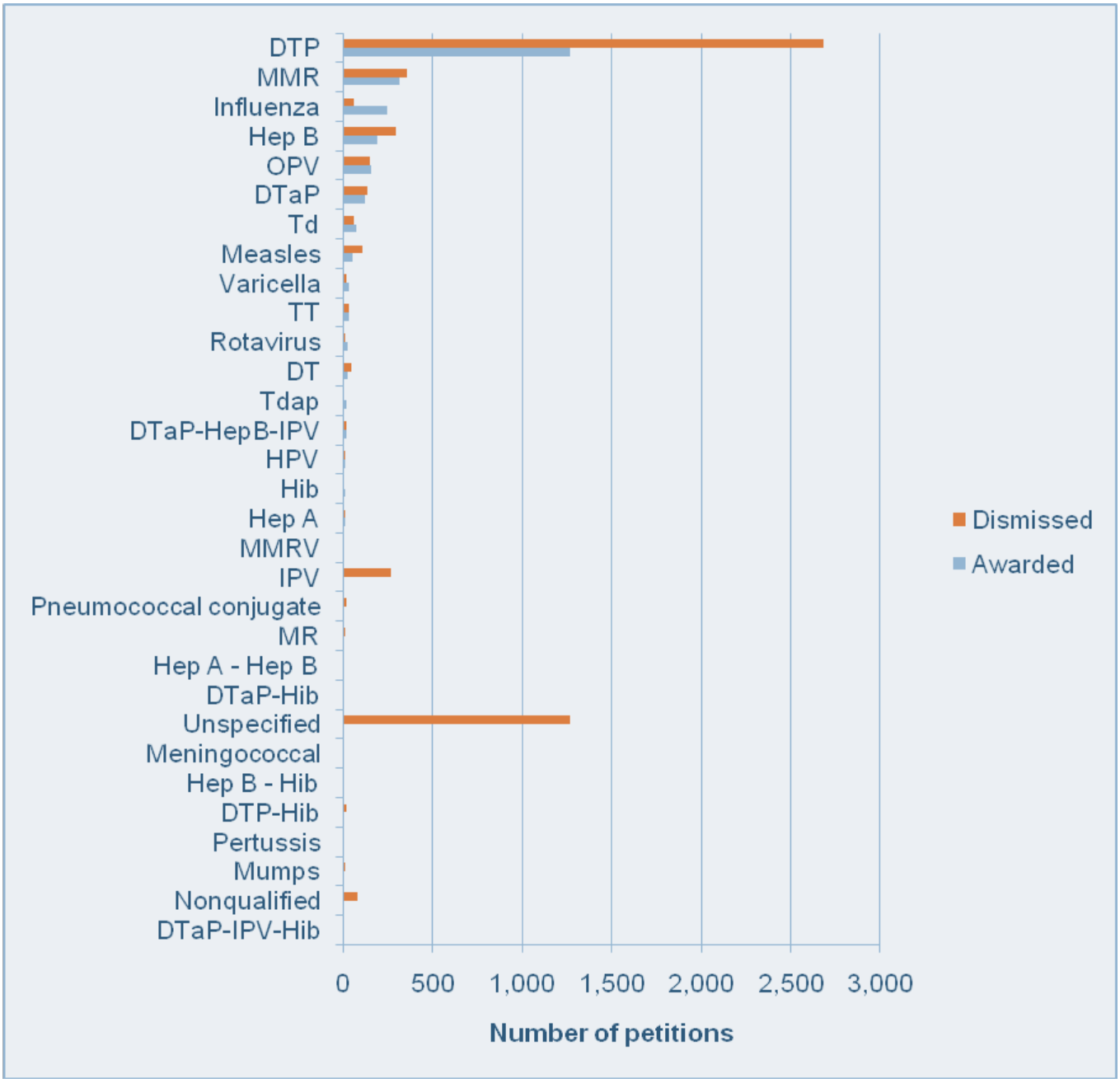


FIGURE 23. NUMBER OF PETITIONS TO THE VICP AND NUMBER OF AWARDS GRANTED BY VACCINE TYPE, FROM 1988 - 2010

National vaccine injury compensation programs, other than in the US

Nineteen countries have some form of vaccine injury compensation program (See **Figure 24**)[30]. Germany was the first country to introduce a program in 1961, and Hungary adopted a program in 2005. All but two of these programs are administered by the national or state governments. In the other two countries (Sweden and Finland) the programs are administered by the vaccine industry through voluntary contributions to insurance. In all countries, except Taiwan, compensation is awarded from the national treasury. Taiwan, like the US, created a trust fund from an excise tax of Taiwan $1.00 / dose on the sale of vaccines. In all cases, these countries' vaccine-injury compensation programs require causation to be demonstrated by a standard of "more likely than not," a standard that is lower than in tort law.

Some schemes cover only mandatory vaccines while others cover any licensed vaccine. Eligibility criteria vary between programs, but most require proof of disability of some duration to be compensable.

All programs, except in the UK, compensate for medical expenses, disability pension, and death benefits. The UK provides a lump sum payment of £120,000. Some programs also compensate for pain and suffering, but none compensate for legal costs.

Most programs aim to settle claims in a timely fashion and some countries are mandated to resolve claims within six months. Unlike the US program, which uses an Injury Table to determine eligibility, most countries rely on the Bradford Hill criteria to establish causality.

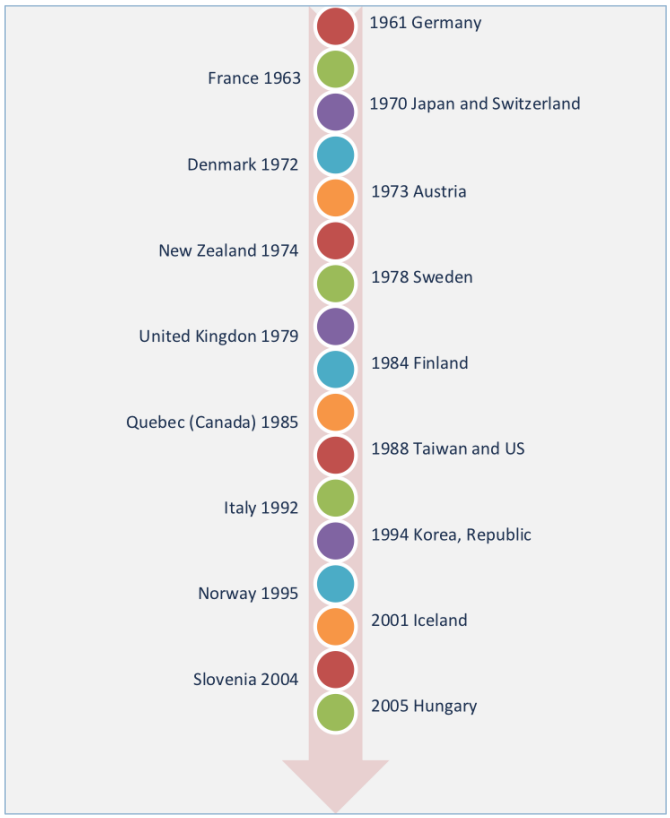


FIGURE 24. COUNTRIES WITH INJURY COMPENSATION PROGRAMS, YEAR INTRODUCED

[30] Looker C & Kelly H. No-fault compensation following adverse events attributed to vaccination: a review of international programmes. *Bull World Health Organ* 2011; 89:371–378. http://www.who.int/bulletin/volumes/89/5/10-081901.pdf

1.6 Cost-effectiveness analyses and evaluation

Cost analyses are often used in healthcare. 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 25**).

Several methods can be used to quantify the value of immunization programs (See **Figure 26**). 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 12**)[31]:

- 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 12. 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% / 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[32].

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

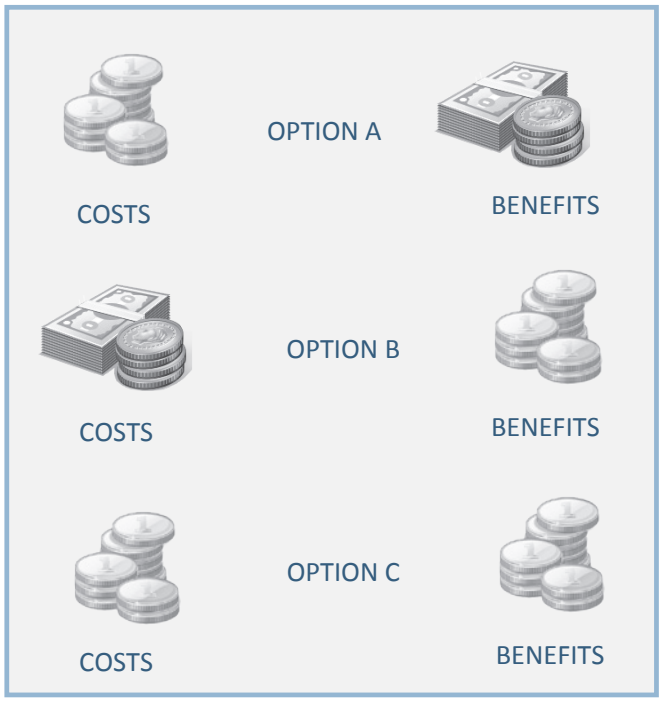


FIGURE 25. COST BENEFIT ANALYSES ASSIST IN DETERMINING WHICH PROGRAM OPTIONS AND PROVIDE THE GREATEST VALUE

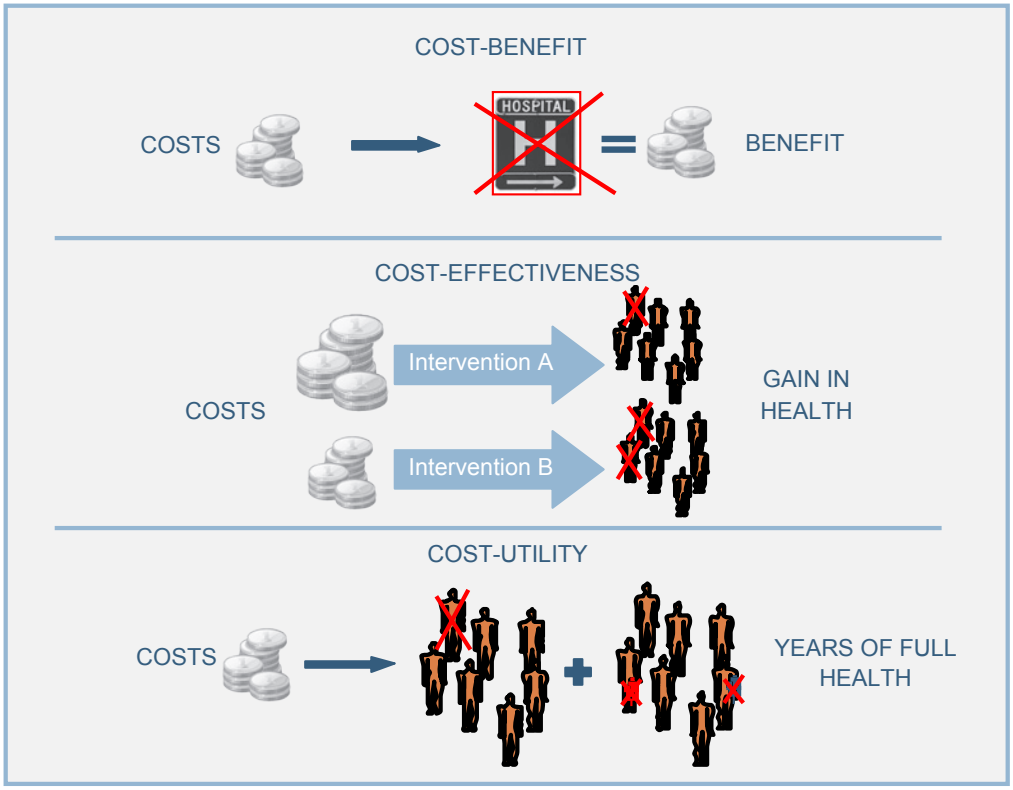


FIGURE 26. TYPES OF ECONOMIC ANALYSES COMMONLY USED TO ASSESS IMMUNIZATION PROGRAMS

The benefits: 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, such as 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 healthcare 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 27**)[33].

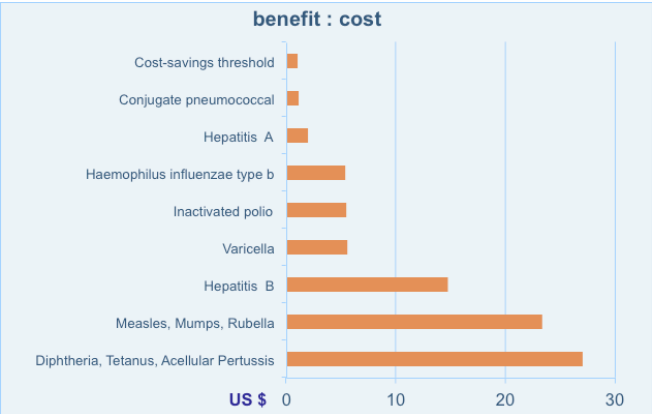


FIGURE 27. COST-SAVING BENEFIT: COST RATIOS FOR SOME VACCINES IN THE US

Benefit : cost ratios vary according to the healthcare 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[34].

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 a 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 Hepatitis B vaccines, instead of administering separate injections[35].

Compared to other government interventions, including other interventions in health, the cost-effectiveness of most vaccines is exceptionally high (See **Figure 28**)[36]. 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[37].

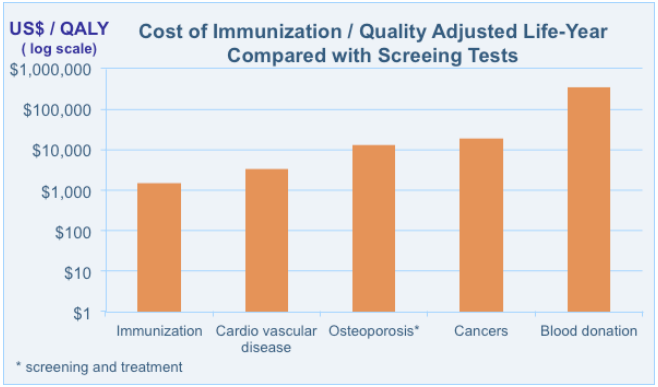


FIGURE 28. COST-EFFECTIVENESS OF IMMUNIZATION COMPARED TO COMMONLY USED SCREENING TESTS IN THE US

[33]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.
[34]World Health Organization. Immunization. http://www.who.int/topics/immunization/en/
[35]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.
[36]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
[37]World Health Organization. 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 26**).

Disability-adjusted-life-years (DALY) or quality-adjusted-life-years (QALY) 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.

DALY and QALY 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 29 shows the relative cost utility of some vaccines in the US[38,39,40].

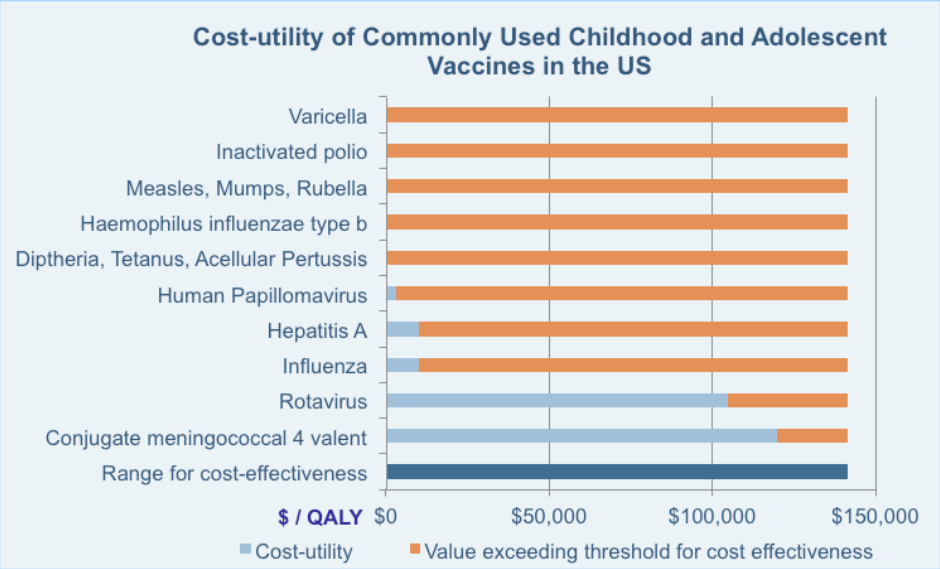


FIGURE 29. COST-EFFECTIVENESS OF CHILDHOOD AND ADOLESCENT VACCINES IN THE US. VACCINES <$0 / QALY ARE COST SAVING. ALL VACCINES SHOWN EXCEED THE THRESHOLD FOR COST-EFFECTIVENESS. (LOWEST COSTS WERE USED IF FROM A RANGE; COST FOR HUMAN PAPILLOMAVIRUS VACCINE IS FOR IMMUNIZATION OF 12 YEAR-OLD GIRLS)

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

1.7 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 healthcare 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 30**)[41]:

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 healthcare 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);

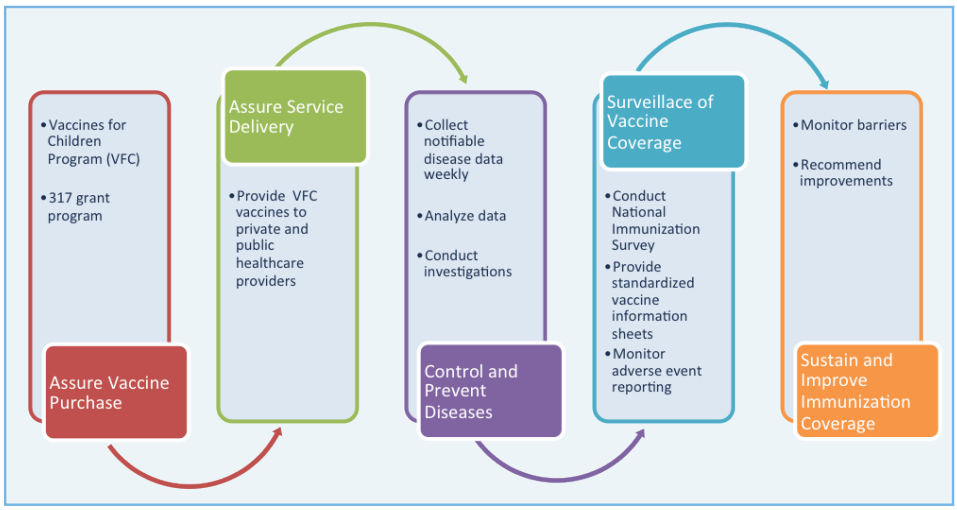


FIGURE 30. KEY GOVERNMENT ROLES IN IMMUNIZATION SUPPORTED BY IMMUNIZATION FINANCE POLICIES AND PRACTICES

[41]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 Health Management Organizations (HMOs) also assess immunization coverage using a standardized program through the Health Plan Employer Data Information Set (HEDIS);

- Immunization Information Systems (previously called immunization registries) are confidential computerized databases that record vaccine doses administered by participating healthcare 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, such as 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, such as the UK, have a strong, centralized, comprehensive health system that includes responsibility for immunization. In the UK, the national government provides for 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, such as the European Center for Disease Prevention and Control (ECDC), strengthen surveillance within the European Union 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 31**).

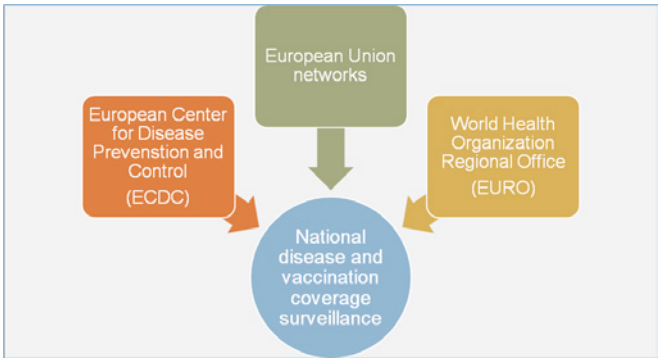


FIGURE 31.SUPPORT MECHANISMS IN EUROPE FOR NATIONAL SURVEILLANCE OF VACCINE-PREVENTABLE DISEASES AND VACCINATION COVERAGE

Immunization policies and implementation are determined within each country. They are not subject to EU legislation. But vaccines can be licensed in other European Union 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 the three regions.

The Asia-Pacific region does not have a regional vaccination support program, such as 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. Ironically, some of the lowest-income countries in the region recommend the greatest number of vaccines (See **Figure 32**)[42].

[42]Tsai TFand Xu ZY. Immunization in the Asia-Pacific region. pp 1525-1539. In Vaccines 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.

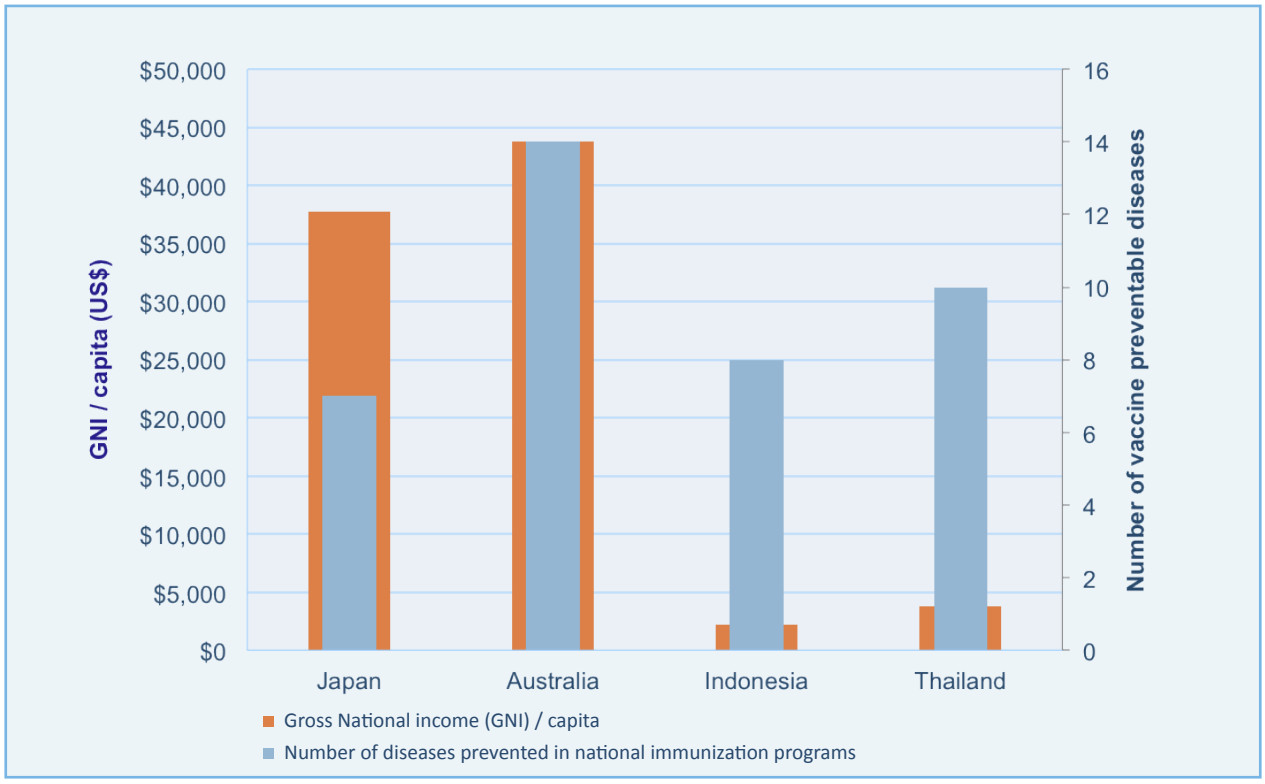


FIGURE 32. DISPARITY IN THE NUMBER OF DISEASES PREVENTED IN NATIONAL IMMUNIZATION PROGRAMS IN COUNTRIES WITH DIFFERENT LEVELS OF GROSS NATIONAL INCOME / CAPITA IN THE ASIA-PACIFIC REGION

1.8 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[43]. The nature and composition of these committees vary 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[44]. It issues recommendations for vaccines that are used by healthcare 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 33**).

[43]World Health Organization. Immunizations, Vaccines and Biologicals. National advisory committees on immunization. http://www.who.int/immunization/sage/national_advisory_committees/en/index.html
[44]US Centers for Disease Control and Prevention. Vaccines & Immunizations. Recommendations and Guidelines: Advisory Committee on Immunization Practices (ACIP). About ACIP. http://www.cdc.gov/vaccines/recs/acip/#about

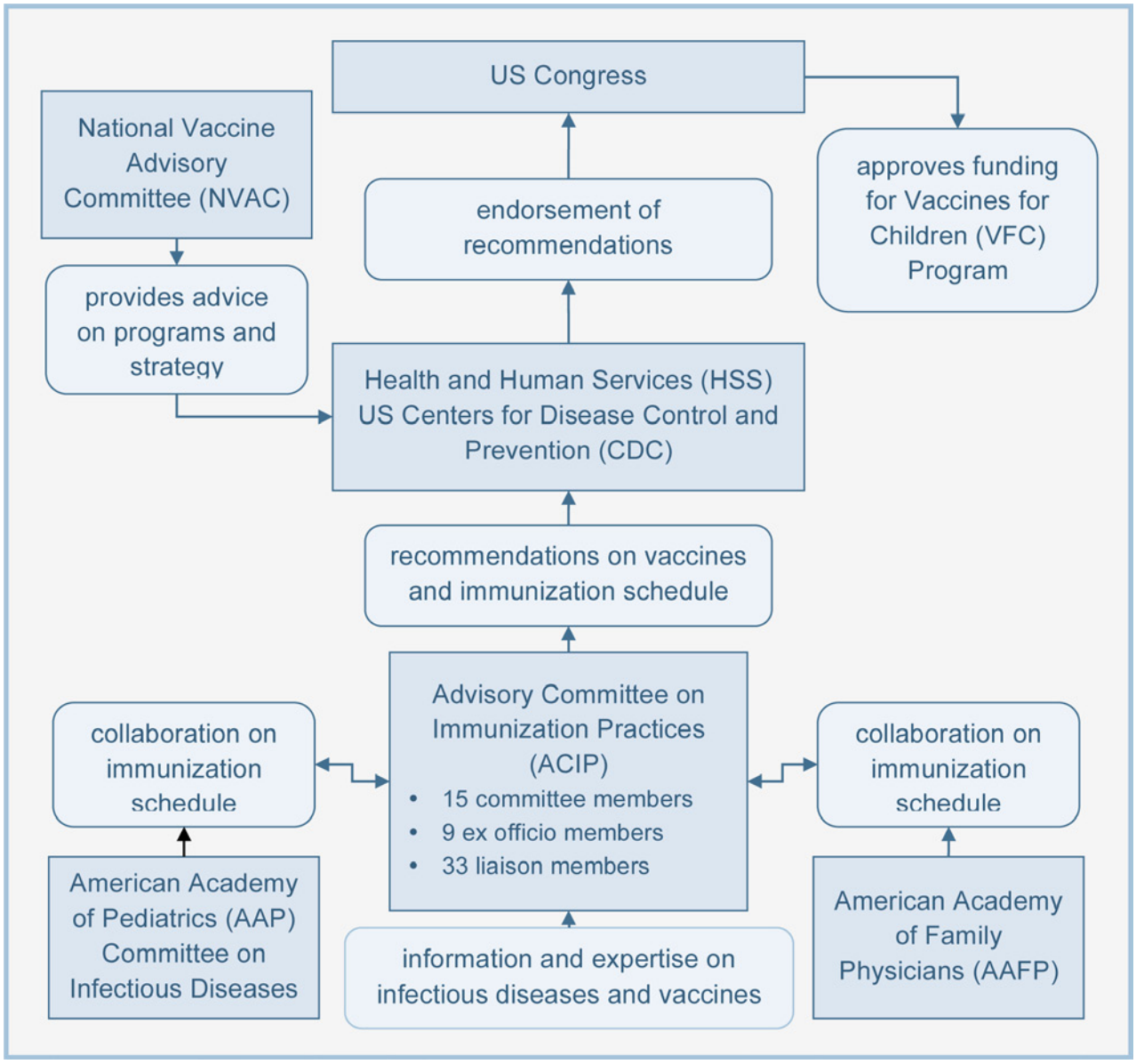


FIGURE 33. ORGANIZATION AND RECOMMENDATION PROCESS OF THE US ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP) AND ITS PARTNERS

The 15 ACIP members are appointed by the Secretary of HHS for a term of two 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 34** and **Figure 35**).

FIGURE 34. BROAD ARRAY OF REPRESENTATION IN THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Once ACIP's recommendations have been accepted by HSS and CDC, recommended vaccines are funded by the Vaccines for Children Program (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.

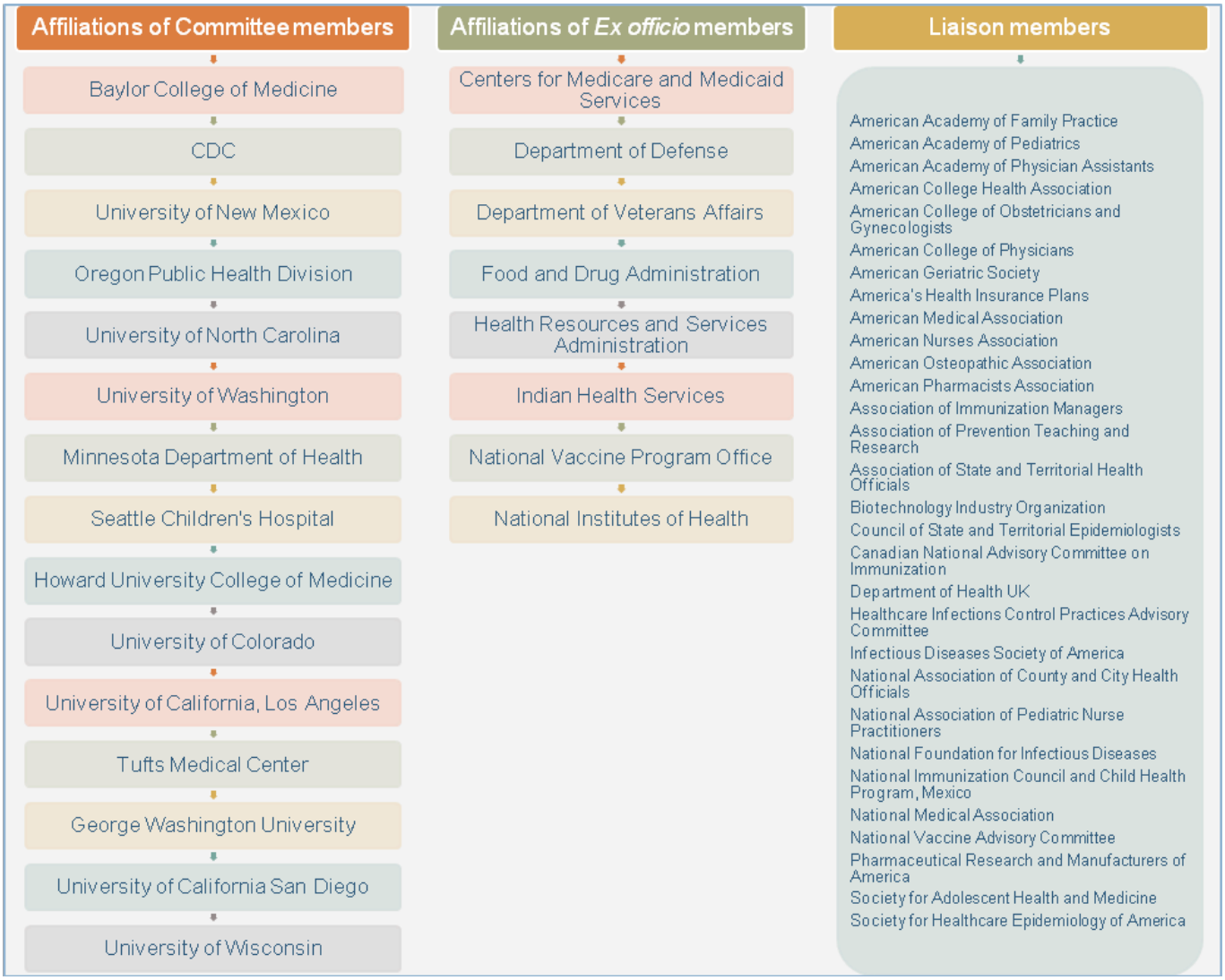


FIGURE 35. AFFILIATIONS OF MEMBERS OF THE US ACIP IN 2011 SHOWING REPRESENTATION FROM A WIDE DIVERSITY OF INSTITUTIONS AND ORGANIZATIONS

How Australia recommends immunizations

The Australian Technical Advisory Group on Immunization (ATAGI) is the national immunization technical advisory group for Australia[45]. 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)[46] (See **Figure 36**).

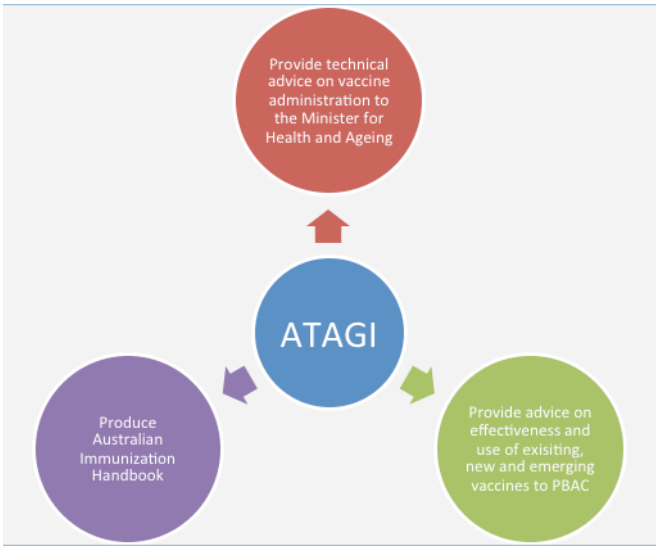


FIGURE 36. FUNCTIONS OF THE AUSTRALIAN TECHNICAL ADVISORY GROUP ON IMMUNIZATION (ATAGI)

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 is required, the decision goes to the government's cabinet.

In addition to providing the Minister of 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[47]. Member affiliations are shown in **Figure 37**.

[45]Australian Government. Department of Health and Ageing. Immunisation Advisory Bodies. Australian Technical Advisory Group on Immunisation (ATAGI). http://www.health.gov.au/internet/immunise/publishing.nsf/content/advisory-bodies
[46]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
[47]Australian Government. Department of Health and Ageing. Immunisation advisers appointed. http://www.health.gov.au/internet/ministers/publishing.nsf/Content/health-mediarel-yr2005-ta-abb128.htm?OpenDocument&yr=2005&mth=10

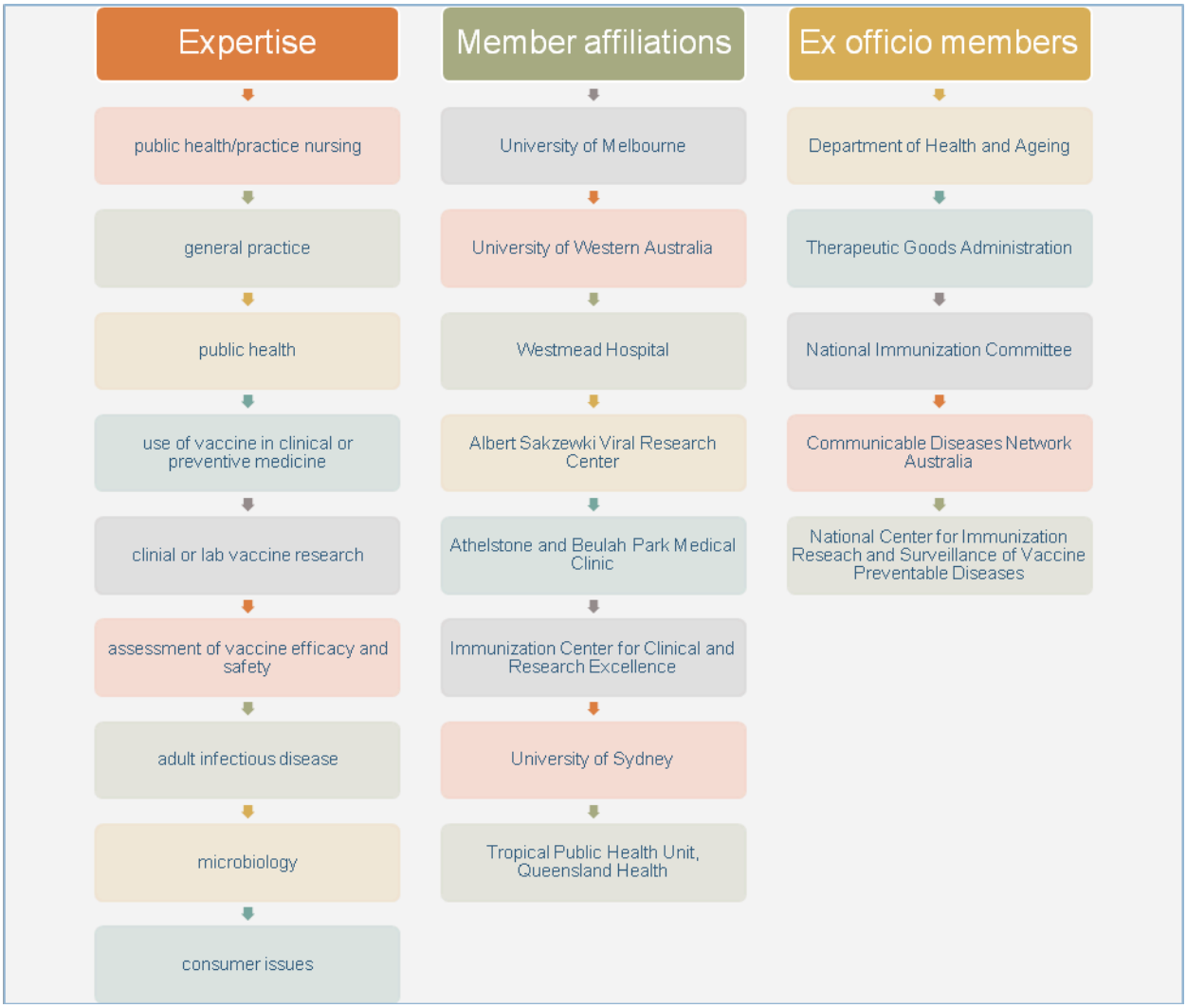


FIGURE 37. AFFILIATIONS OF MEMBERS OF THE AUSTRALIAN TECHNICAL ADVISORY GROUP ON IMMUNISATION (ATAGI)

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 (STIKO and the Joint Committee on Vaccines and Immunization (JCVI), respectively) (See **Table 13**). 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 Immunization	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 13. SAMPLE LIST OF SOME NATIONAL IMMUNIZATION TECHNICAL ADVISORY GROUPS (NITAGS)

In the Asia-Pacific region, many countries have expert immunization committees: the Taiwan Advisory Committee on Immunization Practices (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 national immunization technical advisory groups (NITAGs) is shown in **Table 13**[48].

How supra-national organizations recommend immunizations

The WHO provides leadership on global health matters for the members of the United Nations. 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[49].

For countries that do not have their own national immunization technical advisory groups (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 the ACIP, the SAGE has affiliate members who participate as observers (e.g. Unicef, GAVI, WHO regional offices, vaccine companies). Affiliations of members are shown in **Figure 38**.

[48]World Health Organization. Immunizations, Vaccines and Biologicals.National Advisory Committees. http://www.who.int/immunization/sage/national_advisory_committees/en/index1.html
[49]World Health Organization. Strategic Advisory Group of Experts – Terms of Reference. March 29, 2011. http://www.who.int/immunization/sage/SAGE_TOR_part_1_Annex_3_29_Mar_2011.pdf

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.intwer). For specific issues, the SAGE may constitute time-limited working groups.

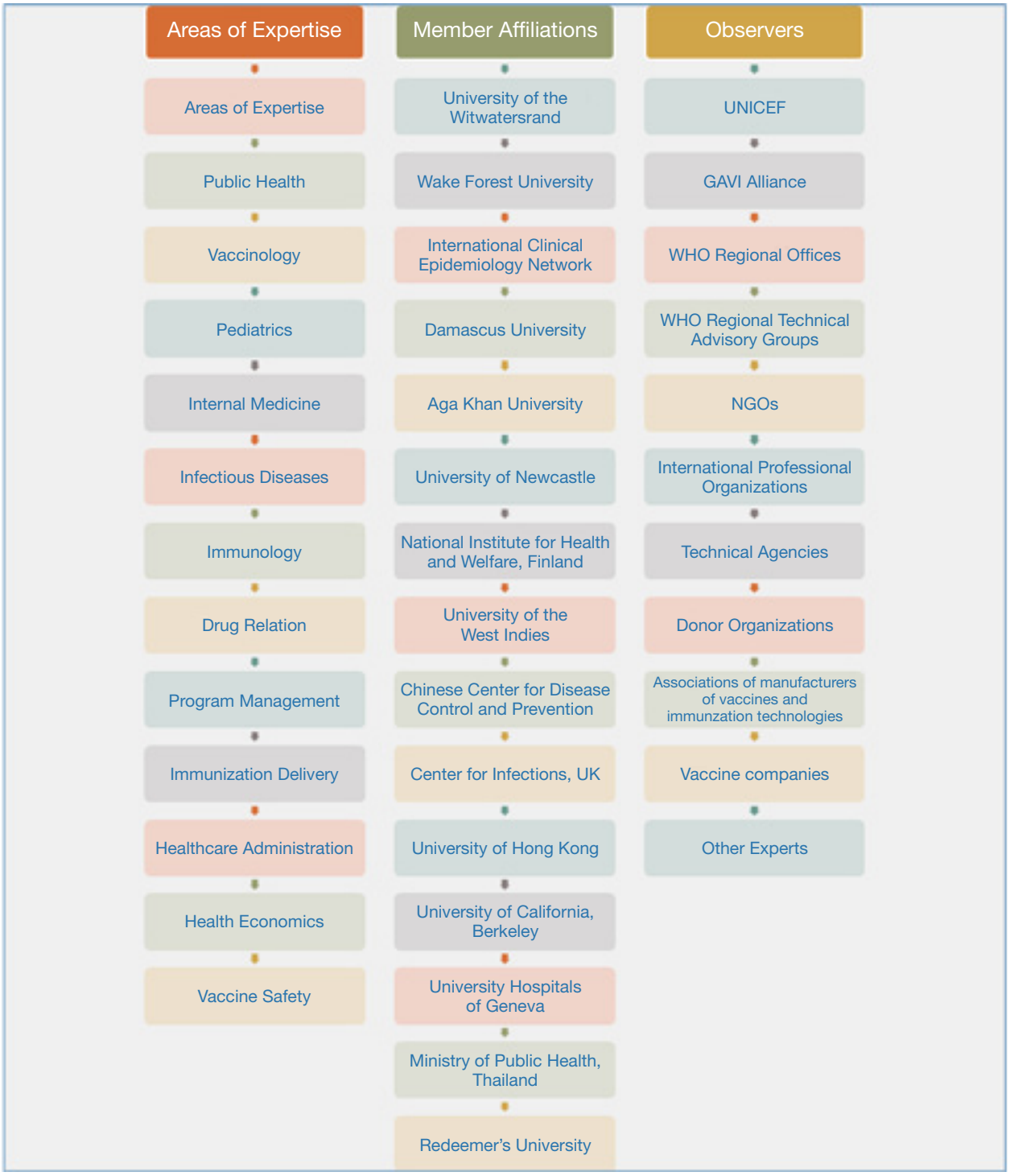


FIGURE 38. AFFILIATIONS OF CURRENT MEMBERS OF WORLD HEALTH ORGANIZATION'S STRATEGIC ADVISORY GROUP OF EXPERTS (SAGE)[50]

[50]World Health Organization. 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[51]. 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.

[51]World Health Organization. Immunization, Vaccines and Biologicals. WHO vaccine position papers. http://www.who.int/immunization/position_papers/en/

Vaccine implementation varies between countries, but, generally, those with similar levels of income have comparable immunization systems. One exception is Japan. Japan has a level of wealth similar to countries in Western Europe, 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 past 25 years have been developed in the US[52].

2.1 The global vaccine market

The vaccine market represented about 3% of the pharmaceutical market, at about $28 billion in 2010[53]. Five manufacturers (Merck & Co, GlaxoSmithKline, Sanofi Pasteur, Pfizer, and Novartis) account for the majority of the market (79.4% in 2010) (See **Figure 39**)[54].

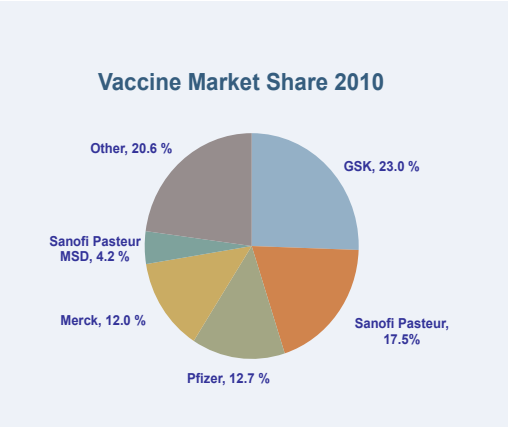


FIGURE 39. THE DOMINANT SUPPLIERS INF THE GLOBAL VACCINE MARKET 2010

The pediatric vaccine market accounted for about 52% of the total vaccine market in 2009. Sales of influenza vaccines, including H1N1 vaccine, were approximately $5 billion in 2010, accounting for about 18% of the vaccine market.

Growth in the market is expected to continue at around 10% compound annual growth rate (CAR) over the next five years. The pediatric market is expected to grow slightly faster than the adult vaccine market, at 11% versus 8.2% (See **Figure 40**)[55]. By comparison, the pharmaceutical market grew by 4 – 6% in 2010 and is expected to grow at 4 – 7% through 2013[56].

The growth in the vaccine market is driven by the sales of recently developed vaccines and by new vaccine markets. Several vaccines now generate more than $1 billion in global sales (See **Figure 41**)[57] and the Global Alliance for Vaccines and Immunization (GAVI Alliance) is expected to expend more than $1 billion per year on vaccines.

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

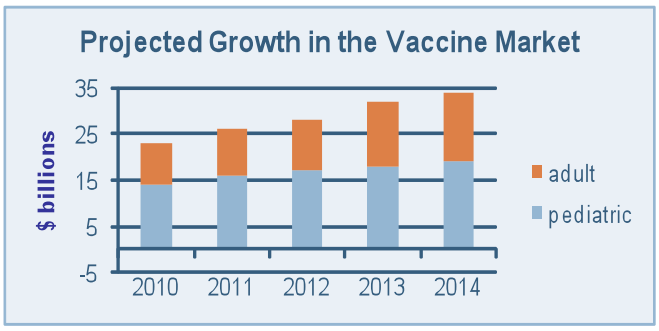


FIGURE 40. PROJECTED GROWTH OF THE VACCINE MARKET BY ADULT AND PEDIATRIC SEGMENTS

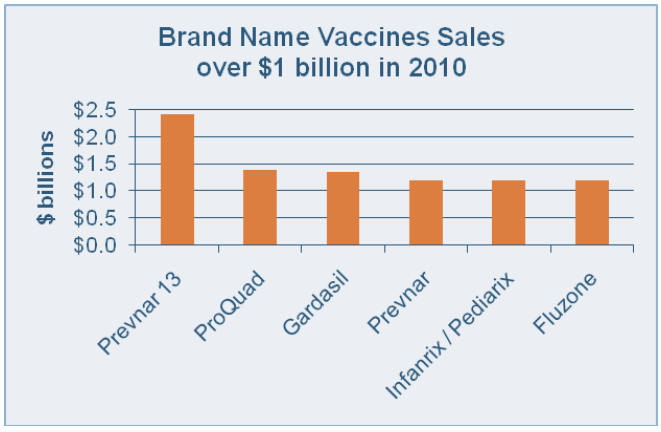


FIGURE 41. BRAND NAME VACCINES THAT GENERATED MORE THAN $1 BILLION IN SALES IN 2010.

[52]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.
[53]Knol. Global Vaccine market 2010. Top vaccine companies and blockbuster vaccines. http://knol.google.com/k/krishan-maggon/global-vaccine-market-2010/3fy5eowy8suq3/152#
[54]Hiller A. Vaccines continue to bolster pharma market. PharmPro. December 2, 2010. http://www.pharmpro.com/articles/2010/12/busines-Vaccines-Continue-to-Bolster-Pharma-Market/
[55]Hiller A. Vaccines continue to bolster pharma market. PharmPro. December 2, 2010. http://www.pharmpro.com/articles/2010/12/busines-Vaccines-Continue-to-Bolster-Pharma-Market/
[56]Pharmaceutical Drug Manufacturers. Pharmaceutical market trends 2010. http://www.pharmaceutical-drug-manufacturers.com/articles/pharmaceutical-market-trends-2010.html
[57]Knol. Global Vaccine market 2010. Top vaccine companies and blockbuster vaccines. http://knol.google.com/k/krishan-maggon/global-vaccine-market-2010/3fy5eowy8suq3/152#

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-tenth of vaccine candidates achieve licensure. The high failure rate is due to the unpredictability of the biological organisms 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 42**):

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

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

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 organisms, 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 43**)[58].

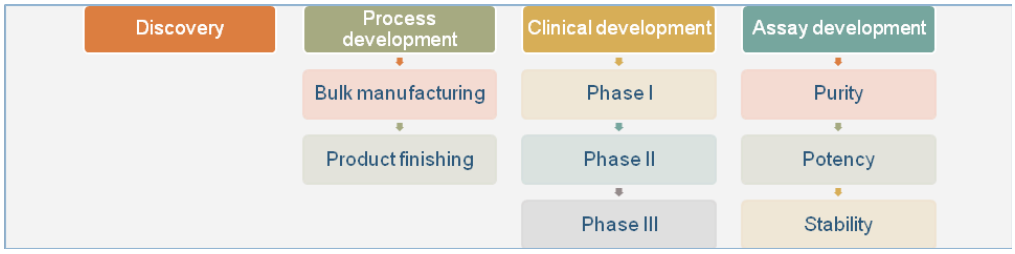


FIGURE 42. DIFFERENT TYPES OF DEVELOPMENT NECESSARY TO REACH THE VACCINE LICENSING STAGE

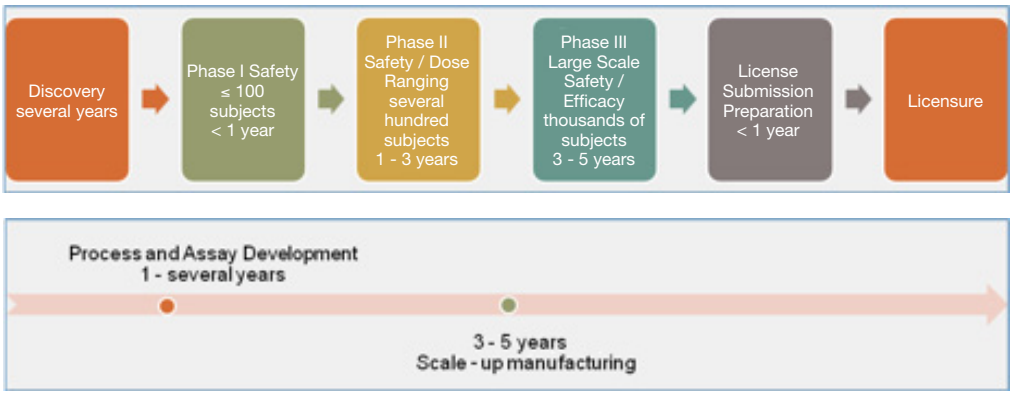


FIGURE 43. VACCINE DEVELOPMENT PROCESS OVER A PERIOD OF UP TO 15 YEARS AT A COST OF UP TO $1 BILLION

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 44**)[59]:

Phase I – early safety and immunogenicity trials that involve ≤100 subjects and can be completed in under one year;

Phase II – safety, dose ranging, and immunogenicity trials that involve several hundred 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 44. THE FOUR PHASES OF CLINICAL DEVELOPMENT OF VACCINES

[58]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

[59]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 the 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[60]. 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.

[60]GlaxoSmithKline. European Medicines Agency maintains position on the continued use of Rotarix™ (rotavirus vaccine). Media Center, May 21, 2010. http://www.gsk.com/media/pressreleases/2010/2010_pressrelease_10048.htm

2.3 Vaccine manufacturing

The manufacture of vaccines is achieved from the propagation of living organisms. 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 45**):

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

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

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

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 healthcare providers. (See **Figure 46**).

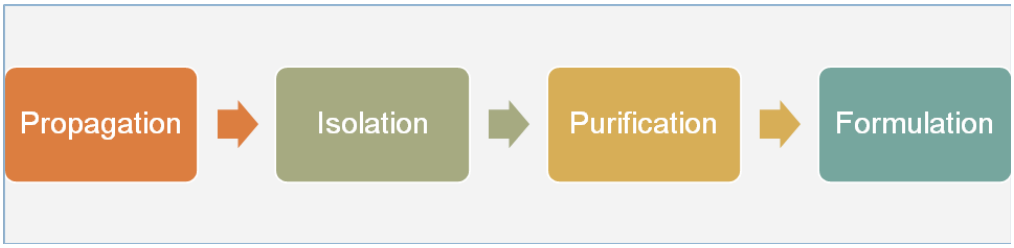


FIGURE 45. THE FOUR STEPS IN THE PRODUCTION OF VACCINES

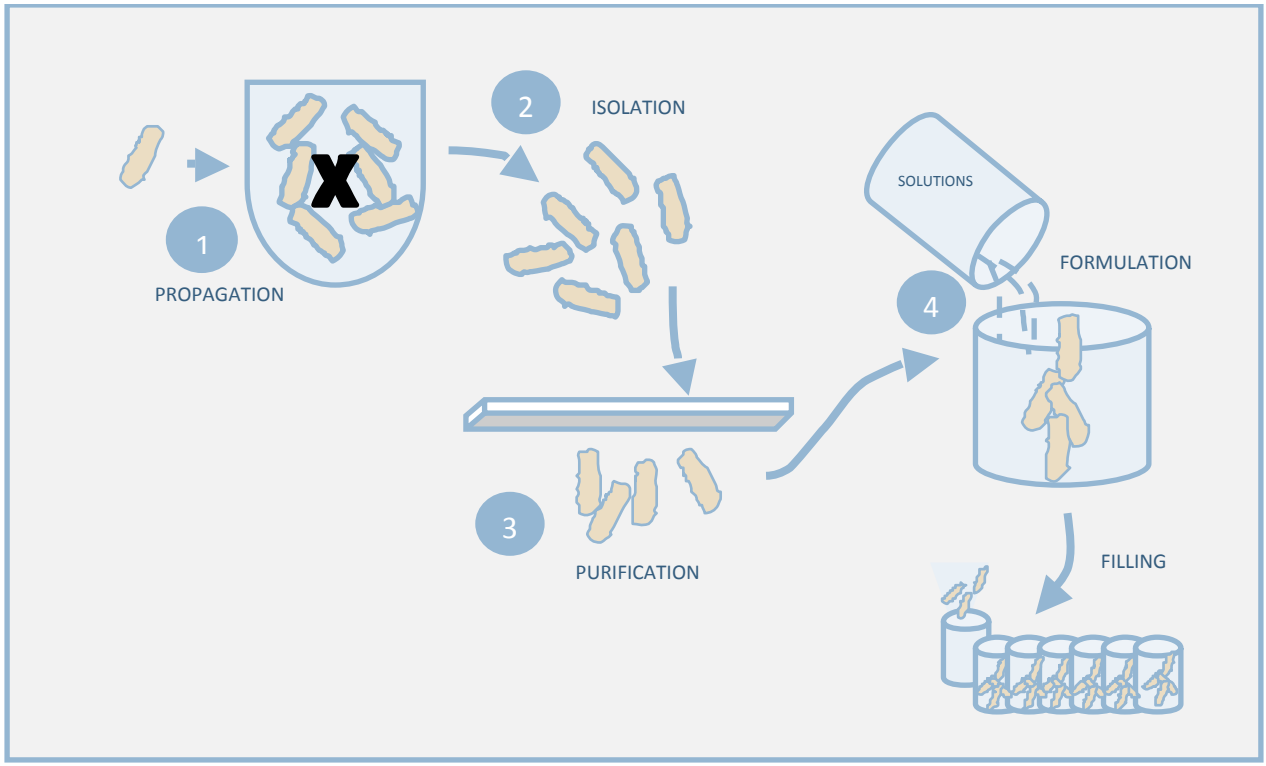


FIGURE 46. PROCESSES INVOLVED AT EACH OF THE FOUR STEPS OF VACCINE MANUFACTURING

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, 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-*Haemophilus influenzae* type b-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**)[61]. 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 ones. 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[62].

Vaccine manufacture is highly capital intensive. A manufacturing facility alone will cost up to €500 million (about ¥52.6 billion at September 2011)[63]. As 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, such as vaccine packaging, up to two years may be required to install and validate new packaging machinery. Building a new manufacturing facility takes on average five years to complete and validate with regulatory authorities (See **Figure 47**).

Image 6. Vaccine manufacturing in the 2000s

[61]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.
[62]GlaxoSmithKline. Global Vaccines Public Policy Issues. Addressing developing world production – technology transfer. December 2009. http://www.gsk.com/policies/Technology-Transfer-Vaccines.pdf
[63]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/

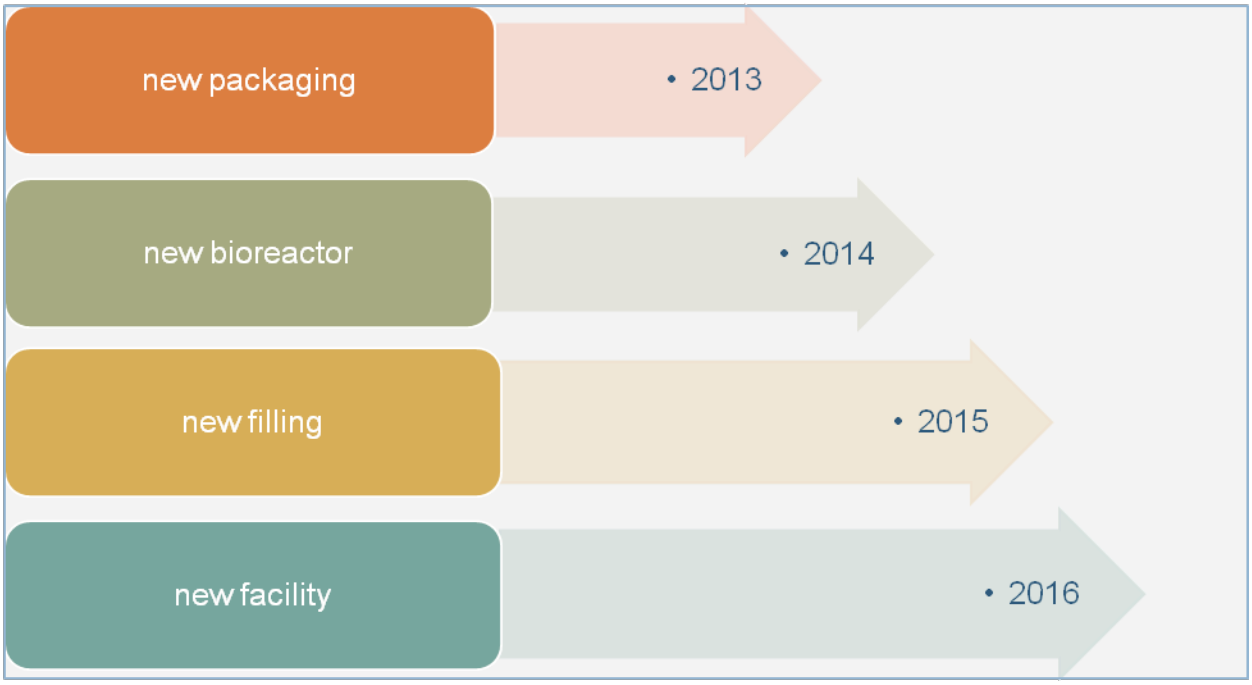


FIGURE 47. TYPICAL TIMELINES TO INSTALL AND VALIDATE NEW INDUSTRIAL CAPACITY FOR DECISIONS MADE IN 2011

2.4 Vaccine registration and approval

Because of their biological nature and that 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 one and two years to complete (See **Figure 48**). 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 test for:

- safety;
- identity;
- purity;
- potency; and,
- sterility.

Regulators also monitor the consistency of product from one production batch to the next (See **Figure 49**). Inactivation and attenuation are also checked to ensure that the product does not expose to risk. Regulators 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 mice or guinea pigs.

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

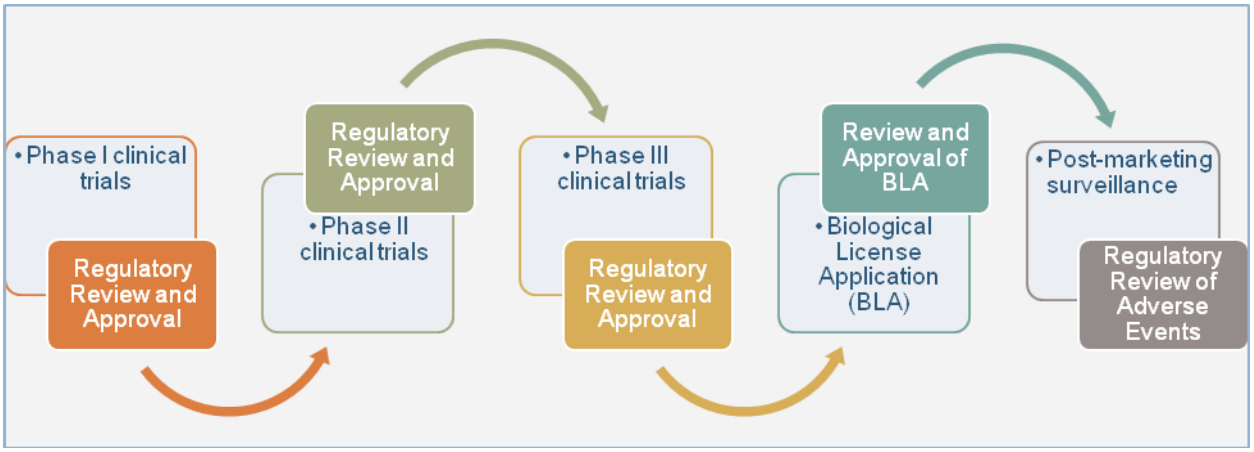


FIGURE 48. REGULATORY PROCESS FOR VACCINES UNDER DEVELOPMENT

FIGURE 49. REGULATORY TESTING OF LICENSED VACCINES

extraneous materials, including moisture and pyrogenic substances. The products used in the manufacture of the vaccine must also meet standards of purity.

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 require viral seeds and cell substrates used in vaccine production to be tested to ensure that they do not introduce contaminants. Cell substrates are well characterized to ensure that they are as safe as possible.

Regulators also regularly inspect manufacturing facilities to ensure compliance with current Good Manufacturing Processes (GMPs). GMPs are a set of guidelines that ensure consistency in 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[64]. Quality testing may account for as much as 70% of the time to manufacture[65].

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 Food and Drug Administration's Center for Biologics Evaluation and Research (CBER). Vaccine developers must apply to CBER for permission to both develop and sell vaccines (See **Figure 50**).

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 51**). The endpoints for vaccine licensure include vaccine safety and efficacy, but safety must be demonstrated at each phase of the study.

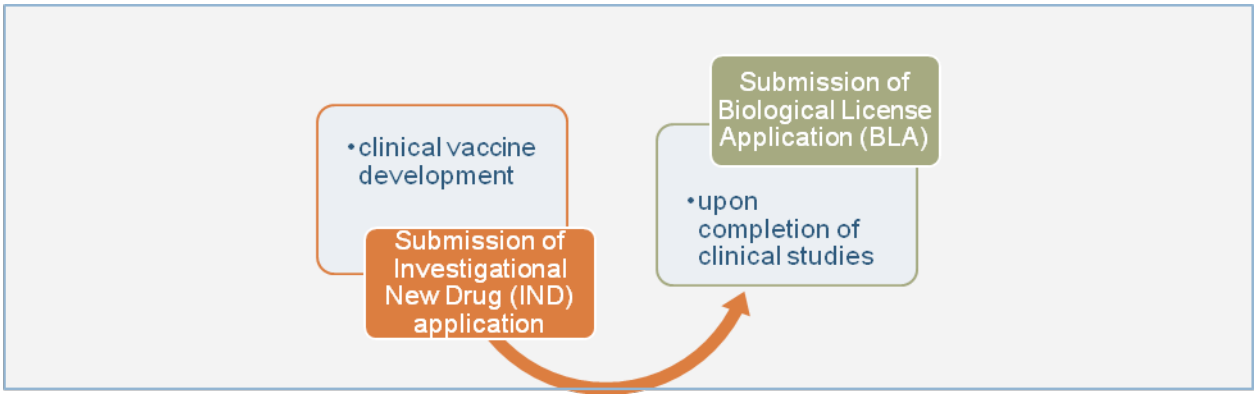


FIGURE 50. PERMISSIONS THAT MUST BE SOUGHT FROM THE FDA'S CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER) FOR THE DEVELOPMENT AND SALES OF VACCINES

[64]GlaxoSmithKline. Global Vaccines Public Policy Issues. Addressing developing world production – technology transfer. December 2009. http://www.gsk.com/policies/Technology-Transfer-Vaccines.pdf
[65]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 51. REQUIREMENTS FOR AN INVESTIGATIONAL NEW DRUG 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 14**. 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 14. REQUIREMENTS FOR A BIOLOGICS LICENSE APPLICATION (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 two 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 52**.

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, such as the European Union's Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (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 alternatively 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 International Conference on Harmonization (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 52. AREAS INSPECTED BY THE CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (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 depend 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 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 National Technical Advisory Groups (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 Advisory Committee on Immunization Practices (ACIP) are to provide advice that will reduce the incidence of disease and increase safe use of vaccines. The committee members are appointed by the Secretary of Health and Human Services (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 Vaccines for Children program (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 53**). Historically, HHS and the CDC have endorsed all ACIP recommendations.

In addition, the section 317 Federal Grant Program, appropriated annually by Congress, can be used to ensure coverage of both children and adults who would otherwise not have access to ACIP recommended vaccines, through the public or private sectors.

In the US, most private insurers cover ACIP recommended vaccines and about 55% of children have insurance coverage for immunization. Under the Affordable Healthcare Act, health insurers must now provide ACIP recommended vaccines at no out-of-pocket expense to the policyholder, and insurers cannot charge premiums for vaccines.

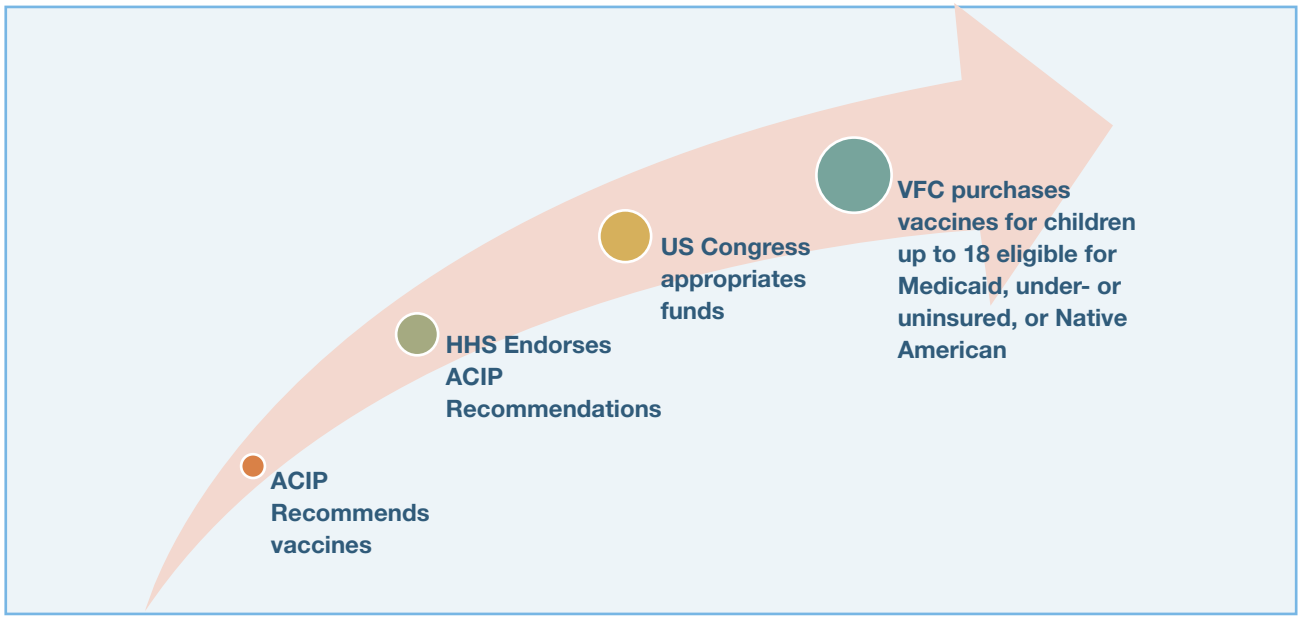


FIGURE 53. FUNDING FOR THE VACCINES FOR CHILDREN (VFC) PROGRAM IN THE US

The goals of the Advisory Committee on Immunization Practices (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 Australian Technical Advisory Group on Immunisation (ATAGI) and an economic assessment of the candidate vaccine by the Pharmaceuticals Benefits Advisory Committee (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 is required (See **Figure 54**).

The National Immunisation Committee, in turn, is responsible for the implementation of the Immunise Australia Program. The Immunise Australia Program provides vaccines at no charge through the National Immunisation Program (NIP) Schedule, which currently includes 16 vaccines[66].

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 55**).

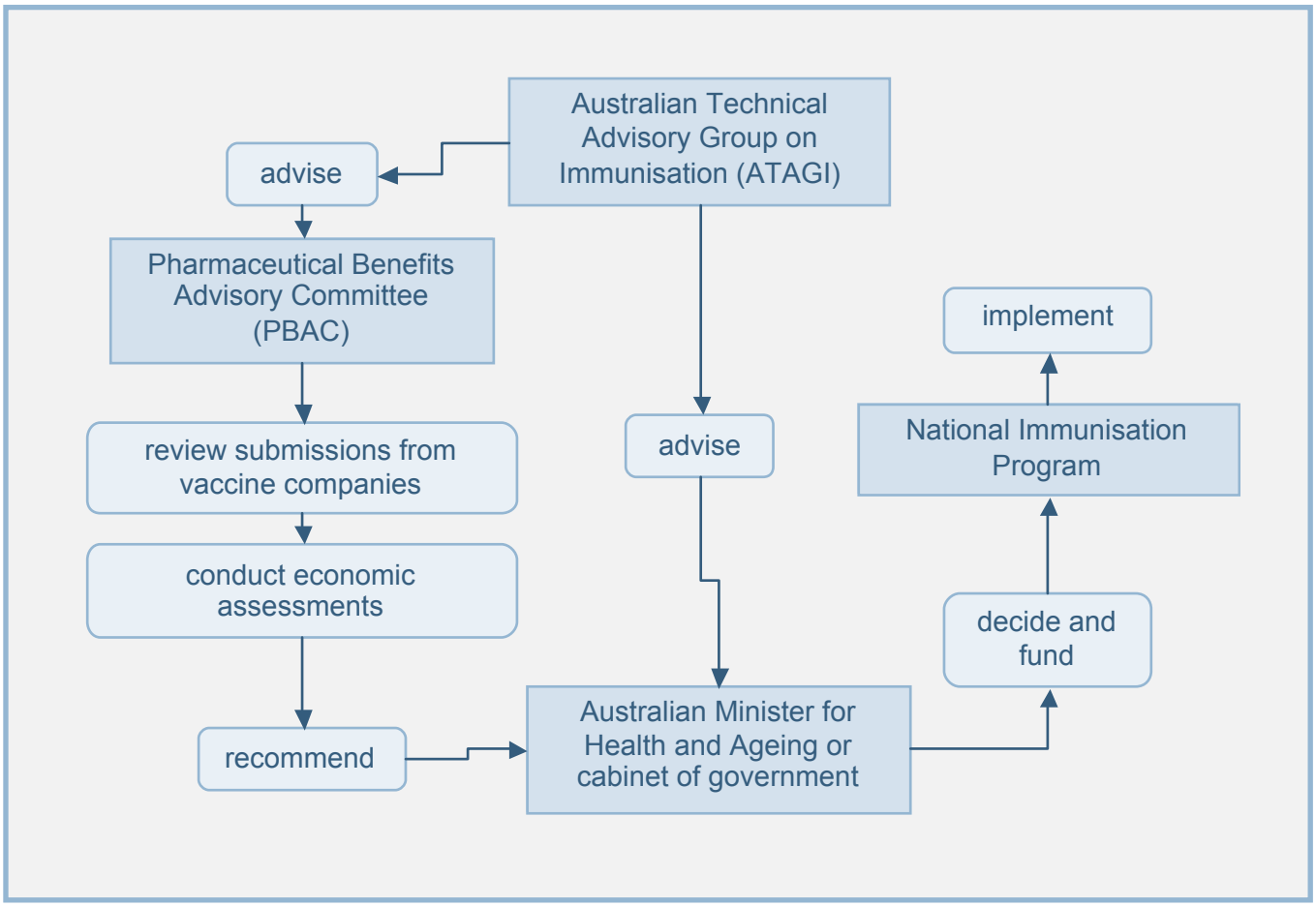


FIGURE 54. DECISION-MAKING PROCESS FOR VACCINE FUNDING IN AUSTRALIA

[66]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

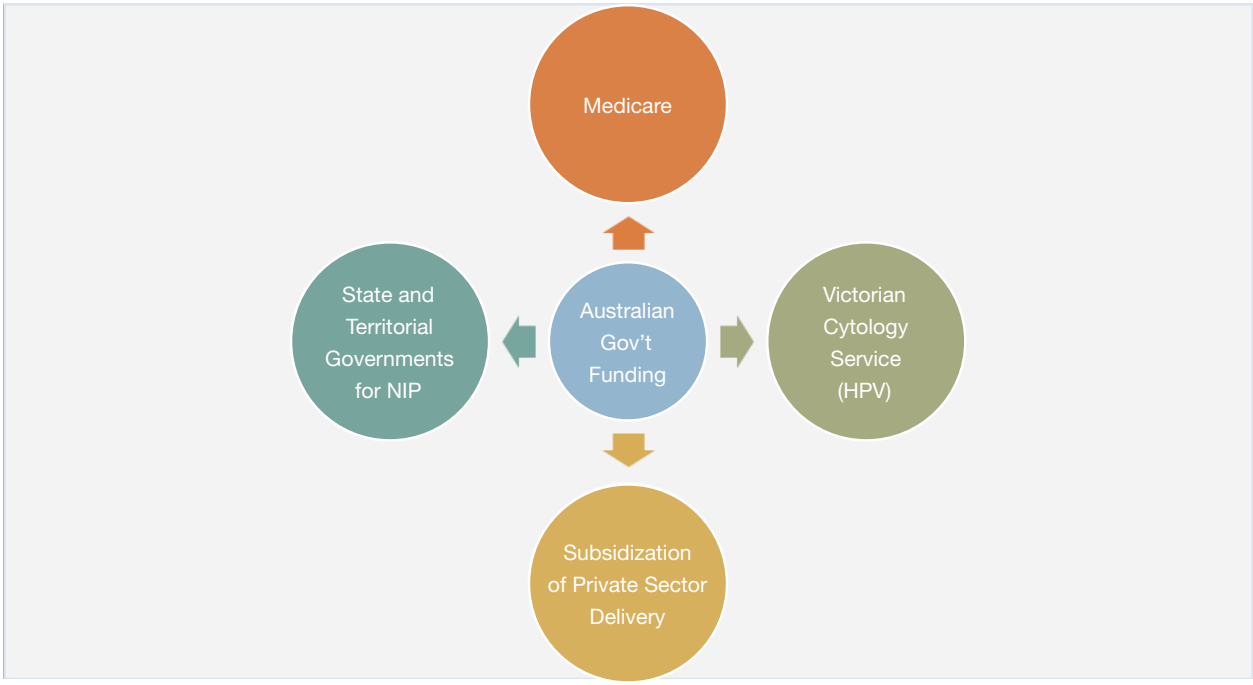


FIGURE 55. CHANNELS OF GOVERNMENT FUNDING FOR IMMUNIZATION IN AUSTRALIA

2.5.3 Other

Most industrialized countries have similar advisory groups (see **Table 13**, section 1.8) 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, such as 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 the 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[67]

Poliomyelitis is a paralyzing, sometimes fatal, viral disease that dates back more than 3000 years (See **Image 7** and **Image 8**). But the disease was not described in 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/POLIOANDPREVENTION.ASPX

In 1931, Jean Mcnamara and Frank Burnet 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, John Enders, Thomas Weller and Frederick Robbins won a Nobel Prize for demonstrating how a virus could be cultured in order to produce a vaccine.

The disease is spread by the oral-fecal route (See **Figure 56**).

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.

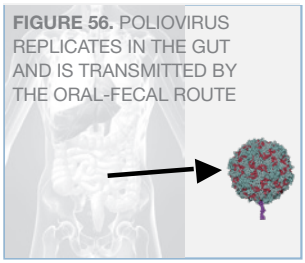


FIGURE 56. POLIOVIRUS REPLICATES IN THE GUT AND IS TRANSMITTED BY THE ORAL-FECAL ROUTE

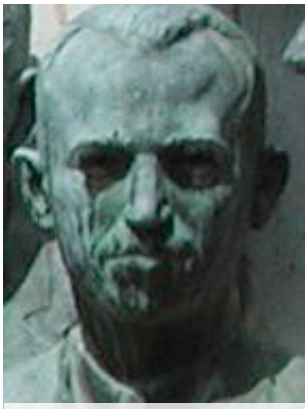


Image 9. Bust of Jonas Salk

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 within a few years. Sweden introduced a vaccine in 1957 and by 1962 had stopped wild polio transmission.

Iceland introduced a 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 (See **Figure 57**)[69].

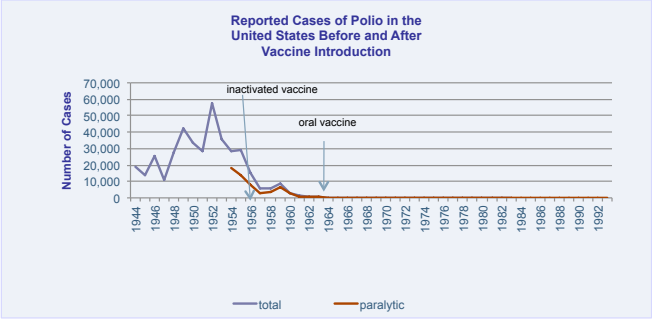


FIGURE 57. IMPACT OF IMMUNIZATION ON CASES OF POLIO IN THE US

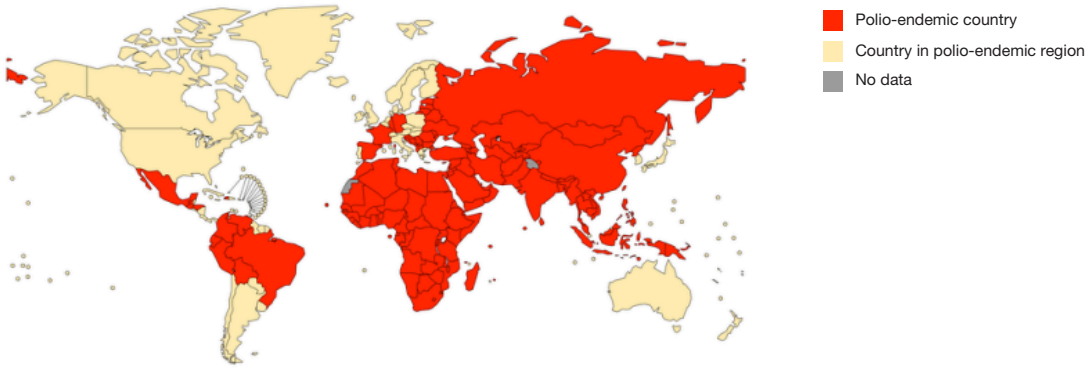
By 1994, 2000, and 2002 wild polio transmission was certified eliminated in all of the Americas, the Western Pacific, and Europe, respectively[70]. In 2010 polio was endemic in only four countries: Afghanistan, India, Nigeria and Pakistan[71]. Wild polio type 2 virus has been eradicated, but vaccine-derived type 2 virus has recently spread in Nigeria. Wild type 1 and 3 polioviruses continue to be transmitted in endemic and neighboring countries. By mid-2011, the number of cases reported globally was approximately 300[72] (See **Figure 58**, **Figure 59**, **Figure 60**). Countries reporting cases in 2011 are shown in **Figure 60** and **Figure 61**[73].

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.

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[74]. Globally, polio eradication is estimated to have incremental net benefits of $40–50 billion between 1988 and 2035[75].

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.

[67]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.
[68]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.
[69]US Centers for Disease Control and Prevention. MMWR Summary of notifiable diseases, United States, 1993. http://www.cdc.gov/mmwr/preview/mmwrhtml/00035381.htm
[70]Global Polio Eradication. History of Polio. http://www.polioeradication.org/Polioandprevention/Historyofpolio.aspx
[71]Global Polio Eradication. Infected countries. http://www.polioeradication.org/Infectedcountries.aspx
[72]Global Polio Eradication. Data and monitoring. http://www.polioeradication.org/Dataandmonitoring.aspx
[73]Global Polio Eradication. Data and monitoring. Polio this week. http://www.polioeradication.org/Dataandmonitoring/Poliothisweek.aspx
[74]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.
[75]Duintjer Debbens RJ, Pallansch MA, Cochi SL, et al. Economic analysis of the global polio eradication initiative. Vaccine 2010; 29: 334-343.

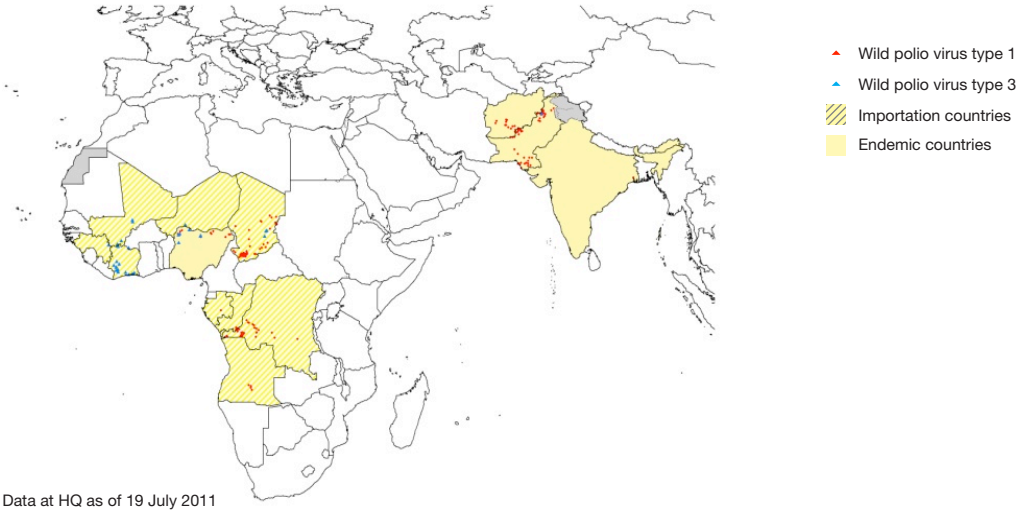


Data is projected to 2008 WHO legal template

FIGURE 58. IN 1988, 125 COUNTRIES HAD RECURRING (ENDEMIC) POLIO DISEASE (COUNTRIES IN RED), BEFORE AN ACCELERATED IMMUNIZATION ERADICATION PROGRAM BEGAN

Data is projected to 2008 WHO legal template

FIGURE 59. IN 2010, ONLY FOUR COUNTRIES CONTINUED TO BE CLASSIFIED AS HAVING RECURRENT (ENDEMIC) POLIO DISEASE (COUNTRIES IN RED)



Data at HQ as of 19 July 2011

FIGURE 60. TOTAL NUMBER OF CASES OF POLIO DISEASE IN 2011 (RED DOTS ARE POLIO TYPE 1; BLUE DOTS ARE POLIO TYPE 3) (COLORED COUNTRIES ARE THE SAME FOUR ENDEMIC COUNTRIES AS IN 2006 AND COUNTRIES WHERE CASES HAVE BEEN IMPORTED)

3.2 Haemophilus influenzae type b (Hib)

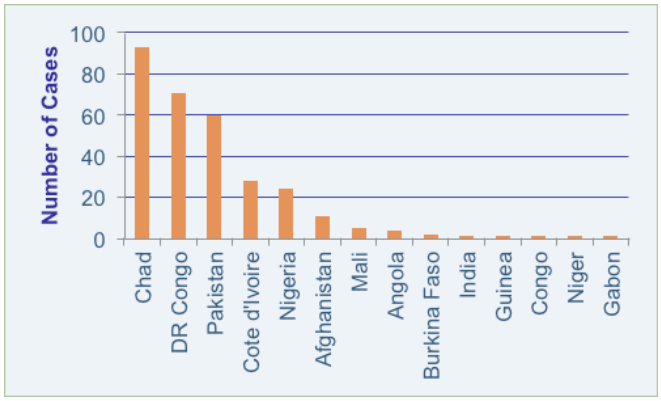


FIGURE 61. COUNTRIES REPORTING CASES OF POLIO IN 2011 (AS OF JULY 2011)

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 influenza*. Type b accounts for 95% of all serious diseases caused by this organism. Non encapsulated, non-typable forms of the bacteria also exist.

The organism is carried in the pharynx and spread by respiratory droplets (**Figure 62**).

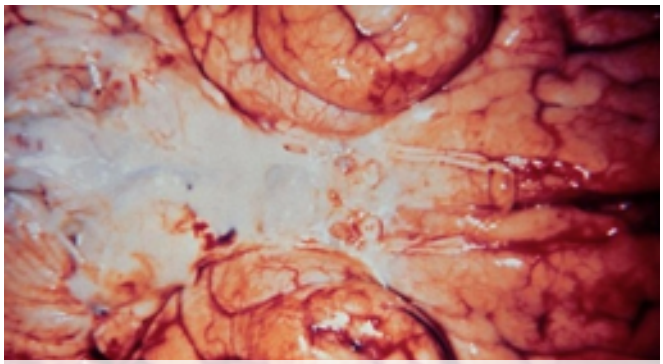


Image 11. Purulent meningitis from Haemophilus influenzae type B. Source CDC Public Health image library

The Impact of the Disease[76, 77, 78]

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

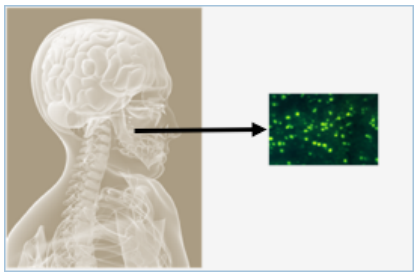


FIGURE 62. NASOPHARYNGEAL CARRIAGE AND AEROSOL SPREAD OF HAEMOPHILUS INFLUENZAE TYPE B.
SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY

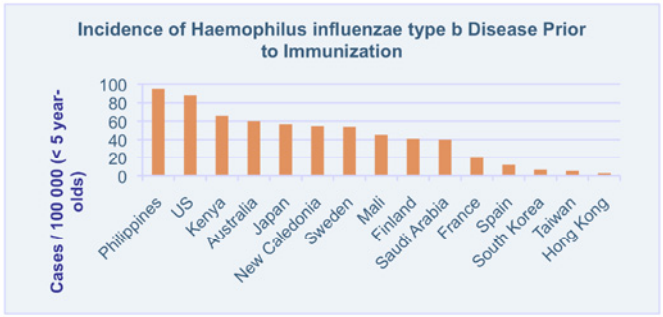


FIGURE 63. INCIDENCE OF HEAM

[76]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.
[77]Hib Initiative. Research and Surveillance. http://www.hibaction.org/research.php#disease_burden
[78]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.

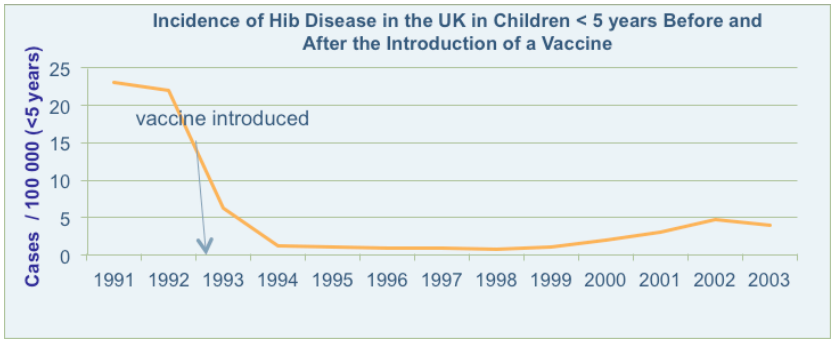


FIGURE 64. ALMOST IMMEDIATE IMPACT OF CONJUGATE HIB VACCINE ON THE INCIDENCE OF HIB IN < 5 YEARSS-OLDS IN THE UK

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%[79]. 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 10**)[80].

In the UK, the incidence of disease declined immediately after the introduction of a vaccine in a 3 dose primary series (See **Figure 64**)[81]. The incidence rose slightly in the late 1990s, but has since fallen again since the introduction of a 4th booster dose at 12 months of age. Most countries deliver three 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 12**). 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.

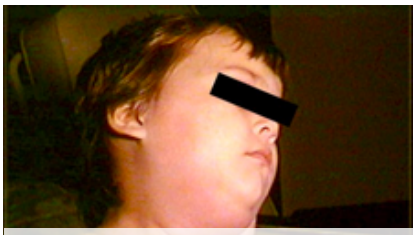


Image 11. Purulent meningitis from Haemophilus influenzae type B. Source CDC Public Health image library: HTTP://PHIL.CDC.GOV/PHIL/DETAILS.ASP?PID=130

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

[79] Wikipedia. Hib vaccine. http://en.wikipedia.org/wiki/Hib_vaccine#Impact
[80] 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.
[81] 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

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 / 1000 mumps cases in Japan

TABLE 15. COMPLICATIONS AND FREQUENCIES OF MUMPS COMPLICATIONS

The Cause[82]

Mumps is a viral disease first described by Hippocrates in the 5th 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 65**).

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 / 1000 in Japan[83]. In 2005, Kawashima, et al, found that the number of cases of deafness from mumps was steadily increasing in Japan[84]. The number of cases in 1987 was estimated at 300, but had jumped to 650 by 2001. The increase in number of cases of deafness correlated with an increase in the incidence of mumps.

Complications of mumps are summarized in **Table 15**.

The Vaccine[85]

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

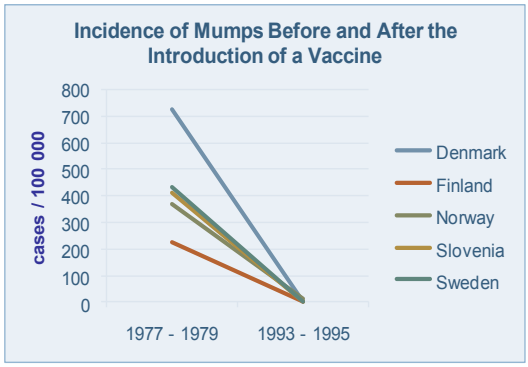


FIGURE 66. DECLINE IN INCIDENCE OF MUMPS FOLLOWING THE INTRODUCTION OF A VACCINE IN A TWO-DOSE SCHEDULE

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 have used mumps vaccine have experienced similar declines in cases (See **Figure 66**)[86].

[82]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.
[83]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.
[84]Kawashima Y, Ihara K, Nakamura M et al. Epidemiological study of mumps deafness in Japan. Auris Nasus Larynx 2005; 32: 125-128.
[85]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.
[86]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.

The efficacy of mumps vaccines varies by stain, 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[87].

3.4 Measles eradication, global

The Cause[88]

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 14**). 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 67**).

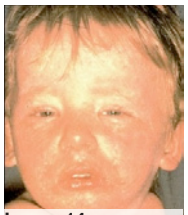


Image 14. Measles rash. Source: CDC

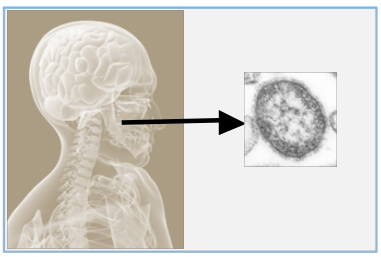


FIGURE 67. TRANSMISSION OF MEASLES VIRUS IS BY AEROSOL ROUTE.
SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY
HTTP://PHIL.CDC.GOV/PHIL/DETAILS.ASP?PID=8429

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[89]

The case-fatality rate in industrialized countries is about 1–3 deaths / 1000 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.

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.

[87]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.
[88]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.
[89]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.
mmwrhtml/mm5453a1.htm

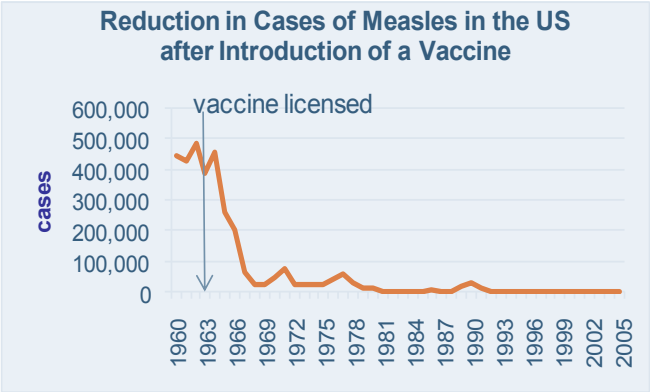


FIGURE 68. DECLINE IN CASES OF MEASLES IN THE US AFTER INTRODUCTION OF A VACCINE

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[90]. Most industrialized countries introduced measles vaccines in the 1960s and have since experienced remarkable declines in disease incidence (See **Figure 68**.)[91, 92].

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[93]. 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[94].

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: the Americas by 2000; Europe and Middle East by 2010; western Pacific by 2012, and Africa by 2020. The Americas has 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 primar-

[90]American Academy of Pediatrics. Why Immunize? http://www.aap.org/advocacy/releases/whyimmunize.htm
[91]Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 1994. MMWR 1995; 43:1. http://www.cdc.gov/mmwr/preview/mmwrhtml/00039679.htm
[92]Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 2005. MMWR 2007; 54: 2-92. http://www.cdc.gov/mmwr/preview/
[93]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.
[94]Applied economics. Immunisation programs: measles and Hib disease. http://www.appliedeconomics.com.au/pubs/reports/health/ph05.htm

ily from persons who have travelled to the US and spread their infection.

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 69**)[95].

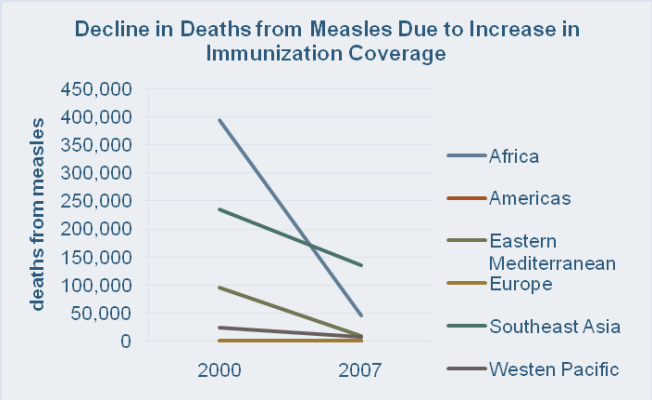


FIGURE 69. DECLINE IN THE NUMBER OF DEATHS FROM MEASLES DUE TO INCREASED IMMUNIZATION COVERAGE

3.5 Rotavirus

The Cause

Rotavirus is a highly contagious common viral disease spread by oral-fecal route (See **Figure 70**).

It is the most common cause of severe diarrhea in infants and young children (See **Image 15**). 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 6 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[96]. These viruses multiply in the gut, and transmission of the disease is from person to person contact—not from contaminated water and food (See **Figure 70**).

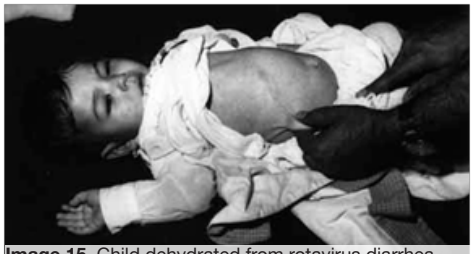


Image 15. Child dehydrated from rotavirus diarrhea. Source: WHO, D Mahalanabis HTTP://WWW.VACCINEINFORMATION.ORG/ROTAVIRUS/PHOTOS.ASP

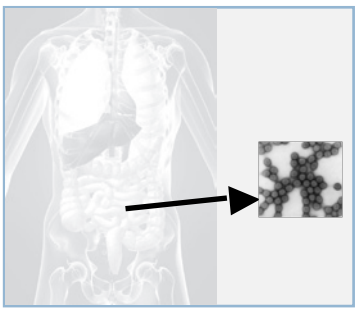


FIGURE 70. TRANSMISSION OF ROTAVIRUS BY FECALE-ORAL ROUTE. SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY HTTP://PHIL.CDC.GOV/PHIL/DETAILS.ASP?PID=197

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[97]. Globally, rotaviruses kill over 500,000 children every year and account for about 25% of deaths from all diarrheal diseases (SEE **Figure 71**)[98]. 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.

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,

[95]Centers for Disease Control and Prevention. 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
[96]Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children recommendations of the Advisory Committee on Immunization Practices (ACIP)/ MMWR 2009; 58: 1- 25. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5802a1.htm
[97]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.
[98]Tate JE, Patel MM, Steele AD, et al. Global impact of rotavirus vaccines. Expert Rev Vaccines 2010; 9: 395-407

1.9 million will be hospitalized, and 13.5 million will require an outpatient visit (See **Figure 72**)[99].

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 five (pentavalent) live-reassortant human-bovine viruses (Merck, RotaTeq™). Both are administered orally, in two and three doses, given before 24 and 32 weeks, respectively.

The first rotavirus vaccine licensed for use in humans was made from simian-human reassortant rotaviruses. Carefull study of adverse events following immunization showed that this vaccine was associated with a higher risk of the extremely rare event of intestinal folding (intussusception) (15 cases / 1 million 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 16**).

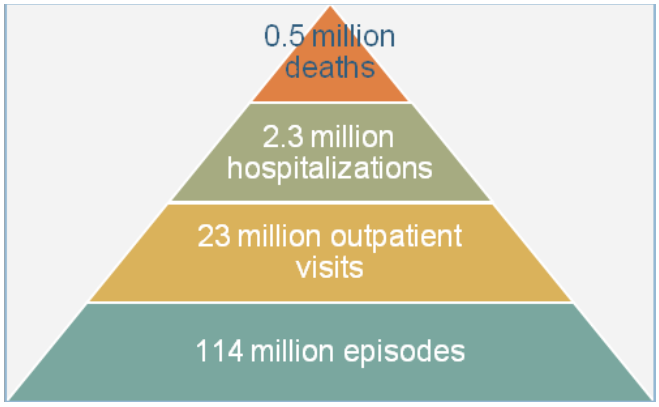


FIGURE 71. GLOBAL BURDEN OF ROTAVIRUS DISEASE

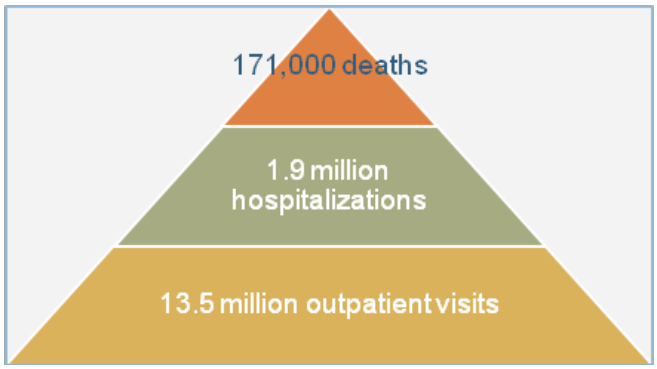


FIGURE 72. IMPACT OF ROTAVIRUS ASIA IN THE ABSENCE OF IMMUNIZATION

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

TABLE 16. RISK OF INTUSSUSCEPTION IS NOT ELEVATED FOLLOWING ROTAVIRUS VACCINATION WITH LICENSED LIVE HUMAN-BOVINE REASSORTANT AND HUMAN LIVE-ATTENUATED VACCINES

[99]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 temporal 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 17**).

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 17. 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) [100, 101]

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% to 63% in children < 1 year of age (See **Figure 73**)[103].

The impact of rotavirus vaccines has been almost immediate in countries where they have been introduced (See **Figure 74**)[104].

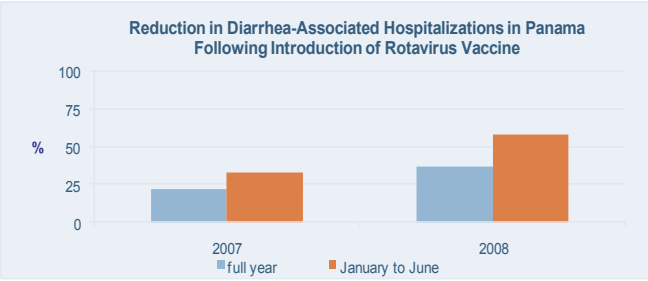


FIGURE 73. REDUCTION IN HOSPITALIZATION FOR ANY-CAUSE DIARRHEA IN CHILDREN < 5 YEARS IN PANAMA, FOLLOWING INTRODUCTION OF A ROTAVIRUS VACCINE IN 2006

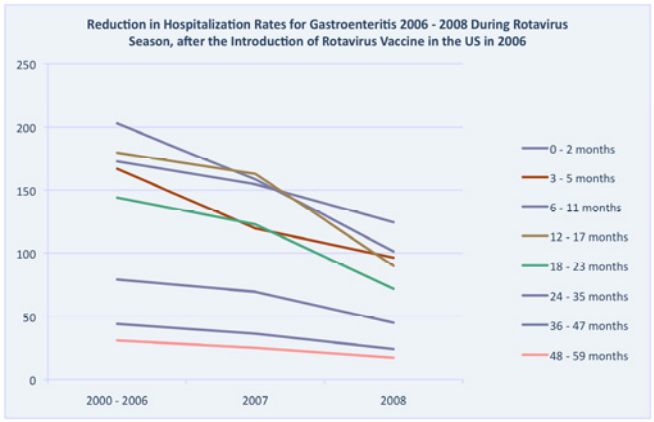


FIGURE 74. REDUCTION IN HOSPITALIZATION RATES FOR GASTROENTERITIS BY AGE GROUP DURING ROTAVIRUS SEASON IN THE US, FOLLOWING INTRODUCTION OF ROTAVIRUS VACCINE

[100]Merck. RotaTeq prescribing information. July 2011. http://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf
[101]GSK Source. Rotarix prescribing information. February 2011. https://www.gsksource.com/gskprm/en/US/adirect/gskprm?cmd=ProductDetailPage&product_id=1244173585205&featureKey=600594#nlmhighlights
[102]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
[103]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.
[104]Curns AT, Steiner CA, Barrett M et al. Reduction in acute gastroenteritis hsopitalizations amond 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 both Latin America[105] and Europe[106] and Australia[107] and the US[108] (See **Table 18**).

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	• 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 18. IMPACT OF ROTAVIRUS IMMUNIZATION IN SELECT COUNTRIES[106, 107, 108, 109, 110, 111, 112, 113]

[105]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 accumulate experience. Pediatr Infect Dis J 2011; 30: s61-s66.
[106]Braeckman T, Herck KV, Raes M, et al. Rotavirus vaccines in Belgium – policy and impact. Pediatr Infect Dis J 2011; 30: s21-s24.
[107]Buttery JP, Lambert SB, Grimwood K, et al. Rediction 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.
[108]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.
[109]Tate JE, Patel MM, Steele AD, et al. Global impact of rotavirus vaccines. Expert Rev Vaccines 2010; 9: 395-407.
[110]Tate JE, Mutuc JD, Panozzo CA, et al. Sustained decline in rotavirus detections in teh United States following the introduction of rotavirus vaccine in 2006. Pediatr Infect Dis J 2011; 30: s30-s34.
[111]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.
[112]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.
[113]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 2010, 14 countries in Latin America were using rotavirus vaccines[114]. 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)[115].

Image 16. President Bolanos of Nicaragua adminisering 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[116]. 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[117]. The vaccine has since prevented 77% of very severe cases of rotavirus diarrhea[118] in Nicaragua and cut hospital admissions and emergency room visits by 50%[119]. In children less than 1 year of age, vaccine was 88% effective against hospitalization from rotavirus gastroenteritis[120].

3.6 Human Papillomavirus (HPV)

The Cause

Human Papillomaviruses (HPV) 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 75**).

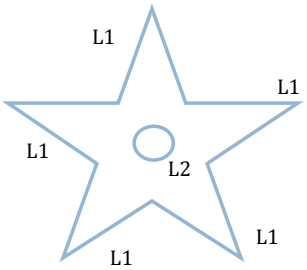


FIGURE 75. SINGLE PENTAMERE OF HUMAN PAPILLOMAVIRUS (WHOLE VIRUS HAS 72 PENTAMETERS)

[114]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 accumulate experience. Pediatr Infect Dis J 2011; 30: s61-s66.
[115]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
[116]Merck. Nicaraguan vaccination program. http://www.merck.com/responsibility/access/access-feature-nicaraguan.html
[117]PATH Rotavirus Vaccine Project - Summary Report. http://www.rotavirusvaccine.org/files/RVP_SummaryReport_Final.pdf
[118]View Change.Org. Living proof: Nicaragua – a vaccine's remarkable impact. http://www.viewchange.org/videos/living-proof-nicaragua-a-vaccines-remarkable-impact
[119]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
[120]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 (See **Figure 77**). Types 6 and 11 cause 90% of genital warts. These virus types are transmitted sexually (See **Figure 78**).

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 19**)[121].

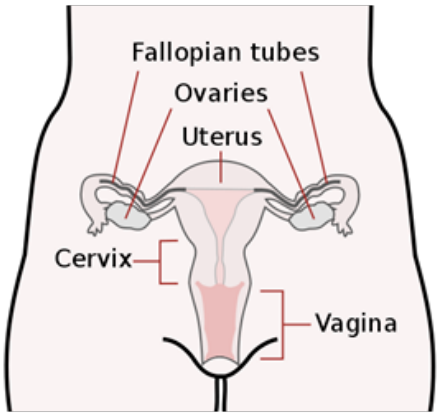


FIGURE 72. IMPACT OF ROTAVIRUS ASIA IN THE ABSENCE OF IMMUNIZATION

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

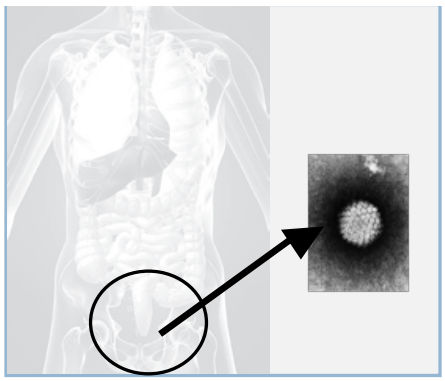


FIGURE 77. GENITAL AND HIGH-RISK GENTIAL HPVs ARE TRANSMITTED SEXUALLY. SOURCE: NIH-VISUALS OLINE. LABORATORY OF TUMOR VIRUS BIOLOGY

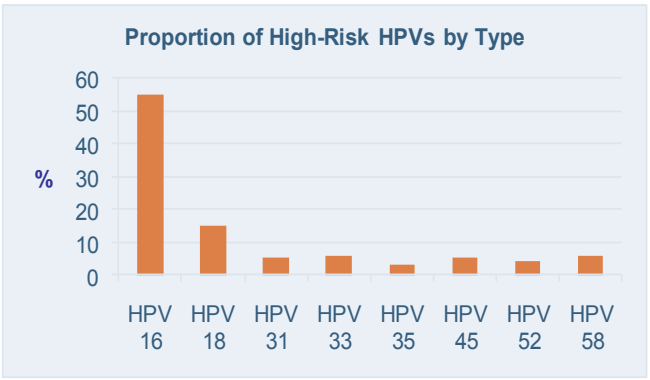


FIGURE 78. GLOBAL DISTRIBUTION OF HIGH-RISK HPVs BY TYPE (VALUES ARE APPROXIMATE)

[121]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.

The Impact of the Disease[122]

Globally, cervical cancer is the 2nd or 3rd 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[123]. 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 five years. About 52–58% of cervical cancers are caused by HPV

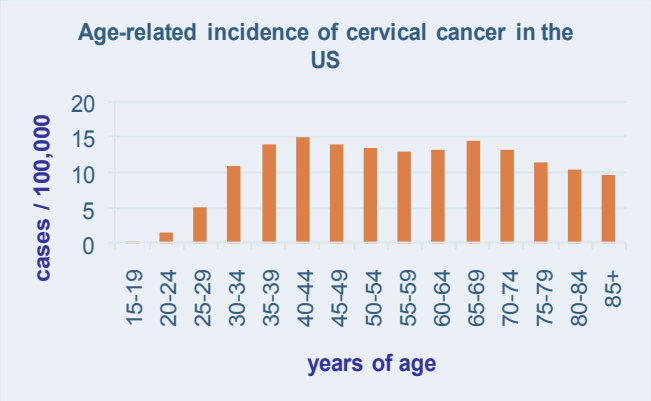


FIGURE 79. AGE-RELATED INCIDENCE OF CERVICAL CANCER IN THE US

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 78**)[124].

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 79**)[125]. In 2011, about 12,710 new cases of cervical cancer and about 4,290 deaths are expected to occur in the US[126].

The Vaccine[127]

A vaccine for use in humans was developed by using the L1 protein which makes up the shell (capsid) of the virus (See **Figure 75**). The star shaped L1 proteins (pentameres) self assemble into virus-like particles (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 three doses over six 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[128].

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)[129].

[122]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.
[123]World Health Organization. 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
[124]World Health Organization. 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
[125]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
[126]National Cancer Institute. Cervical cancer. http://www.cancer.gov/cancertopics/types/cervical
[127]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.
[128]MerckVaccines.com. Gardasil indications. http://www.merckvaccines.com/Products/Gardasil/Pages/indications.aspx
[129]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.

Country	Year added to immunization schedule	Immunization schedule
Australia	2007	girls and women 12-26 years for an initial period of three years; routine for girls 12-13 years;
Canada	2007	routine for girls 11-14 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
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
Sweden	2010	voluntary for girls 10-12 years
United Kingdom	2008	routine for girls 12-13 years; catch-up for girls up to 18 years of age
United States	2007	routine for girls 11–12 years; catch-up for girls and women 13–26 years; boys 9–26 years (2010)

TABLE 20. COUNTRIES WITH HUMAN PAPILLOMAVIRUS VACCINE IN IMMUNIZATION SCHEDULES[130]

On the basis of clinical trial data, several countries introduced HPV vaccine into national immunization programs shortly after they were licensed (See **Table 20**).

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 that 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% three years after vaccine introduction[131], and the prevalence of genital warts in the vaccinated population has decreased by 59%[132]. Evidence is growing for the ability of vaccine HPV types to cross-protect against some other high-risk HPV types.

[130]Wikipedia. HPV vaccine. http://en.wikipedia.org/wiki/HPV_vaccine
[131]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.
[132]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

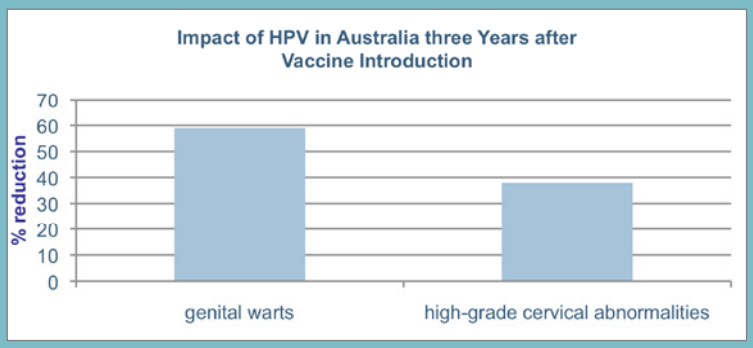
Australia introduced HPV vaccine in 2007. Between 2007 and 2009 Australia conducted a national catch-up campaign. 72% of girls aged 14 and 15 and nearly 66% of girls aged 16 and 17 were vaccinated with three doses[133].

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[134, 135].

How the reduction in infections will impact cervical cancer is difficult to assess. Not all infections 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%, three years after vaccine introduction[136]. And the prevalence of genital warts in the vaccinated population has decreased by 59%[137].



[133]Australian Government. Department of Health and Ageing. Human Papillomavirus (HPV). http://www.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-hpv
[134]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
[135]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.
[136]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.
[137]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

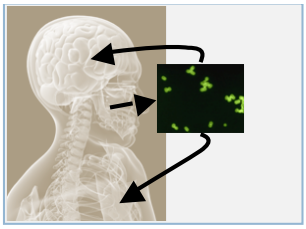


Figure 80. Pneumococci colonize the back of the nose. When they spread to other organs in the body they cause illness.

SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY HTTP://EN.WIKIPEDIA.ORG/WIKI/FILE:PNEUMOCOCCUS_CDC_PHIL_ID1003.JPG

Pneumococci 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 80**). 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.

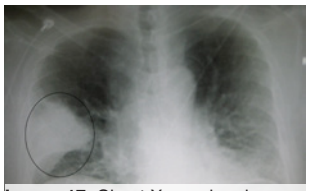


Image 17. Chest X-ray showing pneumococcal lobar pneumonia

Pneumococci were first identified in 1881 and were recognized as cause of lobar pneumonia (See **Image 17**). Today, pneumococci have been classified in more than 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.

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[138]. 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[139]. 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[137] and 63,000 cases of invasive pneumococcal disease were estimated to have occurred annually[140]. About 17,000 of these cases occurred in children under 5 years of age[141]. The US experienced about 6,100 deaths from invasive pneumococcal disease each year. About 700 cases of meningitis and 200 deaths occurred annually in children under 5 years of age (See **Table 21**).

The incidence of invasive pneumococcal disease is highest in infants and young children. **Table 22** 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.

[138]National Foundation for Infectious Diseases. Facts about pneumococcal disease. http://www.nfid.org/factsheets/pneumofacts.shtml
[139]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.
[140]Centers for Disease Control and Prevention. What would happen if we stopped vaccinations? Pneumococcal. http://www.cdc.gov/vaccines/vac-gen/whatifstop.htm#pneumo
[141]Centers for Disease Control and Prevention. Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000; 49 (RR-9): 1 – 35.
[142]Centers for Disease Control and Prevention. Pneumococcal disease and pneumococcal vaccines. May 2009. www.cdc.gov/vaccines/pubs/pinkbook/downloads/Slides/Pneumo11.ppt

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

TABLE 21. FREQUENCY OF PNEUMOCOCCAL SYNDROMES IN THE US IN CHILDREN < 5 YEARS, PRIOR TO CHILDHOOD PNEUMOCOCCAL IMMUNIZATION[142]

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 22. INCIDENCE OF INVASIVE PNEUMOCOCCAL DISEASE IN YOUNG CHILDREN IN SELECT COUNTRIES[143,144,145,146,147]

In addition, some ethnic groups may be particularly vulnerable (See **Table 23**).

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 23. INCIDENCE OF INVASIVE PULMONARY DISEASE IN CHILDREN IN THE US IN 1998, PRIOR TO THE INTRODUCTION OF A CHILDHOOD PNEUMOCOCCAL VACCINE[148]

[143]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

[144]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.

[145]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.

[146]Ispahani P, Slack R, Donald F, et al. Twenty year surveillance of invasive pneumococcal disease in Nottingham: serogroups responsible and implication fro immunization. Arch Dis Child 2004; 89: 757-762.

[147]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.

[148]Centers for Disease Control and Prevention. Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000; 49 (RR-9): 1 – 35.

Next to the very young, the elderly experience the highest incidence of invasive pneumococcal disease (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.

Mortality rates from IPD in the US are approximately 7–28% for all age groups and as high as 11–44% for the elderly[149]. 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 24**). The 23-valent vaccine protected against > 85% of the strains that caused invasive pneumococcal disease 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 invasive pneumococcal disease in US infants and young children (See **Table 25**). 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 invasive pneumococcal disease 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 81**)[150].

In addition, childhood conjugate pneumococcal immunization programs have had a herd effect, impacting the incidence of disease in unvaccinated age groups (See **Figure 82**)[151]. By 2003, there were 30,000 fewer cases of invasive pneumococcal disease in the US, including 20,000 fewer in children and adults who did not receive the vaccine[152]!

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 24. 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 25. PNEUMOCOCCAL TYPES CONTAINED IN 7-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

[149]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.
[150]Centers for Disease Control and Prevention. Pneumococcal disease and pneumococcal vaccines. May 2009. www.cdc.gov/vaccines/pubs/pinkbook/downloads/Slides/Pneumo11.ppt
[151]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.

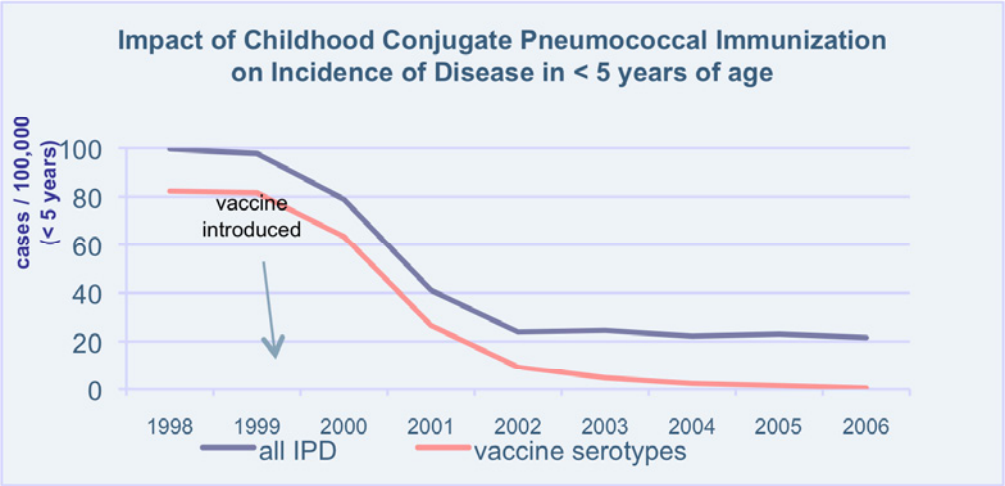


FIGURE 81. DIRECT IMPACT OF CONJUGATE PNEUMOCOCCAL IMMUNIZATION ON INCIDENCE OF PNEUMOCOCCAL DISEASE IN < 5 YEARS OF AGE

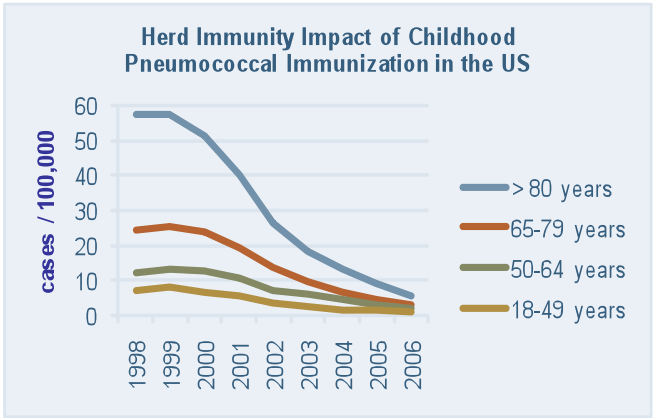


FIGURE 82. IMPACT OF CHILDHOOD PNEUMOCOCCAL

3.8 Varicella Zoster virus (VZV)

The Cause[153]

Varicella zoster virus (VZV) causes two diseases: varicella (chickenpox) and herpes zoster (shingles). Varicella is a disease resembling smallpox (See **Image 18**). 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 the same virus[154].

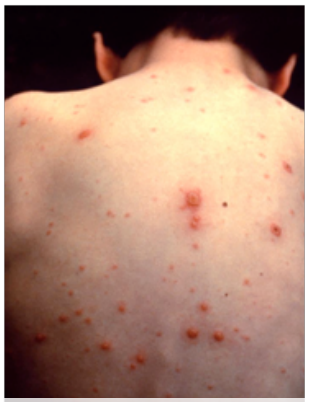


Image 18. Typical pustular lesions of varicella in a child.
SOURCE: CDC PUBLIC HEALTH IMAGE LIBRARY HTTP://PHIL.CDC.GOV/PHIL/DETAILS.ASP

Varicella is transmitted by the viruses contained in the skin lesions, or from the upper respiratory tract through air (See **Figure 83**). 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.

Herpes zoster is a painful vesicular rash localized to a portion of the body such as around the waist (See **Image 19**).

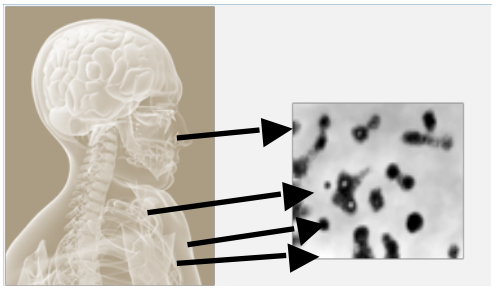


Figure 83. Transmission of varicella-zoster virus from varicella is airborne from skin lesions or upper respiratory tract.

SOURCE: E PALMER CDC PUBLIC HEALTH IMAGE LIBRARY HTTP://PHIL.CDC.GOV/PHIL/DETAILS.ASP

The Impact of the Disease

Varicella

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 26**). There were approximately 4 million cases of varicella annually and about 11,000 to 13,500 hospitalizations in the US.

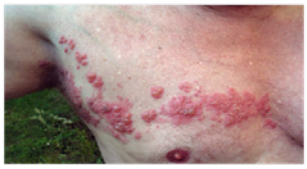


Image 19. Herpes zoster showing vesicular rash localized over the right chest.
SOURCE: FISLE HTTP://EN.WIKIPEDIA.ORG/WIKI/FILE:HERPES_ZOSTER_CHEST.PNG

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 26. INCIDENCE OF VARICELLA IN SELECT COUNTRIES PRIOR TO THE INTRODUCTION OF VARICELLA VACCINATION[152]

[152]Centers for Disease Control and Prevention. What would happen if we stopped vaccinations? Pneumococcal. http://www.cdc.gov/vaccines/vac-gen/whatifstop.htm#pneumo
[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.
[154] 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 more than 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[155]. 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 more than 90% from a single dose and over 98% after two doses. Effectiveness trials of vaccines post-licensure confirm rates as high as 100% against moderate or severe disease[156].

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

TABLE 27. COUNTRIES THAT HAVE UNIVERSAL CHILDHOOD VARICELLA IMMUNIZATION PROGRAMS

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 27**).

The US ACIP recommends a two-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 85**)[157]. Direct expenses for hospitalizations and care for varicella had decreased by 74% by 2005.

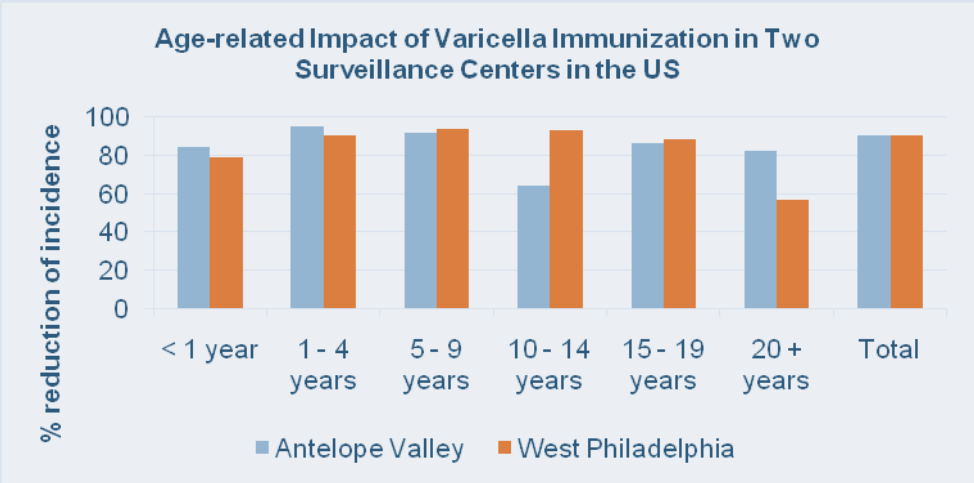


FIGURE 84. IMPACT OF VARICELLA IMMNIZATION BY AGE IN TWO SURVEILLANCE CENTERS IN THE US.

[155]Levin MJ. Zoster vaccine. pp 1057-1068. In Vaccines 5th edition, S Plotkin, W Orenstein and P Offit, Eds, Saunders Elsevier, China, 2008.
[156]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.
[157]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[158]

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.

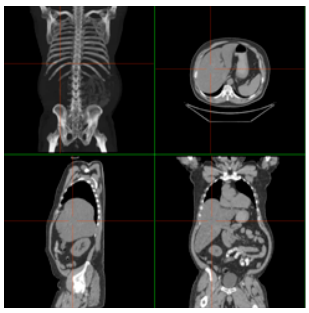


Image 20. CT scan showing enlargement of the liver as often occurs in chronic hepatitis B infections.

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 antigen (HBsAg) persist in the blood for at least six months. Chronic hepatitis B increases the risk of hepatocellular carcinoma (cancer of the liver) and cirrhosis (See **Image 20**).

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 85**). 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.

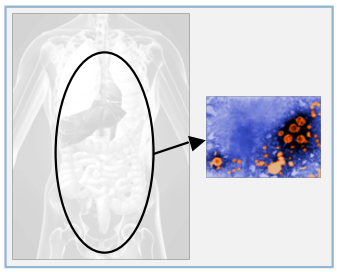


Figure 85. Transmission of hepatitis B virus is from body fluids and sexual contact

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 86**)[159]. 25% of adults with chronic hepatitis B who became infected during childhood will die of liver cancer or liver cirrhosis.

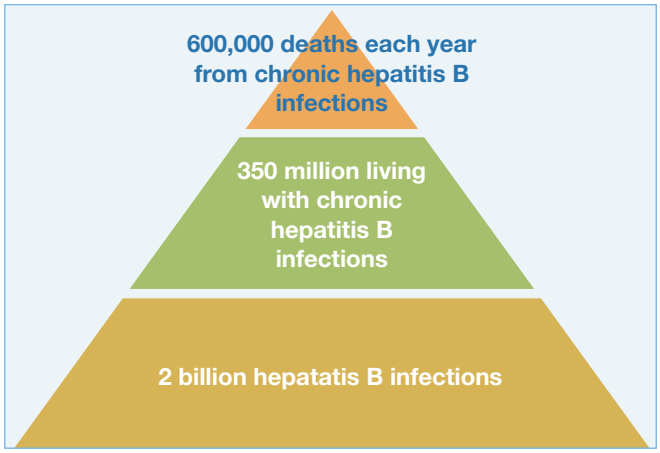


FIGURE 86. GLOBAL IMPORTANCE OF HEPATITIS B

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[160].

The prevalence of chronic infections is much higher in these regions: 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.

[158]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.
[159]World Health Organization. Media center. Hepatitis B. Fact sheet n°204. August 2008. http://www.who.int/mediacentre/factsheets/fs204/en/index.html
[160]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 three or four doses in a primary series by injection. More than 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 common 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[161].

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 87**).

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 88**).

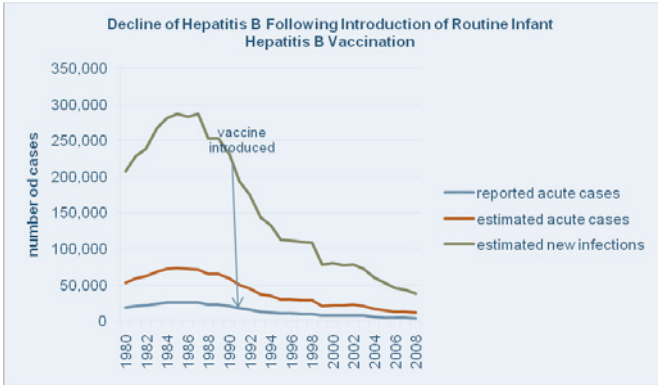


FIGURE 87. IMPACT OF ROUTINE INFANT HEPATITIS B IMMUNIZATION IN THE US[162]

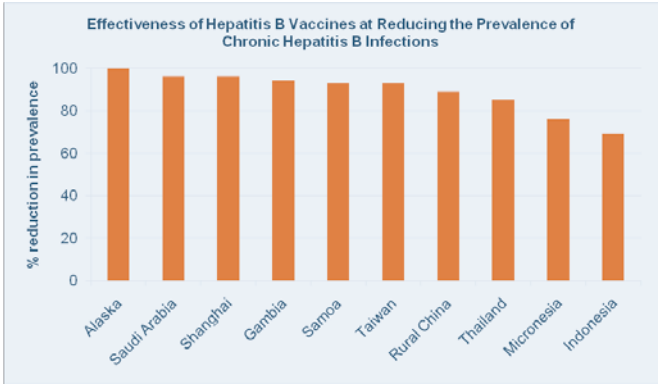


FIGURE 88. EFFECTIVENESS OF HEPATITIS B VACCINES AT REDUCING THE PREVALENCE OF CHRONIC HEPATITIS B INFECTIONS IN SELECT COUNTRIES[163]

[161]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.
[162]Centers for Disease Control and Prevention. 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
[163]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

More than 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 World Health Assembly 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 Expanded Programme on Immunization (EPI)[164].

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 28**).

Universal recommendations			
Antigen	Children	Adolescents	
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 28. WORLD HEALTH ORGANIZATION RECOMMENDATIONS FOR IMMUNIZATION[165]

[163]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.
[164]World Health Organization. Immunization service delivery and accelerated disease control. Expanded programme on immunization. http://www.who.int/immunization_delivery/en/
[165]World Health Organization.Table 1. Recommended Routine Immunization – Summary of WHO Position Papers. October 21, 2010. http://www.who.int/immunization/policy/Immunization_routine_table1.pdf

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, *Haemophilus influenzae* type b, measles, mumps, rubella, and varicella), it saves $5.30 and society saves $16.50[166]. Every 26 days, the US saves the equivalent of its entire investment in the smallpox eradication program from savings on treatment of disease alone[167].

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 2nd 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 eight to 16 diseases, in the last 20 years (See **Table 29**).

“In 1991, a new objective was set: to ensure that 90% of children had completed the full series of vaccinations by their 2nd birthday.

[166]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.
[167]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	√	√				√								

TABLE 29. CHILDHOOD IMMUNIZATION SCHEDULE IN THE US (EXCLUDING CATCH-UP SCHEDULE)[168]

	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
Measles, Mumps, Rubella						√					√			
Varicella						√					√			
Hepatitis A						√				high-risk				
Meningoccal conjugate										high-risk			√	
Human Papillomavirus													girls	

[168]Centers for Disease Control and Prevention. Vaccines & Immunizations. Recommendations and guidelines: 2011 child and adolescent immunization schedules for persons aged 0 – 6 years, 7 – 18 years, and "catch-up schedule".http://www.cdc.gov/vaccines/recs/schedules/child-schedule.htm

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 30**).

Antigen	19-26 years	27-49 years	50-59 years	60-64 years	≥ 65 years
Influenza	1 dose annually				
Tetanus, Diphtheria, Acellular Pertusis / Tetanus, Diphtheria	1dose of Tdap then Td every 10 years				Td every 10 years
Varicella	2 doses if no evidence of immunity				
Human Papillomavirus	3 doses (females) if not yet received				
Herpes zoster				1 dose	
Measles, Mumps, Rubella	1 or 2 doses		1 dose high-risk		
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 30. ADULT IMMUNIZATION SCHEDULE IN THE US[169]

[169]US Department of Health and Human Services and Centers for Disease Control and Prevention. Recommended adult immunization schedule United States 2011. http://www.cdc.gov/vaccines/recs/schedules/downloads/adult/adult-schedule.pdf

4.3 European Union

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 European Union's European Center for Disease Prevention and Control (ECDC) and the WHO's European Regional Office (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 31** below.

Country / year last updated	BCG (tuberculosis)	Diphtheria, Tetanus, Acellular Pertussis	Haemophilus iinfluenzae 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 31. CHILDHOOD VACCINES USED IN EUROPEAN COUNTRIES (LAST UPDATE OF SCHEDULE RANGE FROM DEC 2006 – JULY 2011)[170]

[170]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 US (See **Table 32**).

	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 32. AUSTRALIAN CHILDHOOD IMMUNIZATION SCHEDULE[171]

The adult Australian immunization schedule provides for pneumococcal and influenza vaccines. Influenza is not part of the routine childhood immunization schedule (See **Table 33**).

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

TABLE 33. AUSTRALIAN ADULT IMMUNIZATION SCHEDULE[172]

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

4.5 Japan

Like in many industrialized countries, vaccines in the childhood immunization schedule in Japan are provided at no cost in public health centers. But Japan has been slow to adopt many of the newest vaccines from the last 10 – 15 years and its immunization schedule resembles the schedule of a country of much lower economic status. A table of Japan's childhood immunization schedule relative to countries in the region with comparable or much lower levels of wealth is shown in **Table 34** below.

	Japan	Australia	Korea, South	Singapore	Indonesia	Thailand	USA
Gross National Income / capita (US$)	37,780	43,770	18,830	37,220	2,230	37,760	47,240
BCG (tuberculosis)	√		√	√	√	√	
Diphtheria, Tetanus, Pertussis					√	√	
Diphtheris, Tetanus, Acellular Pertussis	√	√	√	√			√
Oral Polio	√			√	√	√	
Inactivated Polio		√	√		√		√
Haemophilus influenzae type b	√	√					√
Hepatitis B		√	√	√	√	√	√
Measles					√	√	
Measles, Rubella or combination	√						
Measles. Mumps, Rubella		√	√	√		√	√
Japanese Encephalitis Virus	√		√			√	
Tetanus					√		
Diphtheria, Tetanus	√				√		
Tetanus, Diphtheria			√			√	
Tetanus, Diphtheria, Acellular Pertussis				√			√
Pneumococcal conjugate		√		√			√
Varicella		√	√				√
Meningococcal C conjugate		√					
Meningococcal A,C,W,Y conjugate						high risk	√
Human Papillomavirus	√	√					√
Rotavirus	√	√					√
Hepatitis A		high risk					√
Typhoid			high risk				
Influenza	√	high risk	high risk	√			√

TABLE 34. JAPAN'S CHILDHOOD IMMUNIZATION SCHEDULE COMPARED TO OTHER COUNTRIES IN THE REGION AND THE US[173]

[173]World Health Organization. WHO Vaccine Preventable Diseases Monitoring System. http://apps.who.int/immunization_monitoring/en/globalsummary/countryprofileselect.cfm

4.5.1 Current situation in Japan

Japan was one of only a few pioneering countries in vaccine development. Several vaccines were developed first in Japan and later produced or further adapted in other countries. Ironically, Japan has lagged behind most countries of similar economic development in both vaccine policy and implementation. Over the last several decades, the US and countries in the European Union have outpaced Japan in developing policies and practices for the introduction of new vaccines.

Initiatives, such as the Childhood Immunization Initiative of the early 1990s, helped the US 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.

Likewise, 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. At the start of the 2000s, many developing countries had not updated their immunization programs and policies from the 1970s when they were first launched. 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.

The relatively high incidence of deafness from mumps in Japan, when the US and countries in Europe have virtually eliminated the disease, highlights the divergence in immunization policy and implementation between Japan and countries of similar economic status. In the absence of a renewed or reinvigorated emphasis on immunization in Japan, the contrast in public health outcomes may become increasingly apparent. 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.

Therefore, Japan has recently undertaken to reform vaccine policy and practice, as evidenced by the activities of the Vaccine Committee of the Ministry of Health, Labor and Welfare.

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. 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 2011, the global leaders in vaccine research and development reported the vaccines shown in **Table 35** 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)
			cell-cultured influenza vaccine; pediatric influenza vaccine
Novartis	cytomegalovirus	*Pseudomonas aeruginosa*	
	group B *Streptococcus*	meningococcal B	
	HIV	cell-cultured influenza	
	pneumococcal	conjugate meningococcal A, B, C, Y, W135	
Pfizer	3 and 4-valent *Staphylococcus aureas*	Alzheimer's disease	
		adolescent and infant meningococcal B	
Sanofi Pasteur	rotavirus	6-valent pediatric combination (diphtheria, tetanus, pertussis, polio, hepatitis B, and *Haemophilus influenzae* type b)	4-valent pediatric combination (diphtheria, tetatnus, pertussis, polio)
	pneumococcal	*Clostridium difficile*	6-valent pediatric combination (diphtheria, tetanus, pertussis, polio, hepatitis B, and *Haemophilus influenzae* type b)
	Pseudomonas aeruginosa	rabies post-exposure prophylaxis	4-valent inactivated influenza
	tuberculosis	rabies	4-valent dengue
		4-valent meningococcal a, C, Y, W135 conjugate	
GlaxoSmithKline	cell-cultured influenza	7-valent pediatric combination (diphtheria, tetanus, pertussis, polio, hepatitis B, *Haemophilus influenzae* type b, and meningococcal C conjugate)	4-valent inactivated influenza
	HIV	measles, mumps, rubella	Herpes Zoster
		pneumococcal conjugate	
		HIV	
		tuberculosis	

TABLE 35. VACCINES UNDER DEVELOPMENT BY GLOBAL VACCINE LEADERS, BY CLINICAL PHASE OF DEVELOPMENT[174,175,176,177,178]

[174]Merck. Merck pipeline. July 29, 2011. http://www.merck.com/research/pipeline/home.html
[175]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
[176]Pfizer. Pfizer pipeline – our medicines in development. Aug 11, 2011. http://www.pfizer.com/research/product_pipeline/product_pipeline.jsp
[177]Novartis. Welcome to Novartis vaccines. Pipeline. 2011. http://www.novartisvaccines.com/products-diseases/pipeline.shtml
[178]GlaxoSmithKline. Product development pipeline. Feb 2011. http://www.gsk.com/investors/product_pipeline/docs/gsk-pipeline-2011.pdf

In addition, in its report of 2006, the WHO noted vaccine research and development in specific disease areas (See **Table 36**). Some of these trials have now been completed. Others have been discontinued. Some have progressed to a further stage of development.

> 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.

Disease Area	Vaccine
Diarrheal diseases	Cholera
	Escherichia coli
	Rotavirus
	Shigella
	Typhoid fever
Respiratory diseases	Influenza
	Parainfluenza virus type 3
	Respiratory syncytial virus
	Severe Acute Respiratory Syndrome (SARS)
	Pneumococcal
	Tuberculosis
Bacterial diseases	Anthrax
	Meningococcal A, C, Y, W135
	Meningococcal B
	Plague
	Group A *Streptococcus*
	Group B *Streptococcus*
Sexually transmitted diseases	*Chlamydia trachomatis*
	Herpes simplex type 2
	HIV
Vector-borne diseases	Dengue fever
	Japanese encephalitis
	West Nile virus
Parasitic diseases	Hookworm
	Leishmania
	Malaria
	Schistosomiasis
Hepatitis and cancers	*Helicobacter pylori*
	Hepatitis B
	Hepatitis C
	Hepatitis E
	Human Papillomavirus
	Epstein-Barr virus
Enterovirus	Polio

TABLE 36. VACCINE RESEARCH AND DEVELOPMENT BY DISEASE AREA[179]

[179]World Health Organization. Immunizations and Vaccine Research. New vaccines against infectious diseases: research and development status. Updated Feb 2006. http://www.who.int/vaccine_research/documents/en/Status_Table.pdf

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