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

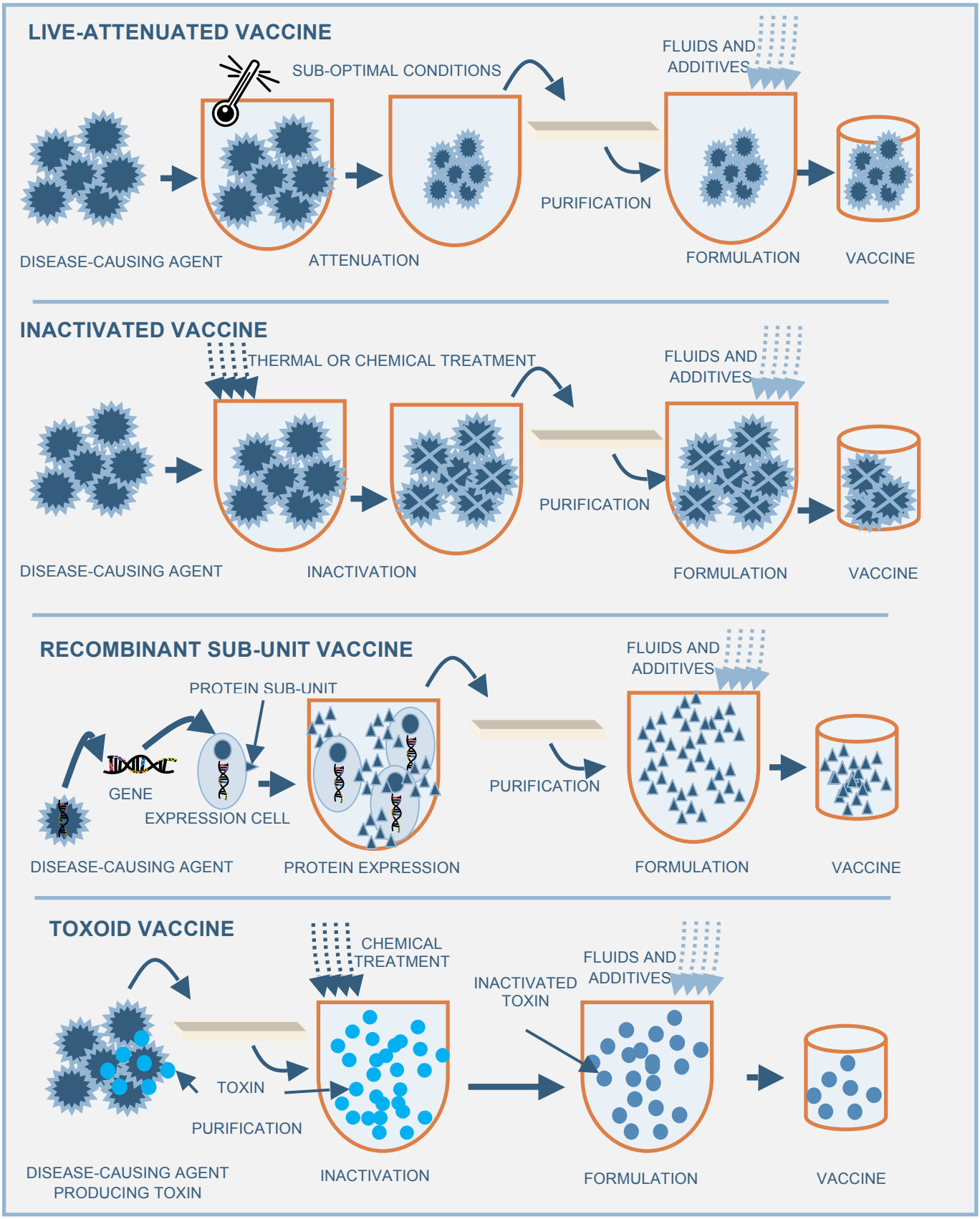
LIVE-ATTENUATED VACCINE
SUB-OPTIMAL CONDITIONS
FLUIDS AND ADDITIVES
PURIFICATION
DISEASE-CAUSING AGENT
ATTENUATION
FORMULATION
VACCINE
INACTIVATED VACCINE
THERMAL OR CHEMICAL TREATMENT
FLUIDS AND ADDITIVES
PURIFICATION
DISEASE-CAUSING AGENT
INACTIVATION
FORMULATION
VACCINE
RECOMBINANT SUB-UNIT VACCINE
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

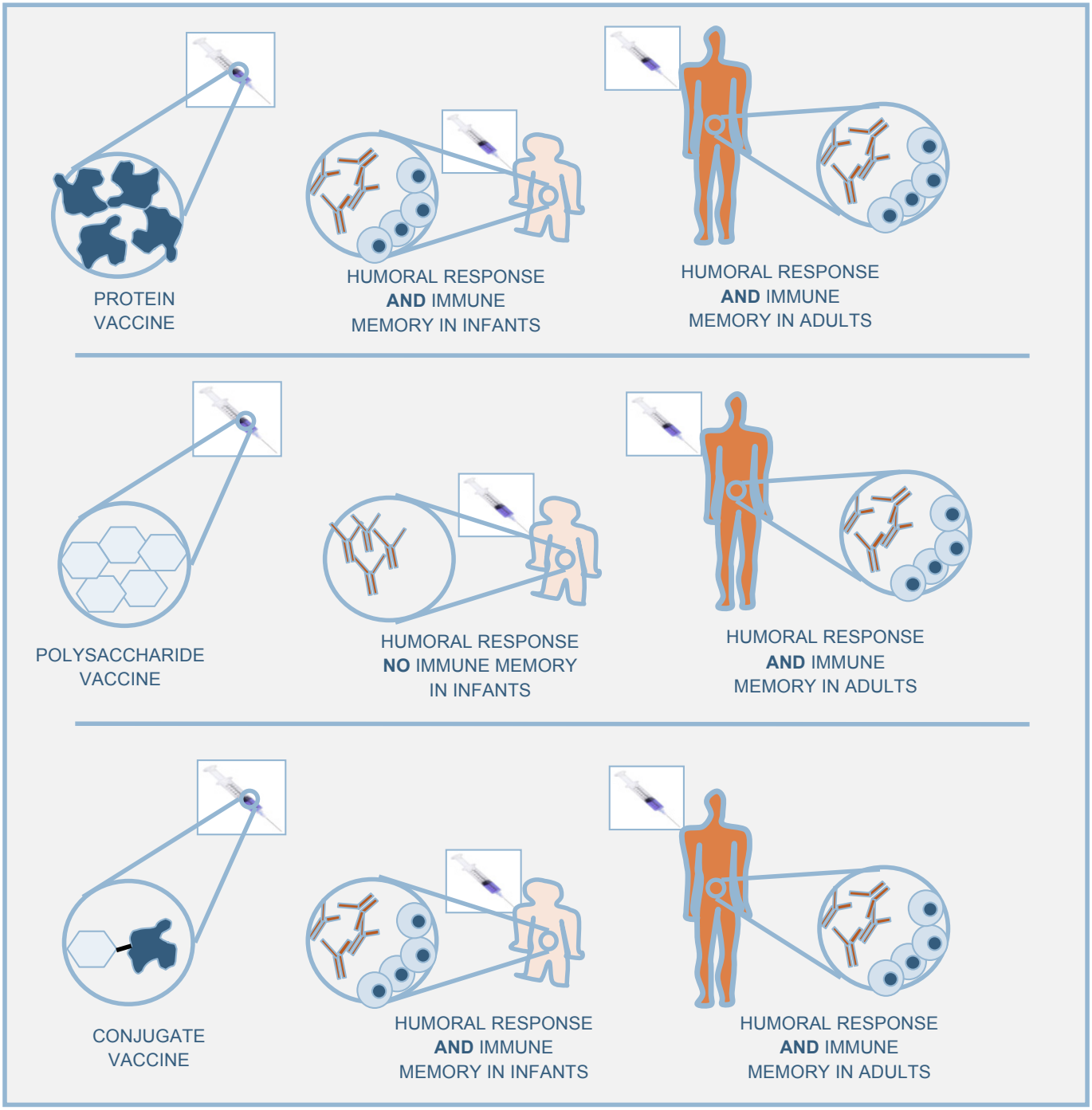

FIGURE 2

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**).

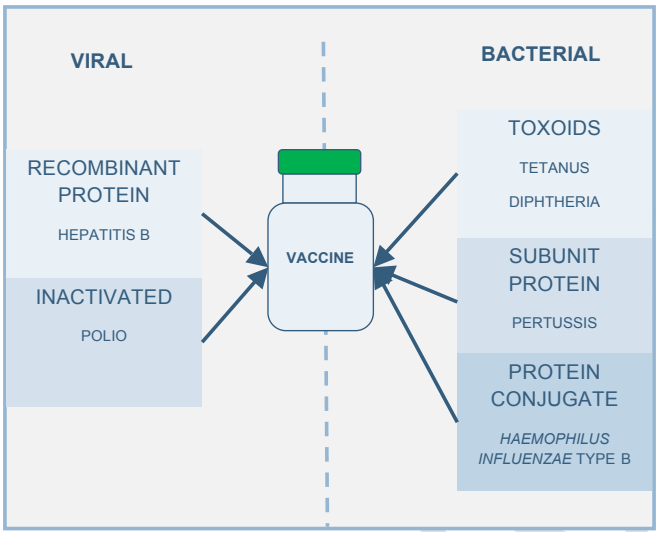

FIGURE 3. COMMON COMBINATION PEDIATRIC VACCINE CONTAINING MULTIPLE ANTIGENS OF MULTIPLE VACCINE TYPES

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**).

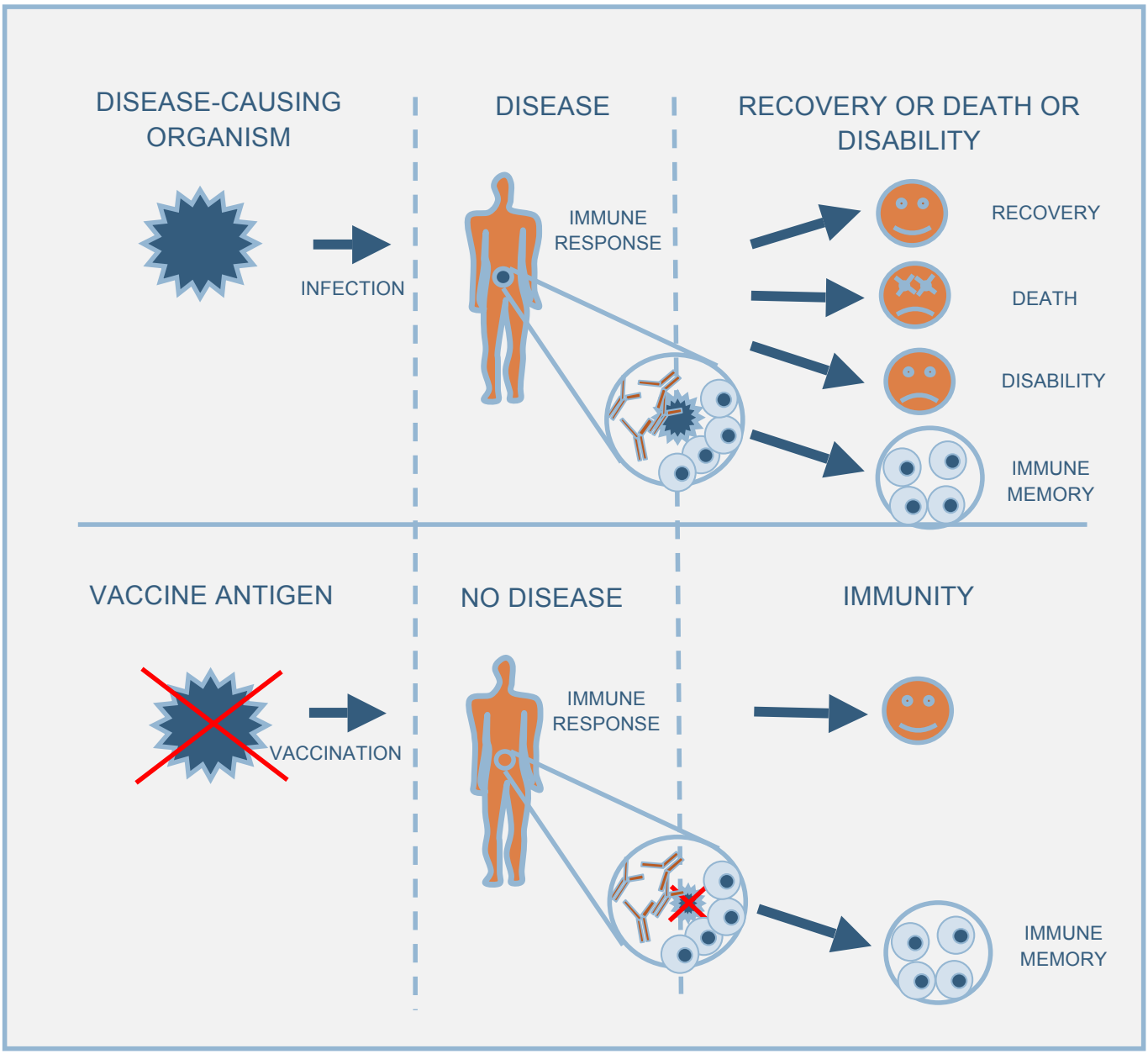

FIGURE 4. COMPARISON OF THE IMMUNE RESPONSE TO A DISEASES-CAUSING ORGANISM AND TO A VACCINE

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**).

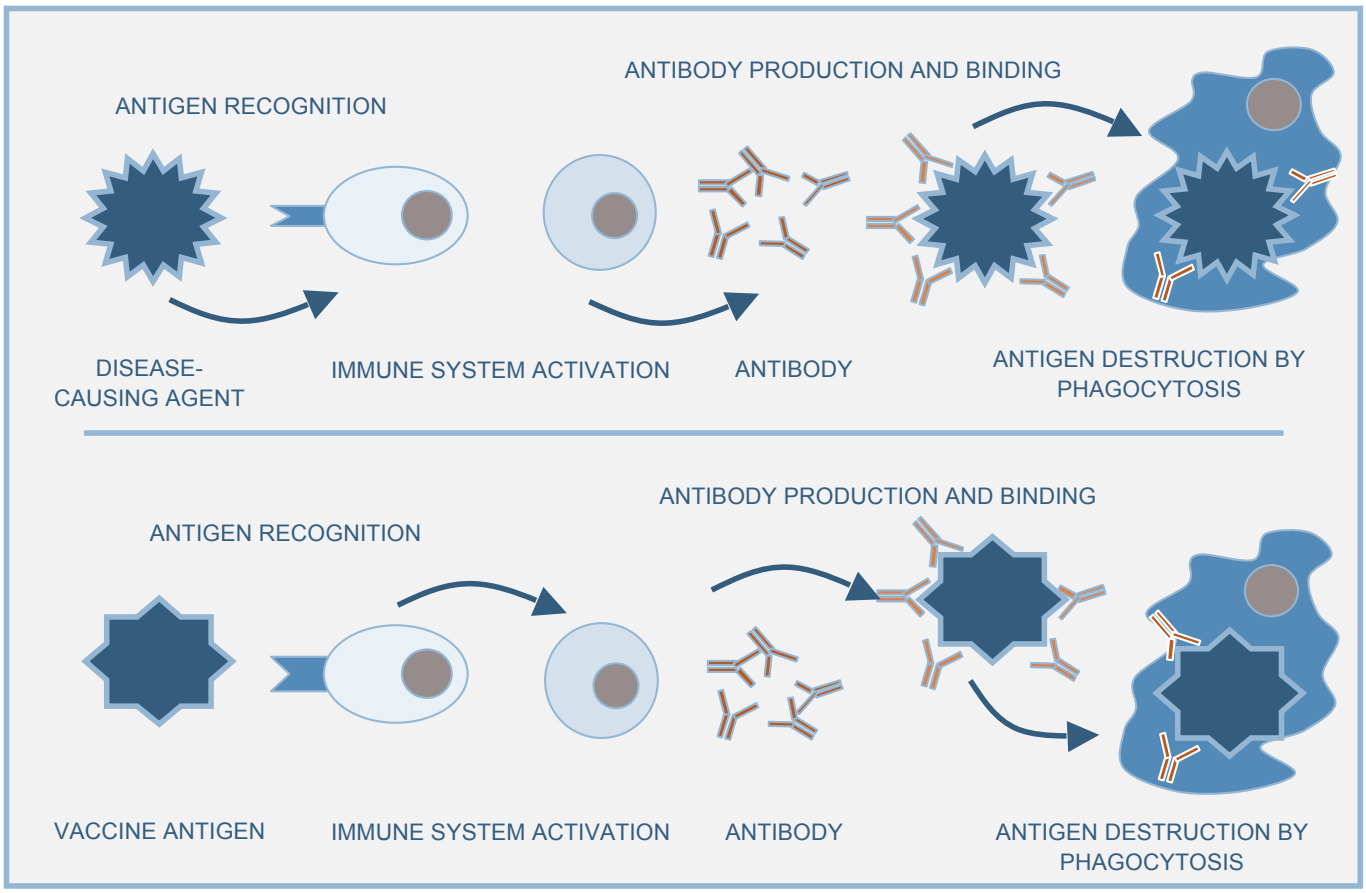

FIGURE 5. ANTIBODY DESTRUCTION OF ANTIGEN

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.

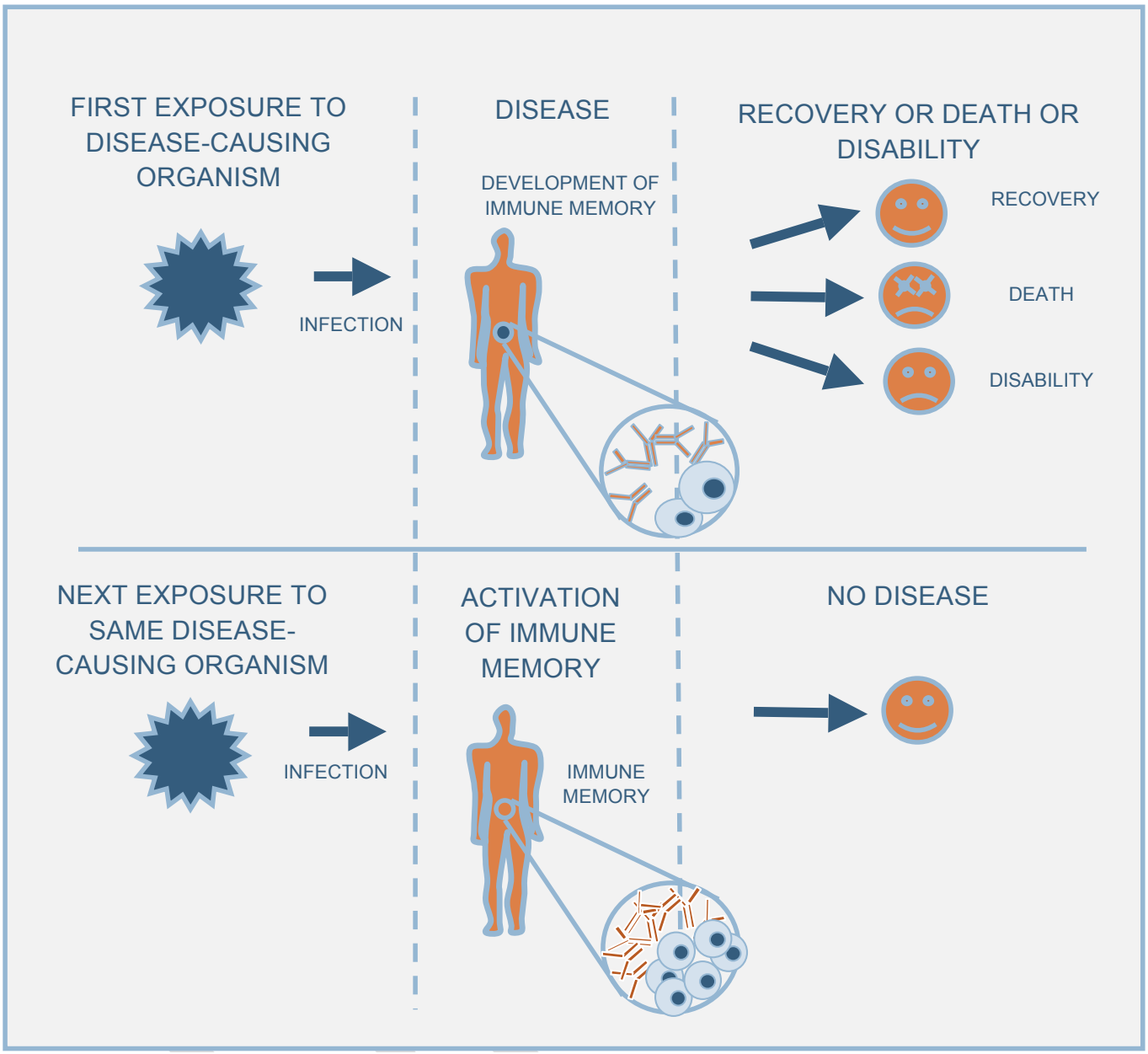

FIGURE 4. COMPARISON OF THE IMMUNE RESPONSE TO A DISEASES-CAUSING ORGANISM AND TO A VACCINE

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.

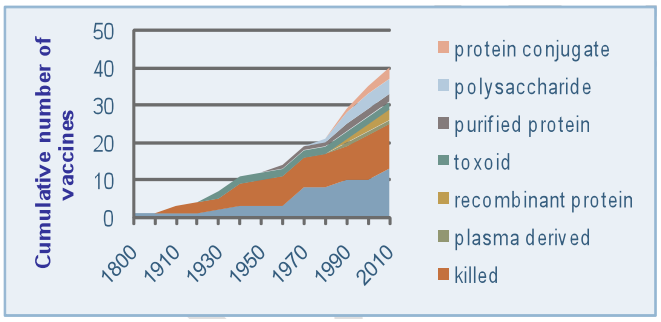

FIGURE 7. CUMULATIVE NUMBER OF VACCINES DEVELOPED SINCE THE FIRST VACCINE IN 1798, BY TYPE

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/

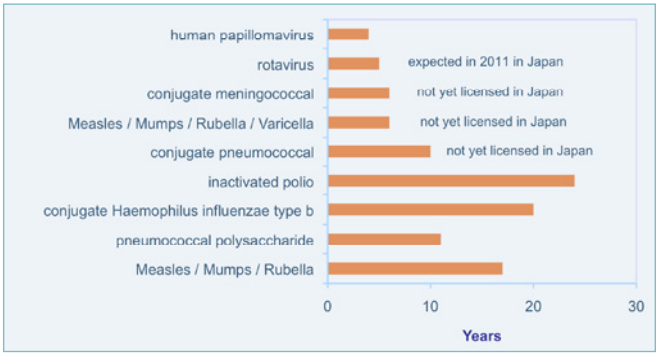

FIGURE 8. NUMBER OF YEARS BETWEEN THE GRANTING OF VACCINE LICENSES IN THE US AND THE GRANTING OF VACCINE LICENSES IN JAPAN (FOR SOME VACCINES)

“

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**).

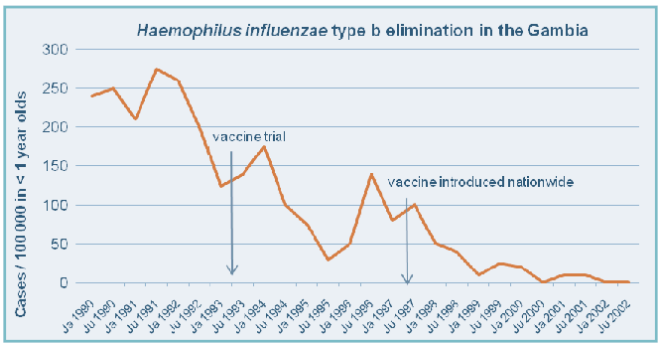

FIGURE 10. IMPACT OF IMMUNIZATION ON HIB DISEASE IN THE GAMBIA (ADAPTED – DATA ARE APPROXIMATE)[8]

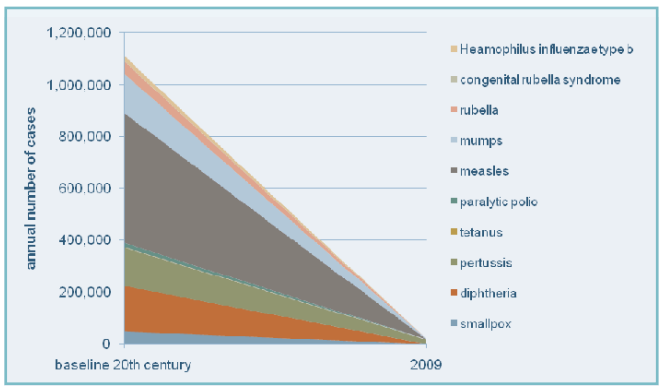

FIGURE 9. IMPACT OF IMMUNIZATION ON THE NUMBER OF ANNUAL CASES OF DISEASE IN THE USA[6,7]

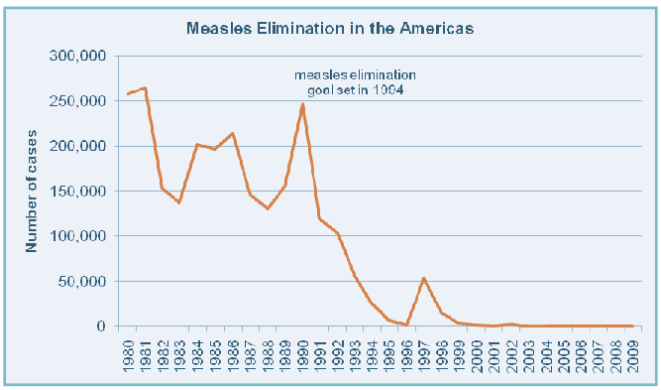

FIGURE 11. MEASLES ELIMINATION IN THE AMERICAS FROM EFFORTS IN IMMUNIZATION[9,10]

[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).

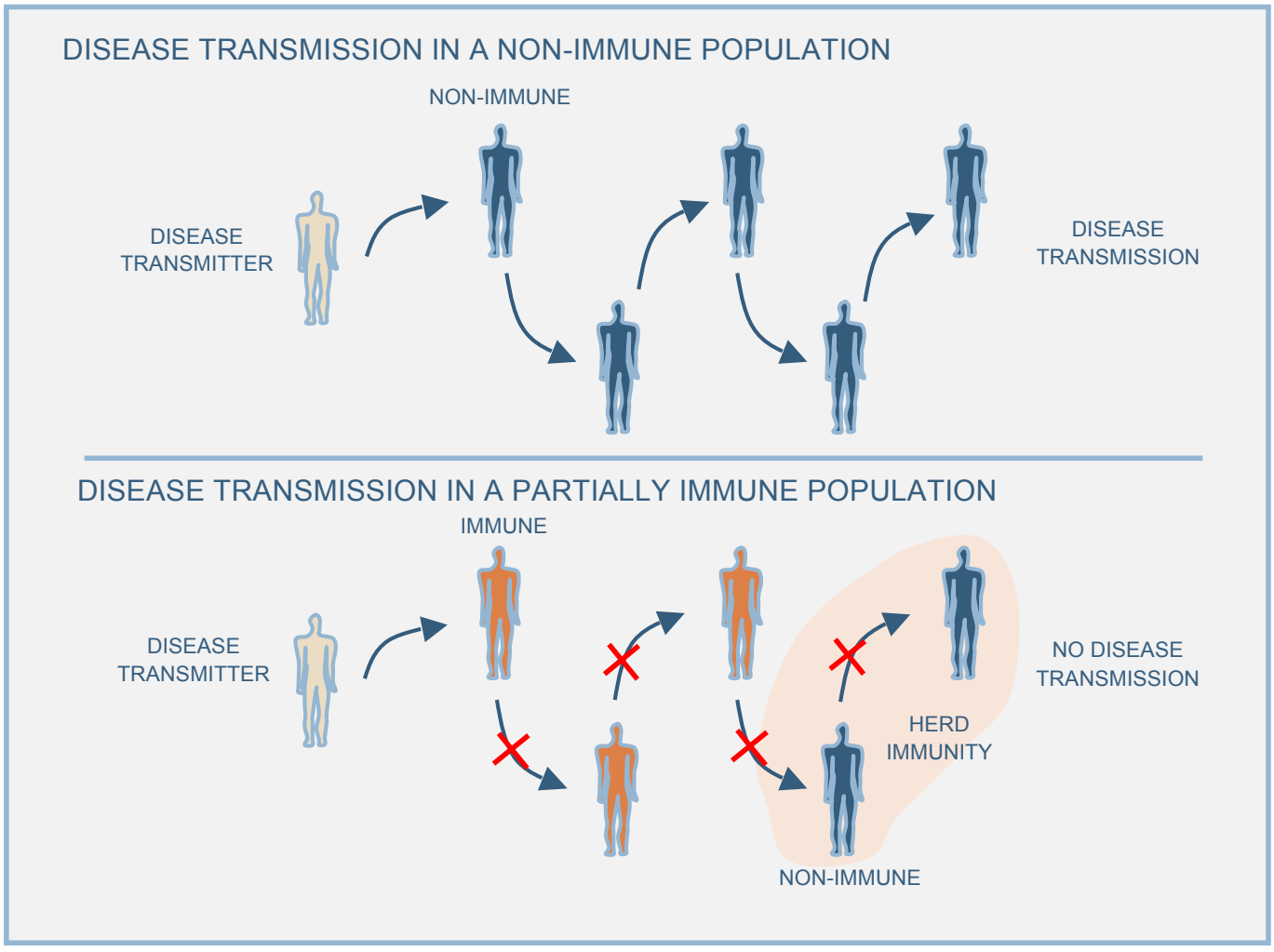

FIGURE 12. HERD IMMUNITY

[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

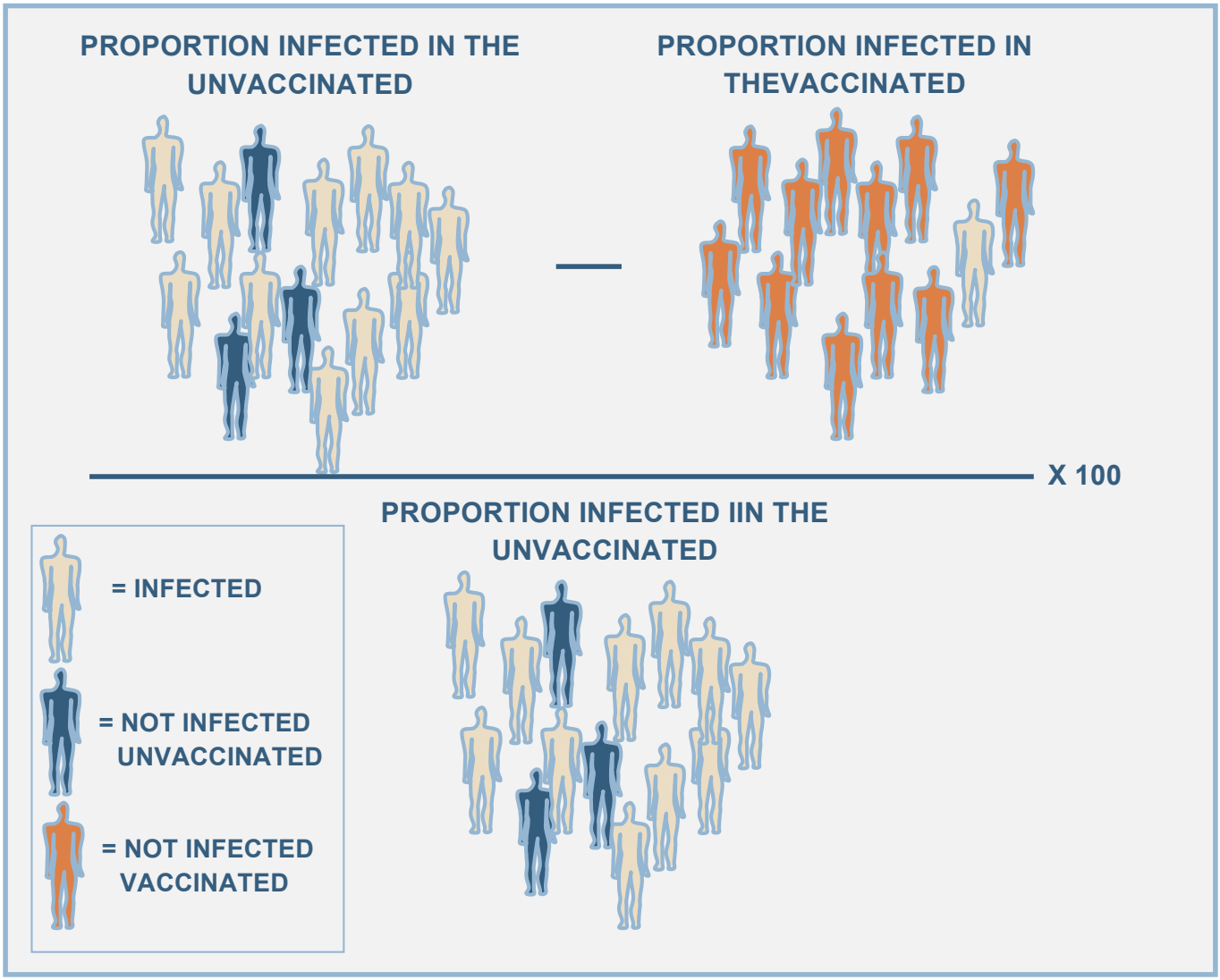
PROPORTION INFECTED IN THE UNVACCINATED
PROPORTION INFECTED IN THEVACCINATED
X 100
PROPORTION INFECTED IIN THE UNVACCINATED
= INFECTED
= NOT INFECTED UNVACCINATED
= NOT INFECTED VACCINATED

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**).

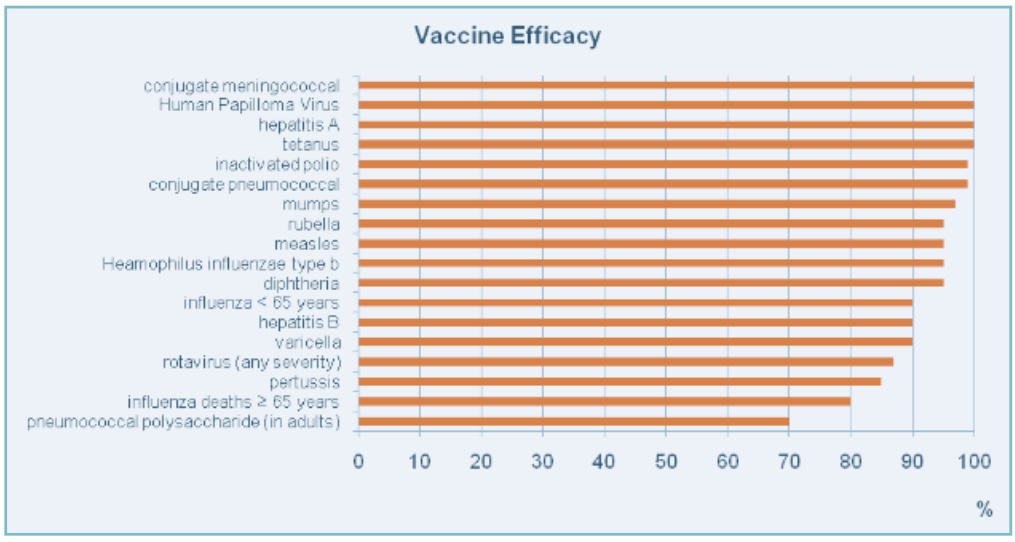

FIGURE 14. OBSERVED EFFICACIES OF SOME VACCINES (MAXIMUM VALUES ARE SHOWN FOR RANGES)[13]

[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.

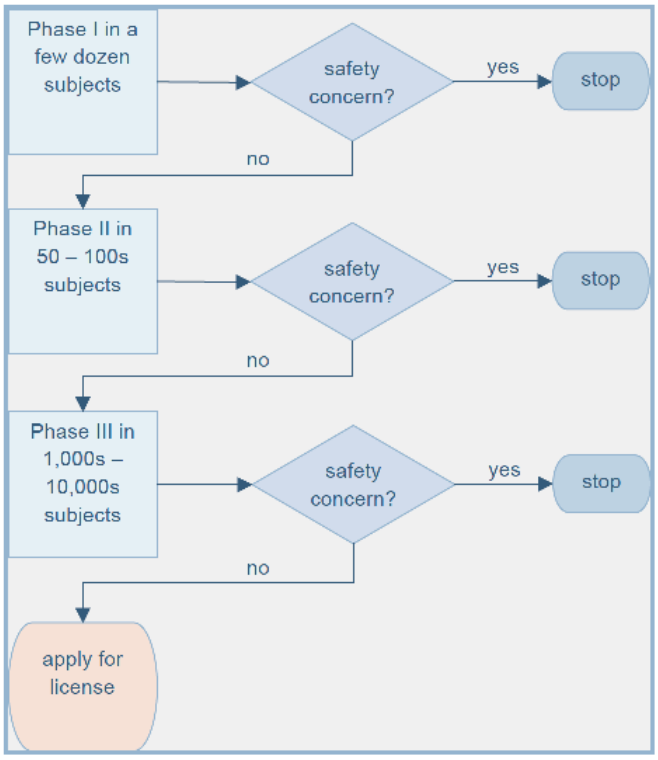

FIGURE 15. SAFETY TESTING OF VACCINES IN THREE PHASES OF CLINICAL TRIALS

[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).

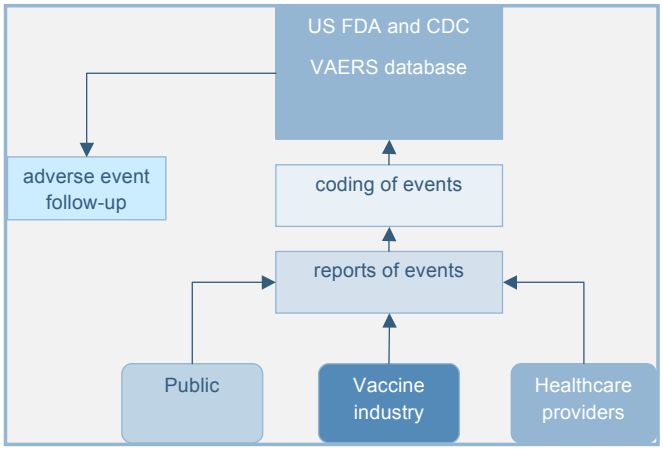

FIGURE 16. US VACCINE ADVERSE EVENT REPORTING SYSTEM (EXAMPLE OF A SPONTANEOUS SURVEILLANCE SYSTEM)

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**).

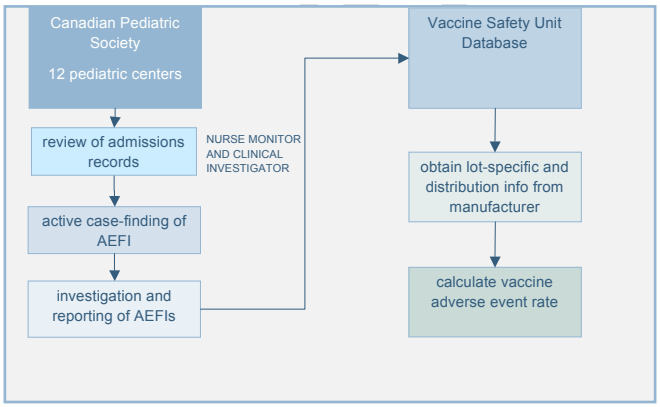

FIGURE 17. CANADIAN IMPACT SURVEILLANCE SYSTEM (EXAMPLE OF AN ACTIVE SURVEILLANCE SYSTEM)

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.

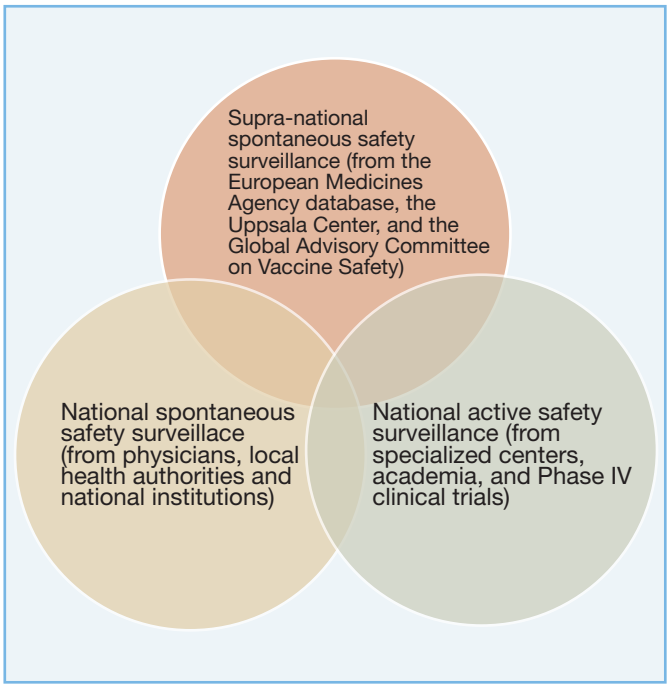

FIGURE 18. NATIONAL AND SUPRA-NATIONAL VACCINE SAFETY SURVEILLANCE IN EUROPE

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].

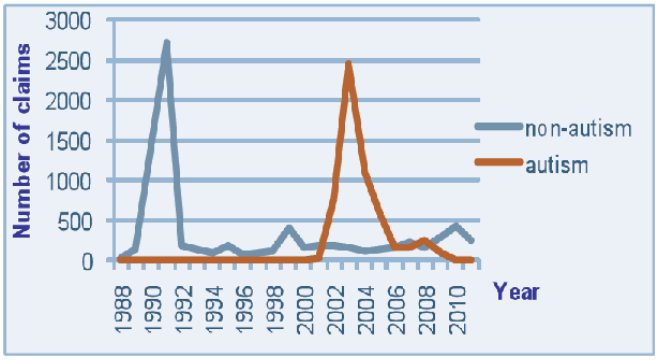

FIGURE 19.

> 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

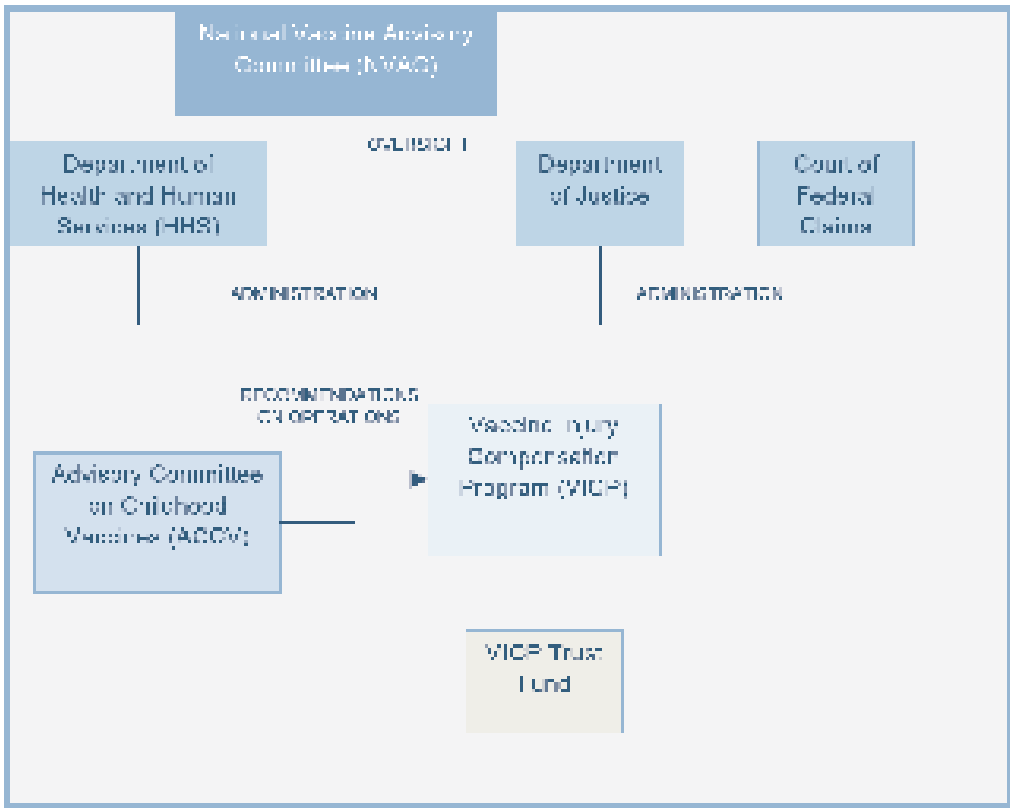

FIGURE 20. ORGANIZATION OF VACCINE INJURY COMPENSATION PROGRAM IN THE US

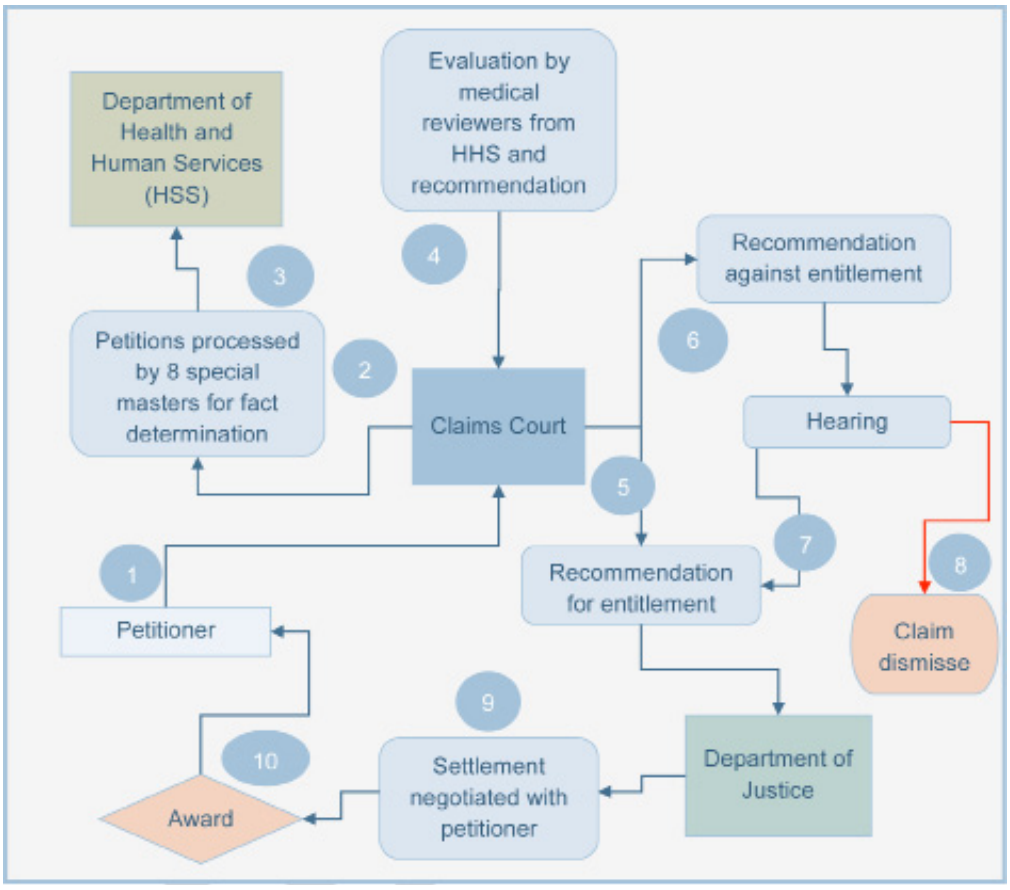

FIGURE 21. VACCINE INJURY COMPENSATION CLAIM PROCESS IN THE US

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**.

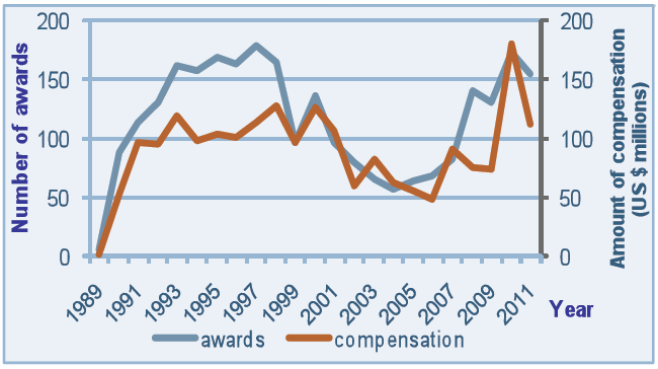

FIGURE 22. ANNUAL NUMBER OF VICP AWARDS AND ANNUAL AMOUNTS OF COMPENSATION AWARDED FROM THE VICP TRUST FUND

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

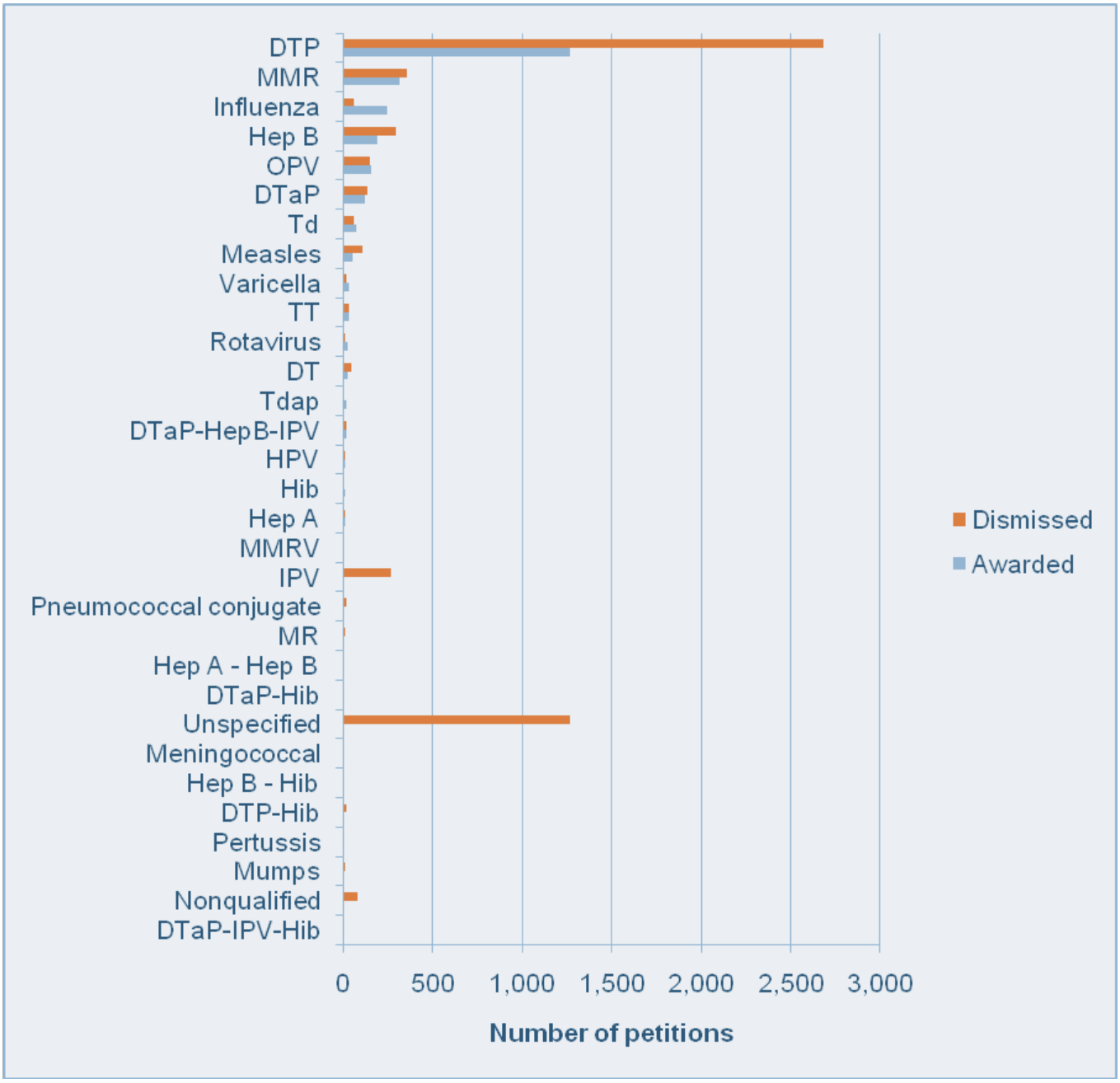

FIGURE 23. NUMBER OF PETITIONS TO THE VICP AND NUMBER OF AWARDS GRANTED BY VACCINE TYPE, FROM 1988 - 2010

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.

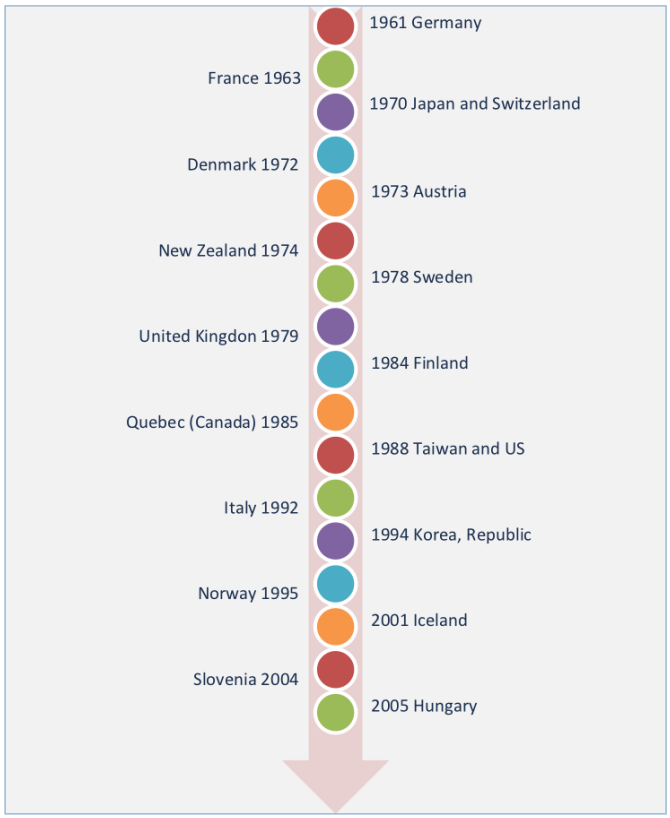

FIGURE 24. COUNTRIES WITH INJURY COMPENSATION PROGRAMS, YEAR INTRODUCED

[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.

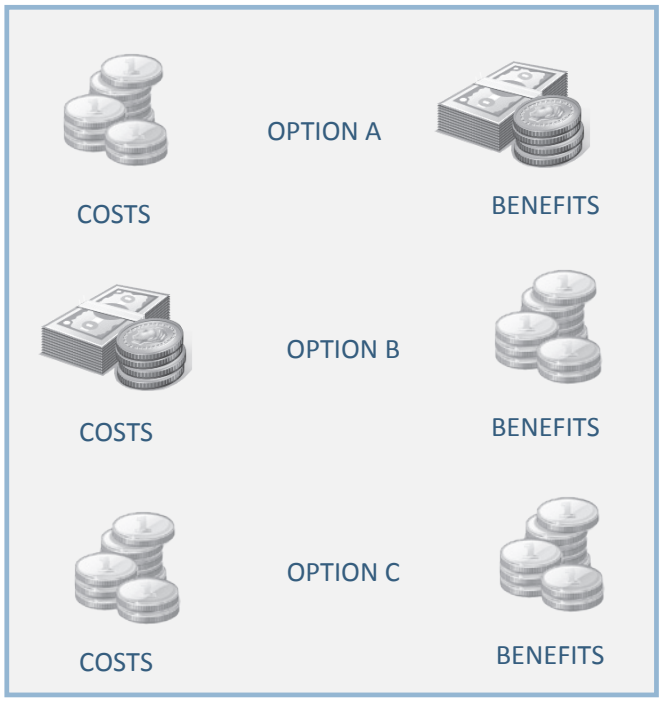

FIGURE 25. COST BENEFIT ANALYSES ASSIST IN DETERMINING WHICH PROGRAM OPTIONS AND PROVIDE THE GREATEST VALUE

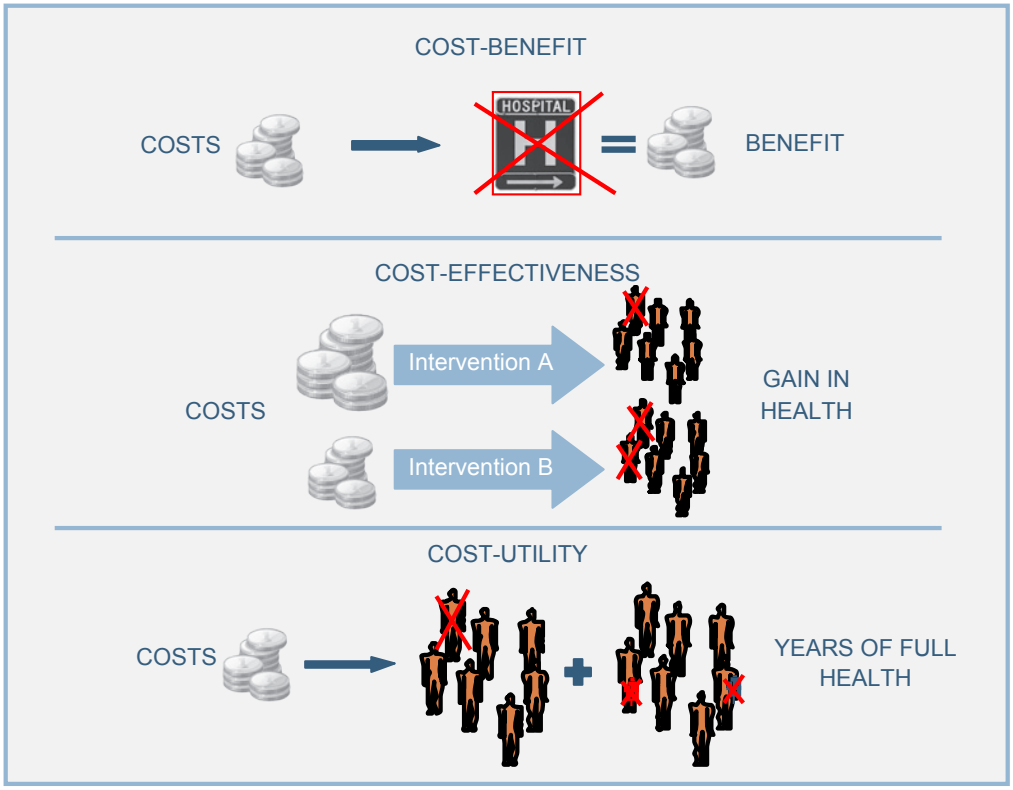

FIGURE 26. TYPES OF ECONOMIC ANALYSES COMMONLY USED TO ASSESS IMMUNIZATION PROGRAMS

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].

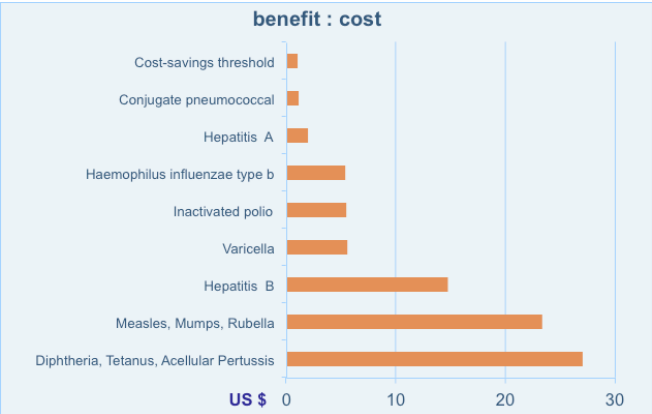

FIGURE 27. COST-SAVING BENEFIT: COST RATIOS FOR SOME VACCINES IN THE US

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].

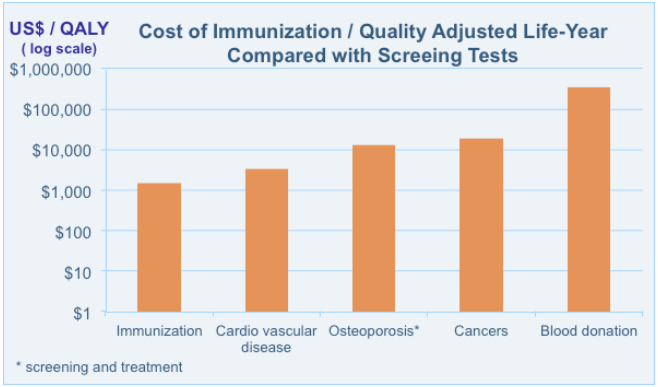

FIGURE 28. COST-EFFECTIVENESS OF IMMUNIZATION COMPARED TO COMMONLY USED SCREENING TESTS IN THE US

[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].

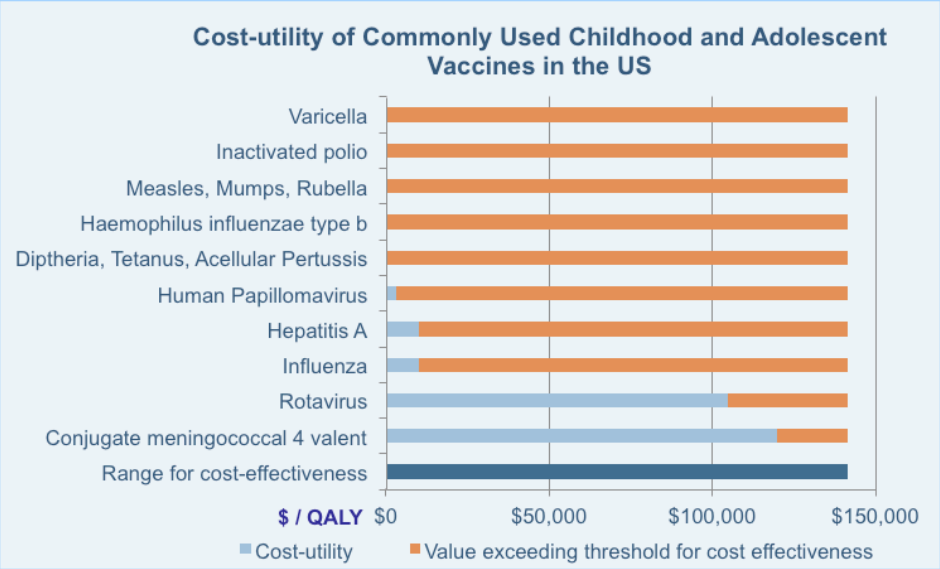

FIGURE 29. COST-EFFECTIVENESS OF CHILDHOOD AND ADOLESCENT VACCINES IN THE US. VACCINES <$0 / QALY ARE COST SAVING. ALL VACCINES SHOWN EXCEED THE THRESHOLD FOR COST-EFFECTIVENESS. (LOWEST COSTS WERE USED IF FROM A RANGE; COST FOR HUMAN PAPILLOMAVIRUS VACCINE IS FOR IMMUNIZATION OF 12 YEAR-OLD GIRLS)

[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);

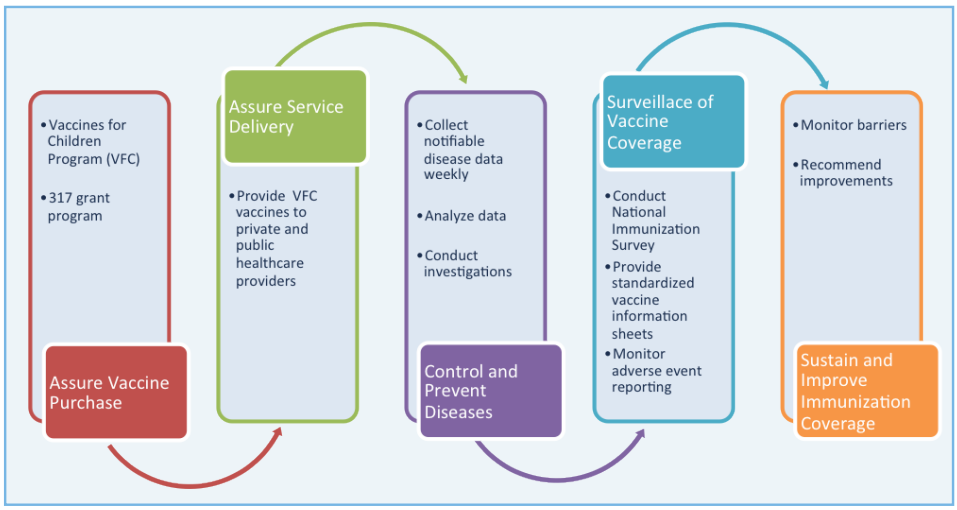

FIGURE 30. KEY GOVERNMENT ROLES IN IMMUNIZATION SUPPORTED BY IMMUNIZATION FINANCE POLICIES AND PRACTICES

[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**).

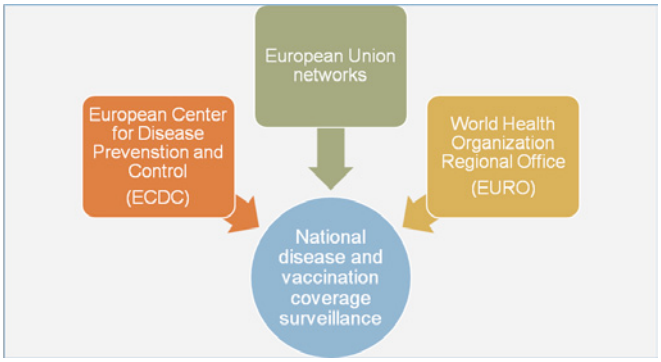

FIGURE 31.SUPPORT MECHANISMS IN EUROPE FOR NATIONAL SURVEILLANCE OF VACCINE-PREVENTABLE DISEASES AND VACCINATION COVERAGE

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.

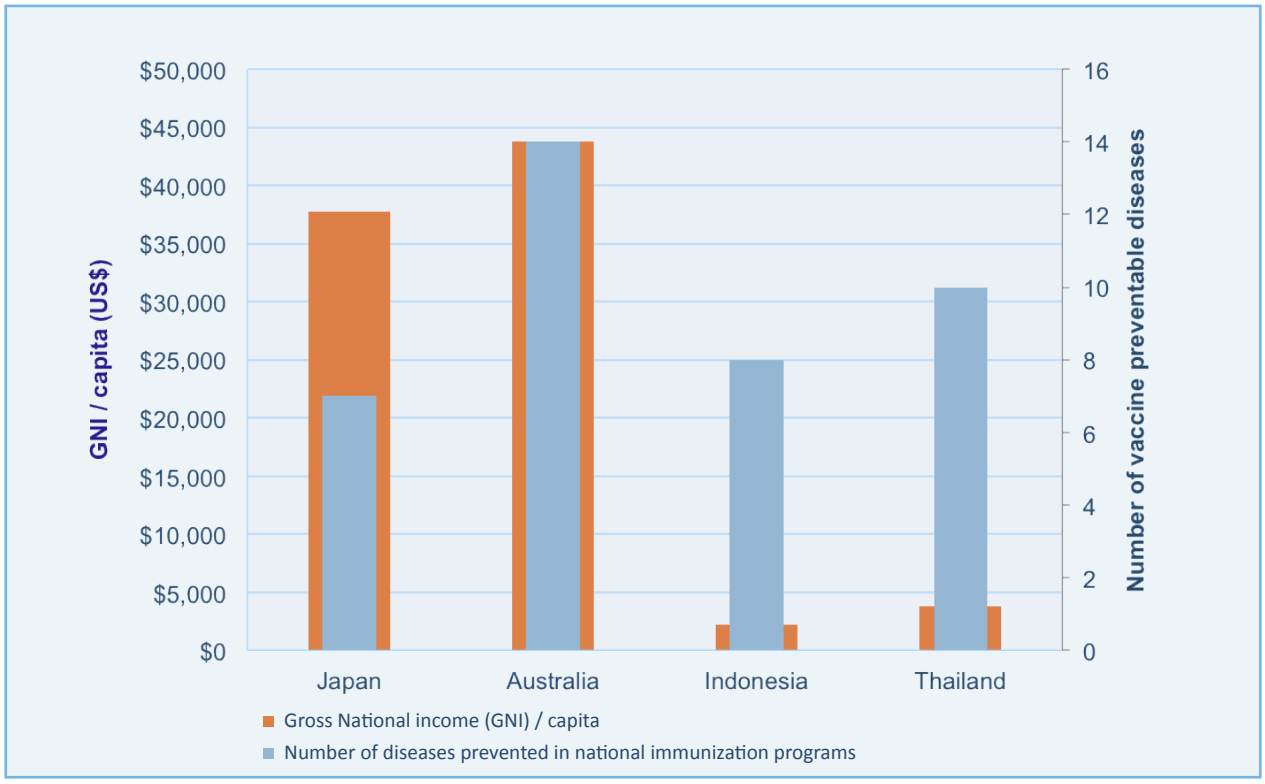

FIGURE 32. DISPARITY IN THE NUMBER OF DISEASES PREVENTED IN NATIONAL IMMUNIZATION PROGRAMS IN COUNTRIES WITH DIFFERENT LEVELS OF GROSS NATIONAL INCOME / CAPITA IN THE ASIA-PACIFIC REGION

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

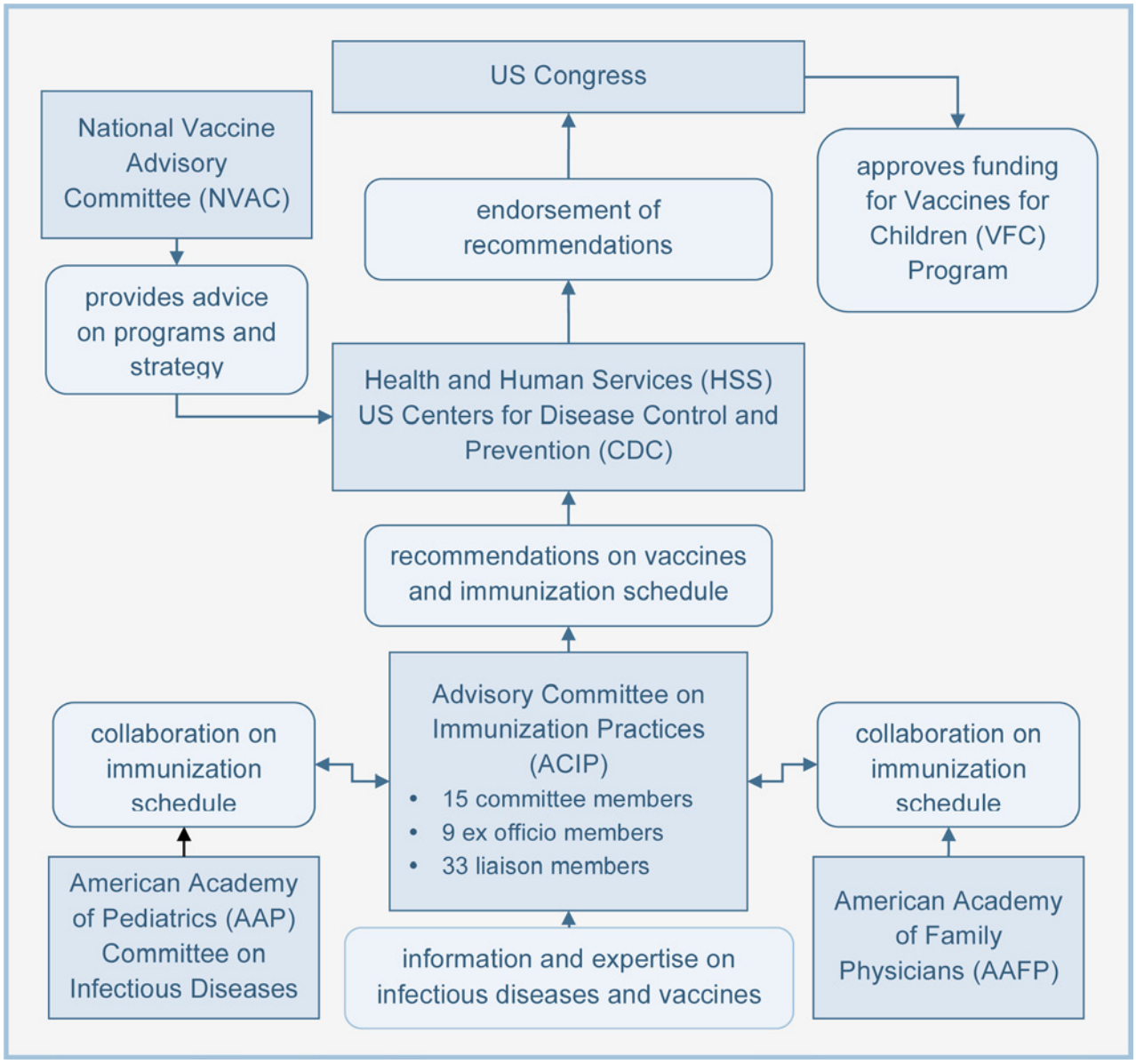

FIGURE 33. ORGANIZATION AND RECOMMENDATION PROCESS OF THE US ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP) AND ITS PARTNERS

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.

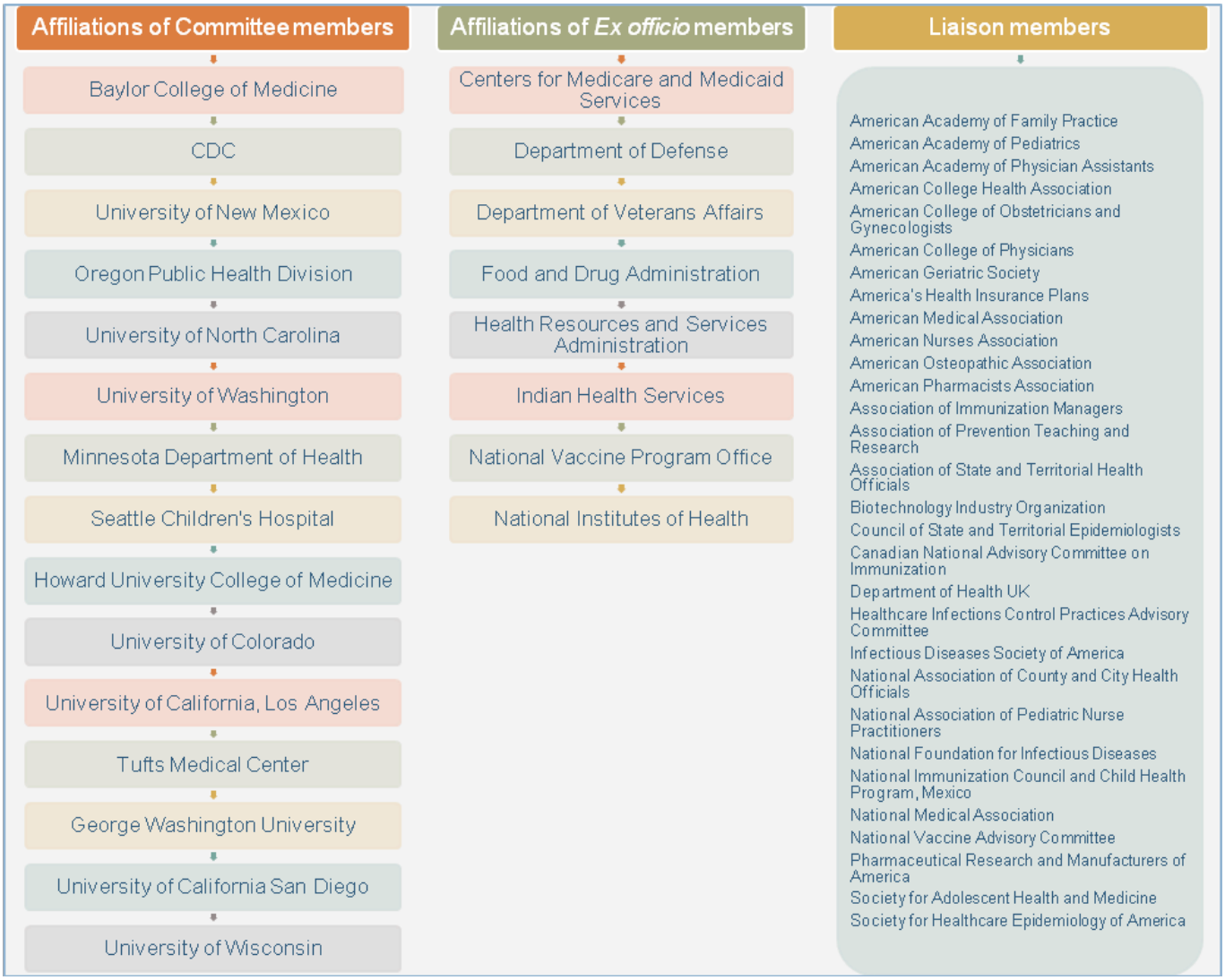

FIGURE 35. AFFILIATIONS OF MEMBERS OF THE US ACIP IN 2011 SHOWING REPRESENTATION FROM A WIDE DIVERSITY OF INSTITUTIONS AND ORGANIZATIONS

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**).

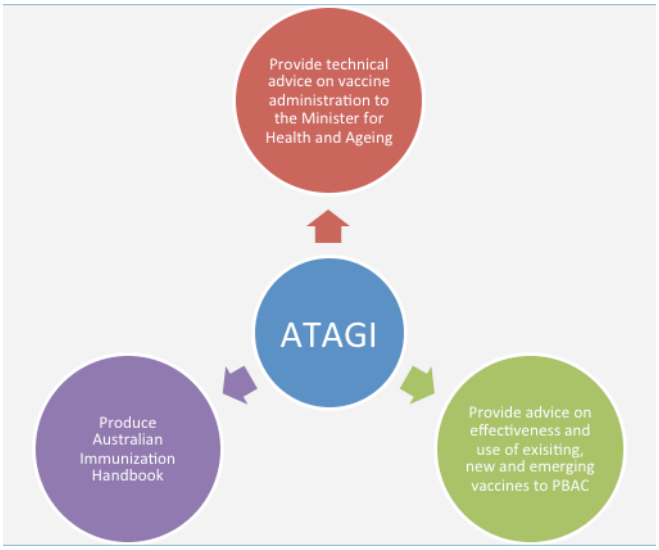

FIGURE 36. FUNCTIONS OF THE AUSTRALIAN TECHNICAL ADVISORY GROUP ON IMMUNIZATION (ATAGI)

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

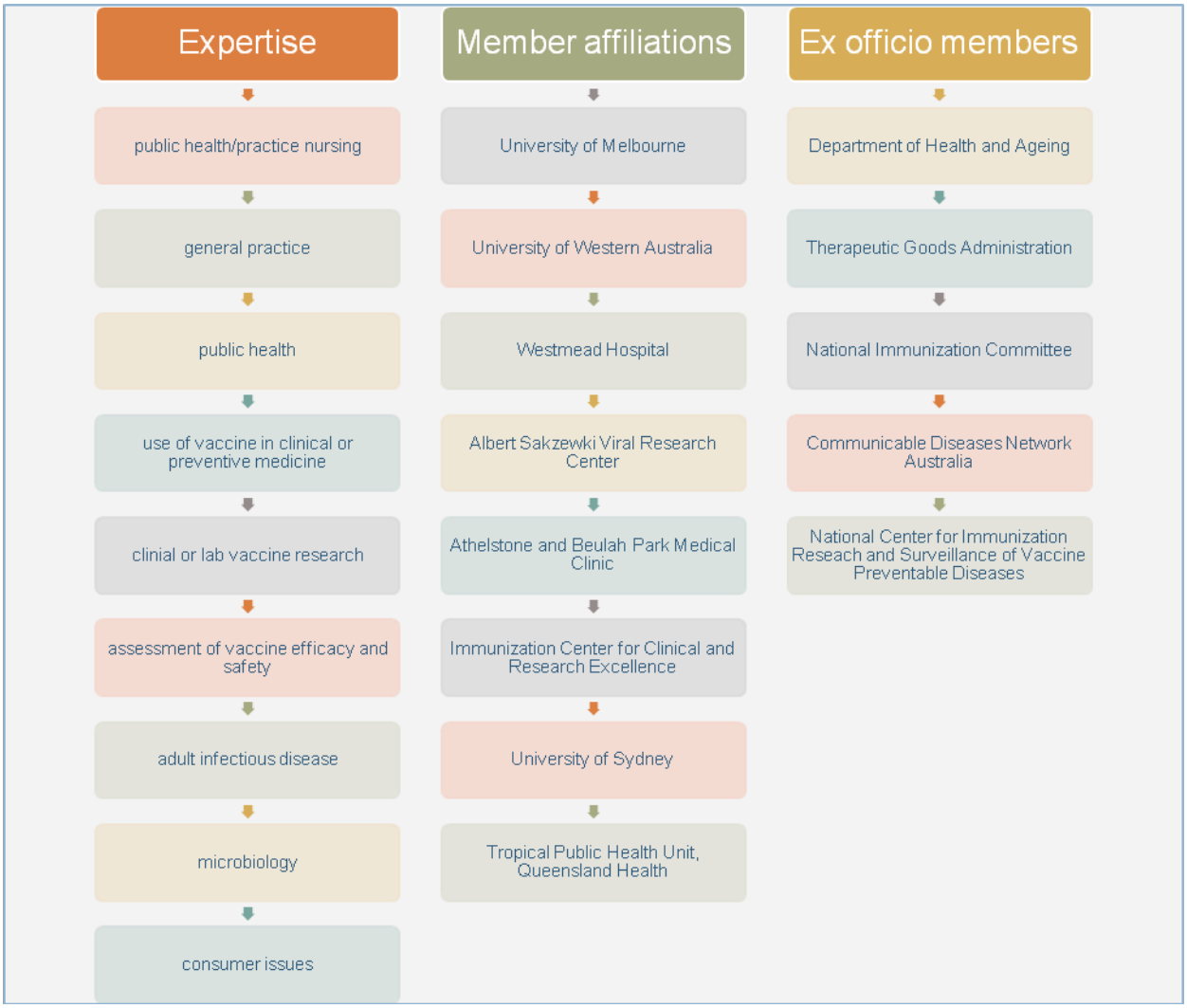

FIGURE 37. AFFILIATIONS OF MEMBERS OF THE AUSTRALIAN TECHNICAL ADVISORY GROUP ON IMMUNISATION (ATAGI)

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.

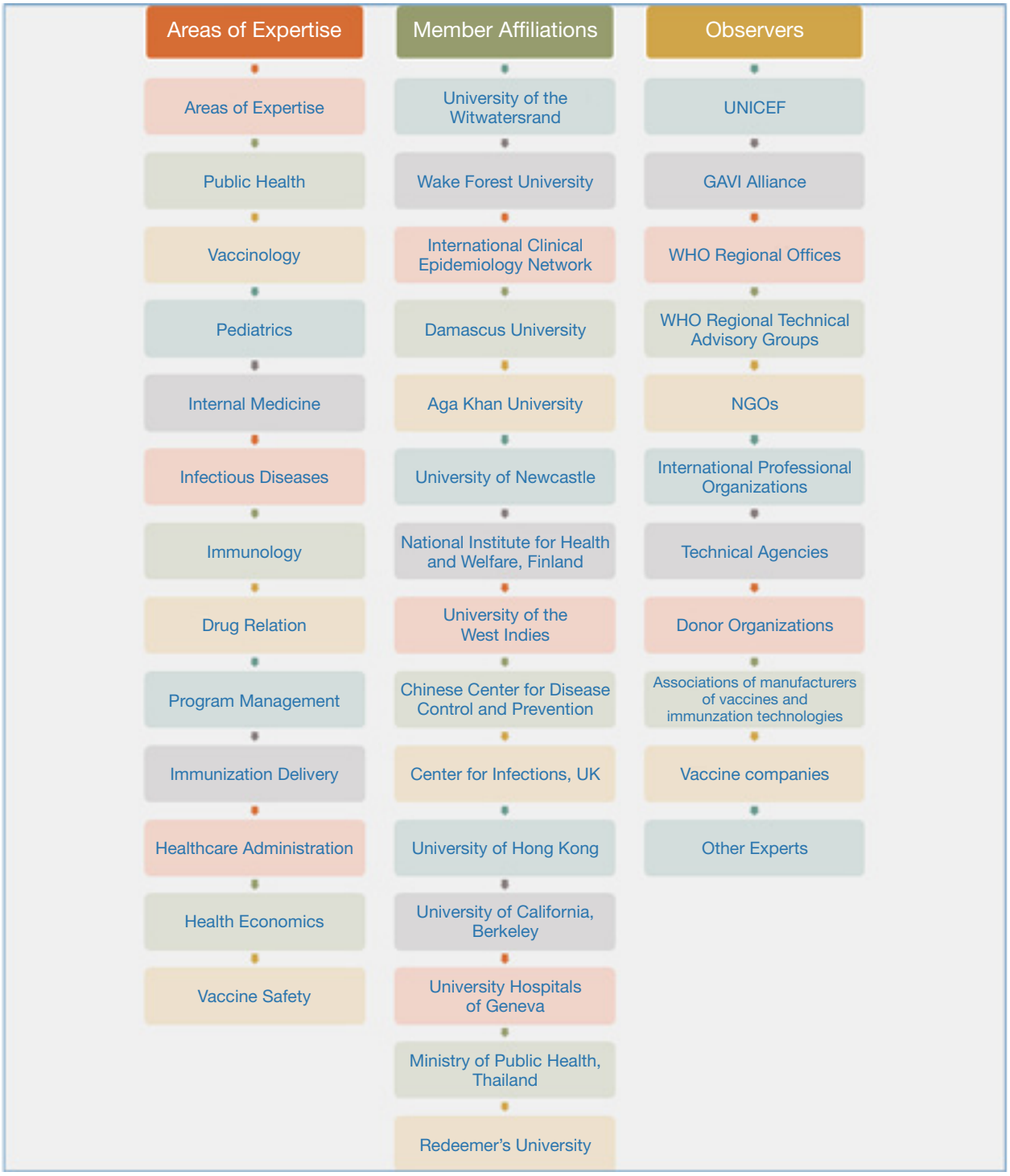

FIGURE 38. AFFILIATIONS OF CURRENT MEMBERS OF WORLD HEALTH ORGANIZATION'S STRATEGIC ADVISORY GROUP OF EXPERTS (SAGE)[50]

[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/

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