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VACCINATION



EUROPEAN FEDERATION
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Vaccination and the immune system

How do vaccines work?

Vaccination involves the introduction into the body of entire microorganisms (pathogens) or part of them, which are presented to the cells of the immune system that learns to recognize and fight them during infection. Traditional vaccines contain viruses and bacteria that have been (a) killed-inactivated, (b) attenuated (weakened) or (c) otherwise modified to produce immunity to a specific infectious disease or diseases by stimulating, for instance, the production of antibodies.

Immunity is the body's successful defence against a pathogen. When a person is exposed to a disease, the immune system attempts to fight against it by producing antibodies and highly specific cells that can target the pathogen. When someone has produced sufficient antibodies to fight the disease, immunity results, providing protection against the disease for many months, for years or even for a lifetime. If someone later comes into contact again with that same pathogen, antibodies circulating in the bloodstream begin to increase, either preventing the disease from developing or decreasing its severity, while antibodies and highly specific cells can eliminate the pathogen from the body. Through "immunological memory", it is estimated that the immune system can remember or recognise and effectively combat hundreds of thousands, possibly millions, of different organisms.



Classic or traditional types of vaccines:

- **Live-attenuated (weakened) vaccines** - contain modified strains of a pathogen (bacteria or viruses) that have been weakened but are able to multiply within the host and remain antigenic enough to induce a strong immune response (e.g., varicella-zoster vaccine, oral poliovirus (OPV) vaccine, or yellow fever virus vaccine).

Heterologous vaccines - a sub-group of live attenuated vaccines is produced from strains that are pathogenic in animals but not in humans. The only example to date is the cowpox virus that protects against smallpox in man.

- **Killed-inactivated vaccines** - bacteria or viruses that are killed or inactivated by chemical treatment or heat (e.g., inactivated poliovirus (IPV) vaccine, pertussis vaccine, rabies vaccine, or hepatitis A virus vaccine).
- **Sub-unit vaccines** - contain a very small part of a microorganism (bacterial or viral), selected for its ability to initiate a specific immune response, which is then isolated and purified (e.g., *Haemophilus influenzae* type b vaccine or acellular pertussis vaccine).

Toxoids - an important sub-group of sub-unit vaccines, like diphtheria toxoid, that contain a chemically modified bacterial toxin that has retained its immunogenic properties, stimulating formation of antibodies that bind and neutralise the corresponding bacterial toxin if encountered on infection with the pathogen.

Vaccinology into the 21st century

During the last twenty years, vaccinology underwent dramatic changes in its biotechnology production methods, some of which include the development of *combination vaccines* (e.g., Diphtheria-Tetanus-Pertussis (DTP), Measles-Mumps-Rubella (MMR), and *protein-conjugated bacterial polysaccharides* against *Haemophilus influenzae* type b (Hib), meningococcal or pneumococcal diseases.

Genetic engineering, one of the greatest discoveries of the 20th century, has contributed to the development of recombinant yeast to produce hepatitis B surface antigen vaccine, as well as antigens for pertussis and cholera vaccines that are produced in bacteria. By isolating the gene coding for a protective protein antigen, the gene that is inserted into the cells of bacterial, yeast, or animal origin can then produce protein in large quantities [1].

Early research into the study of *attenuated vectors* during the 1980s suggested that some naturally or artificially attenuated organisms could carry genetic information from pathogens and, during replication in animals, could transcribe, translate, and present that information to the immune system of the host. Researchers demonstrated that many microorganisms (bacteria, viruses or parasites) could be used as vectors. The *Bacille de Calmette-Guérin* (BCG) against tuberculosis, and attenuated salmonella are two of the most commonly used bacteria. Among the viruses, poxviruses, adenoviruses, alphaviruses and other agents have also undergone investigation [1].



Edible vaccines prepared through the food chain via fruits or vegetables containing antigens are currently being tested against pathogens like *Escherichia coli* or the hepatitis B virus. The challenge in using plant or plant virus recombinants as effective vaccines is to determine "how to stimulate immunity to the antigens or pathogens without breaking tolerance against food antigens" [1].

DNA plasmid technology involves "inserting foreign genetic information into a bacterial plasmid that is expressed on injection into the muscle or skin of the host" [1].

New vaccine research and manufacture: preventive and therapeutic applications

Today, around 80% of the world's vaccines are manufactured in Europe, a region that plays a key role in the research and development of preventive as well as therapeutic vaccines. During the last twenty years, the extraordinary pace of innovative vaccine development has been the result of new knowledge and technology that has emerged from basic research, e.g., use of recombinant DNA and hybridoma technologies.

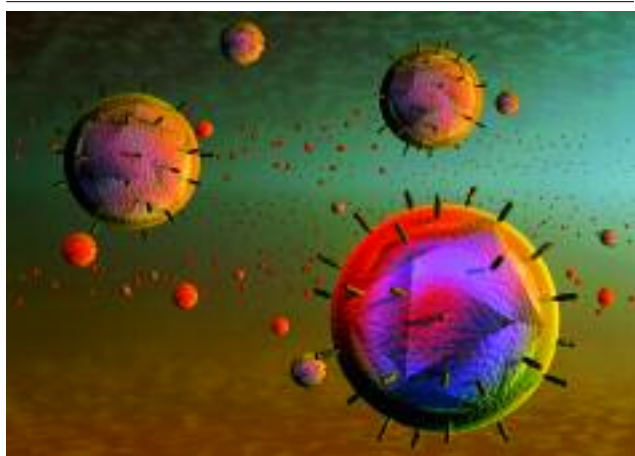
Accelerated vaccine R&D is one of the common goals among vaccine manufacturers, driven primarily by the need to:

- **develop vaccine adjuvants** (agents that are used in vaccine formulations to enhance, modify, prolong or accelerate immune response to vaccine antigens). In addition to gel-type adjuvants, usually prepared from aluminium salts (alum), newer types are being investigated, and include microbial (e.g., bacterial DNA), particulate (e.g., using virosome technology), oil-emulsion and surfactant based, synthetic, cytokines, or genetic adjuvants;
- **ensure compliance** with increased regulatory and safety requirements for vaccine manufacture;
- **develop combination vaccines** to reduce number of injections per visit, and total number of injections overall, resulting in:
 - reduced exposures to possible injection pain;
 - less time spent in doctor visits;
 - less waste and increased injection safety with fewer syringes;
 - reduced immunisation programme costs;
 - improved vaccination coverage and compliance;
 - facilitated introduction of new antigens into existing immunisation programmes;
 - and
 - facilitate data collection through improved documentation.
- **create new vaccine delivery systems:**
 - to reduce patient injection discomfort (e.g., through mucosal, topical or edible vaccines).

Vaccines in the pipeline

The vaccine industry is actively engaged in research and development of new vaccines, including use of DNA plasmid technology and immunotherapy. A number of vaccines in development target diseases that are difficult to treat, such as HIV/AIDS, cancer, Alzheimer's disease, and rheumatic disorders, among others. Pathogens that are currently targeted by vaccines in development include:

- Dengue fever virus
- Hepatitis B virus *
- Hepatitis C virus
- Hepatitis E virus
- Herpes simplex virus
- Human immunodeficiency virus (HIV)
- Human papillomavirus (HPV)
- Influenza virus *
- *Mycobacterium tuberculosis* (the cause of tuberculosis) *
- *Neisseria meningitidis* serogroups A, C, W 135 and Y, through the development of combined tetravalent conjugate vaccines
- *Neisseria meningitidis* serogroup B (the cause of meningococcal B disease)
- *Plasmodium falciparum* (the cause of malaria)
- *Pseudomonas aeruginosa* (infections with this pathogen severely affect the lungs of cystic fibrosis patients)
- Respiratory syncytial virus (RSV), an important airborne virus that causes bronchitis and bronchiolitis
- Rotavirus
- *Streptococcus pneumoniae* *
- Varicella-zoster virus *



Hepatitis C viruses

* While a safe and effective vaccine against this pathogen is already on the market, a newer generation vaccine is also currently in development.

Other new vaccine technology developments in Europe

- Further development of new adjuvants;
- A new production technology for developing influenza vaccines based on cell cultures. (Traditional influenza vaccines require chicken eggs for producing the vaccine. Using readily available cell cultures should make it possible to start up vaccine production at any time, independent of the availability of eggs.);
- Development of a new improved vaccine delivery system that will painlessly deliver vaccines into the skin, without needles, as dry powder formulations;
- A third-generation hepatitis B vaccine containing two new antigenic regions of the virus envelope included in the currently marketed second-generation vaccines;
- A new vaccine product for combined immunisation against measles, mumps and rubella (MMR), produced entirely in the human diploid cell culture strain; and
- Development of new orally administered live-attenuated bacterial vaccines for immunisation against gastrointestinal diseases.

What vaccination has achieved: success stories

Vaccination has safely and effectively prevented more disease and death due to infectious agents than any other public health intervention, aside from improved sanitation and provision of clean water [2]. Among the various international disease eradication programmes that were launched during the 20th century, the only programme that has been successful so far has been vaccine-based – the eradication of smallpox. Global elimination of polio could be a second possible achievement within the next decade [3].

Eradication of smallpox

The eradication of smallpox is one of the greatest achievements in the history of vaccinology. At the end of the 18th century, approximately 400,000 people a year were dying in Europe from smallpox infection, one of the most highly contagious and virulent diseases to affect humans. It is estimated that smallpox was responsible for between 8% and 20% of all deaths during the 18th century, also causing complications that increased the probability of death from other types of diseases [4].

Controlling smallpox with widespread vaccination measures during the 19th and 20th centuries resulted in eventual elimination of the disease. In 1980 the World Health Assembly announced that smallpox had been eradicated worldwide. While a number of factors were important, smallpox eradication would not have been possible without widespread vaccination.

Smallpox is not only of historical interest, but also of current concern regarding the possible deliberate release of biological agents, such as the smallpox virus, through acts of terrorism or war. Many new challenges confront the vaccine industry, not least of which are potential biological threats that will require heavy demands on vaccine production and supply in order to protect those who are potentially at risk or directly exposed to biological attack.

Progress in eliminating polio

Eradication of wild poliovirus from the Western hemisphere is also largely due to immunisation. The World Health Organization declared the region of the Americas polio-free in 1991 and, more recently, the European Region was declared polio-free in June 2002. As polio eradication efforts accelerate, the number of countries that are free of polio continues to increase. Since 1988, the number of polio cases in the world has decreased by more than 99%, from an estimated 350,000 to less than 1,000 each year.

In parallel with world polio immunisation programmes is ongoing and intensive research into the virological and immunological aspects of polio. Polio research has contributed to major scientific breakthroughs, such as reassembling the poliovirus from its constituents in a cell-free test-tube system, and has contributed significantly to the knowledge of other types of viruses.

Childhood immunisation: impact of conjugate vaccines on paediatric disease

Certain bacteria that cause some diseases (e.g., pneumococcal pneumonia, certain types of meningitis, and invasive Hib disease) have an outer coating of polysaccharide, which is the primary factor for virulence of the pathogen. This coating allows the pathogen to escape attack by specialised cells of the immune system, and it also cannot be recognised by the immune system of children under the age of two years. Older, traditional polysaccharide vaccines were not effective in eliciting protective antibodies against these bacteria among children under the age of two years. A major challenge for vaccine manufacturers was to develop a vaccine in which a protein is chemically linked (i.e., conjugated) to the purified polysaccharides of the outer coating of the disease-causing bacteria. The immune system responds appropriately to the antigen once it has been chemically linked to the protein.

The first conjugate vaccine was developed in the 1980s against *Haemophilus influenzae* type b (Hib). Invasive Hib disease can be fatal in a small percentage of children (<5%), and can lead to complications such as meningitis and epiglottitis that can cause long-term neurological disability. Through appropriately elevated vaccine coverage levels among infants and children, invasive Hib disease has been virtually eliminated within several industrialised countries.

1796	Smallpox (live-attenuated)*
1885	Rabies (killed-inactivated)*
1896	Cholera (killed-inactivated)* Typhoid (killed-inactivated)*
1923	Diphtheria (D) (toxoid)
1926	Pertussis (Pw), whole cell (killed-inactivated)
1927	Tetanus (T) (toxoid) Tuberculosis (BCG) (live-attenuated)
1928	Yellow fever (live-attenuated)
1936	Influenza (killed-inactivated)*
1937	Tickborne encephalitis (killed-inactivated)*
1945	Japanese B encephalitis (killed-inactivated)
1955	Polio (IPV) (killed-inactivated)
1957	DTPw
1958	Polio (OPV), oral polio vaccine (live-attenuated)
1961	DT-IPV
1963	Measles (M) (live-attenuated)
1966	DTPw-IPV
1967	Mumps (M) (live-attenuated)
1969	Rubella (R) (live-attenuated)
1970	MMR
1974	Meningococcal disease (serogroup A – polysaccharide)
1975	Meningococcal disease (serogroup C – polysaccharide) Meningococcal disease (serogroups A&C – polysaccharide)
1976	Pneumococcal disease (14 serotypes – polysaccharide)
1981	Typhoid (live-attenuated)* Hepatitis B (HB) (protein) Pertussis acellular (Pa)
1983	Pneumococcal disease (23 serotypes – polysaccharide)
1984	Varicella-zoster (live-attenuated)
1985	HB (protein/recombinant DNA)
1986	Influenza (subunit)
1988	Haemophilus influenzae type b (Hib) (polysaccharide-protein conjugate) Typhoid (polysaccharide)
1991	Hepatitis A (HA) (killed-inactivated)
1992	DTPw-IPV-Hib
1993	DTPa
1994	HA (subunit, adjuvanted)
1996	DTPw-HB HB-HA
1997	DTPa-Hib DTPa-IPV-Hib
1997	Influenza (subunit, adjuvanted)
1999	DTPa Meningococcal disease (serogroup C – polysaccharide-protein conjugate)
2000	HA-Typhoid (polysaccharide) DTPa-IPV DTPa-IPV-HB DTPa-IPV-HB-Hib Pneumococcal disease (7 serotypes – polysaccharide-protein conjugate)
2001	Pseudomonal disease (8 serotypes – polysaccharide-protein conjugate)
2003	Influenza (live-attenuated) Meningococcal disease (serogroups ACW – polysaccharide)
2004	Rotavirus (live attenuated)

*A newer vaccine is available

Introduction of vaccines: historical time-line

Development of the Hib conjugate vaccine paved the way for development of other conjugate vaccines to protect children under the age of two years from meningococcal and pneumococcal diseases.

In November 1999, the United Kingdom was the first country in the world to license and market *meningococcal C conjugate vaccines*. Beginning in 1999, the UK carried out an extensive immunisation campaign against meningococcal disease, which resulted in a 90% reduction of the disease among infants, children, and adolescents who received the new meningococcal C conjugate vaccine.

In February 2000, a *pneumococcal conjugate vaccine* against invasive pneumococcal disease was first licensed in the United States, and in Europe in 2001, providing protection for the first time to young children, and hampering the carriage and blocking the transmission of the invasive strains of the *S. pneumoniae* bacteria.

- In developing countries, pneumococcal disease causes approximately 1.2 million deaths of young children annually, mainly due to pneumonia [5]
- In industrialised countries, the incidence of invasive pneumococcal disease (meningitis and bacteraemia) is as high as 250 cases per 100,000 in children less than two years of age [6]
- In Europe, *S. pneumoniae* bacteria are responsible for 25% to 50% of bacterial meningitis in children [7].

Positive impact of vaccination programmes: Examples - United Kingdom

Tables 1 and 2 show the dramatic reductions in death and disease in the United Kingdom following the introduction of vaccines in UK public health programmes.

Disease	Diphtheria		Tetanus		Pertussis		Hib meningitis**	
Year	1939*	1996	1960*	1996	1956*	1996	1991*	1996
Number of cases (all ages)	47,061	12	NA***	8	94,410	2,387	417	38
Number of deaths (all ages)	2,133	0	32	0	92	2	22	0

*Last year before vaccination, ***Haemophilus influenzae* type b meningitis, ***Not a notifiable disease until 1968
Sources: Office for National Statistics, Public Health Laboratory Service

TABLE 1 Incidence of diphtheria, tetanus, pertussis (whooping cough), and Hib meningitis in the United Kingdom prior to and following the introduction of vaccination

Disease	Measles		Mumps**		Rubella**		CRS***		TB	
Year	1967*	1996	1989*	1996	1989*	1996	1971*	1996	1952*	1996
Number of cases (all ages)	460,407	5,613	20,713	1,924	14,750	9,081	162	21	48,093	5,859
Number of deaths (all ages)	99	0	0	0	2	0	0	0	10,590	420

*Last year before vaccination, **1989 was the first full year of notification for mumps and rubella, ***Cases of congenital rubella syndrome and terminations related to rubella infection
Sources: Office for National Statistics, Public Health Laboratory Service

TABLE 2 Incidence of measles, mumps, rubella (German measles), congenital rubella syndrome (CRS), and tuberculosis (TB) in the United Kingdom prior to and following the introduction of vaccination

Adults and travellers' vaccines

Vaccination can help the elderly to avoid influenza and pneumococcal disease. Influenza virus infection is so closely associated with pneumococcal disease in older people, that influenza prevention is one of the main strategies available in preventing

pneumococcal pneumonia. In addition, vaccination with pneumococcal polysaccharide vaccine is also recommended in many countries for the elderly in whom the disease remains a major cause of morbidity and mortality.

Vaccines are also available to those travelling to countries where the risk of typhoid, hepatitis A and hepatitis B, and certain strains of meningococcal meningitis is high, as well as for polio, diphtheria and yellow fever.

Addressing the needs of developing countries

There are still many challenges that need to be overcome before all people benefit from vaccinations protecting them against infectious diseases. Access to immunisation varies greatly across the world. A child in a developing country is ten times more likely to die of a vaccine-preventable disease than a child from an industrialised country. In some areas of the world, up to 70% of children do not receive the full set of paediatric immunisations: the lowest coverage is found in sub-Saharan Africa. In Africa as a whole, over 40% of children are not immunised against measles, a major cause of infant mortality that kills a child each minute.

A number of factors combine to challenge vaccination efforts – including lack of funding, political priorities, lack of adequate health care infrastructure, and missed immunisation opportunities for mobile populations and those caught up in wars.

What industry is doing

The European vaccine industry is the largest supplier to UNICEF of vital paediatric vaccines, including polio vaccines. The successful development of novel vaccines like those against tropical diseases requires extensive collaboration between scientists and institutions, usually in the disease-endemic countries and the vaccine industry. To that end, the European vaccine industry is working in partnership with the public sector in joint R&D activities, in clinical trials partnerships, and in cooperation with international vaccine distributors and other non-governmental organisations.

R&D

- International Aids Vaccine Initiative (IAVI)
- Malaria Vaccine Initiative (MVI)
- The African Malaria Vaccine Testing Network / African Malaria Network (AMVTN / AMNET)
- Children's Vaccine Program (CVP) at PATH (Program for Appropriate Technology in Health)
- National Institutes of Health (NIH)
- Centers for Disease Control and Prevention (CDC)
- US Agency for International Development (USAID)

Procurement & delivery

- United Nations Children's Fund (UNICEF)
- World Health Organization (WHO)
- Global Alliance for Vaccines and Immunization (GAVI)
- Pan American Health Organization (PAHO)

Vaccine R&D for developing countries

While R&D for an HIV/AIDS vaccine is a major undertaking, other vaccines are being developed for diseases that particularly burden developing countries, such as dengue fever, leishmaniasis, rotavirus, malaria, and tuberculosis, among others. The European vaccine industry has also developed vaccines specifically designed for the needs of developing countries, such as combined paediatric vaccines against diphtheria, tetanus, pertussis, hepatitis B and invasive Hib disease.



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