17 Vaccines and vaccination

history and present developments

The word vaccination literally means: (in)oculation with cow pox (vacca = cow). Since nowadays dozens of vaccines are around, this term is rather old fashioned now. A better term is: Actively evoked immunity'. The principle: adminstration of a (part of an) antigen of a micro organism, or the whole killed or attenuated organism, in order to arouse an immune reaction, without provoking the real disease. Several components can be administered theoretically, but in practice the choice is often restricted. And this has consequences for the possible side effects and for the response to the vaccine. See table.

Table: Vaccine components (source: Hui95).

Component	**Bacterial infection**	**Viral infection**
Live attenuated	tuberculosis, typhoid [1]	mumps (NL; bof), meazles, rubeola (NL: BMR); poliomyelitis [1], yellow fever
Killed or inactivated		
Whole micro-organisms	Pertussis, typhoid [2]	hepatitis A, influenza, poliomyelitis [2]
subunit vaccines		influenza, hepatitis B
soluble capsular polysaccharides	Pneumococcal and meningococcal infections, infections by *Haemophilus influenzae* type b	
conjugated capsular polysaccharides	infecties door *Haemophilus influenzae* type b	
Recombinant DNA-vaccine		hepatitis B
Toxoid	diphtheria, tetanus	

[1] parenteral (injection) vaccine; in NL for typhoid as well as poliomyelitis (Salk vaccine)

[2] oral vaccine; in NL only for typhoid, not for poliomyelitis (Sabin vaccine).

As long as a millennium ago this principle was already applied in China against a dreaded viral infection: smallpox. Finely ground not-too-fresh pox crusts were blown high up into the nose of the vaccinee, after which mostly a moderate form of smallpox occurred. It was stated that less than one in one hundred vaccinees died from the preventive measure. That is quite different from the real smallpox, that everyone met in his life and that killed about 30 percent of the patients. In India the method was changed into bringing pox material into a scratch in the under arm. The Arab Medicine spread the method to Constantinople, North-Africa, and

deeper into Africa. In Turkey the wife of the British ambassador got acquainted with the variolation and introduced it into Western-Europe (1721). However, also by other roads the ‘oculation’ reached the West.

More on the fascinating small pox story can be read in the smallpox article in the appendices.

In the second half of the nineteenth century both Koch and Pasteur succeed in producing a vaccine against the bacterium that causes anthrax in cattle. Moreover Pasteur develops a vaccine against the virus that causes rabies. After that the race is on. Much of the suffering caused by children’s diseases can be banned by vaccinations. The child mortality that was so high in the Europe of the nineteenth century (when your great grandparents were born) dwindled. For instance Behring and Roux developed an anti diphtheria vaccine, that yearly saved the lives of ten thousands of children.

But there are also setbacks. Koch promises a vaccine against the tuberculosis bacterium that he detected in 1881. He does not succeed. And even the present day BCG vaccine against tuberculosis is not a real success, it protects only about 30 percent of the vaccinees. And there are more vaccines that after a long period of trying still are not satisfying (see table).

A number of frequently occurring infectious diseases urge us to expand our arsenal. But despite our extended knowledge of the structure and functions of micro organisms on the one hand and the our immune system on the other hand, it is a tough struggle. In the following table a number of candidates are mentioned. They impose a large disease burden, just like some diseases mentioned in the last table in association with a bad or moderate vaccine. (data about them are partially in the table).

Table: The present vaccines that are generally distributed in NL, the microorganisms they abate, the target population, and the effectiveness. Italics = bacteria. The first eight are distributed in the National Vaccination Programme (NL: het Rijksvaccinatieprogramma (RVP)) for children aged 0 and 1 year. The first five in NL: DKTP/Hib and the last three: BMR. (source: Hui95, Eve92).

Disease	**Micro-organism**	**Target population**	**Effectiveness**
Diphtheria	*Corynebacterium diphtheriae*	babies; booster for adults	Very good
Pertussis (NL: kinkhoest)	*Bordetella Pertussis*	babies	Moderate and much debated
Tetanus	*Clostridium tetani*	babies; booster for adults	Very good
Poliomyelitis	polio virus	babies; booster for adults	Very good
Invasive haemo-philus-afflictions (e.g. meningitis)	*Haemophilus influenzae* type b (Hib)	babies	Very good
Mumps (NL: bof)	mumps virus	1 year old	Very good
Measles	measles virus	1 year old	Very good
Rubella (NL: rode hond)	rubella virus	1 year old	Very good
Influenza (NL: griep)	influenza virus	The elderly, ill people	Moderate; changing epidemical types and no full protection
Tuberculosis (Bacille Calmette/Guerin: BCG)	*Mycobacterium tuberculosis*	The professionaly exposed (medical personell); travellers	poor (mopreover future diagnostics are disturbed)
Pneumococcal infections (pneumonia, septicaemia, meningitis)	*Streptococcus pneumoniae*	The elderly, the ill, and people without spleen (NL: milt)	Rather poor (reponse varying and many sero-types not in vaccine)
Yellow fever	Yellow fever virus	Travellers	Very good
Rabies	rabies virus	The exposed (after bite of e.g. dog, fox or bat)	Very good
Cholera	*Vibrio cholerae*	travellers	Very poor
Typhoid	*Salmonella typhi*	Travellers	moderate (several pathogenic types)
Hepatitis A	hepatitis A virus (HAV)	Travellers	Very good
Hepatitis B	hepatitis B virus (HBV)	The professiomnally exposed (medical personell)	Very good
Meningococcal infections (e.g. meningitis, septicaemia)	*Neisseria meningi-tidis* serogroups A, C, W en Y	Travellers	good (however: in NL mainly infections by serogroup B)
Varicella (NL: waterpokken	varicella virus and later (exacerbation) herpes zoster virus	in the future to all babies together with BMR ?	Good; but in Nederland not yet approved)

Table: Vaccines that are wanted but do not (yet) exist. Some will prove to be never attained. Disease, causal organism, and problems met in vaccine research (source: Eve92).

Disease	**Causal organism**	**Problems met in vaccine research**
Leprosy (NL: melaatsheid)	Mycobacterium leprae	Akin to tuberculosis: poor reponse to bacterial antigenes
AIDS (Acquired Immunodeficiency Syndrome)	Humane Immunodeficiency virus (HIV)	Hypervariability of the protein capsule; the virus activates continuously different parts of its genome and the changing expression confuses the immune system. Moerover: mutations. Antibodies are fast out of date
Malaria	Severel types of plasmodium	Similar to HIV: hypervariability of the surface of this parasite. Antibodies can quickly render useless
Gonorrhea	*Neisseria gonorrhoeae*	Mainly a mucous membrane infection. Vaccines will only be affective agains invading bacteria
Syphilis	*Treponema pallidum*	Poor response to the presented antigen
Worm diseases	Several worms	Extremely diverse range of antigens
Caries	Several bacteria in the mouth	There exist many caries stimulating bacteria. Moreover this is a superficial process and a vaccine will mainly act against invading bacteria
Cervical carcinoma	Genital humane papilloma virus (HPV)	Only some of the >80 types (particularly 16 en 18) are supposed to cause cell degeneration which degenerates into cancer

Particularly for developing countries it is of great importance that accelerated development of vaccines takes place. And this should also be the case for other strategies against diseases that nowadays are still a large burden, especially for children. In 1988 an 'International Task Force for Disease Eradication' (ITFDE) was founded (WHO: EPI). This organization aims at the eradication of some important infectious diseases, as has already been the case with smallpox. The infectious diseases have to meet a few conditions for this favour.

- What are the transmission routes?
- Are there reservoirs outside man?
- Is the abatement safe and affordable?

Is the disease severe enough to arouse broad political and financial support for the eradication efforts?

In the following two tables we see respectively eight general infectious diseases that are chosen by ITFDE and seven children's diseases that are it's target. By the way: a disease is a children's disease if:

- The transmission and spreading occur very effectively and acquaintance takes place at young age.
- The affliction evokes a strong response from the immune system.
- The acquired immunity lasts long or even life long.

In the table there is only for three of the eight diseases/clusters a good vaccine available (hepatitis B, rabies, and yellow fever) and for one a bad vaccine (tuberculosis). The next table renders more optimism: against all seven of these children's diseases there is a good vaccine. However, as we already saw in the case of smallpox:, vaccination is only one of the means to reach eradication. For, as a matter of fact, the immunization of all individuals is nice, but if one succeeds to destroy the source, then that is even nicer. In the case of tetanus or rabies the reservoirs are so enormous that this will never succeed but , for instance, in the case of leprosy there is a chance.

The WHO and the ITFDE hope to eradicate the polio virus and the Guinea worm in the foreseeable future. With some optimism they added mumps, rubella, and hepatitis A to that list in the beginning of the nineties. Hepatitis B, endemic syphilis (and other treponematoses) and neonatal tetanus is considered not to be eliminable but constrainable in the near future. In the case of onchocerciasis it is expected that the dreaded river blindness will be preventable and rabies is foreseeably banned from urban areas. More somber are the perspectives concerning tuberculosis (especially now that AIDS so much fuels this disease, particularly in Africa), leprosy, yellow fever, measles, diphtheria, and whooping cough.

Table: Nine infectious diseases which are candidate for world wide eradication (IFTDE) (source: CDC, MMWR 1990, 1992).

Disease	**Global morbidity and mortality per year**	**Main obstructions**	**Conclusion**
Dracontiasis (Guinea worm)	10 millon persons infected; low mortality	Lack of public and political interest; lacking funds	Eradication feasible
Onchocerciasis (river blindness)	18 million ill; 340,000 blinds	Vector control is expensive; adult worms cannot be killed	Blindness can be prevented by treatment of the patients
Endemic syphilis & other trepo-nematoses	2,5 million cases	Neglected by politicians and financers	The chain of transmissions is to be interrupted
Hepatitis B	250,000 deaths per year	Many carriers, prenatal infection; general vaccination of children would be urged (vaccine = ok)	Not yet eradicable; possibly feasible in next decades
Rabies	52,000 deaths	No effective method of administration of the (good) vaccine to contaminated wild animals	in urban areas eradicable
Tuberculosis	8-10 million new cases; 2-3 million deaths	In need of better diagnostic tests, chemotherapy en vaccines; broader implementation of present therapy	Not eradicable now
Leprosy	11-12 million cases	In need of better diagnostic tests and chemotherapy; social stigma; potential reservoir in armadillo's	nu niet uit te roeien
Yellow fever	> 10,000 deaths	Sylvatic reservoir; vaccine good but not heat resistent	nu niet uit te roeien
Hepatitis A	Tens of millions cases/ jaar; low case fatality rate	Survives long in water; there is a good vaccine	Possibly eradicable by mass vaccination

Table: Seven pediatric infections which are candidate for world wide eradication (IFTDE). (source: CDC, MMWR 1990, 1992).

Disease	**Mondial morbidity and mortality / year**	**Main obstructions**	**Conclusion**
poliomyelitis [1]	250,000 paralysis cases; 25,000 deaths	Technically possible; more involvement is still needed	eradicable
mumps [2]	Not known	Lack of data in developing countries; diagnostics are difficult	potentially eradicable
Rubella [3]	Not known	Lack of data in developing countries; diagnostics are difficult	potentially eradicable
Neonatal tetanus	770,000 deaths	Endless reservoir in Nature	Not eradicable now; transmission might be eliminated
measles [4]	2 million deaths, mainly children	Effective vaccine for the (very) young is still lacking; high costs; underestima-tion of severity by the public	Not eradicable now
diphtheria	Not known	Difficult diagnosticse met meerdere doses; veel dragers	Not eradicable now
pertussis (kinkhoest)	60 million ill and 700,000 deaths	Very contagious; infections at young age; vaccination with several doses	Not eradicable now

1. most infections are in young children; the serious complications and sequelae (NL: restverschijnselen) are in elder children and adults.
2. pediatric infection that eventually for boys leads to infertility in adult life.
3. pediatric infection, but potentially damaging the embryo of infected women during the first three months of pregnancy.
4. virtually always a disease of young children; more serious course in elder children and adults.