Principles of vaccination
vaccination stimulates protective adaptive immune response – this priming expands the pool of specific memory cells
subsequent natural infection induces fast, vigorous responses
harmless forms of the immunogen are used to vaccinate – these can be killed or modified living organisms, subcellular fragments, or toxoids
vaccine adjuvants enhance immune responses
vaccines must be safe, affordable, and produce herd immunity

Figure 18.1 Principles of vaccination.

The main antigenic preparations

type of antigen		vaccine examples
living organisms	natural	vaccinia (for smallpox) vole bacillus (for tuberculosis; historical)
	attenuated	polio (Sabin; oral polio vaccine)*, measles*, mumps*, rubella*, yellow fever 17D, varicella-zoster (human herpesvirus 3), BCG (for tuberculosis)*
intact but non-living organisms	viruses	polio (Salk)*, rabies, influenza, hepatitis A, typhus
	bacteria	*pertussis, typhoid, cholera, plague
subcellular fragments	capsular polysaccharides	pneumococcus, meningococcus, *Haemophilus influenzae*
	surface antigen	hepatitis B*
toxoids		tetanus*, diphtheria*
recombinant DNA-based	gene cloned and expressed	hepatitis B (yeast-derived)*
	genes expressed in vectors	experimental
	naked DNA	experimental
anti-idiotype		experimental

*standard in most countries

Figure 18.2 A wide range of antigenic preparations are used as vaccines.

Live attenuated vaccines

disease		remarks
viruses	polio	types 2 and 3 may revert; also killed vaccine
	measles	80% effective
	mumps	
	rubella	now given to both sexes
	yellow fever	stable since 1937
	varicella-zoster	mainly in leukemia
	hepatitis A	also killed vaccine
bacteria	tuberculosis	stable since 1921; also some protection against leprosy

Figure 18.3 Attenuated vaccines are available for many, but not all, infections. In general it has proved easier to attenuate viruses than bacteria.

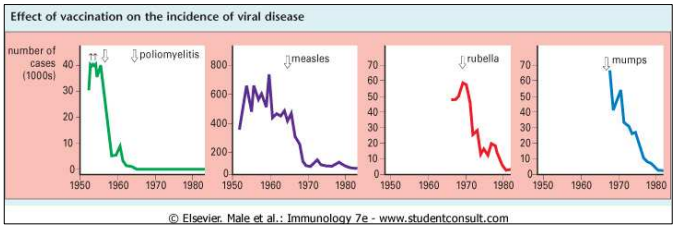

Figure 18.4 The effect of vaccination on the incidence of various viral diseases in the USA has been that most infections have shown a dramatic downward trend since the introduction of a vaccine (arrows).

Killed (whole organism) vaccines

disease		remarks
viruses	polio	preferred in Scandinavia; safe in immunocompromised
	rabies	can be given post-exposure, with passive antiserum
	influenza	strain-specific
	hepatitis A	also attenuated vaccine
bacteria	pertussis	potential to cause brain damage (controversial)
	typhoid	about 70% protection
	cholera	protection dubious; may be combined with toxin subunit
	plague	short-term protection only
	Q fever	good protection

Figure 18.5 The principal vaccines using killed whole organisms.

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Toxin-based vaccines

organism	vaccine	remarks
Clostridium tetani	inactivated toxin (formalin)	three doses, alum-precipitated; boost every 10 years
Corynebacterium diphtheriae		usually given with tetanus
Vibrio cholerae	toxin, B subunit	sometimes combined with whole killed organisms
Clostridium perfringens	inactivated toxin (formalin)	for newborn lambs

Figure 18.6 The principal toxin-based vaccines. Note that there are no vaccines against the numerous staphylococcal and streptococcal exotoxins, or against bacterial endotoxins such as lipopolysaccharides.

Subunit vaccines

	organism	remarks
virus	hepatitis B virus	surface antigen can be purified from blood of carriers or produced in yeast by recombinant DNA technology
bacteria	*Neisseria meningitidis*	capsular polysaccharides or conjugates of group A and C are effective; group B is non-immunogenic
	Streptococcus pneumoniae	84 serotypes; capsular polysaccharide vaccines contain 23 serotypes; conjugates with five or seven bacterial serotypes are being tested
	Haemophilus influenzae B	good conjugate vaccines now available

Figure 18.7 Conjugate vaccines are replacing pure polysaccharides. N. meningitidis type B is non-immunogenic in humans because the capsular polysaccharide cross-reacts with self carbohydrates towards which the host is immunologically tolerant.

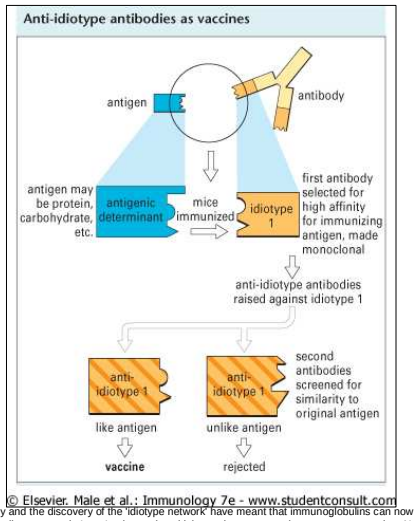

Figure 18.8 Monoclonal antibody technology and the discovery of the 'idiotype network' have meant that immunoglobulins can now be used as 'surrogate' antigens. In the case of a carbohydrate or lipid antigen, this allows a protein 'copy' to be made, which may have some advantages as a vaccine. Note also that a monoclonal anti-idiotype can act as a mimic of a discontinuous B cell epitope.

Adjuvants

adjuvant type	routinely used in humans	experimental* or too toxic for human use†
inorganic salts	aluminum hydroxide (alhydrogel) aluminum phosphate calcium phosphate	beryllium hydroxide
delivery systems		liposomes* ISCOMs* block polymers slow-release formulations*
bacterial products	*Bordetella pertussis* (with diphtheria, tetanus toxoids)	BCG *Mycobacterium bovis* and oil† (complete Freund's adjuvant) muramyl dipeptide (MDP)†
natural mediators (cytokines)		IL-1 IL-2 IL-12 IFNγ
ISCOMs, immune-stimulating complexes		

Figure 18.9 A variety of foreign and endogenous substances can act as adjuvants, but only aluminum and calcium salts and pertussis are routinely used in clinical practice.

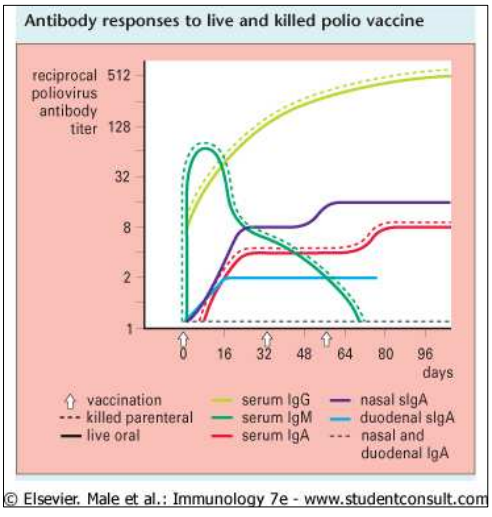

Figure 18.10 The antibody response to orally administered live attenuated polio vaccine (solid lines) and intramuscularly administered killed polio vaccine (broken lines). The live vaccine induces the production of secretory IgA (sIgA) in addition to serum antibodies, whereas the killed vaccine induces no nasal or duodenal sIgA. As sIgA is the immunoglobulin of the mucosa-associated lymphoid tissue (MALT) system (see Chapter 2), the live vaccine confers protection at the portal of entry of the virus, the gastrointestinal mucosa. (Courtesy of Professor JR Pattison, Ch. 26 in Brostoff J, et al., eds. Clinical immunology. London: Mosby; 1991)

Safety problems with vaccine

type of vaccine	potential safety problems	examples
attenuated vaccines	reversion to wild type	especially polio types 2 and 3
	severe disease in immunodeficient patients	vaccinia, BCG, measles
	persistent infection	varicella-zoster
	hypersensitivity to viral antigens	measles
	hypersensitivity to egg antigens	measles, mumps
killed vaccines	vaccine not killed	polio accidents in the past
	yeast contaminant	hepatitis B
	contamination with animal viruses	polio
	contamination with endotoxin	pertussis

Figure 18.11 The potential safety problems encountered with vaccines emphasize the need for continuous monitoring of both production and administration.

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Vaccines in general use

disease	vaccine	remarks
tetanus diphtheria pertussis polio (DTPP)	toxoid toxoid killed whole killed (Salk) or attenuated (Sabin)	given together in three doses between 2 and 6 months; tetanus and diphtheria boosted every 10 years
measles mumps rubella	attenuated	given together (MMR) at 12–18 months
Haemophilus influenzae type b	polysaccharide	new; may be given with DTPP

Figure 18.12 Vaccines that are currently given, as far as is possible, to all individuals.

Vaccines restricted to certain groups

disease	vaccine	eligible groups
tuberculosis	BCG	tropics – at birth; UK – 10–14 years; USA – at-risk only
hepatitis B	surface antigen	at risk (medical, nursing staff, etc.); drug addicts; male homosexuals; known contacts of carriers
rabies	killed	at risk (animal workers); postexposure
meningitis yellow fever typhoid, cholera hepatitis A	polysaccharide attenuated killed or mutant killed or attenuated	travelers
influenza	killed	at risk; elderly
pneumococcal pneumonia	polysaccharide	elderly
varicella-zoster	attenuated	leukemic children

Figure 18.13 Vaccines that are currently restricted to certain groups.

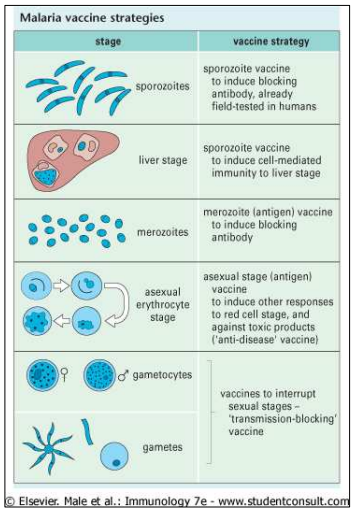

Figure 18.14 A number of different approaches to malaria vaccines are being investigated, reflecting the complexity of both the life cycle of malaria and immunity to it.

Major diseases for which no vaccines are available

	disease	problems
viruses	HIV	antigenic variation; immunosuppression?
	herpes viruses	risk of reactivation? (but varicella-zoster appears safe)
	adenoviruses, rhinoviruses	multiple serotypes
bacteria	staphylococci group A streptococci	early vaccines ineffective (antibiotics originally better)
	Mycobacterium leprae	(BCG gives some protection)
	Treponema pallidum (syphilis)	ignorance of effective immunity
	Chlamydia spp.	early vaccines ineffective
fungi	*Candida* spp. *Pneumocystis* spp.	ignorance of effective immunity
protozoa	malaria	antigenic variation
	trypanosomiasis – sleeping sickness; Chagas' disease	extreme antigenic variation; immunopathology; autoimmunity; trials encouraging
	leishmaniasis	
worms	schistosomiasis	(trials in animals encouraging)
	onchocerciasis	ignorance of effective immunity

Figure 18.15 For some serious diseases there is currently no effective vaccine. The predominant problem is the lack of understanding of how to induce effective immunity.

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Passive immunization

disease	source of antibody	indication
diphtheria, tetanus	human, horse	prophylaxis, treatment
varicella-zoster	human	treatment in immunodeficiencies
gas gangrene, botulism, snake bite, scorpion sting	horse	post-exposure
rabies	human	post-exposure (plus vaccine)
hepatitis B	human	post-exposure
hepatitis A, measles	pooled human immunoglobulin	prophylaxis (travel), post-exposure

Figure 18.16 Although not so commonly used as 50 years ago, injections of specific antibody can still be a life-saving treatment in specific clinical conditions.

Non-specific immunotherapy

source		remarks
microbial	filtered bacterial cultures	used by Coley (1909) against tumors
	BCG	some activity against tumors
cytokines	IFNα	effective for chronic hepatitis B, hepatitis C, herpes zoster, wart virus, prophylactic against common cold (also some tumors)
	IFNγ	effective in some cases of chronic granulomatous disease, lepromatous leprosy, leishmaniasis (cutaneous)
	IL-2	leishmaniasis (cutaneous)
	G-CSF	bone marrow restoration after cytotoxic drugs
cytokine inhibitors	TNF antagonists	septic shock
	IL-1 antagonists	severe (cerebral) malaria?
	IL-10	

G-CSF, granulocyte colony stimulating factor; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor

Figure 18.17 Non-specific stimulation or inhibition of particular components of the immune system may sometimes be of benefit.

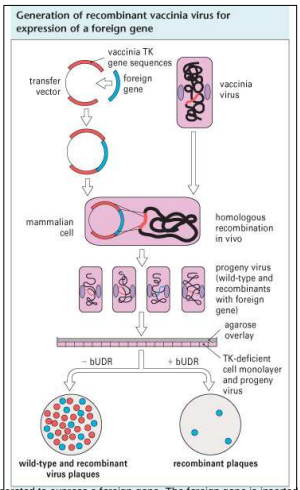

Figure 18.18 Recombinant vaccinia virus can be generated to express a foreign gene. The foreign gene is inserted into vaccinia's thymidine kinase (TK) gene so that recombinant virus plaques can be distinguished from wild-type virus plaques by virus uptake of thymidine from the culture medium or intracellular pool for DNA synthesis; the recombinant virus cannot produce TK, because the gene has been interrupted and so must use the separate pathway for de-novo synthesis of thymidine. In the presence of bromodeoxyuridine (bUDR), a thymidine analog that blocks DNA synthesis when it is incorporated into DNA, wild-type virus replication is blocked but recombinant virus replication continues, using de-novo synthesis of thymidine. The cell monolayer must be TK deficient so that recombinant virus cannot use the cells' TK to take up bUDR. (Courtesy of Dr DJ Rowlands, Ch. 26 in Brostoff J., et al., eds. Clinical Immunology, London: Mosby; 1991)