Vaccination

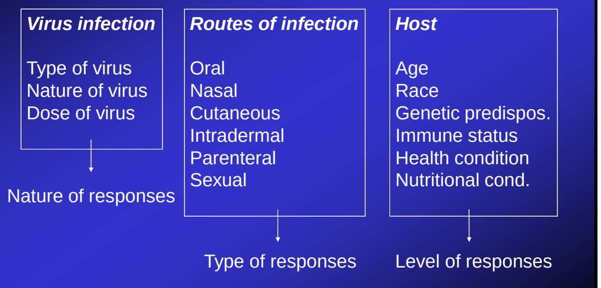
- Vaccination:
  - Practice of artificially inducing immunity
- Goal of vaccination:
  - Stimulate both cell mediated and antibody mediated immunity that will protect the vaccinated person against future exposure to pathogen
  - Want the vaccine to have:
    - Maximum realism
    - Minimum danger

Three major sites for viral replication

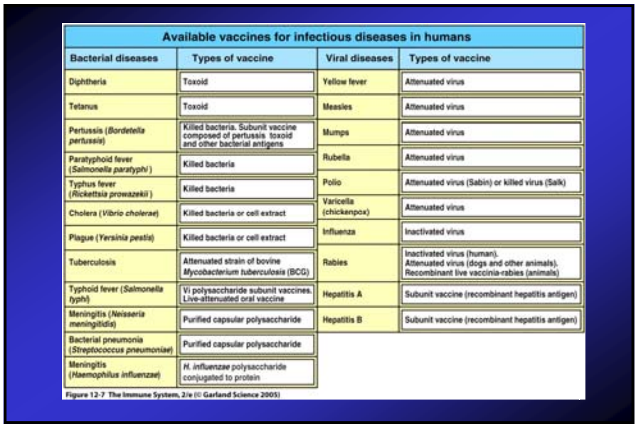
- Mucosal surfaces of respiratory tract and GI tract. **Rhino; myxo; corona; parainfluenza; respiratory syncytial; rota**
- Infection at mucosal surfaces followed by spread systemically via blood and/or neurones to target organs: **picorna; measles; mumps; HSV; varicella; hepatitis A and B**
- Direct infection of blood stream via needle or bites and then spread to target organs: **hepatitis B; alpha; flavi; bunya; rhabdo**

Local immunity via IgA very important in 1 and 2.

Immune mechanisms against viral infection

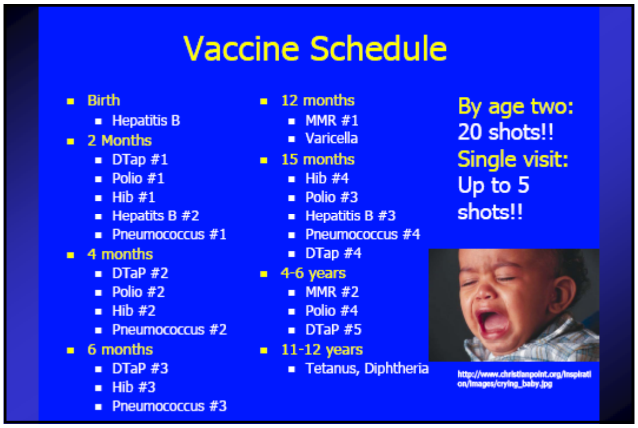


Virus infection	***Routes of infection***	***Host***
Type of virus Nature of virus Dose of virus	Oral Nasal Cutaneous Intradermal Parenteral Sexual	Age Race Genetic predispos. Immune status Health condition Nutritional cond.
Nature of responses	Type of responses	Level of responses



Available vaccines for infectious diseases in humans			
Bacterial diseases	**Types of vaccine**	**Viral diseases**	**Types of vaccine**
Diphtheria	Toxoid	Yellow fever	Attenuated virus
Tetanus	Toxoid	Measles	Attenuated virus
Pertussis (*Bordetella pertussis*)	Killed bacteria. Subunit vaccine composed of pertussis toxoid and other bacterial antigens	Mumps	Attenuated virus
Paratyphoid fever (*Salmonella paratyphi*)	Killed bacteria	Rubella	Attenuated virus
Typhus fever (*Rickettsia prowazekii*)	Killed bacteria	Polio	Attenuated virus (Sabin) or killed virus (Salk)
Cholera (*Vibrio cholerae*)	Killed bacteria or cell extract	Varicella (chickenpox)	Attenuated virus
Plague (*Yersinia pestis*)	Killed bacteria or cell extract	Influenza	Inactivated virus
Tuberculosis	Attenuated strain of bovine *Mycobacterium tuberculosis* (BCG)	Rabies	Inactivated virus (human). Attenuated virus (dogs and other animals). Recombinant live vaccinia-rabies (animals)
Typhoid fever (*Salmonella typhi*)	Vi polysaccharide subunit vaccines. Live-attenuated oral vaccine	Hepatitis A	Subunit vaccine (recombinant hepatitis antigen)
Meningitis (*Neisseria meningitidis*)	Purified capsular polysaccharide	Hepatitis B	Subunit vaccine (recombinant hepatitis antigen)
Bacterial pneumonia (*Streptococcus pneumoniae*)	Purified capsular polysaccharide		
Meningitis (*Haemophilus influenzae*)	*H. influenzae* polysaccharide conjugated to protein		

Figure 12-7 The Immune System, 2/e (© Garland Science 2005)



Vaccine Schedule

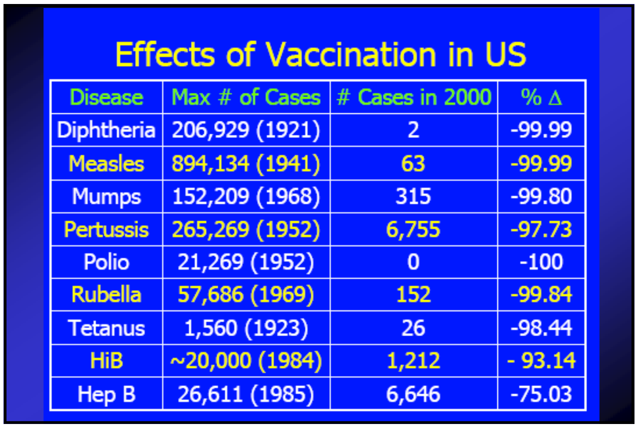
- Birth
  - Hepatitis B
- 2 Months
  - DTap #1
  - Polio #1
  - Hib #1
  - Hepatits B #2
  - Pneumococcus #1
- 4 months
  - DTaP #2
  - Polio #2
  - Hib #2
  - Pneumococcus #2
- 6 months
  - DTaP #3
  - Hib #3
  - Pneumococcus #3
- 12 months
  - MMR #1
  - Varicella
- 15 months
  - Hib #4
  - Polio #3
  - Hepatitis B #3
  - Pneumococcus #4
  - DTap #4
- 4-6 years
  - MMR #2
  - Polio #4
  - DTaP #5
- 11-12 years
  - Tetanus, Diphtheria

By age two:
20 shots!!
Single visit:
Up to 5
shots!!

http://www.christianpoint.org/inspiration/images/crying_baby.jpg

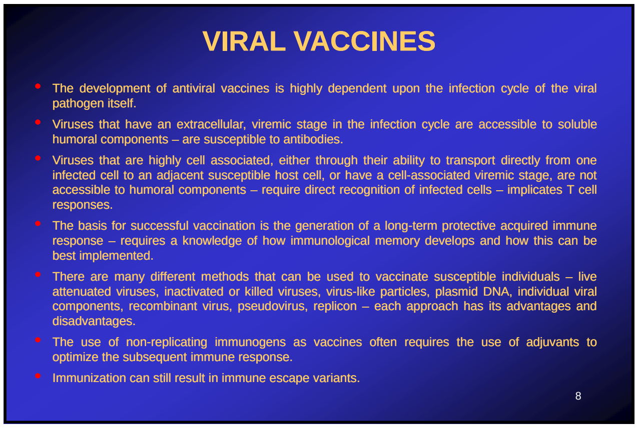
Current licensed vaccines

Virus	Serotypes	Live	Inactivated	Doses	Injection	Attenuation
Adenovirus	2,4,7	+		1	Oral	
Japanese enc.	1	+		2	P	BHK
Measles	1	+		1+R	P	CE
Mumps	1	+		1	P	CE
Polio	1,2,3	+		1	O	MKC
Rotavirus	1,2,3,4	+		3	O	Reassortant RRV
Smallpox	1	+		1	ID	Natural Jenner
Varizella	1	+		1	P	MKC
Yellow fever	1	+		1	P	CE
Hepatitis A	1		+	2	P	
Hepatitis B	1		VLP	3	P	
Influenza	A,B		+	1	P	
Japanese enc.	1		+	3+R	P	
Polio	1,2,3		+	2	P	
Rabies	1		+	x	P	
Tick-borne enc.	1		+	2+R	P	



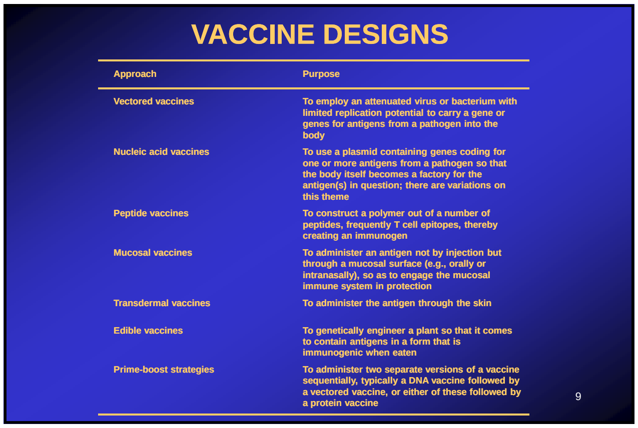
Effects of Vaccination in US

Disease	Max # of Cases	# Cases in 2000	% Δ
Diphtheria	206,929 (1921)	2	-99.99
Measles	894,134 (1941)	63	-99.99
Mumps	152,209 (1968)	315	-99.80
Pertussis	265,269 (1952)	6,755	-97.73
Polio	21,269 (1952)	0	-100
Rubella	57,686 (1969)	152	-99.84
Tetanus	1,560 (1923)	26	-98.44
HiB	~20,000 (1984)	1,212	- 93.14
Hep B	26,611 (1985)	6,646	-75.03



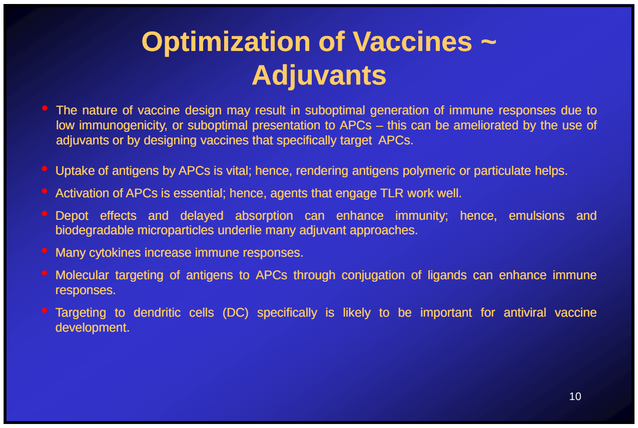
VIRAL VACCINES

- The development of antiviral vaccines is highly dependent upon the infection cycle of the viral pathogen itself.
- Viruses that have an extracellular, viremic stage in the infection cycle are accessible to soluble humoral components – are susceptible to antibodies.
- Viruses that are highly cell associated, either through their ability to transport directly from one infected cell to an adjacent susceptible host cell, or have a cell-associated viremic stage, are not accessible to humoral components – require direct recognition of infected cells – implicates T cell responses.
- The basis for successful vaccination is the generation of a long-term protective acquired immune response – requires a knowledge of how immunological memory develops and how this can be best implemented.
- There are many different methods that can be used to vaccinate susceptible individuals – live attenuated viruses, inactivated or killed viruses, virus-like particles, plasmid DNA, individual viral components, recombinant virus, pseudovirus, replicon – each approach has its advantages and disadvantages.
- The use of non-replicating immunogens as vaccines often requires the use of adjuvants to optimize the subsequent immune response.
- Immunization can still result in immune escape variants.



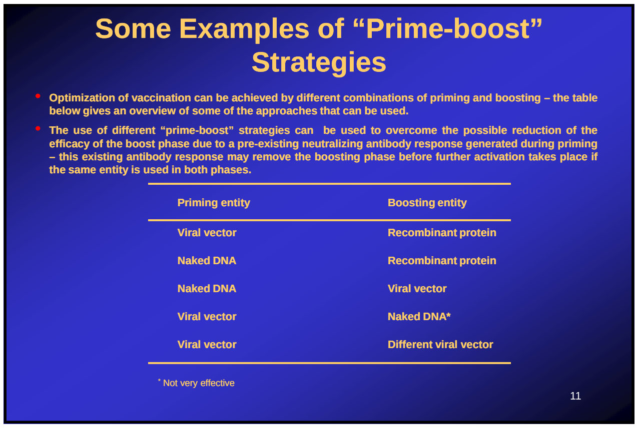
VACCINE DESIGNS

Approach	Purpose
Vectored vaccines	To employ an attenuated virus or bacterium with limited replication potential to carry a gene or genes for antigens from a pathogen into the body
Nucleic acid vaccines	To use a plasmid containing genes coding for one or more antigens from a pathogen so that the body itself becomes a factory for the antigen(s) in question; there are variations on this theme
Peptide vaccines	To construct a polymer out of a number of peptides, frequently T cell epitopes, thereby creating an immunogen
Mucosal vaccines	To administer an antigen not by injection but through a mucosal surface (e.g., orally or intranasally), so as to engage the mucosal immune system in protection
Transdermal vaccines	To administer the antigen through the skin
Edible vaccines	To genetically engineer a plant so that it comes to contain antigens in a form that is immunogenic when eaten
Prime-boost strategies	To administer two separate versions of a vaccine sequentially, typically a DNA vaccine followed by a vectored vaccine, or either of these followed by a protein vaccine



Optimization of Vaccines ~ Adjuvants

- The nature of vaccine design may result in suboptimal generation of immune responses due to low immunogenicity, or suboptimal presentation to APCs – this can be ameliorated by the use of adjuvants or by designing vaccines that specifically target APCs.
- Uptake of antigens by APCs is vital; hence, rendering antigens polymeric or particulate helps.
- Activation of APCs is essential; hence, agents that engage TLR work well.
- Depot effects and delayed absorption can enhance immunity; hence, emulsions and biodegradable microparticles underlie many adjuvant approaches.
- Many cytokines increase immune responses.
- Molecular targeting of antigens to APCs through conjugation of ligands can enhance immune responses.
- Targeting to dendritic cells (DC) specifically is likely to be important for antiviral vaccine development.

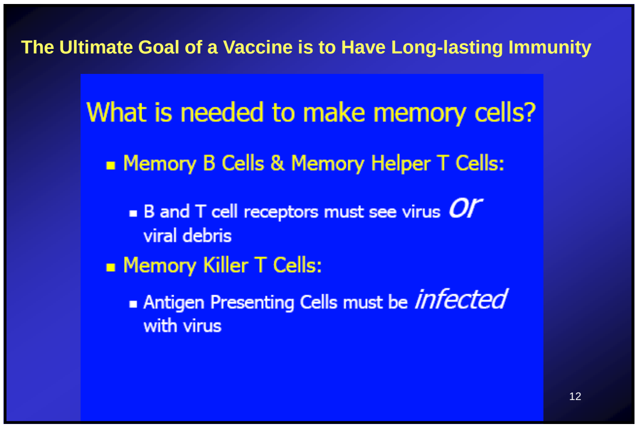


Some Examples of "Prime-boost" Strategies

- Optimization of vaccination can be achieved by different combinations of priming and boosting – the table below gives an overview of some of the approaches that can be used.
- The use of different "prime-boost" strategies can be used to overcome the possible reduction of the efficacy of the boost phase due to a pre-existing neutralizing antibody response generated during priming – this existing antibody response may remove the boosting phase before further activation takes place if the same entity is used in both phases.

Priming entity	Boosting entity
Viral vector	Recombinant protein
Naked DNA	Recombinant protein
Naked DNA	Viral vector
Viral vector	Naked DNA*
Viral vector	Different viral vector

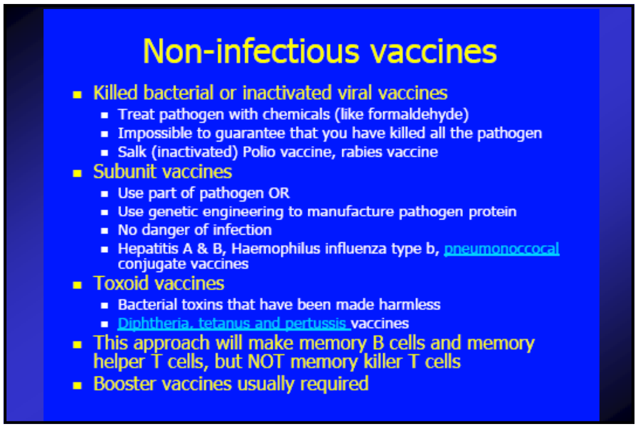
* Not very effective



The Ultimate Goal of a Vaccine is to Have Long-lasting Immunity

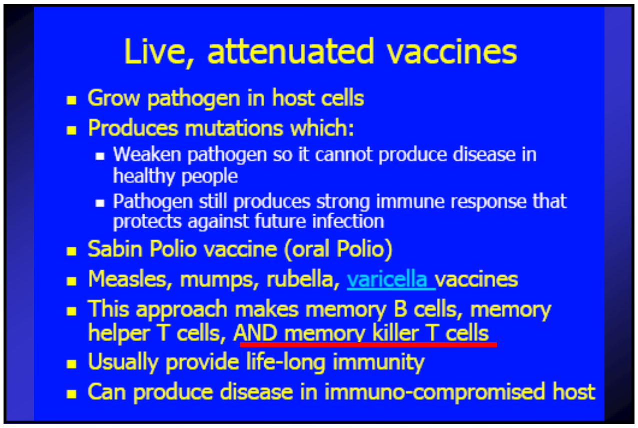
What is needed to make memory cells?

- Memory B Cells & Memory Helper T Cells:
  - B and T cell receptors must see virus *or* viral debris
- Memory Killer T Cells:
  - Antigen Presenting Cells must be *infected* with virus



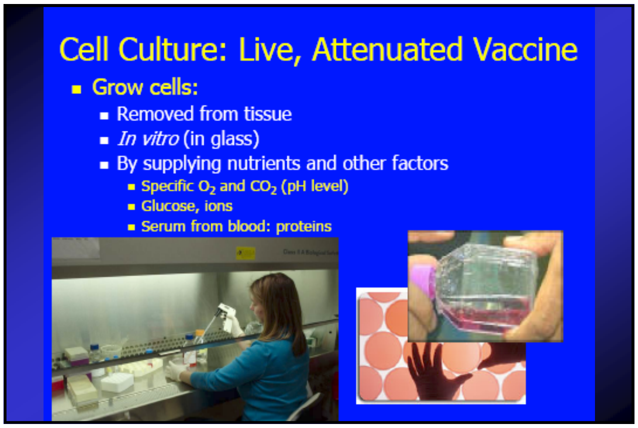
Non-infectious vaccines

- Killed bacterial or inactivated viral vaccines
  - Treat pathogen with chemicals (like formaldehyde)
  - Impossible to guarantee that you have killed all the pathogen
  - Salk (inactivated) Polio vaccine, rabies vaccine
- Subunit vaccines
  - Use part of pathogen OR
  - Use genetic engineering to manufacture pathogen protein
  - No danger of infection
  - Hepatitis A & B, Haemophilus influenza type b, pneumonoccocal conjugate vaccines
- Toxoid vaccines
  - Bacterial toxins that have been made harmless
  - Diphtheria, tetanus and pertussis vaccines
- This approach will make memory B cells and memory helper T cells, but NOT memory killer T cells
- Booster vaccines usually required



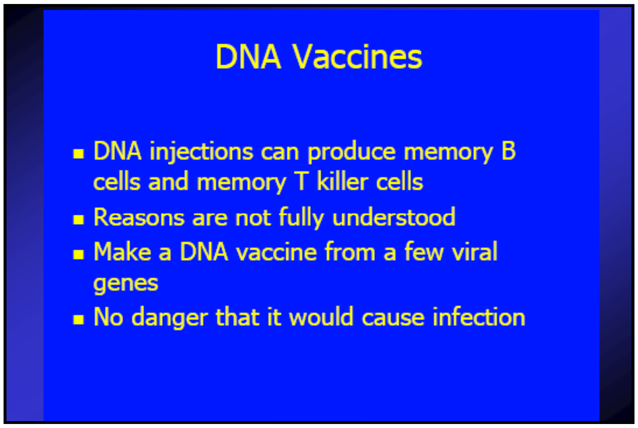
Live, attenuated vaccines

- Grow pathogen in host cells
- Produces mutations which:
  - Weaken pathogen so it cannot produce disease in healthy people
  - Pathogen still produces strong immune response that protects against future infection
- Sabin Polio vaccine (oral Polio)
- Measles, mumps, rubella, varicella vaccines
- This approach makes memory B cells, memory helper T cells, AND memory killer T cells
- Usually provide life-long immunity
- Can produce disease in immuno-compromised host



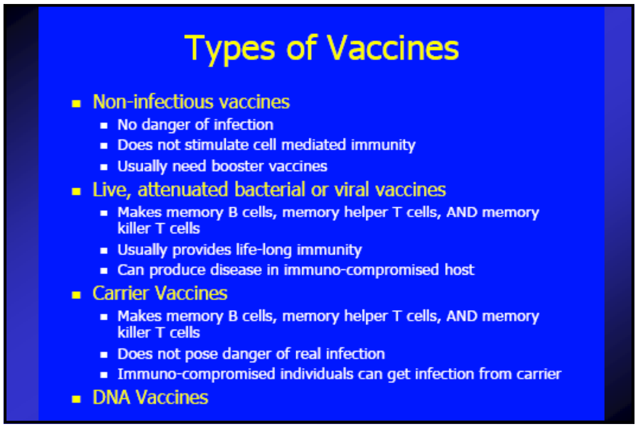
Cell Culture: Live, Attenuated Vaccine

- Grow cells:
  - Removed from tissue
  - *In vitro* (in glass)
  - By supplying nutrients and other factors
    - Specific O_2 and CO_2 (pH level)
    - Glucose, ions
    - Serum from blood: proteins



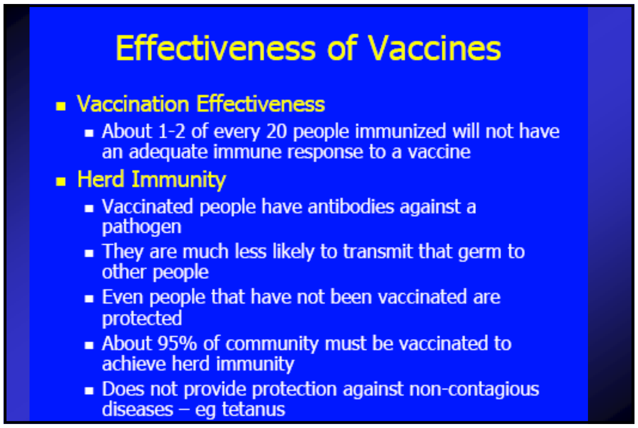
DNA Vaccines

- DNA injections can produce memory B cells and memory T killer cells
- Reasons are not fully understood
- Make a DNA vaccine from a few viral genes
- No danger that it would cause infection



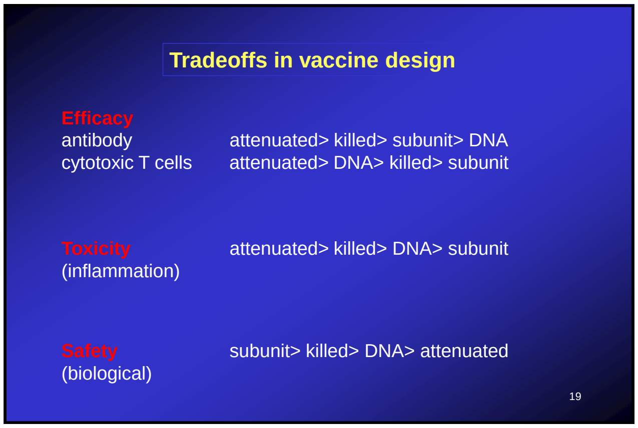
Types of Vaccines

- Non-infectious vaccines
  - No danger of infection
  - Does not stimulate cell mediated immunity
  - Usually need booster vaccines
- Live, attenuated bacterial or viral vaccines
  - Makes memory B cells, memory helper T cells, AND memory killer T cells
  - Usually provides life-long immunity
  - Can produce disease in immuno-compromised host
- Carrier Vaccines
  - Makes memory B cells, memory helper T cells, AND memory killer T cells
  - Does not pose danger of real infection
  - Immuno-compromised individuals can get infection from carrier
- DNA Vaccines



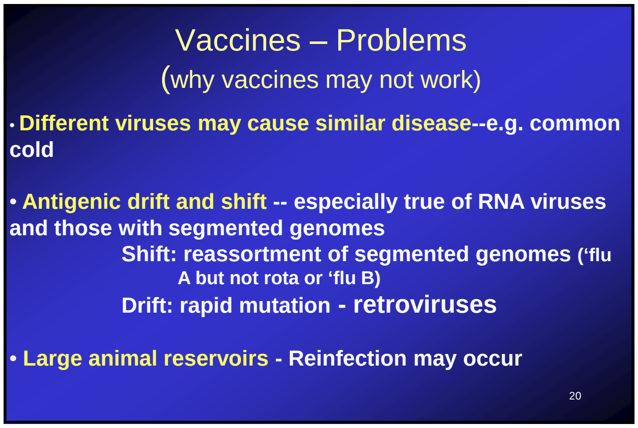
Effectiveness of Vaccines

- Vaccination Effectiveness
  - About 1-2 of every 20 people immunized will not have an adequate immune response to a vaccine
- Herd Immunity
  - Vaccinated people have antibodies against a pathogen
  - They are much less likely to transmit that germ to other people
  - Even people that have not been vaccinated are protected
  - About 95% of community must be vaccinated to achieve herd immunity
  - Does not provide protection against non-contagious diseases – eg tetanus



Tradeoffs in vaccine design

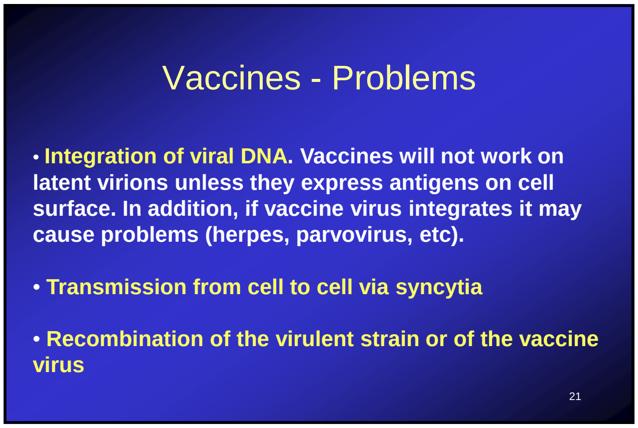
Efficacy	
antibody	attenuated> killed> subunit> DNA
cytotoxic T cells	attenuated> DNA> killed> subunit
Toxicity (inflammation)	attenuated> killed> DNA> subunit
Safety (biological)	subunit> killed> DNA> attenuated



Vaccines – Problems

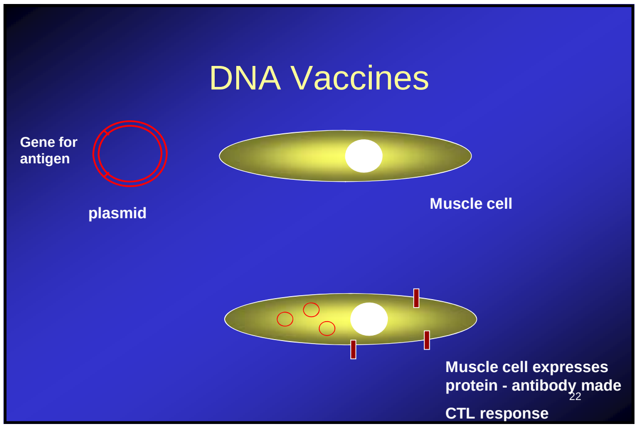
(why vaccines may not work)

- **Different viruses may cause similar disease--e.g. common cold**
- **Antigenic drift and shift -- especially true of RNA viruses and those with segmented genomes**
  - **Shift: reassortment of segmented genomes ('flu A but not rota or 'flu B)**
  - **Drift: rapid mutation - retroviruses**
- **Large animal reservoirs - Reinfection may occur**

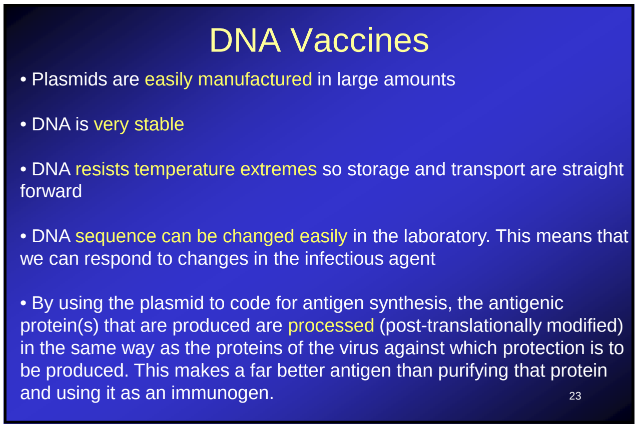


Vaccines - Problems

- **Integration of viral DNA. Vaccines will not work on latent virions unless they express antigens on cell surface. In addition, if vaccine virus integrates it may cause problems (herpes, parvovirus, etc).**
- **Transmission from cell to cell via syncytia**
- **Recombination of the virulent strain or of the vaccine virus**

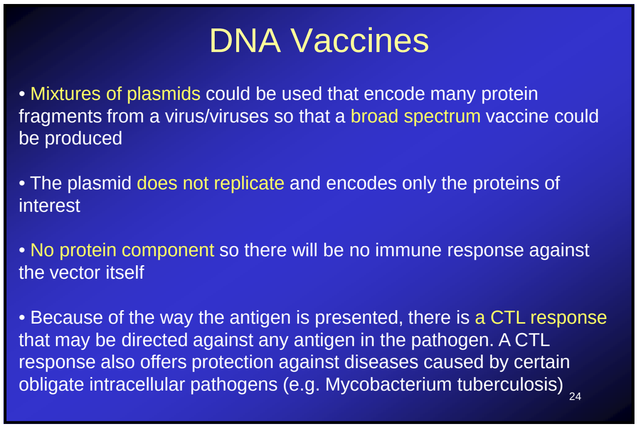


DNA Vaccines



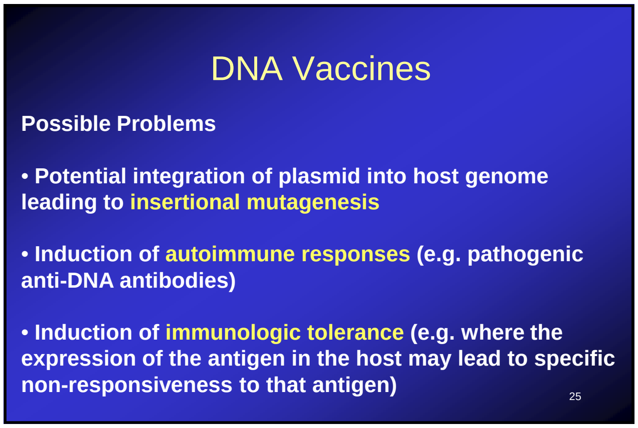
DNA Vaccines

- Plasmids are easily manufactured in large amounts
- DNA is very stable
- DNA resists temperature extremes so storage and transport are straight forward
- DNA sequence can be changed easily in the laboratory. This means that we can respond to changes in the infectious agent
- By using the plasmid to code for antigen synthesis, the antigenic protein(s) that are produced are processed (post-translationally modified) in the same way as the proteins of the virus against which protection is to be produced. This makes a far better antigen than purifying that protein and using it as an immunogen.



DNA Vaccines

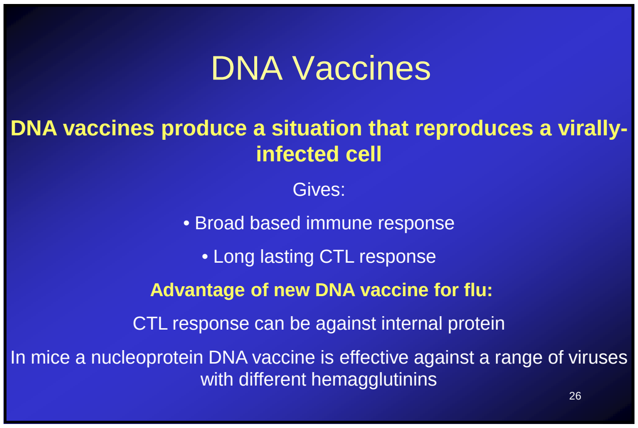
- Mixtures of plasmids could be used that encode many protein fragments from a virus/viruses so that a broad spectrum vaccine could be produced
- The plasmid does not replicate and encodes only the proteins of interest
- No protein component so there will be no immune response against the vector itself
- Because of the way the antigen is presented, there is a CTL response that may be directed against any antigen in the pathogen. A CTL response also offers protection against diseases caused by certain obligate intracellular pathogens (e.g. Mycobacterium tuberculosis)



DNA Vaccines

Possible Problems

- **Potential integration of plasmid into host genome leading to insertional mutagenesis**
- **Induction of autoimmune responses (e.g. pathogenic anti-DNA antibodies)**
- **Induction of immunologic tolerance (e.g. where the expression of the antigen in the host may lead to specific non-responsiveness to that antigen)**



DNA Vaccines

DNA vaccines produce a situation that reproduces a virally-infected cell

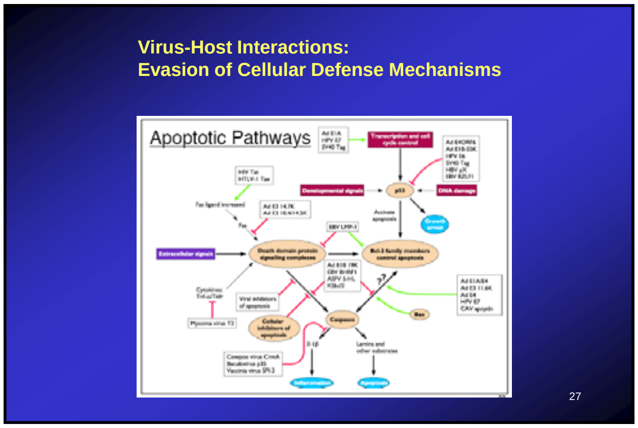
Gives:

- Broad based immune response
- Long lasting CTL response

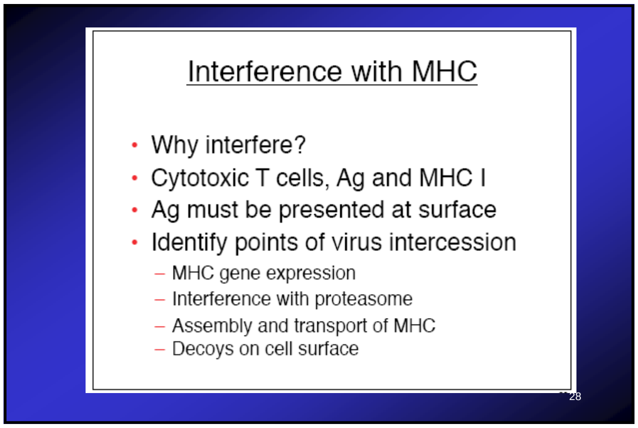
Advantage of new DNA vaccine for flu:

CTL response can be against internal protein

In mice a nucleoprotein DNA vaccine is effective against a range of viruses with different hemagglutinins

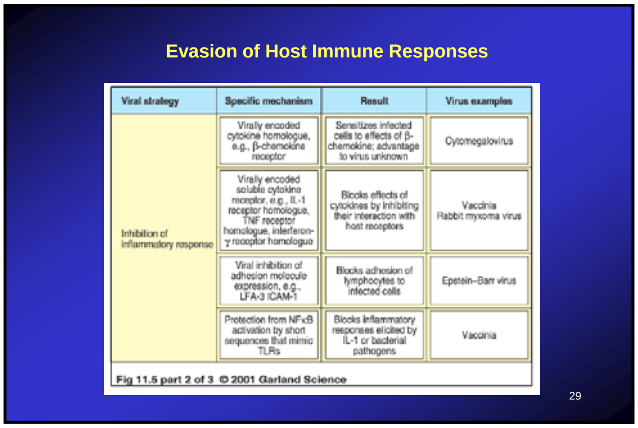


Virus-Host Interactions:
Evasion of Cellular Defense Mechanisms



Interference with MHC

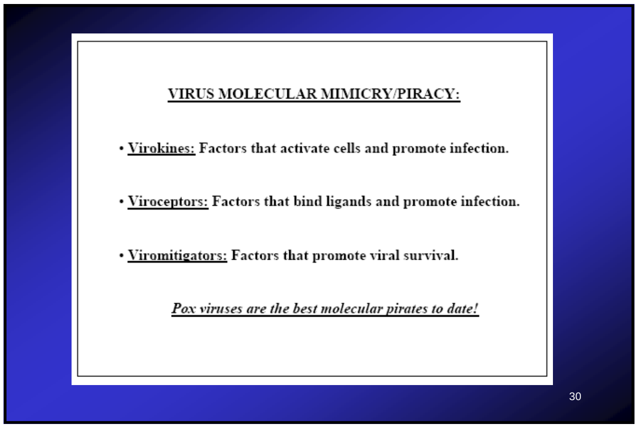
- Why interfere?
- Cytotoxic T cells, Ag and MHC I
- Ag must be presented at surface
- Identify points of virus intercession
  - MHC gene expression
  - Interference with proteasome
  - Assembly and transport of MHC
  - Decoys on cell surface



Evasion of Host Immune Responses

Viral strategy	Specific mechanism	Result	Virus examples
Inhibition of inflammatory response	Virally encoded cytokine homologue, e.g., β-chemokine receptor	Sensitizes infected cells to effects of β-chemokine; advantage to virus unknown	Cytomegalovirus
	Virally encoded soluble cytokine receptor, e.g., IL-1 receptor homologue, TNF receptor homologue, interferon-γ receptor homologue	Blocks effects of cytokines by inhibiting their interaction with host receptors	Vaccinia Rabbit myxoma virus
	Viral inhibition of adhesion molecule expression, e.g., LFA-3 ICAM-1	Blocks adhesion of lymphocytes to infected cells	Epstein–Barr virus
	Protection from NFκB activation by short sequences that mimic TLRs	Blocks inflammatory responses elicited by IL-1 or bacterial pathogens	Vaccinia

Fig 11.5 part 2 of 3 © 2001 Garland Science



VIRUS MOLECULAR MIMICRY/PIRACY:

- **Virokines:** Factors that activate cells and promote infection.
- **Viroceptors:** Factors that bind ligands and promote infection.
- **Viromitigators:** Factors that promote viral survival.

Pox viruses are the best molecular pirates to date!

Summary of the effects of viral infection on Innate Defenses.

- Viruses evade attack by innate cells and factors by hiding inside cells.
- While hiding inside macrophages and lymphocytes and other cells, the virus may block critical functions of the infected cells, such as antigen processing, presentation and activation of macrophage functions.
- Viruses produce products that block complement activation and degrade any activated complement factors (C3b), disrupt MAC.
- Viruses produce receptors and binding proteins that compete for chemokines and prevent their activation of host resistance.
- Viruses can evade natural killer cells by suppressing the expression of surface proteins, including MHC. Viruses may further mask their presence by expressing an MHC homologues that interact with NKIRs on the NK-cells that inactivate the killing of infected cells.
- Viruses can block apoptosis, rendering infected cells immortal.