Vaccination 1

Objectives

- define vaccines and their importance
- discuss current vaccines, their mechanism(s) of protection, and the proof
  - review of B cell biology
- discuss issues of timing and location of protection, herd immunity, vaccine delivery, and vaccines for babies and elderly
- review the types of vaccines (whole vs. subunit), and their pros and cons

Vaccination

- "world's most cost-effective medical procedure for preventing morbidity and mortality caused by infectious disease.."
- represents one of the most important advances in the history of public health
- currently about 20 vaccines licensed for use.

Robinson and Amara 2005

Successful vaccines

Disease	**Max. cases (year)**	**Cases in 2004**
Small pox	over 300m	eradicated 1979
Diptheria	206,939 (1921)	0
Measles	894,134 (1941)	37
Mumps	152,209 (1968)	236
Pertussis	265,269 (1934)	18,957
Polio (paralytic)	21,269 (1952)	0
Rubella	57,686 (1969)	12
Tetanus	1,560 (1923)	26
H. influenza B	~20,000 (1984)	16
Hepatitis B	26,611 (1985)	6,632

Sources: MMWR 53:1213 (2005), Mandell 1995, Abbas 2007

A vaccine..

- "....is a preparation of microbial antigen, often in combination with adjuvants, that is administered to individuals to induce protective immunity against infection"

- Passive vs. Active vaccination
  - passive: antibodies are given directly
  - **active:** immune response is induced by the host

Abbas (2007)

An adjuvant..

- "...is a non-antigenic substance that enhances T cell activation by promoting the accumulation of antigen presenting cells at the site of antigen exposure..."
  - increases expression of co-stimulatory molecules, cytokines, and HLA-peptide complexes on APCs
  - whole vaccines contain "natural" adjuvants

Abbas (2007)

Goal of vaccination

- ...is to mimick infection and induce protective immunity by introducing pathogen components *without causing disease*

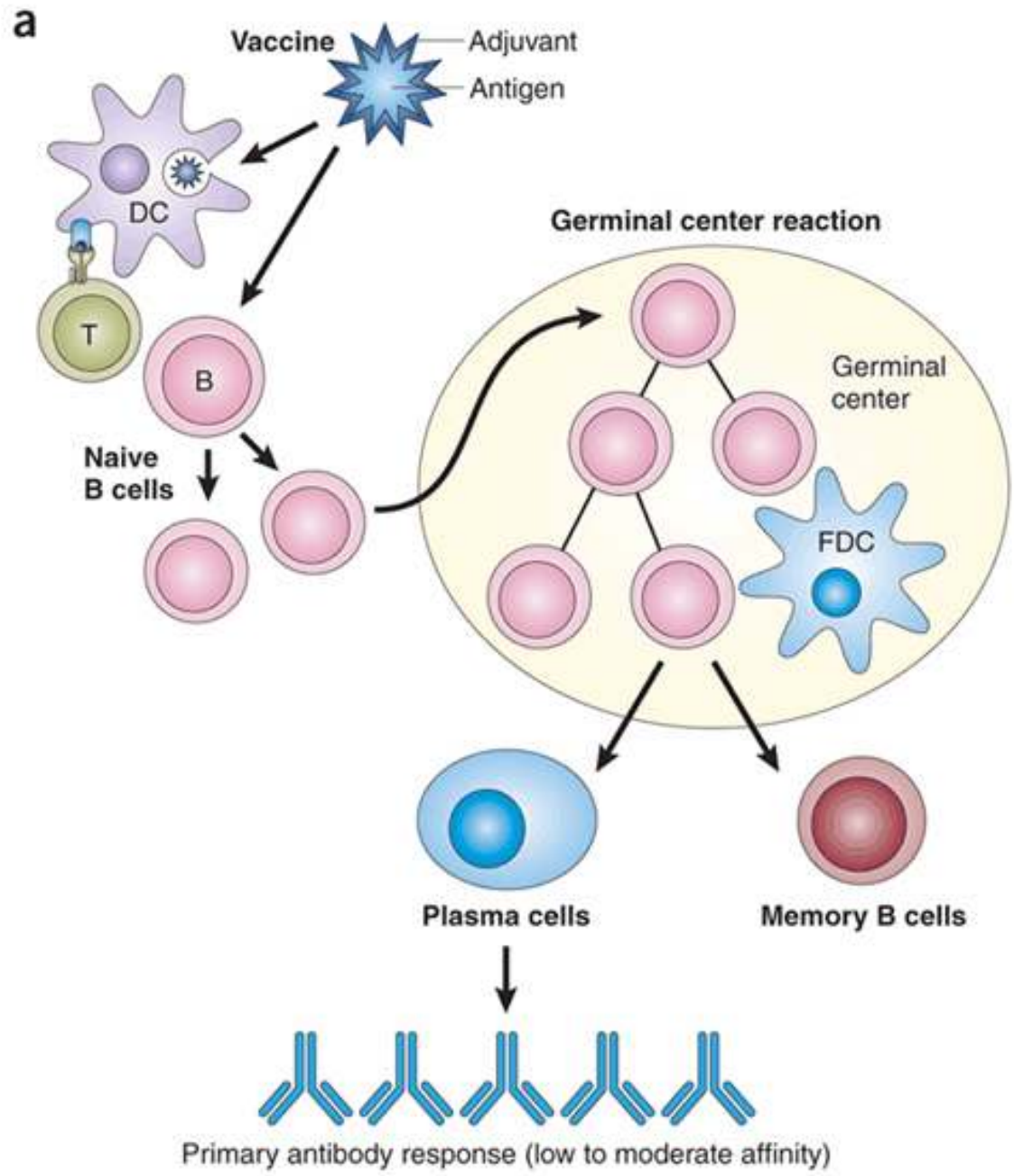
- induces memory, which leads to better and faster responses after exposure to pathogen

- Vaccine design can be either **empirical** or **rationale**
  - Rationale: based on an understanding of protective immunity
  - Empirical: trial and error

Current vaccines

- most current vaccines:
  - have been designed empirically
  - are against extracellular pathogens and viruses that cause acute infection
  - lead to “sterlizing” immunity
- elicit neutralising antibody responses
  - BCG is the only exception => Th1 responses
- best correlate of protection in most -> certain attributes of the ab response
- less is known about the contribution of T cell responses

Vaccine-induced B cell responses



Important points

- antigen-presenting cells capture the vaccine antigen(s)
  - whole vaccines and/or adjuvants
  - analogous to natural infection
- induction of both T and B cell responses
- naïve B cells are optimally induced in germinal centers of lymph nodes by follicular dendritic and CD4+ helper T cells
  - undergo clonal expansion
  - differentiate into plasma cells and memory B cells
  - isotype switch -> IgG
  - produce higher affinity antibodies

Affinity maturation => boosting

- **affinity:** strength of antibody-antigen binding
- antibody genes can undergo random genetic rearrangements leading to selection of the antibodies that can bind with higher affinity to antigen and provide better immunity

- first vaccine dose tends to generate weaker antibodies, while boosting or antigen persistence increases the strength of antibody binding

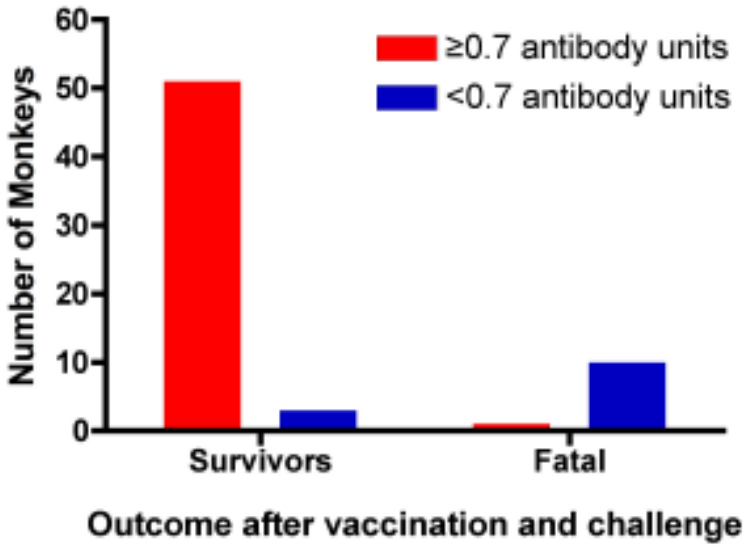
Important points (2)

- memory B cells survive for many years through polyclonal activation
  - regenerate plasma cells
  - duration of protection is linked to B cell memory
- need an appropriate time between first dose and boost
  - allows affinity maturation
  - can potentially be sped up by adjuvants
- dose of antigen is critical
  - higher dose gives better short term responses,
  - lower dose better long term memory

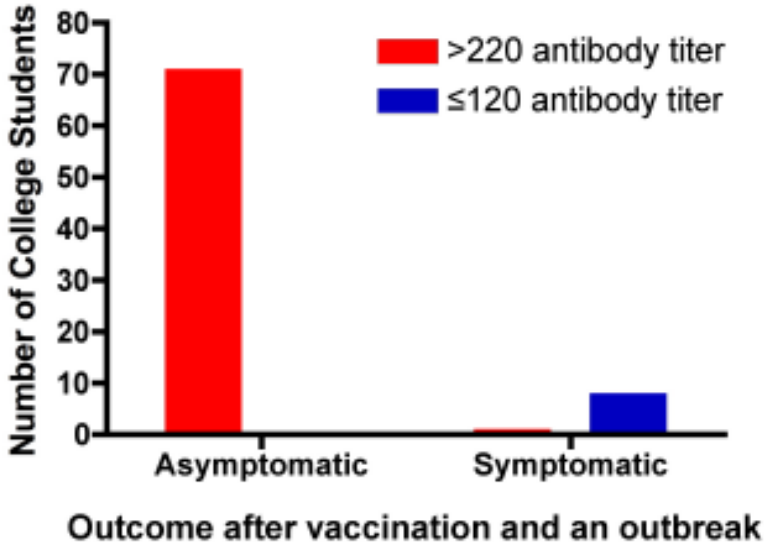
Proof that antibodies protect

- difficult to prove what is protective
  - evidence from human and animal studies
- passive transfer of measles antibodies was found to be protective (1945)
  - similar findings for other pathogens
- often the titer and/or affinity of antibodies predicts protection
  - Titer: concentration of antibodies in serum
  - *H. influenza* B => 0.15ug/ml of high affinity ab protects

Proof that antibodies protect (2)



Yellow Fever Vaccine



Measles Vaccine

Amanna et al 2008

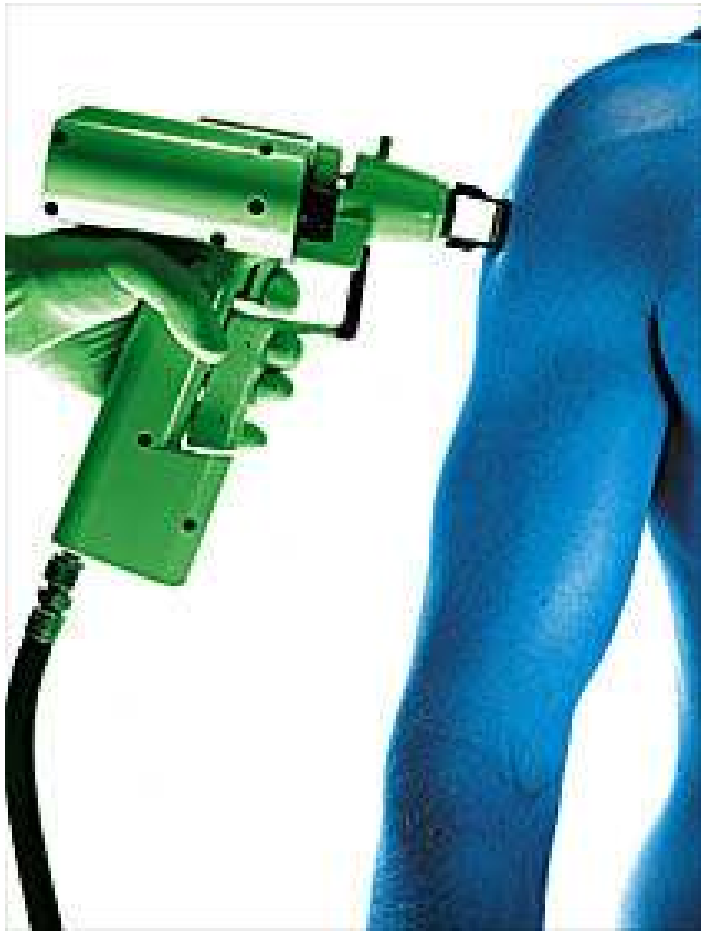
Evidence for protective T cells

- BCG
  - very little antibody response, mostly CD4+ T cell dependent
- Pertussis
  - vaccine can still protect after ab levels decline
- Measles
  - disease severity is reducted in absence of abs
- Influenza
  - T cells are important for cross-reactive protection
  - recognition of less variable viral regions

Herd immunity

- proportion of the population that needs to be immunized to break transmission chains and provide protection to unvaccinated individuals

Vaccine delivery



The Gene Gun

- most are injected intramuscularly
- can be mucosal (oral, nasal)
- some new ideas

OPV vaccine

Timing and location of protection

- responses need to be made rapidly and where the infection challenge occurs
  - mucosal pathogens ideally need mucosal responses
  - ie, influenza, respiratory pathogens
- tetanus
  - need pre-existing antibodies as toxins enter cells rapidly
- hepatitis B
  - antibody response needs to occur before virus becomes established in the liver -> goes intracellular

Babies

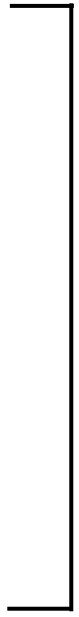
- most susceptible to many diseases, but have an immature immune system
  - especially in the first year of life
  - vaccine responses increase in a step-wise manner with age
  - make poor IgG responses, don't form germinal centers, etc.
- poor duration of immunity
  - but still enough so that boosting works
- maternal antibodies can inhibit or assist vaccine responses in babies
  - competition with baby's B cells, neutralize the vaccine
  - can still get T cell responses, sometimes better

The elderly

- ageing is associated with waning antibodies and a reduced T cell repetoire
- can affect vaccine responses for some vaccines
- may need to alter vaccine regimens for the elderly
  - more or higher doses

Types of vaccines

- attenuated/inactivated
  - BCG, cholera, polio, rabies
- purified antigen
  - tetanus, diptheria
- synthetic antigen
  - hepatitis B
- conjugate vaccines
  - *H. influenza* B, *S. pneumo*
- viral vector*
- DNA vaccine*



"subunit" vaccines

Attenuated vs Inactivated

- render the organism unable to cause disease while retaining immunogenecity
  - repeated passage in cell culture, deletion mutants, etc.
  - has all components of the original pathogen
  - can get both CMI and antibody reponses, plus innate
- Louis Pasteur => attenuation in bacteria
- attenuated viral vaccines most effective
  - often induce life-long immunity
  - can be associated with disease, esp. if host is immunocompromised

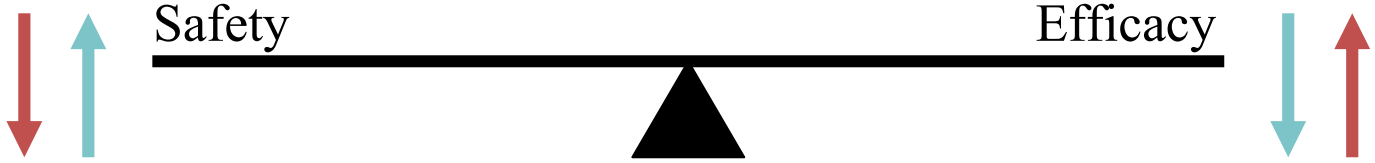
Attenuated vs Inactivated (2)

- polio
  - oral (live) vs injected (inactive) elicit similar ab responses
  - the oral vaccine is mucosal (same as route of infection), decreases intestinal secretion and therefore transmission
  - inactive vaccine is safer (oral can cause paralysis)
- measles
  - live is very effective but causes fever in 20-40%
  - inactive protection not as good, shorter, poorer T cell responses
- influenza
  - traditional vaccine is inactivated
  - new attenuated mucosal vaccine: single dose = protection, good T cell responses, broader recognition, IgA production

Safety vs Efficacy

"Very properly, the greatest emphasis is always placed on administering the vaccine in such a way that no unpleasant reaction ensues, but because vaccination must be safe for all, it is probably ineffective for many..."

- Rene Dubos, *The White Plague: Tuberculosis, Man, and Society* (1952)



Sub-unit vaccines

- use only a portion of the pathogen, usually the part that has been shown to elicit protective responses
- adjuvants are critical for these vaccines
- can be safer -> less of an inflammatory response
- successful examples include purified and synthetic proteins, virus-like particles (HPV)
- under development include viral vectors and DNA (next week)

Conjugate vaccines

- antibody responses to polysacchrides are T-independent
  - typically lower avidity/ shorter duration
  - poor memory
- can increase vaccine efficacy by linking polyS to protein carriers
  - this leads to T and B cell responses and better memory/affinity
- high affinity, complement binding abs are the key correlate of protection

Note that:

- most successful vaccines:
  - elicit neutralising antibody responses and B cell memory
  - antibody quality/quantity critical for protection
  - T cells often induced simultaneously, imp. for long term memory
  - are for acute, extracellular infections
  - have been made empirically
  - are for childhood infections
- For many pathogens => vaccines are under development