Vaccines

Sunday, November 16, 2014
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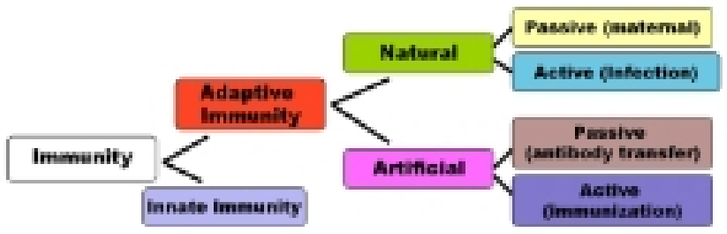
Lecture Outline:
- vaccine history & childimmunization schedule
- acute vs. passive immunization
- qualities of good vaccines
- how vaccines protect:
  - herd immunity
  - historical development
  - future development
  - correlates of protection
- common experimental/clinical vaccines
  - vaccine tech history
  - live attenuated vaccines
  - DNA vaccines
- vaccine-induced immunity
  - primary vs. secondary (memory)
- challenges
  - available vaccines
  - not available vaccines
  - HIV case study
- vaccine formulations (adjuvants)
- mucosal immunity (edible vaccines)

Learning Objectives:
- active vs. passive immunization
- correlates of protection (also know main one for human vaccines)
- inactivated vs. live-attenuated vs. DNA (safest?)
- production of attenuated virus
- immunogen
- herd immunity (main factors affecting whether it will function in a pop)
- challenges of vaccine development
- adjuvant (only approved one?)



Artificial

	ACTIVE	PASSIVE
Definition	Immune system makes Abs/cell-mediated rxns	Abs neutralize Ag given near time of exposure or during infection
Examples	(live, attenuated, DNA)	(cancer tx)
	- SLOW - CANNOT help immuno-suppressed pts - memory - many routes - boosters - not 100% effective	- FAST - can help immuno-suppressed pts (NOT macrophages, neutrophils, & NK deficient) - NO memory - inconsistent (IgG variations) - serum sickness

Qualities of Good ACTIVE Vaccine:
- cheap, safe, stable
- fast
- broad
- long-term
- anti-contagious (no viral shedding)
- maternal transmission to fetus
- beneficial to all
- no boosters
- no needles

Vaccines Protect Against:
- infection (sterile immunity) *"doesn't happen"*
- disease (hospitalization)
- death (cancer)
- transmission (herd immunity)

Historical vs. Future Approach to Vaccine Development:

Historical	Future
"low-hanging fruit"	Beyond "low-hanging fruit"
- empirical approach (trial & error) - live attenuated / inactivated - Ag-specific Abs (smallpox, polio, rabies)	- there is more to vaccine immunity than peak titers - Ab quality - Memory B-Cells - innate immunity - T-Cells (for efficiency)

Herd Immunity

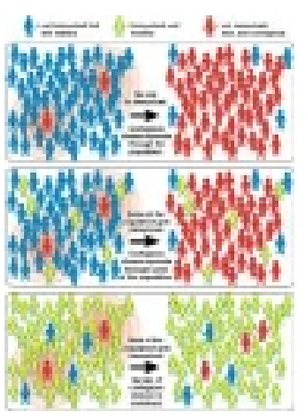
THRESHOLD - # immunized where a disease virtually no longer exists

R_0 - reproduction/virulence; # of newly infected ppl from 1 infected person

E - effectiveness against transmission

V_c - critical vaccination coverage; proportion of pop that must be vaccinated for herd immunity

C - contact parameter; ability to pass infections within community (tight-knit vs. isolated)

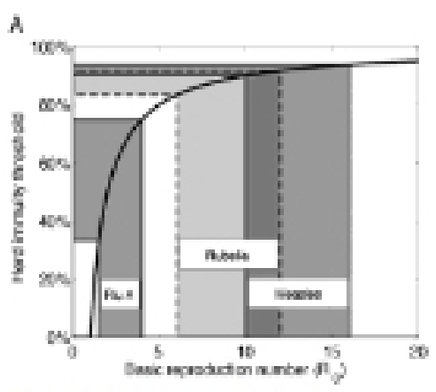


*NONE immunized

*SOME immunized

*MOST immunized

Factors Affecting R_0: (varies per area)
- survival
- infective dose
- contagiousness duration
- contagiousness prior to symptoms
- pop density



* if R_0 = 10, Threshold >80%

EFFECTOR CELLS - activated cells that defend (T-CD4/8, B-Abs, (Innate))
**focus on response function*

***B-Cell Abs** = current main effectors in vaccines*
**smallpox & cowpox share some Ags*

CORRELATES OF PROTECTION - protection is dependent upon presence of marker (T-CD4, B-Abs)
**focus on protection after*

Example:
- *COP to Prevent Disease: X Ab titers*
- *COP to Prevent Infection: X+Y Ab titers*

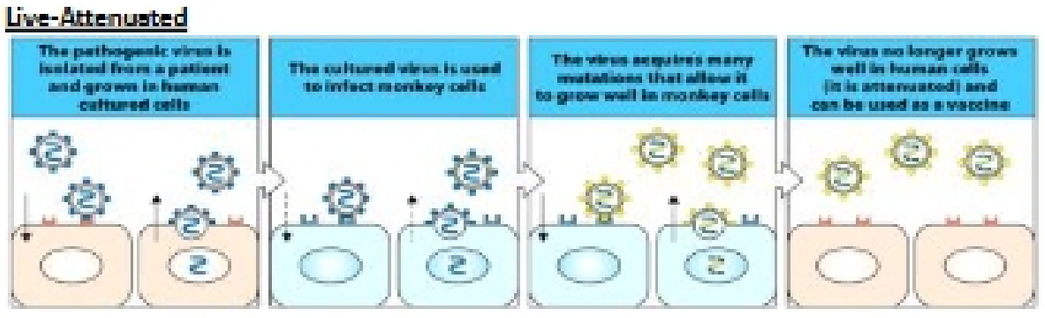
SERUM IgG: main COP for most vaccines; encountered after infection
MUCOSAL IgG: serum IgG that seeps into mucosa
MUCOSAL IgA: only in a few vaccines
- Flu (nasal live attenuated) = IgA + IgG
- Polio Sabin (live attenuated) = IgA + IgG
- Rotavirus (live attenuated) = IgA

T-CELLS: CD4 activates macrophages
Tuberculosis (BCG) = CD4

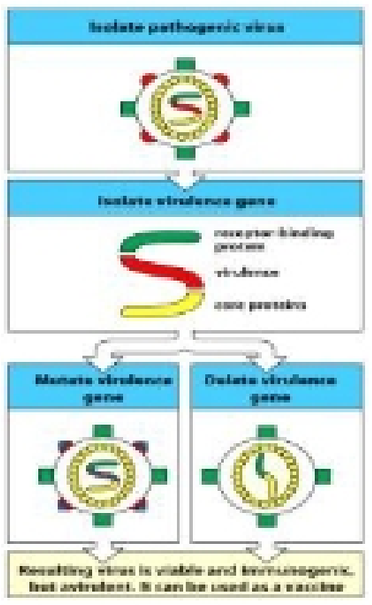
Common Experimental/Clinical Vaccines

LIVE-ATTENUATED - weak (MMR)
INACTIVATED - killed via heat, radiation, chemicals
TOXOID - inactivated toxin (Diptheria/Tetanus)
SUBUNIT - immunogenic portion only (HepB)
COMBO - (DTP, MMR)
CONJUGATE - bacterial polysaccharide:protein; protein enhances immunity to polysaccharide
DNA - roadblocks to success...

Live-Attenuated



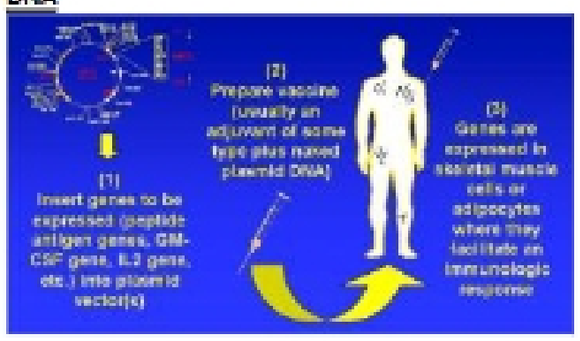
Old Approach: Monkey Mutations
1) isolate human virus
2) infect monkeys
3) monkey mutations
4) attenuation (more effective in monkeys than humans)



New Approach: Manual Mutations **more controlled changes*

1) isolate virus
2) isolate gene
3) mutation/deletion
4) attenuation (low virulence)

DNA



EXPRESSION PLASMID - encodes foreign gene **working very well in small animals, but not humans*

1) insert foreign genes into plasmid vector
2) plasmid DNA + adjuvant
3) Ag gene expression in muscle/fat cells
4) immune response

	Live-Attenuated	Subunit Inactivated	DNA
	- replicate - Abs & Cell-Mediated	- CANNOT replicate - Abs	- synth of Ags only in cells (muscle/fat) - Cell-Mediated
Good	- broad - less boosters - long-term	- CANNOT multiply/revert (safe) - less reactogenic - more technically feasible (defined)	- standardized/simple - long-term
Bad	- residual pathogenesis - uncertain safety before large usage - unstable, reversion - difficult to analyze final product	- needs adjuvant + delivery system - less potent - inconsistent efficacy	- difficult to establish proof-of-principle - less potent

Polio (live-attenuated): undeveloped countries still use live-attenuated version, which can revert back to wild-type & cause Polio outbreak

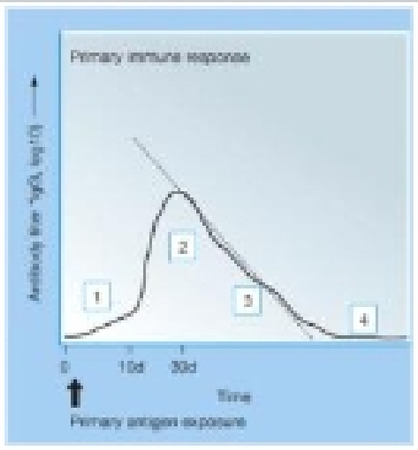
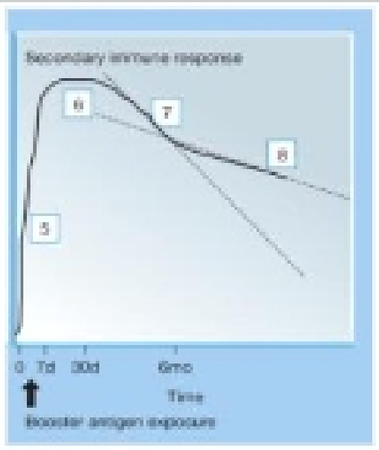
FORMULATION - final vaccine to be administered
1) active substance (Ag/DNA)
2) adjuvant
3) delivery system

ADJUVANT - helpers; stimulates humoral/cell-mediated rxn to increase rxn to Ag (ALUM)
DEPOT/SR = modulate Ag delivery & persistence
IMMUNE-MODULATOR = enhance CD4 (T-helper) responses
DELIVERY SYSTEM - vehicle that ensures Ag presentation; SR

**ALUM - only adjuvant approved in US*

IMMUNOGEN - Ag (protein) that can induce an immune response
****not all Ags are Immunogens***

Primary vs. Secondary Vaccine-Induced Immunity

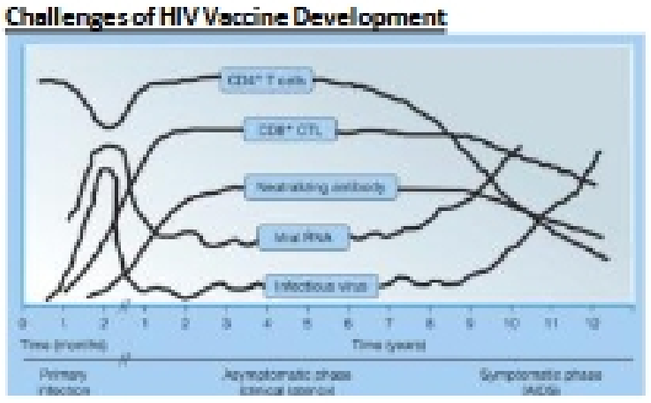
PRIMARY (T-Dependent B-Cell Response, Plasma Cells)	SECONDARY (Memory Cells)
	
1) rapid production of low-IgG Abs 2) B-Cell differentiation into Plasma Cells, secretion of IgG (peak = 4 wks) 3) Plasma Cells die (short half-life) 4) IgG returns to slightly higher than baseline	5) Memory Cells replicate & differentiate into Plasma Cells, secretion of IgG (detectable = 3 days) 6) (peak = 7 days) 7) Plasma Cells die (short half-life) 8) IgG returns to much higher than baseline

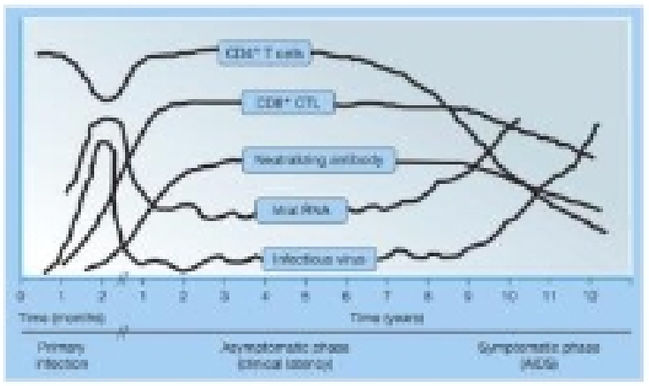
Future Vaccinations

*Current Global Challenges (5.6million deaths/yr): HIV, Malaria, Tuberculosis
*HIV Prevalence: S.Africa

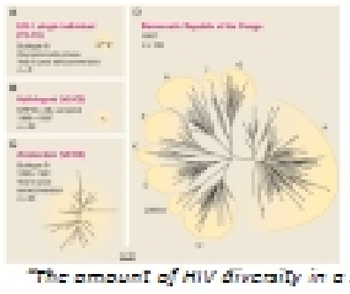
**Smallpox: eradicated*
**Polio: near-eradication*

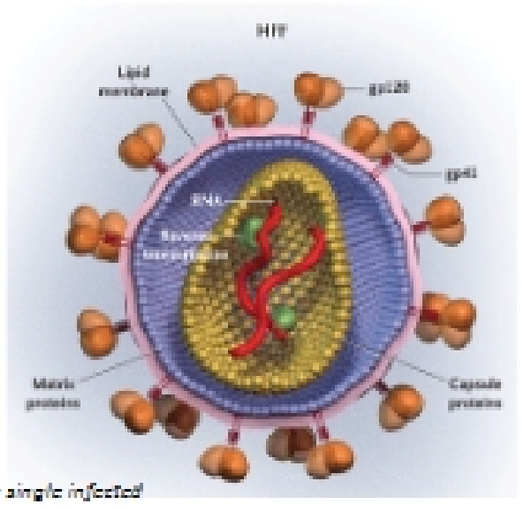
Challenges of HIV Vaccine Development





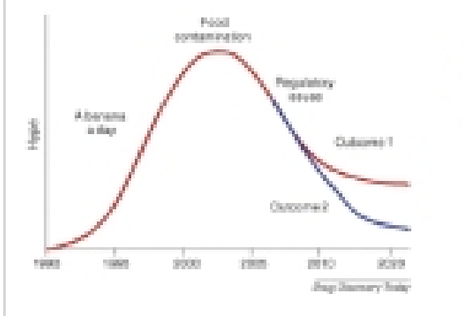
- inadequate natural immune response
- relentlessly progressive (no spontaneous recovery)
- mutations & diversity: Neutralizing Abs unable to keep up
  - mutations
    - REVERSE TRANSCRIPTASE - RNA --> DNA (quick, error-prone)
    - GP120/GP41 - get Ag into cell; major antigenic determinant
  - diversity
    - A) individual
    - B) IV drug users
    - C) small group in Amsterdam
    - D) Congo
- hidden targets of Neutralizing Abs
  - conformation
  - glycosylated
- integration & latency
  - integration: quickly enters genome
  - latency (invisible)
    - established early (days/wks)
    - cannot eradicate during latency





"The amount of HIV diversity in a single infected individual can exceed the variability generated over the course of a global influenza epidemic, the latter of which results in the need for a new vaccine each year"

Mucosal Immunity: Edible Vaccines



Outcome 1: mild resurgence
Outcome 2: if tech is not used
**hype will decrease so much that it may be difficult in terms of negativity to fund plant-based vehicles*