

Successes and Challenges Vaccines for Infectious Diseases

small pox, polio, and beyond...

- small pox
- pertussis
- diphtheria
- polio
- tetanus
- measles
- yellow fever
- mumps
- rubella
- ...ebola

evolving an understanding of infection, pathogens, and pathogenesis

- which illness is which?
- how is it transmitted?
- what is the cause of the illness?
- is immunity acquired after infection?

stages in vaccine development

- pathogen
- means of testing for presence of infection
- correlates of immunity
- protective antigens
- bench
- clinical
- FDA approval
- commercialization and distribution

stages in vaccine development advances follow discoveries

1050 Concept of “immune state”

- variolation (buddhist nun) person to person immunization

1674 Leuwenhook / microscopes : amimacules

1774 attenuation (variolation) Lady Mary Wortley Montague 1721

- live attenuated vaccines Jesley 1774 Jenner 1798
- mimic vaccines (vaccination) ...informed consent..

stages in vaccine development advances follow discoveries

1848 transmission / isolation / sanitation (cholera)

1859 pasteurization / germ theory of disease

1876 Koch pure culture (Frau Hesse/agar)

stages in vaccine development advances follow discoveries

1880 attenuated vaccines

chicken cholera (Pasteur)

anthrax... (also Pasteur)

24 sheep, 1 goat, 6 cows / outcome: 21 v 0

1886: heat killed : hog cholera

(Salmon and Smith, USA)

stages in vaccine development advances follow discoveries

1882 - 1900 “golden age”

isolation / attenuation / heat killed vaccines

1900:

2 attenuated: rabies/small pox

3 whole killed: typhoid, cholera, plague

WW II : toxoids: tetanus

1921- 1922 cell culture (membrane of egg)

stages in vaccine development advances follow discoveries

1921- 1922 cell culture / passaging / attenuating
measles, mumps, rubella, chicken pox
polio (monkey kidney)

1930-1970 isolation techniques: subunit ..Hep B
(the antibody age)

1970-1980 recombinant techniques: Hep B

1973 Doherty and Zinkernagel: MHC restriction

1980's Wiley and others: crystal structure of
MHC /peptide

Vaccine Milestones

<u>Live Att</u>	<u>Killed Whole</u>	<u>Purified Prot</u>	<u>Engineered</u>
1798 smallpox	1896 Typhoid		
1855 rabies	1896 Cholera		
	1897 Plague		
1927 BCG	1926 Pertussis	1923 Tetanus toxoid	
1935 Yellow F	1936 Flu		
	1938 Rickettsia		
vs WW II			
Sabin polio	1954 Salk polio	pneumococcus	1980 Hep B
mumps rubella	rabies	meningococcus	
adeno, varicella	JEE, HepA	H flu, acellular pertussis	
typhoid, measles		Hep B from plasma	

Vaccine Milestones

<u>Live Att</u>	<u>Killed Whole</u>	<u>Purified Prot.</u>	<u>Engin'rd</u>
SIV-nef	Remmune	VaxGen	PMC Cpox Oxford MVA

Small Pox - History

- **which disease is which? -- rash**
orthopox virus, same family as cowpox
- **how is it transmitted?**
aerosol - isolation / mucous membrane to mm- contact
- **history epidemic/endemic**
egyptian paintings/mummies. destroyed
populations in North and South America
in Europe
1700's killed 5 kings and 400,000 people /yr
- **variolation ----> ----> ----> ----> vaccination**
arm to arm, dried material
transmission of syphilis (banned in 1898)
grown on calf flanks, sheep, yaks...now a mixed virus
Lady Mary Wortley Montague 1721
- **Jenner 1798 live attenuated vaccinia**
Jesley 1774 Jenner 1798informed consent..

Small Pox - eradication

- 1798 live attenuated vaccinia described
- 1800 USA: vaccinia arrives in 1800
small pox eliminated by 1897
- 1920 outbreak in FLA in 1920-
102,000 cases in 1921
- 1930's vaccination required for school entry,
15,000 cases by 1951
- 1940's large scale production in cell culture (eggs)
- 1950 PAHO decides to eliminate smallpox in
the Americas-- success by 1958 x Brazil
- 1966 decision to eradicate the disease globally
WHO makes \$2.4 million per year available, standards
- 1977 last case is recorded in Somalia
- 1978 two lab cases
- 1970 no further vaccination required in US
- 1980 declared extinct.....

Small Pox - the future

- two labs still have the virus (USA and Russia)
- 7 labs still make the vaccine
 - efficacy 80%
 - duration of immunity 5 to 10 yrs
- What is the effect of NO LONGER VACCINATING?
- Recombinant vaccinia as a vector

benefits of global eradication

- x - disease prevention**
 - importations to US 1930-1970
 - 36 episodes, 574 cases, 90 deaths
 - in the world: cost \$300 million, saved 1 billion annually
- x - proved that it could be done**
- x - introduced the concept of access to care**
- x - developed technologies in developing world**

Polio / history

- seasonal, epidemic endemic
children mainly affected...Roosevelt
- crippling. Iron lungs for respiratory paralysis
- transmitted oral/fecal
- 1908 produced in monkey brain, first vaccine trials
eventually kidney cells by 1949
- 1936 Sabin tried to grow in non-neural cells
and failed: later found this to be “lab strain”
- 1940 Burnet and Jackson from WEHI grew Mars strain
in pharyngeal tissue
- 1949 three different strains recognized
- 1952 paralytic polio cases 30/100,000 in US

Polio / history (Salk)

1940's Salk developed formalin inactivated virus
did preliminary studies
large trial in Michigan/School of Public Health
1,829,916 children vaccinated:
1955 Vaccine declared safe and 70% effective
opened up for use
millions vaccinated with whole killed vaccine
1955 “Cutter incident” described in A J Pub Hyg
260 cases of post vaccination polio
94 in vaccinees, 126 in family contacts,
40 in community
NOT followed by public outcry: Salk was still the
“standard” until 1960's...added a filtration step

Polio / history (Sabin)

- 1940's vaccine attenuated by passage in tissue culture
- 1950's field trials in Europe (because US had Salk)
 - 200,000 children in Singapore where a Type 1 epidemic was occurring; safe and effective
- 1960 100 million people vaccinated with Sabin in Europe
- US license given (just 10 years from first growth in tissue culture system)
- 1940-1970 NFIP supported vaccines:
 - example of successful foundation-researcher partnership
- 1960 concerns about SV40 raised by Hilleman and Sweet (tumors in hamsters)
- 1970's concerns laid to rest
- 1996 concerns raised again by PCR isolation of SV40 from choroid plexus tumors and mesotheliomas

stages in vaccine development / polio

identify pathogen

antibody, EM. three types (sero types)
picorna virus...clefts in the surface may hide R's

means of testing for presence of infection

antibodies, testing sewage for live virus

identify risk groups

- developing countries
- healthy carrier state

identify correlates of immunity - Ab = dose

enterocytes only transient, CNS target

identify protective antigens -

clinical-- which vaccine to use?

Polio: The future

eradication? (200,000 cases/yr)

- barriers**
- efficacy of vaccines 50-70%
 - vaccination coverage and access to care
 - water borne? fecal contam.
 - resistance to vaccine (polio if Sabin)

reasons to expect success

- two effective vaccines
 - no animal reservoir
- only three types of virus, stable
OPV is expensive, new KPV is ok
but OPV is easy to give