THE UNIVERSITY OF MELBOURNE

Viral vaccines - wins and losses

What is coming sooner?
What is coming later?
What is struggling?

Acknowledgements

- CRC for Vaccine Technology
- The University of Melbourne
- CSL Ltd
- Stephen Kent and Jane Dale

Vaccines – wins and losses

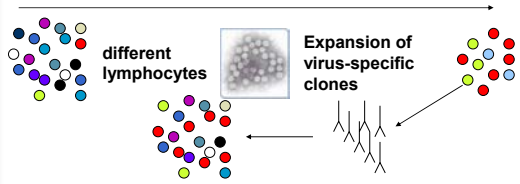
- What is a vaccine?
- How do they work?
- What is needed to make a vaccine?
- 4 case studies:
  - Polio
  - Rotavirus
  - HPV
  - HIV
- Pandemic influenza
- Conclusions

What is a Vaccine ?

- Edward Jenner, late 18th Century
- Smallpox endemic disease, high mortality
- 1780s, Jenner noticed that milkmaids did not carry the scars of smallpox
- He thought that something the milkmaids did made them resistant to smallpox
- He concluded that milkmaids who caught *cowpox*, did not catch smallpox
- pre 'Germ Theory', pre any understanding of immunology or immunological memory

How do Vaccines work ?

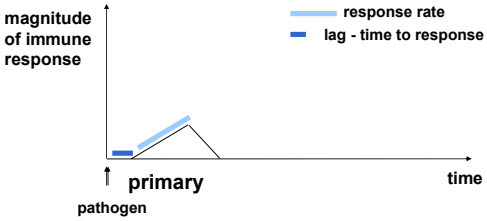
A: Immunological Memory



- An immune response changes the pool of lymphocytes - increases frequency of specific cells, and with an activated phenotype

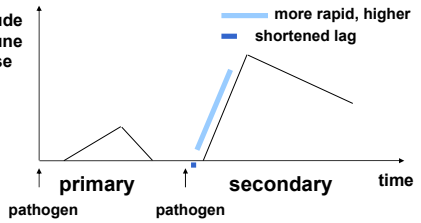
How do Vaccines work ?

- The change in frequency of specific cells = change the kinetics of the immune response
- Organism seen for first time (= primary response)

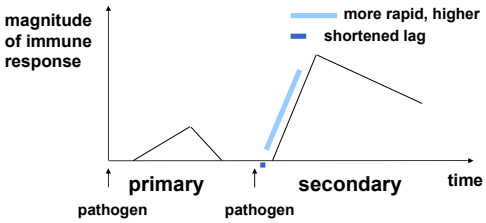


How do Vaccines work ?

- Secondary response
- More rapid, higher immune response



How do Vaccines work ?



What are the different types of Vaccines ?

5 Strategies (now combos = prime-boost)

- *A virus similar to the pathogen is used*
- *The pathogen is cultured, killed, then injected*
- *A less virulent variant of the pathogen is used*
- *Only a part (subunit) of the pathogen is used*
- *A gene encoding an antigen with a strong promoter is injected*

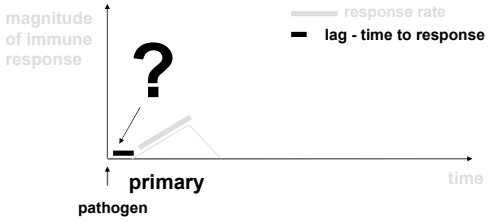
What are the different types of Vaccines ?

The best strategy may not be the same strategy !

- Where the pathogen causes eg. cancer - use a part of the pathogen only eg. Hepatitis B Virus
- Where there is a single component of the pathogen causing the disease, or sufficient for protection - use only that component eg. tetanus, use a form of the toxin; HAs, HBsAg
- Where the safety of a live vaccine cannot be guaranteed - use a non-living vaccine eg. lethal viruses like HIV

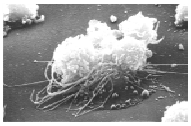
How do Vaccines work ?

- Vaccine immunology = immunology
- How to activate immune cells (DCs + 'danger')
- Maintenance of immunological memory



Activating the immune system

- DCs sense 'danger' through TLR
- TLRs receptors for pathogenic patterns (NA, LPS, flagella…) = 'danger'
- 'Danger' + antigen = DC activation, migration to node, T cells activation/proliferation, T cell migration to periphery
- Once activated, T cells can recognise antigen presented by other cells (eg. macrophages)



Vaccine trends - adjuvants

- Regulators prefer well characterised products
- Safety paramount
- ie. prefer subunit vaccines BUT
- Adjuvants are limited
- GSK bought Corixa $300mn
- CSL has large program on ISCOMS
- Pfizer partnered with Coley

- Good adjuvants now valued + growth adjuvant science (eg. TLRs, formulation..)

What does it take to make a vaccine ?

- Understanding of the disease
- Understanding of the pathogen
- Pre-genetic era - growth of the pathogen or part of the pathogen, culture attenuation (reduction in potency of the pathogen)
- Post-genetic era - growth of an experimental host (eg. *E. coli,* yeast) making part of the pathogen, 'rational' attenuation
- Testing of the vaccine = safe + effective (= $$)
- Use of the vaccine (=$)
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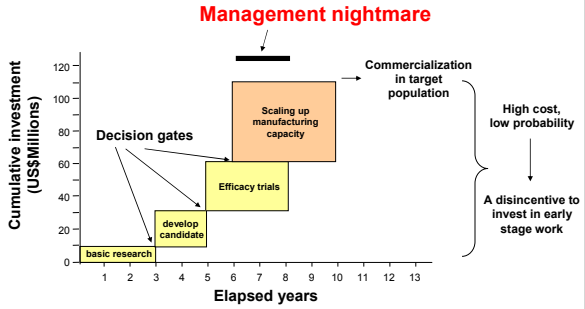
What does it really take?

- Market or perception of market in the US
- Champion
- IP position
- Interest by Biotech and/or Pharma
- $$$ (HPV PIII c.$300mn)

Vaccines – costs and decisions



Amy Batson, Orphan Vaccines 2001

Source: Mercer Management Consultants

Vaccines do not typically prevent infection

Vaccines do not typically prevent infection

- But they do prevent disease and transmission of infection to naives

Vaccines do not typically prevent infection

- But they do prevent disease and transmission of infection to naives
- Implications for HIV, Herpes infections where infection blocking may be essential

Vaccines – wins and losses

- What is a vaccine?
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- **4 case studies:**
  - **Polio**
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  - **HPV**
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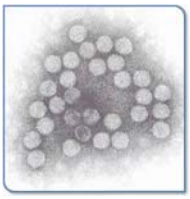
Polio

Key event I – growth of the virus *in vitro*

Weller Enders Robbins



grew poliovirus in 1950

Polio

Polio

Key event II – disease with high public profile

Rancho Los Amigos US, 1950s

Polio

Key Event III – $ + 2 champions

Killed vaccine

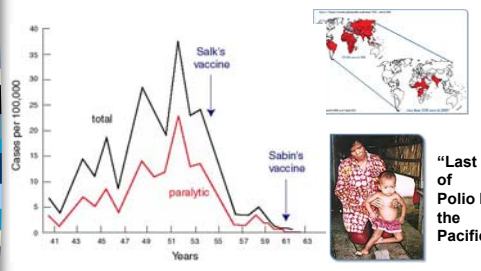
Salk - 1956

Live vaccine

Sabin - 1961

Polio

Key Event IV – rapid implementation



"Last case of Polio In the Pacific"

What does it take to make a vaccine ?

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- Testing of the vaccine = safe + effective (= $$)
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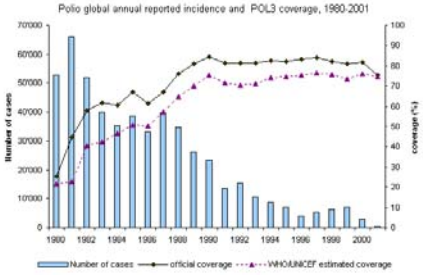
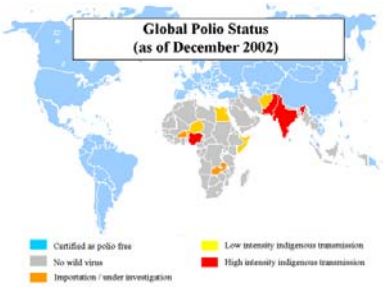
Polio

Key Event V – increased vaccination rates



Polio

Key Event VI – $ global eradication, Rotary..



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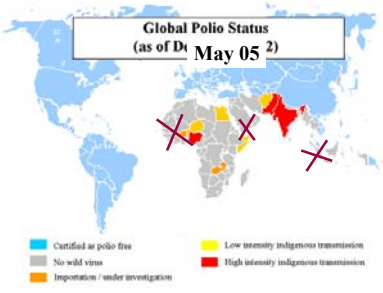
Polio

Key Event VI – political will wavering?



Polio – bottom line

- Disease control is one thing but eradication is another
- Australian government moving to Salk?

Rotavirus

- Most common cause of severe diarrhea among children
- Hospitalization c. 55,000 children USA (20-70 deaths, 400K outpatient, 2.7mn episodes)
- Deaths >600,000 children worldwide
- Incubation period 2 days
- Disease is characterized by vomiting and watery diarrhea for 3 - 8 days
- Immunity after infection is incomplete but repeat infections tend to be less severe

Rotavirus

- **1000 deaths**

Rotavirus vaccines

- Remember: Wyeth's *Rotashield*
- Live, Oral, Tetravalent
- 1 rhesus rotavirus (serotype 3) + 3 rhesus-human reassortant viruses (serotypes 1, 2, and 4)
- Intussusception background 1:2000
- Vaccine added 1:2500/5000
- Vaccine withdrawn voluntarily
- Revised c. 1:9000 additional case
- Developing countries rejected

Rotavirus vaccines

- *Rotashield*
- Protection = 49%, 52%, 83% (68 2nd)
- Severe disease = 80%, 70%, 95% (91)
- Medical intervention = 73%, 65% (82%)
- Overall 54/1127 vs 172/1146
- Approved
- USA to reduce $, ROW to reduce death

Rotavirus vaccines - new

- GSK's *Rotarix*
- Live attenuated monovalent human
- Mexico 2005 + 20 countries Latin America…
- Build safety database ex-USA
- Merck's *RotaTeq*
- Pentavalent human-bovine reassortant
- USA, EU, Asia, Latin America 2005 ? launch
- 70,000 infants, 11 countries

Rotavirus vaccines - new

- New strategy to get vaccine registered in developing world - prove safety profile ex-USA
- “Don’t ask developing world to accept rejected Western medicines”
- Where US market marginal, R&D expenses offset by differential pricing, private-public partnerships (eg. Gates + GSK)

Rotavirus vaccines - equity

Rotavirus vaccines - bottom line

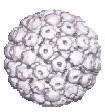
- Vaccines have the potential to significantly impact human health
- Most disease in developing world
- Need developed world to pay for the vaccine
- Establish safety in large developing world cohorts
- Licence first in developing world

HPV

- HPV, small serologically diverse virus
- >100 serotypes
- Cause of genital warts (esp HPV 6, 11)
- Cause of cervical Ca (esp HPV 16, 18, ..31)
- 470,000 cases of cervical Ca WW
- 50% die
- USA 14,000 cervical cancer per year
- No vaccine, barrier methods

HPV vaccines

- Major capsid protein L1 forms VLPs
- VLPs immunogenic
- VLPs expressed in yeast (cf. HBsAg) - Merck
- VLPs expressed in baculovirus - GSK
- Poor models, test in humans
- Merck/CSL vs GSK/Medimmune
- Very protective against homologous serotypes
- Epidemiology

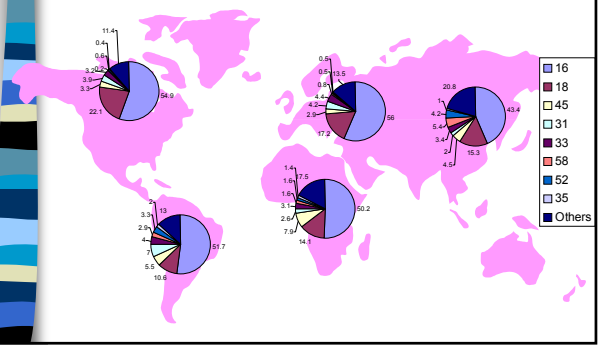


HPV vaccines

- Merck vaccine
- Tetravalent (cervical Ca + warts - 6, 11, 16, 18)
- 0/768 vs 41/765 = 100% effective
- 70% of invasive lesions
- 90% genital warts

- GSK vaccine
- Bivalent (cervical Ca - 16, 18)
- 0/401 vs 10/397 = 100% effective

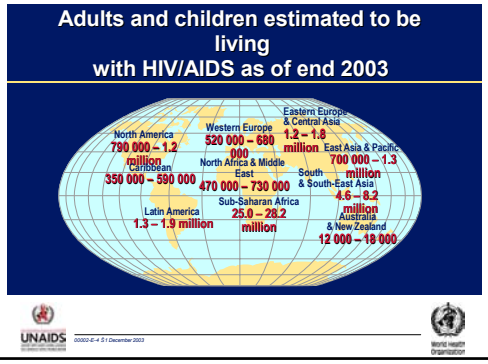
HPV serology



HPV vaccines - bottom line

- Proved relatively simple in design
- Very immunogenic, protective
- Price?
- Age and gender?
- Reimbursement?
- Differential pricing for 'Western' vaccine?

HIV



HIV

14,000 new cases per day

What does it take to make a vaccine ?

- Understanding of the disease inc. immunity
- Understanding of the pathogen
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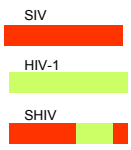
HIV vaccines - problems

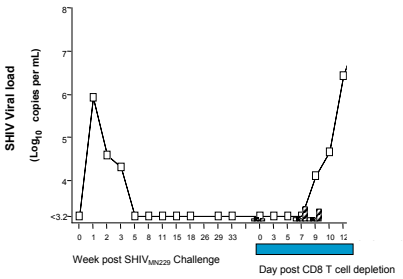
Pathogenic SHIV challenge

- A robust model to study HIV vaccines is the use of SHIV in monkeys
- SHIV is composed of the SIV virus backbone with HIV-1 genes for env, tat and rev
- Administered intrarectally to monkeys to mimic mucosal HIV exposure



HIV vaccines - correlates

SHIV control in macaques (Dale & Kent)



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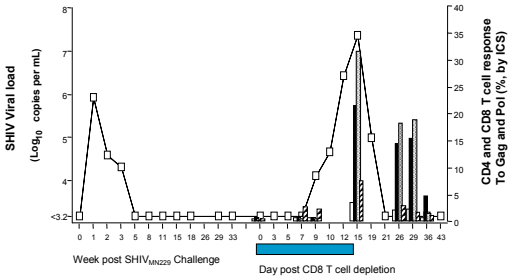
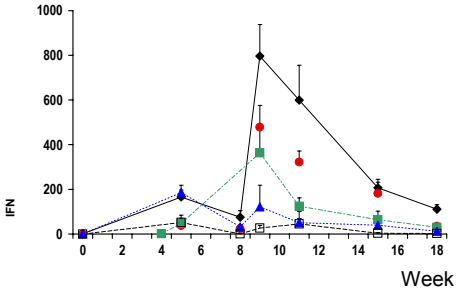


HIV vaccines - correlates

gag CTL responses in macaques (Dale & Kent)



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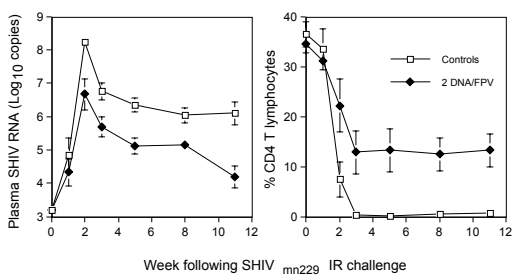

HIV vaccines - correlates?

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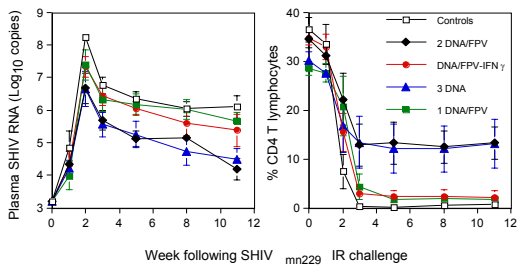

HIV vaccines - correlates

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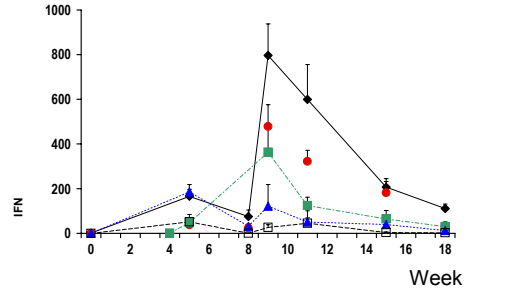
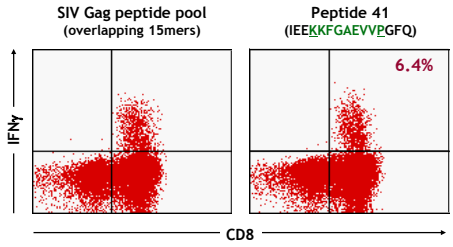


HIV vaccines - CTL escape

Immunodominant CD8+ response
(SHIV, macaques, Dale & Kent)



HIV vaccines - CTL escape

SHIV, macaques, Dale & Kent)

SIV_{mac239}	K K F G A E V V P	
$SHIV_{sf162P3}$	. . . . .	(18/18)
	. . . . .	(11/11) 2 weeks post-challenge

HIV vaccines - CTL escape

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	. . . . .	(11/11) 2 weeks post-challenge
	. R	(18/30)
	. . . . .	(11/30) 2.5 wk p.c.
	. . . . . S	(1/30)
	. R	(25/38)
	. . . . .	(13/38) 3 wk p.c.

HIV vaccines - CTL escape

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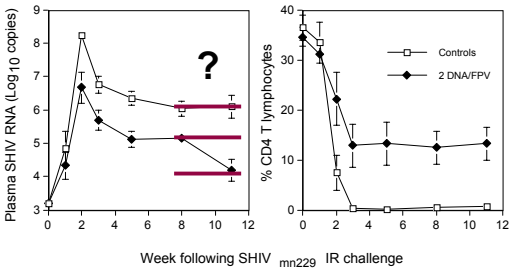
	. . . . . S	(1/30)
	. R	(25/38)
	. . . . .	(13/38) 3 wk p.c.
complete escape	. R	(9/9) 4 weeks post-challenge
	. R	(9/9) 11 weeks post-challenge

HIV vaccines - correlates

SHIV control in macaques (Dale & Kent)



HIV vaccine - bottom line

- Animal models
- Poor natural immunity, long term
- Correlates of protection?
- Has to be simple and cheap
- Has to be deliverable
- Multi-clade, multi-variant
- Possible?

Vaccines – wins and losses

- What is a vaccine?
- How do they work?
- What is needed to make a vaccine?
- 4 case studies:
  - Polio
  - Rotavirus
  - HPV
  - HIV
- **Pandemic influenza**
- Conclusions

Pandemic influenza

- **antibody-based flu vaccines are very effective esp. severe disease, ? except elderly**
- **Takes <u>at least</u> 3 months to develop a new vaccine, sometimes never adapt well to eggs**
- **Australian flu vaccine grown in eggs, chicken virulent strains will present additional hurdles**
- **Will the human-human H5 that arises be similar to current isolates?**
- **Argument for parallel development of CTL-based, broadly reactive vaccines to prevent severe disease (ie. major CTL determinants in matrix)**

Vaccines

- Exciting times
- New vaccines against rotavirus, HPV
- Major challenges with HIV, HCV
- Pandemic flu – will the paradigm be useful in a rapidly lethal outbreak?