Vaccines: Basics & Development

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Abstract

Modern vaccine development requires inputs from many different disciplines – microbiologists (assuming it is an anti-infection vaccine), immunologists, molecular biologists, geneticists and bioinformaticians, before the vaccine reaches production, then biochemists and microbiologists, engineers, marketers, health economists, insurers and ultimately lobbyists to take a vaccine into use. It is an expensive process characterised by a lack of timeliness where new vaccines are involved. The processes for producing an annual influenza virus vaccine will be contrasted with the development of the new multi-serotype dengue fever vaccine that is in late-stage testing. This presentation will highlight some recent innovations in vaccine development, where vaccine development has worked well and where unexpected hurdles have been created by unexpected biological or geographical phenomena. Some newly recognised challenges to vaccine development, such as serotype replacement post pneumococcal vaccination, will also be discussed.
Talk

• What vaccines do
• Vaccines at the crossroads
• Anti-vaccination lobby
• Development process
• How much does it cost, differential pricing
• What and who is involved
• Examples – Bexsero, seasonal flu, dengue
• Issues and opportunities
What vaccines do (and don’t do)

• Vaccines are an important aid in infection control – can be insufficient by themselves

• In cost-effectiveness, run 3rd:
  – Provision of clean water
  – Anti-smoking campaigns
  – Vaccination

• Vaccines may not prevent infection (issue with e.g. HIV where you need sterility), but they usually prevent disease and transmission
Vaccines “at the Crossroads”

• Pharma make vaccines: 5 -> 4 (3 majors)
• Vaccines compete for development capital
• Pharma preference for chronic medications
• Vaccine pricing more subject to payer pressures – tenders, scheduling...
• Prophylaxis harder to value than therapy
• The ‘low hanging fruit’ have been harvested
• Anti-vaccination lobby – unique?
6 Misconceptions re Vaccines (CDC)

- Diseases had already begun to disappear before vaccines were introduced, because of better hygiene and sanitation
- The majority of people who get disease have been vaccinated
- There are "hot lots" of vaccine that have been associated with more adverse events and deaths than others. Parents should find the numbers of these lots and not allow their children to receive vaccines from them
- Vaccines cause many harmful side effects, illnesses, and even death - not to mention possible long-term effects we don't even know about (e.g. DTaP and SIDS)
- Vaccine-preventable diseases have been virtually eliminated from the United States, so there is no need for my child to be vaccinated
- Giving a child multiple vaccinations for different diseases at the same time increases the risk of harmful side effects and can overload the immune system

http://www.cdc.gov/vaccines/vac-gen/6mishome.htm#Diseaseshadalready
Examples

Measles—United States, 1950-2001

<table>
<thead>
<tr>
<th>Disease</th>
<th>Rate</th>
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<tbody>
<tr>
<td>Measles</td>
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<tr>
<td>Pneumonia</td>
<td>6 in 100</td>
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<tr>
<td>Encephalitis</td>
<td>1 in 1,000</td>
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<tr>
<td>Death</td>
<td>1 in 500</td>
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<tr>
<td>Rubella</td>
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<tr>
<td>Congenital Rubella Syndrome</td>
<td>1 in 4</td>
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<tr>
<td>(if woman becomes infected early in pregnancy)</td>
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</tbody>
</table>

MMR Vaccine

- Encephalitis or severe allergic reaction: 1 in 1,000,000

http://www.cdc.gov/vaccines/vac-gen/6mishome.htm#Diseaseshadalready
Pathogen discovery -> Vaccine?

- Rotavirus – discovered 1973 (Bishop & Holmes)
- Rotavirus vaccine – Rotashield (withdrawn)
- RotaTeq (2006 FDA) => 33 years
- Hepatitis A – discovered 1973 (Feinstone)
- HAV vaccine - Havrix (FDA 1995) => 22 years
- HPV – virus 30s/50s, cancer 1976 (zur Hausen)
- HPV vaccine - Gardasil (2006 FDA) => 30 years
- Much shorter for e.g. H1N1, H5 influenza, SARS..
Development process

- ‘Disease economics’ – full cost of disease
- Immunity, ideally “correlates of protection”
- Strategy – live attenuated, antigen, VLP....
- Antigen discovery/genomics/bioinformatics
- Pre-clinical optimisation -> regulation
- Phase 1 – safety and immunogenicity
- Phase 2 – sometimes “proof of concept”
- Phase 3 – protection studies
- Approval
- Phase 4 – post marketing surveillance, lobbying....
How much does it cost?

- HPV - Gardasil

20,000 patients in the US approval

Cost? $750M

Beyond even CSL

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Table 1: Clinical studies

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Vaccine HPV type</th>
<th>Phase</th>
<th>Total sample size (Gardasil™ plus placebo)</th>
<th>Geographic Distribution of Study Populations</th>
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<tbody>
<tr>
<td>001</td>
<td>11</td>
<td>1</td>
<td>140</td>
<td>North America</td>
</tr>
<tr>
<td>002</td>
<td>16</td>
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<tr>
<td>004</td>
<td>16</td>
<td>1</td>
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<td>North America</td>
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<tr>
<td>005</td>
<td>16</td>
<td>2*</td>
<td>2409</td>
<td>North America</td>
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<tr>
<td>006</td>
<td>18</td>
<td>1</td>
<td>40</td>
<td>North America</td>
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<tr>
<td>007</td>
<td>6/11/16/18</td>
<td>2*</td>
<td>1106^</td>
<td>North America, Latin America, Europe</td>
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<tr>
<td>013 (011 + 012) (FUTURE I)</td>
<td>6/11/16/18</td>
<td>3*</td>
<td>5455^</td>
<td>North America, Latin America, South America, Europe, Asia, Australia</td>
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<tr>
<td>015 (FUTURE II)</td>
<td>6/11/16/18</td>
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<td>12167</td>
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<td>939</td>
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* Double-blind, randomized, placebo-controlled studies
^ Includes subjects randomized to different doses of HPV quadrivalent VLP
# Does not include 304 subjects who received HPV monovalent VLP vaccine in a bridging substudy.

Differential Pricing

GAVI Alliance

• Gates funded

• Making vaccines affordable (developing world)

• ‘generic vaccines’ – with IVI, helping in country/region... manufacturing

• Patented vaccines – arguing differential pricing

• HPV - $120/dose -> $4.50/dose (GAVI)

GAVI Alliance

Global number of under-five children unimmunised with three doses of diphtheria, tetanus and pertussis vaccine (DTP3) - See more at:

http://www.gavialliance.org/about/mission/what/#sthash.S0hGQqZo.dpuf
The Equation

Roles in contemporary vaccine development

Pre-clinical

- Microbiologists
- Immunologists
- Molecular biologists
- Geneticists
- Bioinformaticians
Roles in contemporary vaccine development

Pre-clinical

• Microbiologists – antigens, serotypes
• Immunologists – immune responses, adjuvants
• Molecular biologists – design/construction
• Geneticists – field information on variation
• Bioinformaticians – model complex data
Roles in contemporary vaccine development

Clinical and regulatory
- Clinicians
- Biochemists
- Microbiologists
- Engineers
- Marketers
- Health economists
- Insurers
- Lobbyists
Roles in contemporary vaccine development

Clinical and regulatory

• Clinicians – patients inc. diagnosis etc.
• Biochemists – optimisation of rProteins
• Microbiologists – optimisation of rec hosts
• Engineers – fermentation technology
• Marketers – name, packaging, doses..
• Health economists - pricing
• Insurers – who is going to pay?
• Lobbyists – PBS, NHS...
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Meningococcal Disease

http://aapredbook.aappublications.org/content/1/SEC131/SEC217.body
http://www.vaccineinformation.org/meningococcal/photos.asp
Meningococcal Disease

Anne Geddes

Neisseria meningitidis group B vaccine

- *N. meningitidis* has a capsule which provides the serotype (A, B, C, W135, Y commonest)
- Anti-capsule vaccines are usually very effective
- Conjugated vaccines against serotypes A, C, W135, Y produced, work effectively
- Type B capsule, same as *E. coli* K1 capsule, is an autoantigen (poly-alpha[2-->8]-N-acetylneuraminic acid) that cross reacts with human brain
Bexsero 2

• Need to find non-capsular protective antigen(s)
• Novartis used “reverse vaccinology”
Bexsero 3

• ‘heroic’ analysis of all possible antigens -> Bexsero 3+

1 dose (0.5 mL) of BEXSERO contains:

- Neisseria meningitidis Group B Neisseria Heparin Binding Antigen fusion protein\(^1\,2\) (rbe) - 50 micrograms
- Neisseria meningitidis Group B Neisseria Adhesin A protein\(^1\,2\) (rbe) - 50 micrograms
- Neisseria meningitidis Group B Factor H Binding Protein fusion protein\(^1\,2\) (rbe) - 50 micrograms
- Outer membrane vesicles (OMV) from Neisseria meningitidis group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4\(^2\) - 25 micrograms

\(^1\)Produced in *E. coli* cells by recombinant DNA technology. The NHBA (Neisseria Heparin Binding Antigen) is derived from strain NZ98/254 and is fused with accessory protein 953, derived from strain 2996; NadA (Neisseria adhesin A) is derived from strain 2996; fHBP (factor H Binding Protein) is derived from strain MC58 and is fused with accessory protein 936, derived from strain 2996.

• Clinical trials – (2600 2/12 children; 1600 11-17 yrs)
• Abs as surrogate, no protection study – why?

In Australia

- Invasive meningococcal disease is rare but causes public alarm + media attention.
- Meningococcal disease has a peak of incidence in the winter and spring months.
- Influenza virus or *Mycoplasma pneumoniae* infections may predispose to invasive disease - closer personal contact or lack of ventilation may facilitate transmission.
- 3 major serogroups of meningococci cause different patterns of disease.
  - Serogroup A meningococci cause outbreaks of infection in areas such as the meningitis belt of Africa in 8–14 year cycles.
  - Serogroup B meningococcal disease in NZ since 1990 where Maori and Pacific Island people infections were 3- and 6-times higher respectively than for the European population.
  - Serogroup C meningococci are usually associated with sporadic disease.
- Notification of ‘meningitis’ reached a **peak of 33.1 cases per 100 000 in 1942** (2371 cases) as part of a pandemic of serogroup A disease during World War II.
- Steady decline of notifications to <0.5 cases per 100 000 in 1987.
- Notification rate for meningococcal disease to the National Notifiable Diseases Surveillance System (NNDSS) has been slowly increasing over the past 10 years from **1.6 per 100 000 in 1991 to 3.1 per 100 000 in 2000**.
- In **2002** there were 129 notifications in Victoria (1/3 of the national total) of which **47 were serogroup B** and 72 were serogroup C.

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Bexsero 4

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Bexsero 5

- Bottom line – MenB is VERY rare in countries with commercial prospects
- June 2013, the UK Joint Committee on Vaccination and Immunisation (JCVI) indicated that Bexsero failed to meet the QALY test for UK’s cost threshold for vaccine efficiency (this included carer costs, patient costs...)
- JCVI concluded that a three dose course at infancy and then a ‘catch-up’ dose at adolescence would be >£17/dose the QALY breakpoint to make the vaccine cost effective
- JCVI expected Novartis to charge £40 per vaccine dose (figure from ??)
- October 2013 JCVI decided to postpone implementation of the Bexsero vaccine until further studies are conducted
- Lobbying occurred?!
- March 2014 – “Bexsero is to be made available free on the NHS, provided it can be purchased from the manufacturer at "a cost-effective price””
- Bexsero vaccine to be introduced into the childhood vaccination programme after JCVI found it effective in preventing MenB in infants, subject to price
The Bexsero issues in the UK contributed to Novartis reassessing its vaccine business.

April 2014, Novartis sold its vaccine business to GSK for $5.25B + $1.8B royalties.

Novartis to divest influenza separately.

Now large focus of vaccines in 3 companies – GSK, Merck and Sanofi.

Is this healthy for vaccine development?
Vaccine Players

- Essentially 3 but Pfizer with the biggest product (Prev(a)nar)

**Strength in combined Vaccines portfolio, notably in the US**

<table>
<thead>
<tr>
<th>Recommended Immunizations by US CDC</th>
<th>GSK</th>
<th>Novartis</th>
<th>Sanofi</th>
<th>Merck</th>
<th>Pfizer</th>
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<td>Haemophilus influenzae type b (Hib) (pediatric and adult)</td>
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<td>Inactivated Polio (IPV) (pediatric and adult)</td>
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<td>Tetanus, diphtheria, pertussis (Tdap) (pediatric and adult)</td>
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Late stage development programme including: GSK's MMR and Zoster Vaccines, Meningococcal Serogroup B (Bexsero) and MenAB CWY combination post transaction
Vaccine Players

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Late stage development programme including GSK’s MMR and Zoster Vaccines, Meningococcal Serogroup B (Bexsero) and MenABCWY combination post transaction
Influenza – seasonal vaccine

• Average **new** vaccine development – 20+ years
• Influenza vaccine made in <9 months, **every year**
• Influenza subject to antigenic drift
• WHO Meets (Sep -> Southern; Feb -> Northern)
• Best estimate of likely strains (3; 2XA, 1XB -> 4):
  – Adaptation to egg culture (CSL)
  – Production, purification, formulation
  – Limited immunogenicity testing
  – Retail
Influenza – seasonal vaccine

Influenza – seasonal vaccine

- Influenza vaccine underscores that the product is complex and that **the process** is regulated (i.e. strict GMP) cf. drugs (entity)
- “good” and less good matches between predicted strains/vaccine and infections
- Influenza vaccine efficacy (CDC, 2013-2014):
  - 52% for people 65 and older
  - 67% for children 6 months to 17 years

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6307a1.htm?s_cid=mm6307a1_w
Dengue Fever

- Dengue fever is a viral illness
- Spread by the *Aedes aegypti*, found in many tropical areas including parts of Queensland
- 4 types of the dengue virus that cause dengue fever – Dengue Type 1, 2, 3 and 4
- Serotype immunity
- Catching different types of dengue, even years apart, increases the risk of developing severe dengue
- Severe dengue causes bleeding and shock, and can be life threatening (DHF/DSS)
- Deaths in Queensland from severe dengue

Dengue Fever Vaccine

• 50-100 million cases of dengue fever/yr (??)
• 500,000 cases of DHF/DSS
• >20,000 deaths occur each year
• Several vaccines in development
• Sanofi is leading candidate vaccine
• 4 serotypes, live attenuated
• 4000 subject Phase II/III – ¾ serotypes OK (Aug 13)
• 2 Phase III RCTs (40,000 subjects)
• First Phase III “56% protection” (Apr 14)

http://www.who.int/biologicals/vaccines/dengue/en/
Dengue Fever Vaccine

• Sanofi – why dengue? = travellers + differential pricing – “disease economics”
• Sanofi invested >€1B*, so far
• Bloomberg:
  “No country is following the progress of Sanofi’s vaccine as closely as Brazil, which is preparing to host soccer’s World Cup next year and the Olympic Games in 2016. It has almost 450,000 dengue infections a year on average, more than any other country.”

*http://www.reuters.com/article/2014/03/25/us-sanofi-dengue-idUSBREA2O0TD20140325
Issue - Serotype Replacement

- Vaccines which target selected serotypes at risk from serotype replacement
- Prevnar (PC7) originally covered 7 of 91 serotypes *Str. pneumoniae*
- Common serotypes replaced by serotypes absent from the vaccine
- Vaccine increased to 13 serotypes (PC13), view towards reducing replacement - ??
Vaccines what have we learned?

• Vaccine development is getting tougher
• Can be lucrative (e.g. Prevnar – c.$4B in 2013)
• Consolidation of industry (3/4 major players)
• Costs enormous - $1B+, depends on Phase III RCTs
• Phase IIIs (e.g. RotaTeq REST 70,300 infants, PC13 CAPiTA 85,000 adults) are a considerable, risky investment - lack of disease can be a major problem
• Costs to be recovered + profit
• Vaccine Pharma can do a ‘perfect’ job and the disease changes (serotype replacement) or payer resists (UK)
Vaccines - Opportunities

Plenty:

- BBV – HIV, HCV...
- Herpes viruses – HSV, EBV, CMV...
- Better TB, better malaria, better cholera
- iNTS, ETEC, EPEC, Shigella
- STDs
- Hospital bacteria – MRSA, ESBL Kp, Pa
- ------
....and

- Therapeutic vaccines
- Weight loss vaccines
- Addiction vaccines
- ....

- Thanks Bill and Monica
- NHMRC Program Grant