Vaccines: Challenges for the Future
2016

Prof Robert Booy, NCIRS, KRI, MRI, Uni Sydney
The Children’s Hospital at Westmead, Sydney
Rinderpest, or ‘cattle plague,’ becomes only second disease to be eradicated

300 million lives saved in 20th Century due to eradication of small pox

A cow infection can cross-protect - Jenner’s research – derivation of “vaccine”
After the triumphant announcement of the eradication of smallpox in 1980 to the World Health Assembly, the WHO soon switched its attention to polio prevention, instigating in 1988 the Global Polio Eradication Initiative—a highly productive public–private partnership between WHO, Rotary International, the US Centres for Disease Control and Prevention, UNICEF, and the Bill & Melinda Gates Foundation.

By 1999, reports of wild type 2 polio had ceased, while type 3 disease left the world stage in 2012: impressive progress.

Polio of any type has even stopped circulating in the hitherto strongholds of India and Nigeria; the last cases were reported in 2011 and 2014, respectively.

Polio remains endemic only along the border of Pakistan and Afghanistan. Eradication seems in our grasp.
Is it Vaccines that lower disease in our community?
Haemophilus influenzae type B
Gold Coast Hospital

Vaccine introduced
July 1993

Last case
Jan 1995

No cases
1996-2006

H. inf type B

1983 1985 1987 1989 1991 1993 1995 1997 1999 2001 2003 2005
Video: the chain of protection

https://vimeo.com/11641261
http://www.thechainofprotection.org

(10 mins)
Name the patient and the diagnosis

Pregnancy vaccines
Pertussis vaccine for family members
Pertussis

- 90+% protection to infant if Mum vaccinated
- Advice on appropriate action if the dose of dTpa recommended during pregnancy is administered before the third trimester
  - Repeat dose not required; safe
- Vaccination is recommended in each pregnancy regardless of timing of pregnancies
- A history of extensive limb swelling after a booster dose of DTPa is not a contraindication to future recommended doses of pertussis-containing vaccine
What diseases have the highest Ro?

Importance of Herd immunity for the vulnerable
(both of those pictured)
Herpes Zoster

- Localised rash, acute pain
- Systemic symptoms
- Complications
  - Site specific
  - Secondary bacterial infection
  - Dissemination (immunocompromised)
  - Post Herpetic Neuralgia (PHN)
    - = pain persisting > 90 days
- Risk factors for PHN
  - advanced age, severe prodromal pain
  - severe pain/rash in the acute phase

Shingles, derives from the Latin cingulus, a variant of Latin cingulum meaning "girdle"
Zostavax (Seqirus/Merck)

- Live-attenuated vaccine containing the Oka VZV strain
- 14 times more virus than in chickenpox vaccine → T cell boost
- Licensed for use in adults ≥ 50 years of age
- Single dose, no recommendations for a booster…yet

How efficacious? Depends on your age…. 

<table>
<thead>
<tr>
<th>Age group (yrs)</th>
<th>Efficacy against HZ</th>
<th>Efficacy against PHN</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>70%</td>
<td>Not assessed (insufficient cases)</td>
</tr>
<tr>
<td>60-69</td>
<td>64%</td>
<td>66%</td>
</tr>
<tr>
<td>70+</td>
<td>38%</td>
<td>67%</td>
</tr>
<tr>
<td>80+</td>
<td>18%*</td>
<td>Not assessed (fewer participants)</td>
</tr>
</tbody>
</table>

(over 3 years of follow-up); * estimate not statistically significant (ie lower 95%CI < 0)
Immunocompromise and Zostavax
Clarification of advice on the use of live vaccines in people who are immunocompromised, including for persons taking disease modifying anti-rheumatic drugs (DMARDs)

- Live vaccines generally contraindicated
- May be considered in consultation with a specialist
  - e.g. Zoster vaccine may be given to adults receiving low doses of non-biological DMARDs
    - methotrexate <0.4 mg/kg per week,
    - azathioprine ≤3.0 mg/kg per day or
    - mercaptopurine ≤1.5 mg/kg per day
Advice on management of patients with major immunocompromise who inadvertently receive zoster vaccine

• Promptly seek specialist advice to establish the degree of immunocompromise in order to inform appropriate management
  • such as immunoglobulin
  • and/or antiviral therapy
  • or antibiotics
UK, Bill Gates lead $4b vaccination drive

Europe correspondent Rachael Brown, staff

Updated June 21, 2011 12:02:33

The United Kingdom and philanthropist Bill Gates are leading a multi-billion-dollar international campaign to vaccinate children in poorer nations.

Warren Buffett equalled Gates donation!
Ongoing investments..

How good an investment is pneumococcal conjugate vaccine?
3 x $3.50 is TWICE ALL OTHER EPI VACCINES
2 DOSES may be enough: 25% less cost
?? Universal pneumococcal AND flu vaccines
A universal flu vaccine in mice protected the animals against eight different flu strains

*If vaccine works in humans, we might not have to develop new flu vaccines every year*

The NIAID scientists developed a vaccine meant to protect against a number of flu strains - protected 95% of mice against eight different flu strains, compared with 5% of mice that received mock vaccinations

Vaccine was effective for >6 months & worked well in older mice

Lead investigator Dr Taubenberger, chief of the viral pathogenesis and evolution section in the ID Lab at the US National Institute Allergy & Infectious Diseases (NIAID)
### Who Should Have Flu + Pneumococcal Vaccine?

<table>
<thead>
<tr>
<th><strong>INFLUENZA</strong></th>
<th><strong>PNEUMOCOCCAL DISEASE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons aged ≥6 months with predisposing conditions</td>
<td>Conditions associated with the <em>highest</em> increased risk of IPD</td>
</tr>
<tr>
<td><strong>Immunocompromise</strong> those with HIV infection, malignancy or chronic steroid use, are at an increased risk from influenza. They may also have a reduced immune response to the vaccine)</td>
<td>- <strong>Immunocompromise</strong> congenital or acquired immune deficiency, immunosuppressive therapy, haematological, solid organ transplant, HIV</td>
</tr>
<tr>
<td>- Chronic renal failure</td>
<td>- <strong>Chronic renal failure</strong></td>
</tr>
<tr>
<td>- Pregnancy</td>
<td>- Functional or anatomical asplenia (sickle cell disease, congenital or acquired asplenia (e.g. splenectomy), splenic dysfunction)</td>
</tr>
<tr>
<td>- Obesity</td>
<td>- Cochlear implants</td>
</tr>
<tr>
<td>- Chronic neurological conditions</td>
<td>- Intracranial shunts</td>
</tr>
<tr>
<td>Other chronic illnesses</td>
<td>- Proven or presumptive cerebrospinal fluid (CSF) leak</td>
</tr>
<tr>
<td>- <strong>Diabetes Mellitus</strong></td>
<td>- <strong>Diabetes Mellitus</strong></td>
</tr>
<tr>
<td>- <strong>Cardiac Disease</strong></td>
<td>- Chronic Cardiac Disease</td>
</tr>
<tr>
<td>- <strong>Chronic Respiratory</strong></td>
<td>- Chronic Lung Disease</td>
</tr>
<tr>
<td>- Alcoholism</td>
<td>- Alcoholism</td>
</tr>
<tr>
<td>- <strong>Down Syndrome</strong></td>
<td>- <strong>Down Syndrome</strong></td>
</tr>
<tr>
<td>- Haemoglobinopathies</td>
<td>- Chronic Liver Disease</td>
</tr>
<tr>
<td>- Chronic inherited metabolic diseases</td>
<td>- Preterm birth at &lt;28 weeks gestation</td>
</tr>
<tr>
<td>- Long-term aspirin therapy in children</td>
<td>- Tobacco smoking</td>
</tr>
</tbody>
</table>

### Indigenous

- **Indigenous ≥15 years**
  - ≥15 years

- All adults aged ≥65 years - yearly

- Prevenar 13 at age 65
Efficacy of a trivalent influenza vaccine against seasonal strains and against 2009 pandemic H1N1: A randomized, placebo-controlled trial

Outline of rest of talk

- Old vaccines into new countries (developing)
- Vaccines most needed
- New vaccines for Australia
- New technologies
Existing vaccines into developing countries

- Pneumococcal vaccines (eg Africa 7v/13v PCV: Tanzania 2013)
- Hib (huge impact in Kenya; PNG 15 yrs after Aus)
- Rotavirus (poorest countries: 85% of 530,000 early childhood deaths annually)
- Rubella (to decrease rates of Congenital Rubella Syndrome)
- Hepatitis B
- Monovalent hepatitis A vaccine – sub-Saharan Africa
- Polio vaccines (Switching to IPV – and bivalent OPV, without type 2 so to prevent Vaccine-derived paralytic polio disease)
Existing vaccines into developing countries: Issues

- Disease epidemiology
- Vaccine efficacy/effectiveness
  - Reduced impact due to different socioeconomic conditions
  - Different prevalence of disease serotype/strains
- Cost
- Infrastructure
- Implementation (cold chain, administration)
- Vaccine supply
- Coverage achievable
  - changes in disease epidemiology
What would be an ideal vaccine?

- Single dose
- at birth
- life-long
- very safe
- simple eg oral/topical
- cheap
- no cold-chain
- no HCW

A nanopatch vaccine delivery approach could:
- Be more immunogenic – reduce no. of doses
  *Hit the sweet spot where dendritic cells thrive*
- ? Be given in pregnancy and at birth
- Be safer
- Be cheaper
- Remove need for HCW and cold –chain
- AND
  no more needles!/phobia/pain/cross -infection
Lincoln's family weren't to know that a little scratch could kill

The tragic death of eight-year-old Lincoln Flynn to the Australian bat disease, Lyssavirus, has inspired his family to set up a foundation in his honour to raise awareness about the preventable threat that Lyssavirus poses to Australian families.

An ideal vaccine would work even after the exposure to pathogen!
Rabies in Bali/Indonesia: now endemic

- Present in 24 of 33 Indonesian provinces
  - Bali from 2008 - Very slow local action: >130 deaths by 2011 (no PEP)
  - Improved dog vaccination / control & PEP >130,000: has ↓ deaths

- Macaque bites more prominent than dog bites in Bali
  - *No evidence* as yet that they transmit rabies

- Visitors strongly advised: avoid direct contact with dogs, cats, monkeys – *avoid cute animals*

- RIG shortage in developing countries
  - Some still don’t receive RIG in Bali / too late for RIG on return

- Not enough travellers receive pre-travel vaccination
  - *Expensive*
Measles was declared as Eliminated in Australia in 2014

- Of 119 cases in California, at least 39 directly linked to visitors or employees at Disneyland during the holidays
Epidemiological study in children <5 years from East Africa estimated 7vPnC and 13vPnC coverage in 3 African countries Mudhune S and Wamae M.


- 314 invasive pneumococcal samples serotyped:
  - 7v types and 13v types
  - Kenya 46.5% and 79.1%
  - Uganda 55.8% and 79.1%
  - Tanzania 46.2% and 100%

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Measles Cases by Month and Year, WPR, 2008–2013

3rd Regional Verification Commission March 2014
Australia
Republic of Korea
Macao SAR (China)
Mongolia
Have interrupted endemic transmission

Source: National measles and rubella monthly report
Data as of 20 February 2014
Rubella and Congenital Rubella Syndrome

- **Rubella** is a mild febrile maculopapular rash illness
  - 20-50% of infections are asymptomatic
  - Complications of encephalitis and arthritis are rare

- **Rubella infection in early pregnancy**
  - Miscarriages, fetal death, or infants born with congenital defects
  - Clinical presentation is correlated to stage of gestational infection

- **Congenital rubella syndrome**
  - Hearing Impairment, cataracts, heart defects
  - Microcephaly, mental retardation, developmental delay
  - Case-fatality of 20-30% in developing

Child with CRS, autism, mental retardation, and deafness

Surveillance in Bangladesh: CRS and CP
Estimated Number of CRS cases born in 2010

Total: 103,000 CRS cases

Source: Vynnycky, Adams et al (in press)
Quadrivalent conjugate Men vaccines – expensive!!!

Men A Vaccine development for sub-Saharan Africa

A Polysaccharide
produced by SynCo BioPartners, Amsterdam for initial
development then transferred to Serum Institute of India

Development and manufacturing
Serum Institute of India

Lyophilization & stabilization
tech transfer from Aerial in France

Target price US$ <0.50/dose

Conjugation method
developed at CBER/FDA, Bethesda, USA, transferred and scaled-up at Serum Institute of India

MVP Core Team

Tetanus toxoid
Process Development Manufacturing

Conjugation method
Reported meningitis in Burkina Faso: 2008 to 2011 (through week 14)
10 million people vaccinated within 10 days!
Which new vaccine you would most like to see developed?

Why?
PATHOGENS ON THE RAMPAGE
Three of the deadliest diseases on Earth still lack effective vaccines.

- **Malaria**:
  - 627,000 deaths
  - 207M new cases
  - Malaria mortality rates have fallen by 45% globally since 2000

- **Tuberculosis (2011)**:
  - 1.3M deaths
  - 8.6M new cases
- **HIV**:
  - 2.3M new cases
  - 1.6M deaths

Of those who died from HIV in 2012, 320,000 were co-infected with TB and died of TB.

Source: Bourzac et al. Nature 2014
Progress towards development of an HIV vaccine

Prophylactic HIV vaccines: (hopelessly) hopeful?

- Antibody-based or mucosal vaccines
  - Research ongoing
  - some promising results - killing antibody to conserved antigen

- Live attenuated vaccine
  - Not tested in human (safety concern)

- T cell-based vaccines (vector: Adenovirus Type 5)
  - Step Study 2004-7 (Buchbinder et al. Lancet 2008)
    - Multicentred, double-blind RCT of 3000 participants
    - Terminated due to ↑ risk in vacinees
      - Hazard ratio (HR)=3.9 (1.3-11.9) in uncircumcised & Adeno 5 positive
  - Phambili Study 2007, N≈800 in South Africa
    - First interim analysis (Gray et al. Lancet Infect Dis 2011)
      - HR of HIV infection=1.3 (0.8-2.1)
    - 3-yr follow-up analysis (Gray et al. Lancet Infect Dis 2014)
      - HR of HIV infection=1.7 (1.1-2.6)
Prophylactic HIV vaccines: (hopelessly) hopeful?

- T cell-based vaccines (vector: canarypox)
  - The Thailand Trial *(Rerks-Ngarm et al NEJM 2009)*
    - 4 primary doses + 2 boosters of glycoprotein vaccine
    - Vaccine efficacy = 31.2% (1.1-52.1%)

Q: A BIG success?

A: Yes, only when compared with the failure!
Malaria

- “2 million plus” deaths/yr - now nearer 1/2 million
  - mainly children, 90% in Africa
  - 2 billion people exposed to P falciparum
- Increasing drug and insecticide resistance
- Complicated lifecycle, different Antigens expressed at different stages
- Malaria genome sequenced – 5300 gene products (some potential targets)

Most malaria vaccines are *P. falciparum* subunit vaccines
One mosquito antigen
Few *P. vivax* antigens
GSK – RTS, S/AS01 candidate vaccine
Implications for duration of vaccine efficacy: secondary analysis of phase 3 RCT
Lancet Infect Dis 2015

- Modified intention-to-treat analyses
- Followed for a median of 48 months
- RTS,S/AS01 prevented a substantial number of cases of clinical malaria over a 3-4 year period in infants & children **VEs 18%-32%**
- Efficacy was **enhanced by a booster dose**

- Meningitis was reported as a SAE in 22 children: 11 in the R3R group, ten in the R3C group, and one in the C3C group
- R = central Repeat region of *P falciparum* circumsporozoite protein; T for T cell epitope of CSP; and the S for Hep B S Ag.. All combined into a fusion protein
The world's first malaria vaccine has cleared one of the final hurdles prior to being approved for use in Africa August 2015

- The European Medicines Agency has given a positive scientific opinion after assessing its safety & effectiveness
- It represents a 'green light' for the Mosquirix jab, GSK
- The World Health Organization will consider later this year whether to recommend it for children, among whom trials have yielded mixed results
- Mosquirix, otherwise known as the RTS,S vaccine, is the first against a parasite in humans
- Dr Ripley Ballou, head of research at GSK vaccines, said: "This is a hugely significant moment. I've been working on this vaccine for 30 years and this is a dream come true."
Vaccine under consideration for routine use
- 1002 episodes of malaria in 223 vaccinees
- 992 episodes in 224 infants given rabies vaccine
- Negative efficacy in 5\textsuperscript{th} year in children with higher than average exposure to malaria

- ??better to have malaria at an older age immunity to blood borne stage less in vaccinees
- Back to the drawing board?
Tuberculosis

see Doherty, Tropical Medicine and Intl Health 2004;9:818-826
Kaufmann et al, Lancet 2010; 375: 2110–19

- Incidence 8.8 million, deaths 1.8 million (WHO 2002)
- 2 billion latently infected
- Current vaccine M bovis derived bacillus Calmette-Guerin (BCG)
  - protects newborns: early miliary TB / meningitis
  - ineffective in older children/adults
- New vaccines either
  - For naïve individuals (neonates) – priming or prime/boost vaccines
  - For sensitised (latently infected) or vaccinated individuals - booster vaccines
Hiding in the shadows for decades – huge outbreak in Brazil 2015: microcephaly

August 2016: 40 cases in Singapore

1925/6: >500,000 dengue cases in Australia, even Sydney, with 147 deaths
Other vaccines making good progress

- Dengue
  - High mortality due to DHF in endemic areas
  - travel vaccine
- Staph aureus (target high risk eg pre Surgery)
- Ross River Fever
- Clostridium difficile
New Technologies

Box 2 | **New strategies for vaccine development**

**Attenuated vaccines**
- Reverse genetics, temperature-sensitive mutations and reassortment.
- Viral recombinants and deletion mutants.
- Codon de-optimization.
- Control of replication fidelity.
- MicroRNA insertion.
- Replicating vectors that contain genes from pathogens.
- Gene delivery by invasive bacteria.

**Inactivated vaccines**
- DNA plasmids and DNA shuffling.
- Reverse vaccinology.
- Antigen identification by transcriptomics and proteomics.
- Development of fusion proteins.
- Development of new adjuvants (including cytokines).
- Induction of innate immunity.
Recombinant multicomponent Meningococcal B vaccine: 4CMenB = Bexsero® (Novartis)

Bexsero: 4 Antigenic Components Chosen to Achieve Broad Protection

<table>
<thead>
<tr>
<th>Dose</th>
<th>fhbp fusion protein</th>
<th>NadA protein</th>
<th>NHBA fusion protein</th>
<th>OMV*</th>
<th>AP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5ml</td>
<td>50 mcg</td>
<td>50 mcg</td>
<td>50 mcg</td>
<td>25 mcg</td>
<td>0.5 mcg</td>
</tr>
</tbody>
</table>

*From Neisseria meningitidis serogroup B strain NZ 98/254 measured as amount of total protein containing the PorA P1.4.

Today: Happy but happier if she had been vaccinated

Will the vaccine be recommended for routine use?

New Men B vaccine licensed in Australia
Influenza vaccines

Reassortment of Influenza A Viruses

- Alpha 2,3 receptors in respiratory tract
- Non-human virus
- Alpha 2,6 & Alpha 2,3 receptors in respiratory tract
- Reassortant virus
Influenza vaccine research stimulated by increasing recognition of emerging new strains and pandemic potential

- Pandemic influenza
- H5N1 avian influenza
  - High mortality humans
  - And in chickens
- H7N9
  - High mortality humans
  - Low pathogenicity in poultry
  - ‘Wet markets’ in China
Traditional egg-based culture of flu vaccines
New Vaccine Delivery: Intradermal Flu vaccine

Cutaneous flu vaccination by the conventional intradermal route using easier and more reliable methods

“Intanza” Sanofi
Seasonal Influenza vaccine
9ug dose: 18-59 years
Private market
15ug dose: ≥ 60 years
Not on NIP yet

Micro Delivery System
Becton, Dickinson and Co.
Intranasal Administration of FluMist™
Microneedles

- **Stage:** Preclinical development
- **Features**
  - Length formulated to be long enough to penetrate the stratum corneum and viable epidermis but short enough to avoid pain.
  - Needles are dip-coated in vaccine that dries and then rapidly dissolves in skin.

For more information, see: Koutsonanos, DG, Vassilieva, EV, et. al., Delivery of a subunit influenza vaccine to skin with microneedles improves immunogenicity and long-lived protection. Scientific Reports. 2012, April 12; Article number 357, doi: 10.1038/srep00357
Targeted, Needle-Free Vaccinations in Skin using Multilayered, Densely-Packed Dissolving Microprojection Arrays

Kendall MA
Australian Institute for Bioengineering and Nanotechnology

- **Small 2010** Aug 16;6:1785-93

- Targeting of vaccines to abundant immune cell populations within our outer thin skin layers

Dissolving Nanopatch

  - small microneedles
  - *(two orders of magnitude smaller than a standard needle and syringe)*

- Using a commercial trivalent influenza vaccine [Fluvax2008]), the administration of these dissolving patches generate robust systemic immune responses in mice *two orders of magnitude greater*
Mucosal Delivery

- Edible vaccines
- Spray injectors
  - new adjuvants, mucoadhesives
- Intranasal
- Sublingual

Photo credits: Mystic Pharmaceuticals; VeriDoser

Photo Credit: Optinose
www.optinose.com/products/technical-overview
University of Central Florida and Bill and Melinda Gates Foundation help create lettuce vaccines
Edible vaccines could help eradicate disease in the developing world

Barry Marshall

20 years after his discovery that peptic ulcers were caused by a bacteria called Helicobacter pylori, Nobel Prize winner Barry Marshall is using the same bacteria as the base of an edible vaccine that has the potential to eradicate diseases in the developing world.
Questions?