Vaccine Innovation Across the Life-Cycle

Martin Friede
Initiative for Vaccine Research (IVR)
World Health Organization
# Innovation in Vaccines

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth areas</td>
<td>Risk</td>
</tr>
<tr>
<td>Competitive advantage</td>
<td>Sustainability and ROI</td>
</tr>
<tr>
<td>Public health benefit</td>
<td>Barriers</td>
</tr>
<tr>
<td></td>
<td>– Biology</td>
</tr>
<tr>
<td></td>
<td>– Regulatory</td>
</tr>
<tr>
<td></td>
<td>– IP</td>
</tr>
<tr>
<td></td>
<td>– Human stupidity</td>
</tr>
</tbody>
</table>
## Innovation in Vaccines

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Growth areas</td>
<td>- Risk</td>
</tr>
<tr>
<td>- Competitive advantage</td>
<td>- Sustainability and ROI</td>
</tr>
<tr>
<td>- Public health benefit</td>
<td>- Barriers</td>
</tr>
<tr>
<td></td>
<td>- Biology</td>
</tr>
<tr>
<td></td>
<td>- Regulatory</td>
</tr>
<tr>
<td></td>
<td>- IP</td>
</tr>
<tr>
<td></td>
<td>- Human stupidity</td>
</tr>
</tbody>
</table>
Innovation in many forms

- New vaccine (no vaccine against pathogen exists)
- Improved Vaccines:
  - Simplified production (cost of goods, supply, speed)
  - New technology (DNA, RNA, viral vectors)
  - Breadth of protection
  - Longer lasting
  - Reduced schedule
  - Combination vaccines
  - Simplified delivery
# Vaccines, the Life Cycle, and Global Opportunities

<table>
<thead>
<tr>
<th>Birth</th>
<th>Childhood</th>
<th>Adolescent Young Adult</th>
<th>Maternal</th>
<th>Older Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Existing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG, HepB</td>
<td>D,T,P,HepB, HiB,PCV,Rota MR, Influenza</td>
<td>HPV</td>
<td>Influenza</td>
<td>Influenza Zoster (PCV, tetanus)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Desired</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV</td>
<td>GAS Pertussis</td>
<td>HIV, TB, HSV, Chlamydia Gonorrhoea</td>
<td>RSV GBS Zika</td>
<td>Pneumonia E.Coli S. Aureus Pseudomonas</td>
</tr>
<tr>
<td></td>
<td>And.. Better influenza vaccines, Shigella, ETEC, Norovirus,…</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Maternal Immunization

- Tetanus
- Influenza
- Pertussis
- Group B Strep
- RSV
- Zika ?

All at the same time?
GBS vaccines

- Maternal antibody to capsular polysaccharide reduces risk of disease
  - Capsular polysaccharide conjugate vaccines in development (phase II)
    - 5-valent or higher
  - Common protein phase 1.

- Issues:
  - Phase III trial designs (endpoints)
  - Standardised immunogenicity
  - Cost, and cost effectiveness
Respiratory Syncytial Virus (RSV)

- 34 million episodes/yr under 5 yr
- 3.4 million hospitalizations
- 200,000 deaths
- No effective drugs
- Palivizumab monoclonal for high-risk preterms ($10,000/course)
RSV vaccines vaccinate mother or child?

- **1960s: inactivated virus on alum**
  - Severe immunopathology in immunized infants (Th2 response)

- **2000s: multiple candidates**
  - Live attenuated (infant)
  - Virus-like particle (maternal, infant or elderly)
  - Subunit (maternal or infant)
  - Viral vector (eg chimp adenovirus)
  - and passive immunization with monoclonals
63 candidates in pipeline

### Table: RSV Vaccine Pipeline

<table>
<thead>
<tr>
<th>Category</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live-Attenuated</strong></td>
<td>Cadagenex RSV, LID/NIAID/NIH RSV, Pfizer/Universidad Católica de Chile, St. Jude Hospital, Sanofi Pasteur, Sev/RSV</td>
<td>LID/NIAID/NIH RSV AM2-2, LID/NIAID/NIH RSV D46 capsAM2-2, LID/NIAID/NIH RSV caps2</td>
<td>Medimmune, LID/NIAID/NIH RSV D46 capsAM2-2, LID/NIAID/NIH RSV caps2</td>
<td>Medimmune, LID/NIAID/NIH RSV D46 capsAM2-2, LID/NIAID/NIH RSV caps2</td>
</tr>
<tr>
<td><strong>Whole-Inactivated</strong></td>
<td>NanoFlu RSV, AgiVax VLP, Fraunhofer VLP, Mynvax Virome, University of Massachusetts VLP</td>
<td>Novavax RSV F Nanoparticle</td>
<td>Novavax RSV F Nanoparticle</td>
<td>Novavax RSV F Nanoparticle</td>
</tr>
<tr>
<td><strong>Particle-Based</strong></td>
<td>Emory University BLP RSV pre-F, Aigiva VLP, Fraunhofer VLP, Mynvax Virome, University of Massachusetts VLP</td>
<td>Novavax RSV F Nanoparticle</td>
<td>Novavax RSV F Nanoparticle</td>
<td>Novavax RSV F Nanoparticle</td>
</tr>
<tr>
<td><strong>Subunit</strong></td>
<td>GlaxoSmithKline RSV F protein, Janssen Pharmaceutical RSV pre-F Protein, PeptVax RSV peptides, University of Georgia SH protein, University of Illinois RSV F protein, University of Saskatchewan RSV F protein</td>
<td>GlaxoSmithKline RSV post-F Protein, ImmunoVaccine RSV F protein</td>
<td>ImmunoVaccine RSV F protein</td>
<td>Medimmune RSV F protein</td>
</tr>
<tr>
<td><strong>Nucleic Acid</strong></td>
<td>CureVac RNA, GlaxoSmithKline RNA, Invivo Pharmaceuticals DNA</td>
<td>GlaxoSmithKline RNA</td>
<td>Janssen Pharmaceutical MVA</td>
<td>Medimmune RSV F protein</td>
</tr>
<tr>
<td><strong>Gene-Based Vectors</strong></td>
<td>AlphaVax MVA, Emergent BioSolutions MVA, Ruenkhiwi Biopharma Adenovirus, University of Pittsburgh Adenovirus, Adenovirus, Adenovirus</td>
<td>Janssen Pharmaceutical MVA, Adenovirus</td>
<td>Janssen Pharmaceutical Adenovirus</td>
<td>Medimmune Anti-F mAb</td>
</tr>
<tr>
<td><strong>Combination/Imuno-Prophylaxis</strong></td>
<td>Biomedical Research Models DNA prime, particle boost, Fudan University DNA+protein combo</td>
<td>Bavarian Nordic MVA, Ruenkhiwi Biopharma Adenovirus</td>
<td>Bavarian Nordic MVA, Janssen Pharmaceutical Adenovirus</td>
<td>Bavarian Nordic MVA, Janssen Pharmaceutical Adenovirus</td>
</tr>
</tbody>
</table>

**Note:** The table above categorizes RSV candidates into different types based on their development stages. Each category includes various companies and institutions working on RSV vaccines. The pipeline stages range from preclinical to market approved, with specific candidates highlighted for each phase.
Infant Immunization
## WHO EPI Schedule 1984

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>BCG</td>
</tr>
<tr>
<td>6 weeks</td>
<td>DPT, OPV</td>
</tr>
<tr>
<td>10 weeks</td>
<td>DPT, OPV</td>
</tr>
<tr>
<td>14 weeks</td>
<td>DPT, OPV</td>
</tr>
<tr>
<td>9 months</td>
<td>Measles</td>
</tr>
</tbody>
</table>
Since then...

- Hep B 2-3
- Rubella 1-dose
- HiB 3 doses
- PCV 3 doses
- Rotavirus 2-3 doses
- Meningitis
- IPV, mumps, varicella, JE, typhoid,…
DTP3 coverage 2010-2015

16 COUNTRIES HAVE MEASURABLY INCREASED DTP3 COVERAGE SINCE 2010

- 39 Chad
- 56 Papua New Guinea
- 52 Somalia
- 60 Democratic Republic of the Congo (the)
- 61 Ethiopia
- 62 Samoa
- 64 Guinea
- 73 Mauritania
- 74 Comoros (the), Congo (the), Mozambique, Lao People’s Democratic Republic (the)
- 76 Timor-Leste
- 78 Afghanistan
- 79 India
- 78 Bolivia
- 80 Gabon, Mozambique, Congo (the), Comoros (the)
- 83 Togo
- 85 Equatorial Guinea
- 86 Ethiopia
- 87 Venezuela (Bolivarian Republic of)
- 89 Lao People’s Democratic Republic (the)

DTP3 COVERAGE DECLINED BETWEEN 2010 AND 2015 IN 25 COUNTRIES

Improving coverage through technology
Some childhood vaccines in the pipeline

- **Group A Streptococcus** – major source of antibiotic use
  - Rheumatic heart disease, soft tissue infection.
  - Phase III: endpoint?

- **Enterovirus 71**
  - one approved (Sinovac),
  - others in development

- **Norovirus, shigella, ETEC**, 

- **Improved pertussis, ‘flu**
Adolescents, young adults

- HPV
- Pertussis
- New TB
- HIV
- Herpes
- Chlamidya...
HPV: The challenge is to ensure that girls are protected in areas where the risk is greatest.

Data Source: WHO/IVB Database, as at 23 January 2014

Risk of cervical cancer

HPV vaccine introduced
Vaccines for sexually transmitted infections

- Issues
  - Limits to progress with condoms,
  - Asymptomatic
  - Anti-microbial resistance

- Status: Global roadmap to move forward
  - Herpes Simplex
  - Chlamydia trachomatis
  - Neisseria gonorrhoeae
  - Trichomonas vaginalis
  - Treponema pallidum (syphilis)
Older adults

- Tetanus
- Influenza
- Pertussis?
- Herpes Zoster
- Pneumonia
We are living in an Ageing world-wide: contrasting realities

- Is the immune response of the average 65 year-old rural Kenyan the same as that of the average 65 year-old urban Japanese? How do you develop policy??
Leading causes of death, low and middle income countries, by age.

0-4 years

5-14 years

15-44 years

45-59 years

>60 years

Noncommunicable conditions

Injuries

Communicable diseases, maternal and perinatal conditions and nutritional deficiencies

Infectious diseases as triggers of excess mortality?

Importance of a life course vaccination programme
Pneumonia hospital admissions by age

Where are antibiotics most used?

Would vaccinating adults be effective?

Same vaccine or a new one?

Pneumonia hospitalisations across age groups

- Griffin NEJM 2013. 369(2) 155-159
Aging and T Cell Homeostasis

Age-dependent decline in thymic output

Antibody concentrations in young and elderly adults depending on the timepoint of the last vaccination

Hainz et al., *Vaccine* (2005)
Improving efficacy through technology

- Intradermal delivery of influenza
- High dose influenza vaccines
- Adjuvants (Herpes Zoster)
Herpes Zoster

**Risk factors**

- History of chickenpox\(^1\)
- Advancing age and waning immunity\(^1\)
  - VZV-specific immunity declines with age\(^1\)


Image courtesy of Charles E. Crutchfield III, MD. Crutchfield Dermatology, Eagan, MN.
Herpes Zoster Vaccines

- **Merck: Zostovax™**
- **GSK: Shingrix™**

Cunningham NEJM 2016
Other vaccines needed for older adults

- Clostridium difficile
- E. coli
- S. Aureus
- Pseudomonas
- Cancers, Alzheimer's,

Driven by AMR
And then there are surprises which hit all ages… where vaccines are needed
Conclusions

- Vaccines can have a huge impact on health at all ages.
- Innovation will expand the number of vaccines which will permit prevention of a wider number of infectious diseases and antimicrobial use.
- Reaching the populations and sustaining high-level coverage is and will be a challenge that will require innovation, investment and support from all health care sectors.