New Technologies in Vaccination

Rino Rappuoli

Future vaccinology building on present evidence and experience

ECDC-Eurovaccine 2010
Stockolm, December 10 2010
20th Century Vaccines
Development via Pasteur principles

- Killed vaccines & VLPs
- Live attenuated vaccines & Vectors
- Subunit vaccines & recombinant & conjugate vaccines

Isolate
Inactivate
Inject
the causative organism
Pasteur’s sustainable Conquest of Infectious Diseases by Vaccination reduced by more than 97% the incidence of 9 infectious diseases and completely eliminated two diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Max. N° of cases (year)</th>
<th>N° of cases in 2001</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>48,164 (1901-1904)</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>21,269 (1952)</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>206939 (1921)</td>
<td>2</td>
<td>99.99%</td>
</tr>
<tr>
<td>Measles</td>
<td>894134 (1941)</td>
<td>96</td>
<td>99.99%</td>
</tr>
<tr>
<td>Rubella</td>
<td>57686 (1969)</td>
<td>19</td>
<td>99.78%</td>
</tr>
<tr>
<td>Mumps</td>
<td>152209 (1968)</td>
<td>216</td>
<td>99.86%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>265269 (1934)</td>
<td>4788</td>
<td>98.20%</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>20000 (1992)</td>
<td>242</td>
<td>98.79%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1560 (1923)</td>
<td>26</td>
<td>98.44%</td>
</tr>
</tbody>
</table>

The Greatest Revolution in the History of Mankind
Vaccination remains the medical intervention with highest impact on health

Drop in death rate for diseases prevented or treated with innovative medicines (pharmaceuticals)
1965 – 1999

**Infectious Diseases** (polio, measles, Hib, HVB, Hib etc)
- >97%

**VACCINATION**

**THERAPEUTICS**

- Rheumatic fever and rheumatic heart disease: -75%
- Hypertensive heart disease: -67%
- Ulcer of stomach and duodenum: -61%
- Ischemic heart disease: -41%

*Source: EFPIA 1999 – 2002*
Key Questions

In the 20th century vaccines eliminated most childhood diseases using old technologies

- What are vaccines role in the 21st century?
- Should we be excited about vaccines?
In the last 30 years, new technologies have expanded the pool of vaccine targets and improved vaccine safety.
Vaccines will help to address the new major health challenges of the 21st century:

1. 21st century society, "aging society"
2. Emerging infections
3. Poverty
European Life Expectancy
1750 - 2006

Which factors have influenced this change?

Crimmis et al. Attribute the Increase of Life Expectancy to the Conquest of Infectious Diseases

- Less Infectious Diseases
- Reduced infant mortality
- Reduced inflammation
- Increased Life Expectancy
- Reduced Mortality in the Elderly

More recently, Reductions in Cardiovascular and Infant Mortality are the Key Factors Driving Increased Life Expectancy in the U.S.

Life expectancy at birth in years

69.9

Life expectancy at birth: 1960

Increased life expectancy due to reduced cardiovascular mortality

4.9

1.4

0.4

0.3

0.2

-0.2

76.9

Life expectancy at birth: 2000

>50% hereof through better medical care of low birth weight infants

>50% hereof through improvements in medical care, e.g., statins, antihyperintensives, aspirin

Source: Cutler - DM et. al., NEJM 335;9
Life Expectancy is outpacing Prediction

*With an aging society, we need a new model for health care*

Vaccination provided the solution for childhood disease

In the future, vaccination will be the best health insurance for all ages
Today, HIV in Africa illustrates the impact of infectious disease on life expectancy

Source: World Bank World Development Indicators, 2004
Safety from technology

21st Century Vaccines
In the 20th century, Crude Preparations Were Often Associated With Safety Concerns

- **The Cutter IPV incident**  
  Poliomyelitis to 56 children, 5 deaths
- **Smallpox**  
  Generalized vaccinia, encephalitis, myocarditis
- **Oral polio**  
  Paralytic disease in vaccinees and contacts
- **Measles high dose**  
  Increased mortality from all causes in vaccinees
- **DPT (whole cell P)**  
  Febrile seizures and encephalopathy (disproved)
- **Rotavirus (Rotashield)**  
  Intussusception (bowel obstruction)
- **BCG (tuberculosis)**  
  Disseminated BCG infection
- **Thimerosal**  
  Neurodevelopmental delays (disproved)

Vaccines great but dangerous  
“parents are more afraid of vaccines than disease”
In the 21st century eliminated the vaccines with safety concerns

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Concerns</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Cutter IPV incident</td>
<td>Poliomyelitis to 56 children, 5 deaths</td>
<td>Solved</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Generalized vaccinia, encephalitis, myocarditis</td>
<td>Discontinued</td>
</tr>
<tr>
<td>Oral polio</td>
<td>Paralytic disease in vaccinees and contacts</td>
<td>Discontinued</td>
</tr>
<tr>
<td>Measles high dose</td>
<td>Increased mortality from all causes</td>
<td>Discontinued</td>
</tr>
<tr>
<td>DPT (whole cell P)</td>
<td>Febrile seizures and encephalopathy</td>
<td>Discontinued</td>
</tr>
<tr>
<td>Rotavirus (Rotashield)</td>
<td>Intersusception (bowel obstruction)</td>
<td>Discontinued</td>
</tr>
<tr>
<td>BCG (tuberculosis)</td>
<td></td>
<td>Discontinued</td>
</tr>
<tr>
<td>Thimerosal</td>
<td>Neurodevelopmental delays (disproved)</td>
<td>Discontinued</td>
</tr>
</tbody>
</table>

No more serious dangerous effects associated with vaccination.
Vaccines today

- Vaccines today are among the most sophisticated users of 21\textsuperscript{st} century technologies

- The mindset of people is still in the 20\textsuperscript{th} century
New vaccines from technology

Glyco-conjugation
Reverse Vaccinology
Next Generation Technology
Meningococcal disease
a failure of modern medicine, case fatality rate 8-25%

Caused by *Neisseria meningitidis* capsular serogroups A, B, C, Y, W135

Death
Severe disability
Tragedies covered by media

The well-liked child, Evelyn Cortez-Covarrubias, attended school on Friday and complained of a stomachache, Packer said. Her condition quickly worsened and she died three days later.

Dreaming the olympic games like Pistorius
*Neisseria meningitidis* is a bacterium surrounded by a capsular polysaccharide (a polymer of sugars), each with distinct chemical composition.
Polysaccharides are not good vaccine antigens

- Limited immune response
  - Only B cells respond
  - No T cell response
  - No memory
- They do not work in newborns and children
Glyco-conjugation improves the immunogenicity of polysaccharides

A glycoconjugate vaccine against serogroup C was developed in the early 90's
Conjugate vaccines for Meningococcus C eliminated the disease in the UK

Laboratory Confirmed Cases of Serogroup C Meningococcal Disease (England & Wales)

Since the introduction of the UK MenC vaccine in 1999

>10,000 cases prevented
>1,000 deaths prevented
>2,000 permanent sequalea prevented
Menveo® uses the CRM197 protein conjugated to the capsular polysaccharides to induce protection in all ages against serogroups A, C, W, Y.
Meningococcus B capsule is a self antigen and cannot be used for vaccination.
Safety from technology

Glyco-conjugation
Reverse Vaccinology
Next Generation Technology

Empirical approach
- Diphtheria
- Tetanus
- Pertussis
- Rabies
- Influenza
- Smallpox
- Polio

Glyco-conjugation
- MenACWY
- S. pneumoniae
- Hib
- GAS
- GBS
- S. aureus

Reverse vaccinology
- MenB
- GBS
- GAS
- Expec
- S. aureus
- C. difficile

Next generation technologies
- Adjuvants
- Structural vaccinology
- Viral vectors
Reverse vaccinology

*a genomic approach to vaccine discovery*

- 600 potential vaccine candidates identified
- 350 proteins successfully expressed in E.coli
- 91 novel surface-exposed proteins identified
- 28 novel proteins have bactericidal activity

**VACCINE CANDIDATES**
600 antigens identified, 350 tested, 3 candidates selected
4CMenB Vaccine Composition

- Three protein antigens (two fusion proteins and one single polypeptide)
- Outer Membrane Vesicle (OMV) component (NZ PorA is P1.4)

4CMenB is a suspension for injection via pre-filled syringe

<table>
<thead>
<tr>
<th>Dose</th>
<th>OMV</th>
<th>Al³⁺</th>
<th>NHBA-953</th>
<th>936-fHbp</th>
<th>NadA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5ml</td>
<td>25 μg</td>
<td>0.5 mg</td>
<td>50 μg</td>
<td>50 μg</td>
</tr>
</tbody>
</table>
Percentage of Subjects With Bactericidal Titers ≥1:5
*Phase III Study V72P12 in infants*

4CMenB given at 2, 4, 6, and 12 months

<table>
<thead>
<tr>
<th>Strain Antigen</th>
<th>Baseline</th>
<th>Post-primary*</th>
<th>Pre-booster</th>
<th>Post-boost†</th>
</tr>
</thead>
<tbody>
<tr>
<td>44/76-SL fHbp</td>
<td>100</td>
<td>100</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>5/99 NadA</td>
<td>100</td>
<td>99</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>NZ98/254 PorA 1.4</td>
<td>84</td>
<td></td>
<td>95</td>
<td>20</td>
</tr>
</tbody>
</table>

*Blood drawn at 7 months, N=1149-1152.*
†Blood drawn at 13 months, N=421-424.
A new meningococcal Typing Antigen System (MATS) to predict coverage in individual geographies

- Effectiveness of 4CMenB being defined based on local epidemiological surveillance
- Proprietary method (MATS) for assessing effectiveness transferred to collaborating national reference laboratories

Analysis is ongoing – full results expected to be presented at EMGM, Slovenia in May 2011

MATS: Meningococcal Antigen Typing System
Reverse vaccinology allows us to target many pathogens that were difficult or impossible before.

- **Group B Streptococcus**
- **Group A Streptococcus**
- **Pneumococcus**
- **Chlamydia trachomatis and Pneumoniae**
- **Tuberculosis**
- **Gonococcus**
- **Malaria**
- **Porphyromonas gingivalis**
- **Yersinia pestis**
- **Staphylococcus**
- **C. difficile**
- **Pseudomonas**
- **Antibiotic resistant!!!!**
Next generation technology

Glyco-conjugation
Reverse Vaccinology
Next Generation Technology
New vaccine technologies will help to address emerging infections/the role of adjuvants

From June to December 2009 3 H1N1 vaccines were:

- Developed
- Tested in clinical trials
- Licensed

- 180 million doses produced
MF59: An established adjuvant in a European-licensed seasonal trivalent vaccine

- Oil-in-water emulsion adjuvant licensed for use in seasonal influenza vaccine FLUAD®* since 1997
  - More than 100 million commercial doses distributed

- Adjuvanted vaccine provides heterologous responses to drifted strains

- >120 Clinical studies, >200,000 subjects
  - No safety signals in either pharmacovigilance database or meta-analysis of clinical trial database with 6 month subject follow-up (filed with CBER)

- Pediatric studies and efficacy trial in 3,000 subjects

*FLUAD® is a registered trademark of Novartis. FLUAD is not licensed in the United States. FLUAD is recommended for active prophylaxis of influenza in the elderly
## Fluad® Pediatric Efficacy Preliminary Results

*(n=4706 subjects 6-72 m) protection from confirmed PCR flu infection*

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Age</th>
<th>Cases/Vaccinated</th>
<th>VE % (CI)</th>
<th>Target</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy Against Matched Strains</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluad® vs. Non-influenza controls</td>
<td>6 to &lt;36 mos</td>
<td>7/1104 vs. 23/566</td>
<td>84.4 <em>(55.6 to 94.5)</em></td>
<td>Lower CI ≥40</td>
<td>Met</td>
</tr>
<tr>
<td></td>
<td>36 to &lt;72 mos</td>
<td>2/836 vs. 25/426</td>
<td>95.9 <em>(75.4 to 99.3)</em></td>
<td>Lower CI ≥40</td>
<td>Met</td>
</tr>
<tr>
<td>Fluad® vs. TIV</td>
<td>6 &lt;36 mos</td>
<td>7/1104 vs. 27/996</td>
<td>75.4 <em>(31.2 to 91.2)</em></td>
<td>Lower CI ≥10</td>
<td>Met</td>
</tr>
<tr>
<td></td>
<td>36 to &lt;72 mos</td>
<td>2/836 vs. 26/776</td>
<td>92.2 <em>(53.5 to 98.7)</em></td>
<td>Lower CI ≥10</td>
<td>Met</td>
</tr>
<tr>
<td>TIV vs Non-influenza Control</td>
<td>6 &lt;36 mos</td>
<td>27/996 vs. 23/566</td>
<td>36.7 <em>(−24.3 to 67.8)</em></td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Efficacy Against Any Strains</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluad® vs. Non-influenza controls</td>
<td>6 to &lt;36 mos</td>
<td>9/1104 vs. 28/566</td>
<td>81.0 <em>(58.3 to 91.3)</em></td>
<td>Lower CI ≥40</td>
<td>Met</td>
</tr>
<tr>
<td></td>
<td>36 to &lt;72 mos</td>
<td>5/836 vs. 31/426</td>
<td>91.8 <em>(73.5 to 97.5)</em></td>
<td>Lower CI ≥40</td>
<td>Met</td>
</tr>
<tr>
<td>Fluad® vs. TIV</td>
<td>6 to &lt;36 mos</td>
<td>9/1104 vs. 35/996</td>
<td>69.1 <em>(32.6 to 85.8)</em></td>
<td>Lower CI ≥10</td>
<td>Met</td>
</tr>
<tr>
<td></td>
<td>36 to &lt;72 mos</td>
<td>5/836 vs. 31/776</td>
<td>85.8 <em>(50.3 to 96.0)</em></td>
<td>Lower CI ≥10</td>
<td>Met</td>
</tr>
<tr>
<td>TIV vs Non-influenza Control</td>
<td>6 to &lt;36 mos</td>
<td>35/996 vs. 28/566</td>
<td>38.1 <em>(−8.2 to 64.6)</em></td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Vaccination: Addressing major health challenges

21st century society, the “aging society”
Emerging Infections
Poverty
Vaccines against poverty
Subtitle A major challenge for developing countries in the 21st century

- Infectious diseases, in addition to causing morbidity and mortality, are a major contributor to poverty

- In developing countries “they extract a huge toll from the income of each family and throw them into a downward spiral of poverty” (Leslie Roberts, Science 2008)

- Vaccination can control many of the infectious diseases
An Institute to address the gaps in vaccine development

In the recent past, no mechanism was in place to develop vaccines needed only in developing countries

Novartis Vaccines Institute for Global Health (NVGH)

A new non-profit initiative to develop effective and affordable vaccines for neglected infectious diseases of developing countries

- Legal entity started in Feb 2007
- Allan Saul hired as CEO Sept 2007
- Inauguration Feb 22, 2008
Childhood Deaths (28 days to 5 years)

2000 Global data, 6.6 million deaths, 27% DIARRHEA

http://www.who.int/whosis/whostat/EN_WHS08_Full.pdf
Salmonella vaccine

NGVH

- Four programs
  - *Salmonella typhi* (typhoid fever) / Vi conjugate / Phase I Q1 2010
  - *Salmonella paratyphi* / O antigen conjugate / Phase 1 Q4 2011
  - *Salmonella typhimurium* / O antigen conjugate / Phase 1 Q1 2012
  - *Salmonella enteriditis* / O antigen conjugate / Phase 1 Q1 2012

- A conjugate for typhoid fever is expected to enter infant routine vaccination in South-East Asia, a second generation for South-East Asia is a vaccine against *Salmonella typhi* and *paratyphi*

- A combination vaccine against *Salmonella typhimurium* and enterica is expected to enter in routine vaccination in Africa