Vaccines to address the needs of the 21st century society

Rino Rappuoli

Viruses, the invisible enemy,
Sixth world conference on the Future of Science

Venezia, September 20, 2010
Vaccine in the 20th century were developed following the Pasteur principles
Pasteur Started the Greatest Revolution in the History of Mankind

The Sustainable Conquest of Infectious Diseases by Vaccination that reduced by more than 97% the incidence of 9 infectious diseases and eliminated two of them

<table>
<thead>
<tr>
<th>Disease</th>
<th>Max. (N^\circ) of cases (year)</th>
<th>(N^\circ) 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>
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*
Most Successful Vaccines look like a black and white photo nice but old technology
Key questions

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

What is their role in the 21^{st} century?

Should we be excited about vaccines?
We are very excited about Vaccines and building Vaccines research groups globally.

- **Cambridge**, 2008: Global Center of Excellence in Virology
- **Siena**, 2007 and 2011+: Global Center of Excellence in Bacteriology
- **Shanghai**, 2011+: Global Center of Excellence for Unmet Medical Needs in Asia
New technologies during the last 30 years expanded the pool of vaccine targets
Vaccines will help to address the new major health challenges of the 21st century society, “aging society“

1. Emerging infections

2. Poverty
A Study Analyzed the Causes of Increased Average Life Expectancy in European Countries From 1750 to 1900

Which factors have influenced this change?

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

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

- **1960**: 69.9
  - Increased life expectancy due to reduced cardiovascular mortality
  - Reduced infant death
  - Reduction in rate of death due to accident, suicide, homicide
  - Reduction in rate of death due to pneumonia, influenza
  - Reduction in rate of death due to cancer
  - Other causes; e.g., HIV, obesity, others

- **2000**: 76.9
  - >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 Growing Beyond Prediction

Society is Aging

We Need a New Model for Health Care
Vaccination took care of childhood diseases

In the future they will be the best health insurance for all ages
HIV in Africa Is the Tragic Example of the Impact of Infectious Diseases On Life Expectancy

Source: World Bank World Development Indicators, 2004
... In my city, Siena, an unfinished cathedral is the largest existing monument to Infectious Diseases, standing reminder of a flourishing economy and culture wiped out forever in just three months by the 1348 PLAGUE.
Safety of vaccines increased in the 21st century
Vaccine in the 20th century were developed following the Pasteur principles.
In the 20th century, Crude Preparations Were Often Associated With Safety Concerns

- **Smallpox**  
  generalized vaccinia, encephalitis, myocarditis
- **Oral polio**  
  paralytic disease in vaccinees and contacts
- **Measles high dose**  
  increased mortality from all causes in females
- **DPT (whole cell P)**  
  febrile seizures and encephalopathy
- **Rotavirus (Rotashield)**  
  intersusception (bowel obstruction)
- **BCG (tuberculosis)**  
  disseminated BCG infection
- **Thymerosal**  
  developmental delays (disproved)

"parents are more afraid of vaccines than disease"
In the 21st century we discontinued the use of the vaccines with safety concerns:

- **Smallpox**
  - generalized vaccinia, encephalitis, myocarditis
  - **Discontinued**

- **Oral polio**
  - paralytic disease in vaccinees and contacts
  - **Discontinued**

- **Measles high dose**
  - increased mortality from all causes in females
  - **Discontinued**

- **DPT (whole cell P)**
  - febrile seizures and encephalopathy (disproved)
  - **Discontinued**

- **Rotavirus (Rotashield)**
  - intersusception (bowel obstruction)
  - **Discontinued**

- **BCG (tuberculosis)**
  - disseminated BCG infection
  - **Discontinued**

- **Thymerosal**
  - autism, neurodevelopmental delays (disproved)
  - **Discontinued**

No more serious dangerous effects associated with vaccination.
Glyco-conjugation

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

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

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

- Next generation technologies
  - Adjuvants
  - Structural vaccinology
  - Viral Vectors

---

NOVARTIS VACCINES
Meningococcal disease
a failure of modern medicine, case fatality rate 8-25%

Caused by *Neisseria meningitidis* capsular serogroups A, B, C, Y, W<sub>135</sub>
Glyco-conjugation improves the immunogenicity of polysaccharides

A glycoconjugate against serogroup C was developed early 1990’s

C antigen
Conjugate vaccines for Meningococcus C eliminated the disease in the UK

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

Immunization with serogroup C conjugate vaccine in 15-17 yr olds began in November 1999
Conjugate vaccines for Meningococcus C eliminated the disease in the UK

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

Since the UK MenC vaccine introduction in 1999:

> 10,000 cases prevented
> 1,000 deaths prevented
> 2,000 permanent sequelae prevented
Menveo® uses a protein conjugate to the capsular polysaccharide to protect all ages against serogroups A, C, W, Y

A antigen  C antigen  W antigen  Y antigen
Meningococcus B capsule is a self antigen and cannot be used for vaccination.
Reverse Vaccinology

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

- Glyco-conjugation
  - MenACWY
  - S. pneumo
  - 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

In silico vaccine candidates
Express recombinant proteins
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

Antibiotic resistant!!

Staphylococcus
C. difficile
Pseudomonas

[Diagram depicting the connections between these pathogens and the concept of reverse vaccinology]
Next Generation Technologies
Emerging infections

Next generation technologies
Adjuvants
Structural vaccinology
Viral Vectors

Empirical approach
Diphtheria
Tetanus
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

Reverse vaccinology

Viral Vectors
New vaccine technologies will help to address emerging infections/the role of adjuvants

From June to December 2009 3 H1N1 vaccines were:

- Developed
- Test 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 45 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
Vaccine produced quickly but pandemic was faster

Example from US during H1N1 pandemic

Close to 40% of cases occurred in a time when no meaningful vaccine quantities were available

Source: [http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm](http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm) and [http://www.cdc.gov/flu/weekly/index.htm](http://www.cdc.gov/flu/weekly/index.htm); As of Jan16, 2010 the CDC estimated that about 57 million people are infected with 2009 H1N1. Weekly data on influenza positive tests reported to CDC by U.S. WHO/NREVSS collaborating laboratories applied to CDC estimate to arrive at the weekly estimate for number of cases in the US.
Vaccines against poverty

A major challenges 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 projects at NVGH

- Composed of 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.
Per saperne di più sui vaccini