Vaccines on the Global Scale
Learning from the past and aiming at the future

Edwin J. Asturias, MD
Associate Professor of Pediatrics and Epidemiology
Director for Latin America
Center for Global Health, Colorado School of Public Health

Colorado Regional Immunization Summit
CCIC – Grand Junction, October 23, 2015
Disclosures

• Research grants and consulting for Takeda Vaccines and GSK (Novartis)
• Funded by Bill and Melinda Gates Foundation for research on polio

No competing interest for this presentation
Objectives

• Describe the burden and impact of VPDs worldwide
• Apply lessons learned from global experience in vaccine policy
• Summarize current priorities and strategies for universal vaccine coverage
• Understand the new vaccine pipeline and challenges ahead
Childhood deaths reducing worldwide!
Impact of vaccines, malaria prevention and neonatal health
Progress towards reducing child mortality by Region – MDG4

Proportion of countries making progress toward reducing child mortality (% of countries in region)

Source: World Bank staff estimates
Projected under-5 mortality rate in 2030, on the basis of the observed rate of change for each country, 2000–13
Lessons learned from the global use of vaccines

• Eradication is seldom a feasible goal
Situation as of 2015

- 48 cases compared to 221 (22%)
- 36 from Pakistan, 12 Afghanistan
- 13 VDPV cases (36 in 2014)
- None in Africa since 07/14
- No wild PV2 or PV3

Excludes viruses detected from environmental surveillance.
Polio endgame strategy 2013-18

**OBJECTIVE 1**
Poliovirus Detection and Interruption

- Wild poliovirus interruption
- Outbreak response (especially cVDPVs)

**OBJECTIVE 2**
Strengthening Immunization Systems and OPV Withdrawal

- Strengthen Immunization Systems
  - Address pre-requisites for OPV cessation
- Complete IPV introduction and OPV withdrawal
- IPV and OPV in Routine Immunization

**OBJECTIVE 3**
Containment and Certification

- Finalize long-term containment plans
- Complete containment and certification globally

**OBJECTIVE 4**
Legacy Planning

- Consultation
- Mainstream polio functions, infrastructure and learning

* Essential activities (e.g., surveillance, laboratory network and IPV in routine immunization) will be mainstreamed beyond 2019.
Lessons learned from the global use of vaccines

- Eradication is seldom a feasible goal
- Value of vaccines is only obvious when it reaches the most needed
Uptake of Hib and pneumococcal vaccines in high-income versus low-income countries

Hib = Haemophilus influenzae type b. PCV = pneumococcal vaccine.
Dashed line = projected uptake. Solid line = actual uptake.

Mission and strategic goals 2011–2015

To save children’s lives and protect people’s health by increasing access to immunisation in poor countries

1. The vaccine goal
   Accelerate the uptake and use of underused and new vaccines

2. The health systems goal
   Contribute to strengthening the capacity of integrated health systems to deliver immunisation

3. The financing goal
   Increase the predictability of global financing and improve the sustainability of national financing for immunisation

4. The market shaping goal
   Shape vaccine markets to ensure adequate supply of appropriate, quality vaccines at low and sustainable prices
Countries having introduced Hib vaccine in 1997 and 2014

1997
- 29 countries introduced
- 2 countries partially introduced

2014
- 190 countries introduced
- 2 countries partially introduced

Map production: Immunization Vaccines and Biologicals (IVB), World Health Organization.
194 WHO Member States. Date of slide: 28 July 2014
# EPI program success around the world as of 2014 – WHO databases

<table>
<thead>
<tr>
<th>Vaccine Preventable Disease</th>
<th>Global cases (2014)</th>
<th>Estimated Global Deaths (2013)</th>
<th>%Global Vaccine Coverage (2014)</th>
<th>% Reduction from reported peak</th>
<th>Target GVAP &gt;90% coverage (No. of gap countries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>7,321</td>
<td>5,000</td>
<td>86</td>
<td>92</td>
<td>65</td>
</tr>
<tr>
<td>Tetanus neo</td>
<td>2,161</td>
<td>49,000</td>
<td>64</td>
<td>94</td>
<td>24</td>
</tr>
<tr>
<td>Pertussis</td>
<td>139,786</td>
<td>254,000</td>
<td>86</td>
<td>93</td>
<td>65</td>
</tr>
<tr>
<td>Polio</td>
<td>376</td>
<td>&lt;50</td>
<td>86</td>
<td>99</td>
<td>3</td>
</tr>
<tr>
<td>Measles</td>
<td>266,701</td>
<td>145,700</td>
<td>85</td>
<td>94</td>
<td>$16%</td>
</tr>
<tr>
<td>Hib</td>
<td>8,371</td>
<td>10,000</td>
<td>56</td>
<td>98</td>
<td>65</td>
</tr>
</tbody>
</table>

§ children not receiving
Vaccine-Preventable Mortality
Among Children Under 5

- Pneumococcal diseases*: 32%
- Tetanus: 4%
- Measles: 8%
- Pertussis: 13%
- Hib*: 13%
- Rotavirus*: 30%

*WHO estimates
Lessons learned from the global use of vaccines

• Eradication is seldom a feasible goal
• Value of vaccines is only obvious when it reaches the most needed
• Community protection is as important as individual protection
Direct and indirect effect on invasive pneumococcal diseases in the USA after introduction of the 7V pneumococcal conjugate vaccine in children aged < 2 y in 2000
Lessons learned from the global use of vaccines

• Eradication is seldom a feasible goal
• Value of vaccines is only obvious when it reaches the most needed
• Community protection is as important as individual protection
• Reaching the last 10% requires understanding of the determinants of health
73% of the 24 million unimmunized children live in 10 countries

- India, 9.7 million
- Nigeria, 2.4 million
- Indonesia, 1.1 million
- China, 1.2 million
- Pakistan, 0.7 million
- Ethiopia, 0.8 million
- Uganda, 0.5 million
- Niger, 0.4 million
- Bangladesh, 0.4 million
- Congo, Democratic Republic, 0.4 million
- Rest of the world, 6.6 million
Why are vaccines key for global health?

• Most impactful and equitable preventive technology
• Effective at reducing the infectious diseases burden in target populations
• Direct and indirect effects
• Societal value and economic value
Effect of vaccine prevention on earnings and wealth

• Fewer missed school days (better attendance)
• Less long term disability
• Changes in household behavior after survival
• Better cognitive development
  • Philippines: vaccination effect on scores in math, language and cognition
  • Estimated return on investment of 21%
Progress in Introduction of Pneumococcal Conjugate Vaccine Worldwide, 2000–2012

- 36 (73%) of 50 high-income countries introduced PCV
- 13 (37%) of 36 low-income
- 18 (35%) of 52 lower-middle income
Rates of Pneumococcal invasive diseases death around the world 2012
Countries that have introduced pneumococcal conjugate vaccines in their national Immunization programs, by income status* — worldwide, 2012

[Map showing countries with pneumococcal conjugate vaccines by income status]
Global Vaccine Action Plan (GVAP)

• Framework to prevent millions of deaths by 2020 through more equitable access to existing vaccines for people in all communities

• Endorsed at 2012 World Health Assembly

• Developed by Decade of Vaccines (DoV) Collaboration
Beyond preventing 426 million cases of illness and averting 6.4 million deaths in the next 10 years...
Vaccine safety going viral and global

Donald J. Trump
@realDonaldTrump

Healthy young child goes to doctor, gets pumped with massive shot of many vaccines, doesn't feel good and changes - AUTISM. Many such cases!
Perception of Safety of Vaccines according to the Program Effectiveness

Stage 1: Pre-vaccine
Stage 2: Increasing coverage
Stage 3: Loss of confidence
Stage 4: Resumption of confidence
Stage 5: Eradication

- Disease
- Vaccine coverage
- Incidence
- Adverse events
- Maturity of Immunization Programme

Robert T. Chen, CDC
Vaccination Policies and Rates of Exemption from Immunization, 2005–2011
Consequences of exemptions and vaccine safety scares – US (measles)

2015 Measles Cases in the U.S.
January 1 to August 21, 2015

*Provisional data reported to CDC's National Center for Immunization and Respiratory Diseases
Number of cases of measles in Europe and rate of 2 doses of MCV 2011
Although early immunization is still favoured, the manufacturers’ conventional age restrictions on the first and last dose of rotavirus vaccines may have prevented vaccination of many vulnerable children in settings where the DTP doses are given late (i.e. after 15 weeks for DTP1 or after 32 weeks for DTP 2 or DTP3). By allowing infants to receive rotavirus vaccine together with DTP regardless of the time of vaccination, immunization programmes will be able to reach children who were previously excluded from the benefits of rotavirus vaccines. Because of the typical age distribution of RVGE, rotavirus vaccination of children >24 months of age is not recommended.
Parental Vaccine Preferences in Guatemala 2009

- Urban areas more concerned with safety

- Safety overrides decision of number of injections
What is next on vaccines?

- Reduce infectious mortality in children
- Reduce morbidity in young children
- Reduce disability and perinatal infections
- Emerging infections
# Five leading childhood infection killers (aged 1-59 months)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of deaths in 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>570,000</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>63,800</td>
</tr>
<tr>
<td>Syphilis</td>
<td>56,900</td>
</tr>
<tr>
<td>Cholera</td>
<td>45,200</td>
</tr>
<tr>
<td>Respiratory Syncytial virus</td>
<td>41,100</td>
</tr>
</tbody>
</table>
Global Vaccines in the Horizon

• Malaria
  • 2012: *Plasmodium falciparum* 207 million cases and 627,000 deaths
  • Mortality has decreased by 50% due to bed nets and antimalarial treatment
  • Increasing insecticide and resistance
Vaccine efficacy against all episodes of clinical malaria after 3rd dose in children 5-17 months (at 18 month follow up)

Interaction p-value = 0.8100

RTSS Clinical Trials Partnership. PLOS Medicine 2014; 11:e1001685
• **RSV** kills more children <1 year of age than any other single pathogen except malaria

• **Leading cause of hospitalization in children under 5 years of age in the**
## Profile of Candidate RSV Vaccines

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Neutralizing epitopes</th>
<th>MHC pathway</th>
<th>CD8 T cell induction</th>
<th>IL-4</th>
<th>Delivery route</th>
<th>Immune modulation</th>
<th>Replication competence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole-inactivated virus</td>
<td>-</td>
<td>II</td>
<td>-</td>
<td>++</td>
<td>IM</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Post-fusion F or G subunit</td>
<td>+/-</td>
<td>II</td>
<td>-</td>
<td>+/-</td>
<td>IM</td>
<td>-/+</td>
<td>-</td>
</tr>
<tr>
<td>VLPs or virosomes</td>
<td>+</td>
<td>II +/- I</td>
<td>+/-</td>
<td>-/+</td>
<td>IM</td>
<td>-/+</td>
<td>-</td>
</tr>
<tr>
<td>Pre-fusion F subunit</td>
<td>+++</td>
<td>II</td>
<td>-</td>
<td>+/-</td>
<td>IM</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vectors</td>
<td>++</td>
<td>I &amp; II</td>
<td>++</td>
<td>-</td>
<td>IM or nasal</td>
<td>-</td>
<td>- or +</td>
</tr>
<tr>
<td>Naked DNA or RNA</td>
<td>++</td>
<td>I &amp; II</td>
<td>+</td>
<td>-</td>
<td>IM</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Recombinant or chimeric viruses</td>
<td>++</td>
<td>I &amp; II</td>
<td>+</td>
<td>-</td>
<td>nasal</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>WT or attenuated virus</td>
<td>++</td>
<td>I &amp; II</td>
<td>+</td>
<td>-</td>
<td>nasal or IM</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Global Vaccines in the Horizon

• Dengue
  • Most common infectious disease worldwide
  • Incubation 3-7 days: fevers, headaches, pains, fatigue
  • Severe dengue in 1-3%, especially if 2\textsuperscript{nd} infection
  • Prevention limited by using repellents, bed nets and protective clothing
  • One dengue vaccine close to registration
  • 3 dose series: 0-6-12 months
# Dengue Vaccine Candidates

<table>
<thead>
<tr>
<th>Producer (Developer)</th>
<th>Vaccine Type</th>
<th>Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sanofi Pasteur (Acambis)</strong></td>
<td>Live attenuated - chimera 17D yellow fever + DENV</td>
<td><img src="arrow.png" alt="Phase I" /> <img src="arrow.png" alt="Phase II" /> <img src="arrow.png" alt="Phase III" /></td>
</tr>
<tr>
<td><strong>Takeda (CDC, Invirogen)</strong></td>
<td>Live attenuated - chimera DENV-2 + DENV 1,3, 4</td>
<td><img src="arrow.png" alt="Phase I" /> <img src="arrow.png" alt="Phase II" /> <img src="arrow.png" alt="Phase III" /></td>
</tr>
<tr>
<td><strong>Butantan (NIAID)</strong></td>
<td>DENV attenuated - mutations + DENV/DENV chimera</td>
<td><img src="arrow.png" alt="Phase I" /> <img src="arrow.png" alt="Phase II" /> <img src="arrow.png" alt="Phase III" /></td>
</tr>
<tr>
<td><strong>GSK (WRAIR)</strong></td>
<td>Cell culture derived, inactivated</td>
<td><img src="arrow.png" alt="Phase I" /> <img src="arrow.png" alt="Phase II" /></td>
</tr>
<tr>
<td><strong>MERCK (Hawaii Biotech)</strong></td>
<td>Envelop subunits of DENVs</td>
<td><img src="arrow.png" alt="Phase I" /> <img src="arrow.png" alt="Phase II" /></td>
</tr>
</tbody>
</table>
# Results of Efficacy Trials Dengue Vaccine Sanofi Pasteur (per protocol results)

<table>
<thead>
<tr>
<th>DENV specific</th>
<th>Phase IIB–Thailand N= 4,002</th>
<th>Phase III–Asia N= 10,275</th>
<th>Phase III–Latin America N= 20,869</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Efficacy</td>
<td>95% CI</td>
<td>Efficacy</td>
</tr>
<tr>
<td>All DENV’s</td>
<td>30.2</td>
<td>-13–57</td>
<td>56.5</td>
</tr>
<tr>
<td>DENV 1</td>
<td>55.6</td>
<td>22–84</td>
<td>50.0</td>
</tr>
<tr>
<td>DENV 2</td>
<td>9.2</td>
<td>-75–51</td>
<td>35.0</td>
</tr>
<tr>
<td>DENV 3</td>
<td>75.3</td>
<td>-38–100</td>
<td>78.4</td>
</tr>
<tr>
<td>DENV 4</td>
<td>100.0</td>
<td>25–100</td>
<td>75.3</td>
</tr>
</tbody>
</table>

Villar L, et al. NEJM 2015: 372 113-123
Causes of newborn deaths, global data for the year 2013

- Intrapartum-related complications: 24%
- Complications from preterm birth: 35%
- Severe infections: 23%
- Sepsis, meningitis, tetanus: 17%
- Pneumonia: 5%
- Diarrhoea: 1%
- Other: 8%
- Congenital: 10%

Effect of Maternal Influenza vaccination on confirmed cases of Influenza According to Cohort and Study Group in South Africa

A HIV-Uninfected Cohort, Mothers

B HIV-Uninfected Cohort, Infants

C HIV-Infected Cohort, Mothers

D HIV-Infected Cohort, Infants

No. at Risk
IIV3 1062 1047 1007 985 703 159
Placebo 1054 1023 993 964 685 179

No. at Risk
IIV3 1026 1004 981 897
Placebo 1023 993 960 873

No. at Risk
IIV3 100 95 91 86 61 9
Placebo 94 87 78 74 53 7

No. at Risk
IIV3 100 93 86 68
Placebo 88 81 75 66
Estimate of absolute risk of GBS disease in a neonate as a function of capsular IgG in colonized mother
Other vaccines we will hope for

- HIV
- Influenza universal
- Tuberculosis
- CMV
- Ebola
- Pandemic influenza
- Staphylococcus aureus
Facts to remember

1 in 5 children do not have access to life-saving immunizations

$20 can fully vaccinate a child against pneumonia, diarrhea, polio and measles

Vaccines prevent 2 to 3 million deaths annually around the world

Over 22 million infants remain unimmunized in the world each year
Final Remarks on Global Vaccines

• One of the most effective and equitable health preventive technologies
• Use of vaccines is key to their preventive success – reach the unimmunized
• Addressing the safety and societal concerns is a priority in the current age
• New vaccines will bring a new paradigm: community protection is the key