Future Pentavalent and Hexavalent vaccines

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Why new Penta or Hexavalent Vaccines?
### Immunization Schemes for Hepatitis B, DPT, polio and *Haemophilus influenzae* b in South America

<table>
<thead>
<tr>
<th>Age</th>
<th>Argentina</th>
<th>Bolivia</th>
<th>Brazil</th>
<th>Chile</th>
<th>Colombia</th>
<th>Ecuador</th>
<th>Paraguay</th>
<th>Perú</th>
<th>Uruguay</th>
<th>Venezuela</th>
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<tbody>
<tr>
<td>birth</td>
<td>HB1</td>
<td>HB</td>
<td>HB1</td>
<td>HB</td>
<td>HB</td>
<td>HB</td>
<td>HB</td>
<td>HB</td>
<td>HB*</td>
<td>HB+OPV</td>
</tr>
<tr>
<td>1 month</td>
<td>HB2</td>
<td></td>
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<td></td>
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<tr>
<td>2 months</td>
<td>DTwP1-Hib1</td>
<td>DTwP1-Hib1</td>
<td>DTwP1-Hib1</td>
<td>DTwP1-Hib1</td>
<td>DTwP1-Hib1</td>
<td>DTwP1-Hib1</td>
<td>DTwP1-Hib1</td>
<td>DTwP1-Hib1</td>
<td>DTwP1-Hib1</td>
<td>DTwP1-Hib1+HB1</td>
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<tr>
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<td>+OPV1+HB2</td>
<td>+OPV1</td>
<td>+OPV1</td>
<td>+OPV1</td>
<td>+OPV1</td>
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<td>DTwP2-Hib2+HB2</td>
<td>DTwP2-Hib2</td>
<td>DTwP2-Hib2</td>
<td>DTwP2-Hib2</td>
<td>DTwP2-Hib2</td>
<td>DTwP2-Hib2</td>
<td>DTwP2-Hib2</td>
<td>DTwP2-Hib2</td>
<td>DTwP2-Hib2+HB2</td>
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<tr>
<td></td>
<td>+OPV2</td>
<td>+OPV2</td>
<td>+OPV2</td>
<td>+OPV2</td>
<td>+OPV2</td>
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<tr>
<td>6 months</td>
<td>DTwP3-Hib3</td>
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<td>OPV4</td>
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<td>18 months</td>
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<td>DTwP4+OPV4</td>
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<td>DTwP4+OPV4</td>
<td>DTwP4+OPV4</td>
<td>DTwP4+OPV4</td>
<td>DTwP4+HB4/OPV4</td>
</tr>
<tr>
<td>4 years</td>
<td>DTwP5</td>
<td>DTwP5</td>
<td>DTwP5+OPV5</td>
<td>DTwP5+OPV5</td>
<td>DTwP5+OPV5</td>
<td>DTwP4</td>
<td>DTwP5</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>5 years</td>
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<td>6 years</td>
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</tbody>
</table>

- Different schemes.
- Pneumo, Hepatitis A, yellow fever, MMR, chickenpox, flu are injectable vaccines added to some countries
- Oral rotavirus vaccine also added
- …?
Convenience of combined vaccines

- Less injections
- More compliance
- Safer
- No thimerosal
- Cold room space
- Easier for immunization programs: logistics
Whole cell or acellular pertussis?
Reported Events 7 days post immunization of placebo vs GSK Rotarix at 3 concentrations
Side Effects with whole cell Pertussis

• High rate of fever and irritability
• Local reactions
• Transient hypotonic hyporesponsive shock-like syndrome
Meta-analysis reviewing role of acP vaccines demonstrated that during the primary series, the risk of fever was at least 5 times lower with acP vs wP vaccines.

Relative risks expressed in relation to the incidence in wC group

<table>
<thead>
<tr>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.08</td>
<td>0.16</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Favours acellular Favours whole cell

AcP: 5 times less risk not to complete the series due to adverse events

Peto Odds Ratio


This improved safety lead to better compliance. Children vaccinated with acP were 5 times more likely to complete the primary series.
AcP vaccines have shown to be efficacious in EFFICACY TRIALS

- Schematic representation of protective efficacy of different pertussis vaccines (DTaP or DTwP) after primary vaccination

Ref: Edwards and Decker. In: Vaccines. 4th ed; 2004; Plotkin & Cadoz. PIDJ 1997; 16(5)

- 4181 infants randomized to receive one type of vaccine at 2, 4 and 6 mo of age.
- Pertussis Surveillance to whole study area for 1.6 yrs of follow-up.
- acP safer and better tolerated.
- RR of pertussis in acP vs wcP was 1.54 (1.23-1.93).
- In case-control study, vaccine efficacy for pertussis was:
  - 55% (38-68) wcP vs 31% (7-49) acP per protocol
  - 74% (55-85) wcP vs 53% (23-71) acP with PCR
  - 92% (81-97) wcP vs 74% (51-86) acP with WHO definition
- Pertussis rate similar in children <18 months of age; higher rate in > 18 mo children: acP had shorter duration of protection. Booster doses are needed.

Ref: Somondon F et al. Vaccine 1997;15:1606-1612
acP vaccines

• Safer
• Immunogenic
• Similar VE than wcP for younger children
• Boosters are needed to keep high VE
• High cost has limited its introduction to Latin-American countries
• Mexico introduced acP at a national level in 2007.
OPV or IPV?
Polio Eradication Progress, 1988 - 2005

Certified Polio-free regions (113 countries)
Not Certified but non-endemic (73 countries)
Endemic with wild polio virus (6* countries)

* In 2005, no wild viruses occurred in Egypt, but its status remained endemic.

Source: WHO AFP surveillance database
Figure 1  Number of cases of paralytic poliomyelitis in developing countries [1].

Ref: Khan MM. Vaccine 2008;26:2034-2040

- Wild virus type 1
- Wild virus type 3
- Wild virus types 1 & 3

Endemic countries
Case or outbreak following importation (0 - 6 months)

*Excludes viruses detected from environmental surveillance and vaccine derived polio viruses.

Data in WHO HQ as of 25 Mar 2008

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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- district infected with wild polio virus type 1
- district infected with wild polio virus type 3
- district infected with wild polio virus types 1 and 3

*Excludes vaccine derived polio virus and virus detected from environmental surveillance.

<table>
<thead>
<tr>
<th>Status</th>
<th>Country</th>
<th>Date of most recent type 1</th>
<th>Date of most recent type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endemic</td>
<td>India</td>
<td>07-02-2008</td>
<td>17-02-2008</td>
</tr>
<tr>
<td></td>
<td>Nigeria</td>
<td>15-02-2008</td>
<td>04-02-2008</td>
</tr>
<tr>
<td></td>
<td>Afghanistan</td>
<td>10-02-2008</td>
<td>09-02-2008</td>
</tr>
<tr>
<td></td>
<td>Pakistan</td>
<td>25-01-2008</td>
<td>31-12-2007</td>
</tr>
<tr>
<td>Active outbreak</td>
<td>DR Congo</td>
<td>14-02-2005</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Chad</td>
<td>17-11-2007</td>
<td>03-02-2008</td>
</tr>
<tr>
<td></td>
<td>Niger</td>
<td>23-01-2008</td>
<td>31-12-2007</td>
</tr>
<tr>
<td></td>
<td>Nepal</td>
<td>22-12-2005</td>
<td>17-01-2006</td>
</tr>
<tr>
<td></td>
<td>Angola</td>
<td>10-01-2008</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Cameroon</td>
<td>18-11-2007</td>
<td>NA</td>
</tr>
</tbody>
</table>

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No polio outbreaks in Europe, where IPV is being used for years
Detection of outbreaks of Circulating vaccine-derived poliovirus, cVDPVs

* Based on retrospective analysis of isolates

Data reported to WHO as of 11 May 2007
## Risk of polio cases from OPV-derived polio virus

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrus JK et al (1995)</td>
<td>UK</td>
<td>1 / 1.4 million</td>
</tr>
<tr>
<td>CDC (1997)</td>
<td>USA</td>
<td>1 / 2.4 million</td>
</tr>
<tr>
<td>Strebel et al (1994)</td>
<td>Rumania</td>
<td>1 / 183,000</td>
</tr>
<tr>
<td>Lei, Li &amp; Xu (1996)</td>
<td>China</td>
<td>1 / 1.25 million</td>
</tr>
<tr>
<td>Andrus JK et al (1995)</td>
<td>América Latina</td>
<td>1 / 1.5-2.2 million</td>
</tr>
</tbody>
</table>
Search for the enteroviruses that recombine with the OPV strains to give VDPVs

316 stools were collected from healthy children in villages of the Taolagnaro district where the polio cases were detected in 2002.
Molecular Epidemiology of the Madagascar outbreak

- 91 enterovirus isolated:
  - 23 poliovirus
  - 68 non-polio enterovirus: some echovirus, many HEV –C serotypes
- Genetic exchange between poliovirus and CoxA17 and CoxA13.
- Co-evolution of these virus generated high genetic diversity (19 recombinant lineages) in a small area (10x20 Km) involving 316 children.
- Low OPV coverage favored vaccine-related polio cases and recombinant varieties.

Source: Francis Delpeyroux, Pasteur Institute, Paris, France.
Environmental Study in Israel

- Type 2 polio vaccine derivative strain isolated in sewage
- Molecular studies indicated circulation and/or multiplication during > 14 years.
- Strain highly pathogenic in mice model.
- How long OPV-related strains may circulate in the environment?

Chronic Infection in Immune-Deficient Individuals

• A type 1 vaccine-derived polio virus infected a man with immunodeficiency for 10 years. Paralysis occurred during the 7th year of infection.


• A type 2 vaccine-derived poliovirus infected a man with hypogammaglobulinemia for ± 22 years. It could not be eradicated with oral immunoglobulins, breast milk or ribavirin.

Global Immunization 1980-2005, DTP3 coverage

Global coverage at 78% in 2005

192 WHO Member States.
“Developing”* countries with % of districts achieving at least 80% DTP3 coverage, 2005


* 156 developing countries and economies in transition per UN World Economic & Social Survey, 2006 classification

100 % districts (43 countries or 28%)
80-99 % districts (27 countries or 17%)
50-79 % districts (29 countries or 19%)
0-49 % districts (31 countries or 20%)

No data (26 countries or 16%)
DTP3 estimated coverage for 2005
14 countries ≥ 90%; 12 countries < 90%
Not applicable (36 countries)
OPV-induced Immunity is not long lasting

• Seroprevalence study in 780 individuals 7m-39 years of age who had a blood sample taken for other reasons in Montevideo, Uruguay.

• 72-95% of children <2 were protected vs. 20-60% of adults 20 to 39 years of age

• Only 12% of adults had antibodies against the three polio virus.

Ref: Pirez M et al. Abstract
Shall Latin American switch from OPV to IPV?

- Cost-effectiveness study in Monterrey, Mexico indicated that IPV, even costing 10 times higher than OPV, is cost effective.
- It could save money if intensive NIM and mop-up campaigns are stopped.
- Cost-effectiveness study for all developing countries in the world showed that IPV switch will increase a mean of US$1/child.
- Will diminish the problem of OPV virus in the environment and risk of polio outbreaks.
- IPV to all countries and OPV to isolated rural areas?

Khan MM. Vaccine 2008;26:2034-2040
The future for Latin America:

Moving toward pentavalent and hexavalent vaccines more affordable to public markets
New SP Penta/Hexa Vaccines

The sanofi pasteur HepB produced in Pilar Argentina is being used as a component of new sanofi pasteur formulations of DTaP-Hib-HepB and DTaP-Hib-HepB-IPV combination vaccines and they are being tested in clinical trials throughout the world.

Produced from *Hansenula polymorpha* yeast strain.

Technology acquired from Rhein Biotech.

New sanofi pasteur Argentina facilities (Pilar)
## Immunogenicity Assessment of an Investigational HepB vaccine (sanofi pasteur) in Adolescents (2/2)

<table>
<thead>
<tr>
<th></th>
<th>HepB, sp</th>
<th></th>
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<th>Engerix B Pediatrico</th>
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<tbody>
<tr>
<td></td>
<td>D0</td>
<td>D60</td>
<td>D180</td>
<td>D210</td>
<td>D0</td>
<td>D60</td>
<td>D180</td>
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<tr>
<td>≥10 mlU/ml %</td>
<td>0.6</td>
<td>93.0</td>
<td>99.4</td>
<td>100</td>
<td>1.8</td>
<td>74.3</td>
<td>95.3</td>
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<tr>
<td>(95% CIs)</td>
<td>(0.3;3)</td>
<td>(88.1;96.3)</td>
<td>(96.8;100)</td>
<td>(97.9;100)</td>
<td>(0.4;5)</td>
<td>(67.0;80.6)</td>
<td>(91.0;98.0)</td>
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<td>GMT</td>
<td>0.32</td>
<td>89.7</td>
<td>445</td>
<td>8970</td>
<td>0.35</td>
<td>26.5</td>
<td>159</td>
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<tr>
<td>(95% CIs)</td>
<td>(0.30;0.35)</td>
<td>(70.6;114)</td>
<td>(378;525)</td>
<td>(7590;10600)</td>
<td>(0.31;0.39)</td>
<td>(19.0;36.8)</td>
<td>(123;204)</td>
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<td>Sanofi pasteur HepB</td>
<td>Engerix B</td>
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<td>D180</td>
<td>D210</td>
<td>D0</td>
<td>D60</td>
<td>D180</td>
</tr>
<tr>
<td>≥10 mIU/ml % (95% CIs)</td>
<td>91 (86;95)</td>
<td>96 (91;98)</td>
<td>100 (98;100)</td>
<td></td>
<td>56 (48;64)</td>
<td>71 (63;77)</td>
<td>96 (96.8;100)</td>
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<tr>
<td>GMT (95% CIs)</td>
<td>0.35 (0.30;0.41)</td>
<td>88.6 (64.7;121)</td>
<td>164 (126;213)</td>
<td>5870 (4551;7570)</td>
<td>0.39 (0.32;0.47)</td>
<td>9.1 (5.92;13.90)</td>
<td>21.0 (14.5;30.4)</td>
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Estudio A3L04

Estudio de seguridad a gran escala de una vacuna combinada DTaP-IPV-HB-PRP~T, en comparación con Tritanrix-HepB/Hib™ y una vacuna OPV administradas a los 2, 4 y 6 meses de edad en niños latinoamericanos

Dr. Claudio LANATA, Investigador principal en Perú

Dra. Mercedes MACIAS, Investigador principal en México

Estudio de 4 grupos paralelos, randomizado, con observador ciego, multicéntrico del que participan 2.133 lactantes
Study A3L17
Immunogenicity Study of DTaP-IPV-HB-PRP~T Combined Vaccine in Comparison to Infanrix®Hexa, at 2-4-6 Months of Age in Healthy Peruvian Infants

Claudio F. Lanata MD.MPH
Principal Investigator
Instituto de Investigacion Nutricional
Lima, Peru
Thanks!