COMBINATION VACCINES: HOW AND WHY? LESSONS LEARNED.

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Michel De Wilde, MDWConsultant, LLC
STRONG RATIONALE EXISTS FOR COMBINATION VACCINES

- Fewer injections
- Higher rate of compliance with complex vaccination schedule
- Better vaccine coverage
- Timely vaccination - schedule completed on time
- Reduced administration cost
- Lower storage space requirement
- Allows incorporation of additional vaccines in the schedule
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COMBINATIONS HAVE LED TO IMPROVED UPTAKE AND CLINICAL OUTCOMES VS. STANDALONE ALTERNATIVES *(THAILAND EXAMPLE)*

**COMBINATION with HEPB SHOWED COVERAGE AND IMMUNOGENICITY GAINS**

<table>
<thead>
<tr>
<th></th>
<th>DTPw + HB (separately)</th>
<th>Combined DTPw-HB</th>
<th>Net change</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB coverage <em>(3rd dose)</em></td>
<td>83.8%</td>
<td>93.8%</td>
<td>+10%</td>
</tr>
<tr>
<td>Seroconversion rate</td>
<td>88.4%</td>
<td>94.8%</td>
<td>+6.4%</td>
</tr>
</tbody>
</table>

Notes: HB coverage *(3rd dose)* P-value=0.001
Source: Comparative evaluation of a combined DTP-HB vaccine in the EPI in Chiangrai Province, Thailand, Vaccine (2002);
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NEPAL:

- Introduced PCV at 6, 10 weeks and 9 months to avoid 3rd injection (with IPV + Penta) at 14 weeks
- Given reduced interval between 6 and 10-week injections, concerns raised about immunogenicity
- Avoidance of three injections at 14-week visit prioritized

BANGLADESH:

- Bangladesh introduced PCV and IPV to routine immunization schedule in 2015 with Penta
- District EPI managers/mothers influence decision 18-week visit rather than a third injection at 14 weeks

CASE FOR COMBINATION VACCINES? EVOLVING UNDERSTANDING OF ACCEPTANCE OF MULTIPLE INJECTIONS IN DEVELOPING WORLD

Some countries in the developing world are reluctant to have > 2 shots per visit...

...But in the U.S., 3 injections in one visit is the norm

2015 U.S. Immunization Schedule

3 injections given at most visits from 2 to 15 months

4 injections given at 4 to 6 years of age

Some countries in the developing world are reluctant to have > 2 shots per visit...
BUT THERE ARE OTHER CONSIDERATIONS

• **Scientific/Technical**
  - Immunological: “in the child’
  - Physicochemical: “in the vial”
  - Analytical: “in the lab”

• **Commercial**
  - Intellectual Property
  - Access to all valences
  - Access policies and pricing

• **Strategic**
  - Introduction of new vaccines
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SCIENTIFIC CHALLENGES: MULTIPLE TECHNICAL AND IMMUNOLOGICAL BARRIERS CHALLENGE THE SUCCESS OF COMBINATIONS

<table>
<thead>
<tr>
<th>“In the child”</th>
<th>“In the vial”</th>
<th>“In the lab”</th>
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<tbody>
<tr>
<td>Immune interference</td>
<td>Incompatibility of components</td>
<td>Analytical assay tests</td>
</tr>
<tr>
<td>Bystander interference</td>
<td>pH incompatibility over time</td>
<td></td>
</tr>
<tr>
<td>Carrier-induced epitopic</td>
<td>Variable absorption to adjuvant</td>
<td></td>
</tr>
<tr>
<td>suppression</td>
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</table>
COMBO DEVELOPMENT CAN BE CHALLENGING AND IS NOT ALWAYS SUCCESSFUL…

…3 Case studies
CASE STUDY 1: GLOBORIX

**Objective**
- Heptavalent for the Meningitis belt, incorporating MenAC into infant series

**Composition**
- D, T, wcP, HepB, Hib, MenAC-TT

**Challenges**
- Somewhat reduced immunogenicity of Men
- Timing/cost of product mismatched vs the development of MenAfrivac

**Outcome**
- File withdrawn following the Article 58 day 120 questions
## CASE STUDY 2: HEXAVAC

### Objective
- Hexavalent, primarily for Europe but other private markets as well.

### Composition
- D, T, acP, HBV, Hib, IPV

### Challenges
- Reduced HBV titers vs. licensed comparators
- Few SIDS cases temporally associated (causality later excluded)

### Outcome
- Licensed in 2000, suspended by EMA in 2005
- Large commitments for re-introduction, vaccine ultimately withdrawn by manufacturer
### CASE STUDY 3: PROQUAD

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>• Increase compliance and timeliness of MMR and varicella vaccination</td>
</tr>
<tr>
<td></td>
<td>• Reduced number of injections</td>
</tr>
<tr>
<td></td>
<td>• Target HIC market</td>
</tr>
<tr>
<td><strong>Composition</strong></td>
<td>• Measles, Mumps, Rubella, Varicella</td>
</tr>
<tr>
<td><strong>Challenges</strong></td>
<td>• Higher varicella titers required for adequate immunogenicity</td>
</tr>
<tr>
<td></td>
<td>• Elevated febrile seizure risk identified post-licensure</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>• Licensed in 2005</td>
</tr>
<tr>
<td></td>
<td>• In 2009, new ACIP recommendation as a 2nd dose at 4-6 years only</td>
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...BUT SUCCESSFUL COMBINATIONS HAVE LED TO EFFECTIVE VACCINES WITH GLOBAL IMPACT

...2 case studies
CASE STUDY 1: PENTA

Objective

• Pentavalent infant vaccine for L&MICs

Composition

• Diphtheria, Tetanus, wPertussis, HepB, Hib

Advantages

• Emerged as successor to DTP
• Shots reduced from 9 to 3
• Allowed the introduction of Hib

Outcome

• After hiccups, now available in world’s 73 poorest countries from 6 manufacturers
• Increased coverage

Source: Gavi: Pentavalent Vaccine Support
CASE STUDY 2: MMR

**Objective**
- Trivalent pediatric combination for the world

**Composition**
- Measles, Mumps, Rubella

**Advantages**
- Available for >40 years
- Components developed as individual vaccines prior to combination

**Outcome**
- Similar titers elicited vs. standalone vaccines
- Where widely used, >99% reduction in incidence of each disease

Source: Development of Combination Vaccines (Vaccine, 2009); BioSpectrumIndia; UNICEF: Facts for Life; Merckvaccines.com
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- Strategic
  - Introduction of new vaccines
ANTIGEN AVAILABILITY AND INTELLECTUAL PROPERTY HAVE IMPACTED THE DEVELOPMENT OF COMBINATION VACCINES…

<table>
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<tr>
<td>• Combination vaccines first emerged in vaccinology in 1949 when DTP was licensed</td>
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<tr>
<td>• As the number of available vaccines grew and the immunization got crowded, the incentive to reduce the number of injections grew, particularly for the primary schedule in infants</td>
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<tr>
<td>• The stage was set for hexavalent combinations in the 1990s with the availability of HepB and Hib and a shift to IPV</td>
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<table>
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<th>Main drivers</th>
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<tr>
<td><strong>Antigen availability</strong></td>
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<tr>
<td>Initially, no manufacturer had all the valences available to make a hexavalent</td>
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<tr>
<td><strong>Intellectual property</strong></td>
</tr>
<tr>
<td>Vaccines had become commodities but IP covering recHepB became a huge driving force</td>
</tr>
</tbody>
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…AND HAVE SHAPED THE DEVELOPED WORLD VACCINE INDUSTRY!

<table>
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<tr>
<th>Combination strategies varied by player</th>
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<tr>
<td><strong>Sanofi and Merck</strong></td>
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<tr>
<td>• Formed a joint venture in Europe in 1994</td>
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<td>• Started development of Hexavac</td>
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<td><strong>GSK</strong></td>
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<td>• Elected to go “alone”</td>
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<td>• Obtained D and T through a agreement with Chiron Behring</td>
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<td><strong>Other players</strong></td>
</tr>
<tr>
<td>• Excluded from the combo market in the developed world</td>
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<tr>
<td>• e.g. Sclavo/Chiron despite an excellent acP</td>
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**Future developments**

• In the developing world, a lot of movement is taking place already between DCVMs and MNCs; it can be expected that combination vaccines will drive further change in the landscape
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THE INTRODUCTION OF NEW VACCINES WILL FURTHER INCREASE COMPLEXITY

Note: All figures are based on GAVI-funded vaccines only

COMBOS ADDRESS CONCERNS ACROSS EACH OF THESE AREAS

- Simplifying administration by decreasing volumes and combining antigens into fewer shots
- Providing greater access to vaccines in the developing world via material cost savings
- Minimizing cold chain supply challenges by decreasing the number of SKUs and total shipment volume required
GOING FORWARD: CONSIDERATIONS FOR NEW COMBINATIONS

- Epidemiology (age group and geography of burden)
- Technical and immunological risks
  - CMC complexity (formulation, analytical, failure rate)
- Route of administration (oral versus parenteral)
- Regulatory pathway
  - e.g. do correlates exist for all antigens?
  - e.g. article 58 vs local vs other
- Needed partnerships/licenses