GLOBAL VACCINE AND IMMUNIZATION RESEARCH FORUM
NEW COMBINATION VACCINES: HOW AND WHY?

POTENTIAL FUTURE STATES

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Bill & Melinda Gates Foundation
INTRO - WHAT PROBLEM ARE WE TRYING TO SOLVE?

Problem statement

- Planning to **add new vaccines to a system already challenged** to deliver current ones
- Concern that countries might be reaching **“dual max”**: # and timing of “shots” and budget constraints
  - New vaccines in development will require different immunization platforms (e.g., maternal RSV) or will lead to more simultaneous administrations (e.g., ETEC, Shigella)
  - 50% of GAVI countries graduating by 2030. Significant budget increases required to pay for vaccines

Which vaccines could feasibly be combined (new or existing) to mitigate headwinds in the developing world?
IMPORTANT TO EVALUATE VARIOUS LEVERS TO MITIGATE THE “DUAL MAX” ISSUE

**Combo vaccines**
- Combinations
  - Maternal combination
  - Penta-based combination
  - Enteric combination
  - Toddler combination
  - Adolescent combination

**Paradigm changing technologies**
- Multi-dose vaccine at each age (e.g. Micropellets, mRNA)
- One single-dose vaccine at each age (e.g. delayed release technology)

**Policy and schedule change to reduce # doses**
- Dose regimen change
  - HPV: 3 doses to 2; possibly as few as 1
  - PCV: 4 doses to 3; possibly as few as 2 (1+1)?

**Schedule change to accommodate new vx**
- Change EPI visit schedule
  - Adjust visit timing to increase vaccine efficacy and/or reduce # of doses

**Spread # of shots (no dose reduction)**
- E.g. PCV dosing from 3+0 to 2+1
- E.g. Shift one infant MenC dose to adolescent (UK)

**Add new visits**
- Add visit to a “gap” in today’s immunization schedule

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Key topics for today’s discussion
A FUTURE SCHEDULE COULD INVOLVE UP TO 13 ADDITIONAL SHOTS OVER AN ALREADY CROWDED SCHEDULE

SCENARIOS

Current state

Maternal
- Tetanus
- BCG
- HepB
- OPV

Birth
- [PCV]
- Penta
- Rota
- OPV

Infant
- 6 wks
- 10 wks
- 14 wks

Toddler
- 9 mos
- 15-18 mos

Adolescent
- 9-17 yrs

Future additions?

Maternal
- GBS
- (Td)aP
- RSV

Infant
- Rubella (w/ Measles)
- ETEC (oral / injectable), Shigella (oral / injectable)
- Norovirus, Rotavirus (injectable)

Toddler
- Typhoid
- Dengue

Adolescent
- HPV
- HIV, TB, Next generation malaria, universal influenza vaccines

IN FUTURE BASELINE:
- 20 shots*
- 2 oral*

TOTALS
- 7 [12] shots
- 6 oral

Injection burden and delivery challenges preclude future additions from being all standalone vaccines

NOTE: *Calculation assume ETEC and Shigella are injectable. Excludes some regional vaccines and long-term development vaccines (HIV, malaria, TB, universal flu); Totals ignore regional vaccines in current state
## FOR TODAY’S DISCUSSION: POTENTIAL COMBINATIONS FOR THREE MAJOR PLATFORMS

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Birth</th>
<th>Infant: Penta-based</th>
<th>Infant: Enterics</th>
<th>Toddler</th>
<th>Adolescents</th>
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</thead>
<tbody>
<tr>
<td>Global</td>
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<tr>
<td>RSV</td>
<td>Rota</td>
<td></td>
<td>M-R</td>
<td>HPV</td>
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<tr>
<td>(Td)aP</td>
<td>(NRRV)</td>
<td></td>
<td></td>
<td>CMV</td>
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<tr>
<td>Flu (Universal)</td>
<td>PCV</td>
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<td>HBV</td>
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<td>CMV</td>
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<tr>
<td>Regional</td>
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<tr>
<td>Tetanus</td>
<td>MenA (C,W,X) or fHBP</td>
<td></td>
<td>Typhoid</td>
<td>HEV</td>
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<tr>
<td>GBS</td>
<td>ETEC</td>
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<td>JE</td>
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<td></td>
<td>Shigella</td>
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<td>YF</td>
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<td></td>
<td>Typhoid</td>
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<td>MenA (C,W,X)</td>
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<td></td>
<td>Cholera</td>
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### Areas of focus for today’s discussion

- **Why not a first priority platform for combination?**
  - Long-acting immunoglobulins as an alternative (e.g., RSV)
- **Areas of focus for today’s discussion**
  - No clear global combination to develop
  - Beyond HPV, no near term candidates to combine
**MATERNAL PLATFORM**

**Current state**

<table>
<thead>
<tr>
<th>Disease incidence (illustrative overview)</th>
<th>Birth</th>
<th>3 mos</th>
<th>6 mos</th>
<th>9 mos</th>
<th>12 mos</th>
<th>18 mos</th>
<th>21 mos</th>
<th>24 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GBS</strong></td>
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<tr>
<td><strong>Pertussis</strong></td>
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<tr>
<td><strong>RSV</strong></td>
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</tbody>
</table>

- Tetanus is the only vaccine given to mothers in the developing world. High maternal coverage rates difficult without supplemental immunization activities (SIAs)

- 2015 maternal tetanus coverage (based on large catch-up programs, not routine immunization):
  - India: 59%; Nigeria: 44%; Pakistan: 65%

**Rationale for novel combo**

- True burden of these pathogens in developing world under active investigation

- Epidemiology clustered in time, supportive of similar vaccine delivery strategy

- Maternal immunization may be more acceptable if higher impact can be anticipated with combination products

- Similar protein-based and glycoconjugate vaccines have been successfully combined in other licensed products (e.g., DTaP-HBV-Hib based combos)

**Scope**

- **Priority antigens:** Tetanus, RSV, Pertussis, GBS

- **Other potential antigens:** Universal flu, CMV, HEV

Source: Maternal (TT) data based on 2014 country reported coverage rates to WHO
### INFANT: PENTA PLATFORM

<table>
<thead>
<tr>
<th>Current state</th>
<th>Rationale for novel combo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MARKET DYNAMICS:</strong></td>
<td>• Penta is a well-established vaccine delivered at established visits; an antigen added to this existing platform would be expected to achieve similar coverage rates</td>
</tr>
<tr>
<td>• Today’s Penta market is healthy, with adequate supply and low price</td>
<td>• <strong>Rota:</strong> An injectable rota under development with potential efficacy, safety and cost benefits vs. current oral vaccines</td>
</tr>
<tr>
<td>• In 2015, there were six suppliers of Penta, with average price under $2 / dose</td>
<td>• <strong>Polio:</strong> Lower antigen IPV may mitigate cost increase; Reduce # infant injections post-polio elimination if antigen maintained</td>
</tr>
<tr>
<td>• Crucell, Shantha, Panacea, Serum, BioE, BioFarma, and BBIL</td>
<td>• <strong>Meningitis:</strong> MenA-TT (MenAfrivac) introduction into EPI but non-MenA outbreaks occurring (C, W); Penta-Men combo could address # shots and changing epidemiology</td>
</tr>
<tr>
<td><strong>COVERAGE:</strong></td>
<td><strong>Scope</strong></td>
</tr>
<tr>
<td>• Global estimates:</td>
<td>• <strong>Priority antigens:</strong> Penta, IPV, NRRV (P2-VP8*), MenACW</td>
</tr>
<tr>
<td>• Penta: 86% (third dose)</td>
<td>• <strong>Other antigens to consider:</strong> PCV?, fHBP (“MenB”), Typhoid conjugate</td>
</tr>
<tr>
<td>• IPV: 86% (third dose)</td>
<td></td>
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</tbody>
</table>
## INFANT: ENTERICS PLATFORM

### Current state

<table>
<thead>
<tr>
<th>Epidemiological incidence (highest to lowest)</th>
<th>0-11 months of age</th>
<th>12-23 months of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Rotavirus</td>
<td>• Shigella / EIEC</td>
</tr>
<tr>
<td></td>
<td>• Shigella</td>
<td>• Rotavirus</td>
</tr>
<tr>
<td></td>
<td>• ST-ETEC</td>
<td>• ST-ETEC</td>
</tr>
<tr>
<td></td>
<td>• Norovirus GII</td>
<td>• V. cholerae</td>
</tr>
<tr>
<td></td>
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<td>• Norovirus GII</td>
</tr>
</tbody>
</table>

### Rationale for novel combo

- Diarrheal disease burden is clustered across geographies and pathogens, making combination particularly attractive.
- Individually, pathogens have modest to high disease burden.
- Combination could better support argument for new product development.
- Lead candidates developed sequentially, with plan for combination product after ETEC licensure. Is a more aggressive development strategy viable?

### Scope

- **Priority antigens**: Rota, ETEC, Shigella, (Typhoid)
- **Other antigens under consideration**: Norovirus, Cholera

Source: Coverage data based on 2014 UNICEF/WHO estimated coverage rates; Internal data
NEW TECH. HAS POTENTIAL TO CHANGE LONG-TERM PARADIGM OF COMBINATION VACCINES, ENABLING ‘BLUE SKY’ SCENARIOS

1. Frangible seal

ETVAX
Frangible seal
dmLT + buffer

2. Micropellets

Source: Process for Stabilizing an Adjuvant Containing Vaccine Composition (US20090232894)

3. mRNA technology

4. Delayed release

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COMBO VACCINES: SEVERAL SCENARIOS FOR REDUCTION IN SHOTS DEPEND ON DEGREE OF SUCCESS OF COMBOS AND NOVEL TECHNOLOGIES

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<tr>
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<th>Birth</th>
<th>Infant</th>
<th>Toddler</th>
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<th>TOTALS**</th>
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<tr>
<td></td>
<td>BCG</td>
<td>HepB</td>
<td>OPV</td>
<td></td>
<td></td>
<td>7 [12] shots</td>
</tr>
<tr>
<td><strong>Future baseline</strong></td>
<td>GBS-TT</td>
<td>(TdaP)</td>
<td>RSV</td>
<td></td>
<td></td>
<td>20 shots</td>
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<td></td>
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<td></td>
<td>15 shots (-5)</td>
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<tr>
<td><strong>Stretch</strong></td>
<td>GBS-TT / RSV</td>
<td>(TdaP)</td>
<td></td>
<td></td>
<td></td>
<td>9 shots (-11)</td>
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<tr>
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<td>15 shots (-5)</td>
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<td><strong>Blue Sky</strong></td>
<td>GBS-TT- RSV-aP (conjugated)</td>
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<td></td>
<td></td>
<td>5 shots (-15)</td>
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<td><strong>Blue Sky +</strong></td>
<td>GBS-TT- RSV-aP (conjugated)</td>
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**CONCLUSIONS**

- Vaccine development targeting developing world diseases will increase
- Current products in pipeline represent both opportunities and challenges
- To maximize impact and reduce timeframe, must leverage recent vaccinology learnings (# of doses, optimal schedules and combination vaccines)
- Must strategically identify the right combination products (epidemiology, vaccinology, technical and commercial) and seek partnership opportunities early