Product Development Pathway for Novel Influenza Vaccines from the Perspective of a Vaccine Manufacturer

Eighth WHO meeting on development of influenza vaccines that induce broadly protective and long-lasting immune responses

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GSK
My Assigned Objectives

• To describe the GSK perspective regarding product development pathway
  – for conventional seasonal influenza vaccines
  – for influenza vaccines that have incremental improvements, novel mechanisms, but no correlate of protection

• To describe the indication GSK will seek

• To describe how incremental improvements in influenza vaccines or true “universal” influenza vaccines may affect use of the existing vaccines
GSK Experience with Influenza VE Trials

• Since 2005, my group at GSK has conducted 7 clinical endpoint IIV trials – 6 for seasonal vaccines in various age segments and 1 for adjuvanted H1N1pdm09 vaccine

• More than 103,000 subjects were enrolled

• 3 trials failed to confirm their primary objectives and provided lessons:
  – Be conservative about expected event rates
  – Study endpoints that are clinically relevant

• The 4 successful trials also furnished important insights
  – See my summary recommendations
Development of Conventional Seasonal Vaccines
Evidence required for regulatory approval

• Pre-licensure clinical benefit (risk reduction) assessed as vaccine efficacy
  – Immunogenic non-inferiority using an immunogenicity endpoint that is correlated with protection vs std of care (for which efficacy is established)
  – Absolute efficacy
  – Relative efficacy vs std of care
  – Both absolute and relative efficacy
• Lot to lot consistency (using immunogenicity EP)
  – Done in a separate trial to have adequate power and to control Type I error
• Safety (benefit >> known risks) based on adequate exposure vs control, with blinded active surveillance
• Pooled data from several seasons offers more certain evidence for efficacy
Development of Conventional Seasonal Vaccines

Age-specific evidence is required for regulatory approval

- Age affects dosing, immune response, and maybe efficacy
- Adequate data for efficacy and safety in each age segment are a condition of licensure

<table>
<thead>
<tr>
<th>Age segment</th>
<th>Age strata</th>
<th>Control vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children, 6-35 MOA</td>
<td>6-17, 18-35 MOA</td>
<td>PCV or HAV dose 1 Varicella dose 2</td>
</tr>
<tr>
<td>Children 3-17 YOA</td>
<td>3-8, 9-17 YOA</td>
<td>HAV dose 1 Saline dose 2</td>
</tr>
<tr>
<td>Adults 18-64 YOA</td>
<td>18-49, 50-64</td>
<td>Saline</td>
</tr>
<tr>
<td>Elderly adults 65+ YOA</td>
<td>65-74, 75+</td>
<td>Std of care, or dTaP or another vaccine offering benefit</td>
</tr>
</tbody>
</table>
Clinical Endpoints for VE
Extract “Moderate to Severe” from “Any” influenza disease

• GSK has experience in 2 pediatric trials (6 to 35 MOA, 3-8 YOA)
• VE was estimated for Influenza of Any Severity and Moderate to Severe Influenza
• Moderate to severe disease captures clinically consequential illness → most repeat ambulatory care, ED visits, and hospitalizations [rare]
• Mild disease incurs few health costs but contributes to transmission
• Clinical validity of a “Moderate to Severe” case definition for adult disease has not yet been assessed
Influenza Case Definitions for VE Trials
Definitions reflect the investigator’s judgement

- **Influenza–like illness (ILI):** presence of T ≥38.0°C (any route) and at least one of the following: cough, runny nose, nasal congestion or breathing difficulty

- **Lower respiratory illnesses (LRI):** physician-diagnosed pneumonia, lower respiratory tract infection, bronchiolitis, bronchitis or croup (laryngotracheitis).

- **Acute otitis media (AOM):** physician-diagnosed otitis media.

<table>
<thead>
<tr>
<th>“Any” rt-PCR confirmed influenza with one or more of the manifestations below</th>
<th>Moderate to severe disease</th>
<th>Severe disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>T &gt;39°C (any route)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physician-diagnosed AOM</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physician-diagnosed LRI (pneumonia, LRTI, bronchiolitis, bronchitis, croup (laryngotracheities), or</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physician-diagnosed serious extrapulmonary complications of influenza</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hospitalization in ICU</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Supplemental O₂ for &gt;8h</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
## Incidence of Influenza by Severity Category

Studies enrolled healthy children only

<table>
<thead>
<tr>
<th>Influenza Severity</th>
<th>6-35 MOA (unpublished) 5 annual cohorts, N=6012</th>
<th>3-8 YOA (Jain et al, 2013) 1 Annual cohort, N=2584</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (% of total)</td>
<td>Incidence</td>
</tr>
<tr>
<td>Any disease</td>
<td>676</td>
<td>11.24%</td>
</tr>
<tr>
<td>Mild</td>
<td>428 (63.3%)</td>
<td>7.12%</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>248 (36.7%)</td>
<td>4.13%</td>
</tr>
<tr>
<td>Severe</td>
<td>3</td>
<td>0.05%</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>7</td>
<td>0.12%</td>
</tr>
<tr>
<td>Emergency dept care</td>
<td>28</td>
<td>0.47%</td>
</tr>
<tr>
<td>Antibiotic administered</td>
<td></td>
<td>49.2%</td>
</tr>
</tbody>
</table>

60% of VE endpoints are mild; 40% are moderate to severe, with severe outcomes (seizures) or hospitalizations occurring in <2 children per 1000

Severe influenza is infeasible as a 1° endpoint in a multi-season VE study for a universal influenza vaccine.
VE against Disease from Drifted Isolates

- Estimates of VE against drifted and vaccine-matching disease are needed to confirm universal protection against seasonal disease.
- Antigenic analysis by HI test using reference serum (made w/ vaccine strain) against vaccine strain versus field isolates allows classification of H1 and B isolates, but not H3 isolates.

<table>
<thead>
<tr>
<th>Jain et al, NEJM 2013</th>
<th>rt-PCR pos samples confirmed by virus culture</th>
<th>Culture-confirmed samples with result for antigenic characterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1</td>
<td>50/66 = 76%</td>
<td>45/50 = 90%</td>
</tr>
<tr>
<td>H3N2</td>
<td>64/70 = 91%</td>
<td>15/64 = 23%</td>
</tr>
<tr>
<td>B/Vic</td>
<td>69/76 = 91%</td>
<td>67/69 = 97%</td>
</tr>
<tr>
<td>B/Yam</td>
<td>2/2 = 100%</td>
<td>2/2 = 100%</td>
</tr>
</tbody>
</table>

- Antigenic analysis using neutralization titer of reference serum (made w/ vaccine strain) for vaccine strain versus field isolates allows classification of most H3 isolates.
Product Development for Novel 2\textsuperscript{nd} Gen Influenza Vaccines w/o a CoP

• The WHO PPC for universal influenza vaccines solicits vaccine candidates offering:
  – 1) greater protection against drifted influenza A strains than currently available unadjuvanted, inactivated influenza vaccines,
  – 2) protection against severe influenza A virus illness through at least 5y after a primary series,
  – 3) suitability for high risk groups in LMICs

• The vaccines may be initially targeted to pregnant women, children aged 6–59 months, elderly adults, individuals with specific chronic medical conditions, and HC workers
Universal Influenza Vaccines May Be Pandemic Vaccines

- Vaccines that provide protection/priming against influenza A virus subtypes with pandemic potential have exceptional value.
- They could be stockpiled for emergency use.
- Examples of current pandemic threats, defined by BARDA:

<table>
<thead>
<tr>
<th>A subtype</th>
<th>Strain</th>
</tr>
</thead>
<tbody>
<tr>
<td>H5N1</td>
<td>A/Duck/Bangladesh/19097/2013</td>
</tr>
<tr>
<td>H7N9</td>
<td>A/Shanghai/2/2013</td>
</tr>
<tr>
<td>H5N8</td>
<td>A/Gyrfalcon/Washington/41088-6/2014</td>
</tr>
<tr>
<td>H9N2</td>
<td>A/Bangladesh/0994/2011</td>
</tr>
<tr>
<td>H2N3</td>
<td>A/Swine/Missouri/21244514/2006</td>
</tr>
</tbody>
</table>

- Protection could be demonstrated in animal models (by active or passive immunization) and/or by immunogenicity evaluations using *in vitro* functional assays.
Influenza B Cannot be Ignored

- Influenza B is second to H3N2 in causing hospitalization and death among all ages
- Mortality associated with pediatric influenza B infection is greater than that of influenza A*
- Quadrivalent vaccines protecting against both B lineages will be Std of Care by 2020
- Influenza B viruses drift, requiring stain updates, although not as often as H3N2
- A second generation vaccine will have to offer protection against influenza B to fully displace use of the current vaccines

WHO PPC should be revised to reflect the important burden of clinically consequential illness due to influenza B, especially in children

GSK’s Desired Indication

- Active immunization for protection against influenza disease due to type A and type B influenza viruses
  - Protection against influenza A subtypes other than H1 and H3 is based on immunological evidence only
- Duration of protection at 1\textsuperscript{st} licensure might be restricted to 3 years and extended to 5+ years with a supplemental filing
- Initial target groups: adults and children (lower age limit TBD)
- Indications for the elderly, infants less than 6 MOA, and for maternal immunization to afford protection of the newborn are likely to come with supplemental filings
Value of a 2\textsuperscript{nd} Gen Vaccine

Minimum Claims

• Non-inferior VE (relative to Std of Care) against clinically consequential disease for at least 3 years without annual boosting containing strain-matched antigens
  – Superior protection will be an upside
• Protection maintained in spite of virus drift
• Acceptable safety profile
• Incremental cost-effectiveness relative to available vaccines
• Protection/priming against pandemic threats

Generation of evidence supporting these claims will require trials within discrete age segments that randomize subjects to:
• the investigational 2\textsuperscript{nd} generation vaccine, or
• a licensed IIV4 comparator, or
• a non-influenza control
Development Pathway

- Novel 2\textsuperscript{nd} generation vaccines will be developed for global use
- Large vaccine efficacy trials spanning multiple years will be required
- To drive adoption of 2\textsuperscript{nd} gen vaccines, it will be essential to estimate both absolute VE and relative VE against the current standard of care
- Trials conducted in young children will offer the most feasible generation of evidence supporting multi-year protection against diverse A and B isolates
- Clinical endpoint trials are most feasible in countries:
  - With sustained periods of influenza virus transmission
  - Without NIPs that include influenza vaccination of healthy children
  - With appropriate clinical trial infrastructure
Product Development for Novel 2\textsuperscript{nd} Gen Influenza Vaccines – Early Development

• Vaccines will contain an adjuvant, if beneficial
• Composition of vaccines (antigen dose, adjuvant dose) will be selected empirically to optimize immunogenicity vs reactogenicity, using the std of care as a control
• Immunogenicity readouts if not functional, should be correlated with function (passive protection of animals, in vitro neutralization, FcR-mediated protection)
• The breadth of the immune response should be assessed
• Antibody persistence at 1y and subsequent natural boosting should be assessed
• Induction of T cells and B cell memory and/or plasmablasts directed against the vaccine’s protective antigens should be assessed
Product Development for Novel 2nd Gen Influenza Vaccines – Late Development

• Large efficacy trials will be required over 4-5 years to demonstrate durable protection including against drifted strains
• 3-arm studies with a non-influenza vaccine control and a licensed vaccine will be optimal
• The study cohort should be followed and recurrent clinical endpoints should be assessed using appropriate statistical approaches (e.g., Anderson and Gill model*)
• Boosting of treatments must be considered
  – Licensed influenza vaccines are administered annually
  – 2nd gen vaccine candidate can be boosted if interim results indicate failure of protection over time (monitored by an IDMC)
• Virus isolates from cases must be made for antigenic analysis

Unique Aspects of Safety F/U with Adjuvanted Vaccines

• Due to limited experience with vaccines containing novel adjuvants, regulatory authorities will require extended safety f/u in clinical trials
  – Currently, 1y of safety f/u after the last vaccine dose is required

• GSK’s standard is to collect data on the induction or aggravation of Potentially Immune-Mediated Diseases (pIMDs) and Adverse Events of Special Interest (AESIs) *
  – pIMDs: a subset of AEs agreed with US FDA that includes both clear autoimmune diseases and other inflammatory and/or neurologic disorders which may or may not have autoimmune etiologies
  – AESIs: a subset of AEs defined by EMA’s CHMP, relevant to pandemic influenza vaccines, that includes anaphylaxis, Bell’s palsy, convulsion, demyelination, encephalitis, Guillain-Barre syndrome, neuritis and vasculitis

* Vaughn et al. Hum Vaccines Immunotherapeutics, 2014
Transition to 2\textsuperscript{nd} Gen Vaccines

- Transition from IIV3 to IIV4 offers a useful example
- Transition to 2\textsuperscript{nd} gen vaccine will be gradual, conditioned on:
  - Product claims
  - Sequence of licensures, from countries with well established influenza vaccine programs (especially those that target children) to those with less established or no programs
  - Vaccine availability (production volumes)
  - Evidence supporting PH impact
  - Use recommendations (and importance assigned to pandemic protection/priming)
  - Cost and incremental cost effectiveness
- Concurrent use of existing and novel 2nd gen vaccine for at least 10 years to control seasonal influenza while impact data are being generated
  - Public-private partnerships beginning during the development phase can hasten introduction of universal influenza vaccine
  - For better pandemic preparedness, the WHO must create a plan for stockpiling and use of universal vaccines in an evolving influenza pandemic
Development Recommendations

1. Know Std of Care benchmark, to design adequate trials
2. Design candidate to protect against influenza B
3. Use M2S endpoint and initiate VE studies early to confirm PoC
4. Evaluate impact of vaccine on health outcomes: antimicrobial prescribing, ED visits, hospitalization
5. Use time to event statistical model that accounts for recurrent events
6. Collect case isolates and type H3N2s by neutralization
7. Refine tests to measure immune responses to broadly protective epitopes and create reference standards
8. Refine/standardize tests to measure FcR-mediated protection
9. Generate data on potential pandemic protection early on
10. Bank serum from all to find a CoP; assess natural boosting, model antibody decay kinetics
11. Use an IDMC; have measures to assure blinding while interim data are submitted for regulatory approval