LONG-TERM IMMUNOGENICITY OF ADJUVANTED PRE-PANDEMIC INFLUENZA VACCINES (H5N1) IN CHILDREN AND ADULTS

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The H5N1 virus challenge

- H5N1 viruses continue to diversify antigenically1
- Nevertheless, most recent human cases are from clade 1 & 2 viruses2
- There are inactivated influenza vaccines (IIVs) made with A/Vietnam/2004 (clade 1) and A/Indonesia/2005 (clade 2.1)
- Some countries hold stocks of them
- Predicting a more suitable pre-pandemic H5N1 vaccine strain to replace them is not realistic
- Do the existing H5N1 IIVs elicit cross-reactive humoral immunity that persists?

Disclosures and acknowledgements

- I am employed by the GlaxoSmithKline group of companies and I own stocks/options of the GlaxoSmithKline group of companies; my travel to this meeting was funded by GlaxoSmithKline Biologicals SA
- Studies of H5N1 vaccine (made in Quebec) were conducted with support from the US Dept of HHS/BARDA under contract HHSO10020100029C
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GSK’s AS03-adjuvanted H5N1 influenza vaccines

<table>
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<tr>
<th>Manufacturing site</th>
<th>Clade</th>
<th>Strain</th>
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<tr>
<td>Dresden, Germany</td>
<td>2.1</td>
<td>A/Indonesia/05/2005</td>
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<tr>
<td>Quebec, Canada</td>
<td>2.1</td>
<td>A/Indonesia/05/2005</td>
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<tr>
<td>Dresden, Germany</td>
<td>1</td>
<td>A/Vietnam/1194/2004</td>
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AS03 = adjuvant system containing α-tocopherol and squalene in an o/w emulsion

Adult dose = 3.75 μg hemagglutinin antigen = AS03a (11.86 mg α-tocopherol)
Child dose = 1.9 μg hemagglutinin antigen = AS03a (5.93 mg α-tocopherol)

AS03-adjuvanted split virion pre-pandemic influenza vaccines have shown:
- high immunogenicity at a low dose1-3
- broad immune response1-3
- persistent immune response4
- acceptable safety and reactogenicity profile1-3
- equivalent immunogenicity for Quebec process vs Dresden process2

References:
2. WHO 2013: http://www.who.int/influenza/vaccines/virus/201302_h5h7h9_vaccinevirusupdate.pdf
Neutralizing antibodies are the relevant measure of humoral immunity breadth and persistence

- Virus neutralizing antibodies are measured by a microneutralization (MN) assay (7-day incubation, non-neutralized virus detected by HA, positive cut-off 1:28)
- Quantitation of MN antibodies instead of HI antibodies provides more clinically relevant information on potential protection
- Antibody-mediated virus neutralization is an important protective mechanism in vivo
- Directed at diverse epitopes on HA and NA
- Their potency reflects their affinity maturation
- The minimum MN titer for protection against influenza disease is unknown
- However, relatively low MN titers are likely to offer clinical benefit
  - An MN titer of 1:11 in mice after human serum transfer (from recipients of a WVV) was the POI estimated for homologous (A/Vietnam/1203/2004) challenge
  - We define the vaccine response rate (VRR) as attaining an MN titer ≥1.56 (a 24-fold rise in a seronegative subject) → conservatively predictive of clinical benefit

\(^1\) Roels et al, Flu Vacc 2011;6:427–31

2-dose primary vaccination against A/Vietnam elicits an immune response to homologous and heterologous strains persisting for ≥5 months in adults 18–60 yrs

2-dose primary vaccination against A/Indonesia elicits an immune response to homologous and heterologous strains persisting for ≥5 months in adults 18–64 yrs

2-dose primary vaccination against A/Indonesia and A/Vietnam persisting for ≥11 months in children 6 mos–17 yrs

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Slide contains unpublished data

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Langley et al, J Infect Dis 2015;211:1644–53
2 doses of A/Vietnam prime a similar anamnestic response to A/Vietnam and A/Indonesia following an A/Indonesia boost at 6, 12, or 36 months, in adults 18–60 yrs

A dose of A/Vietnam primes a durable anamnestic response to either A/Vietnam or A/Indonesia persisting ≥12 months in adults 18–60 yrs

Summary

- This review shows that AS03-adjuvanted split virion H5N1 vaccines elicit:
  - a strong vaccine homologous response in individuals from 6 months to 64 yrs
  - a cross-clade response (2 vs 1, 1 vs 2) above a conservative protective level
  - a response that persists at a stable or slowly declining level for at least 3 years
  - memory that responds to a homologous or heterologous boost with cross-clade MN antibodies

- What's new
  - Data in children
  - 3yr persistence and boostability as evidence of immune memory
  - Consistency of findings in multiple studies - reinforces immunogenicity profile

- These data support pre-pandemic stockpiling or vaccination for individuals at increased risk of H5N1 exposure

Data limitations and possible future research

- Data limitations
  - The effectiveness of H5N1 vaccines is supported by immunogenicity data only, and by generalization of efficacy data with seasonal influenza vaccines made by the same process
  - The level of MN antibody assumed to be protective, while conservative, has not been validated
  - The studies I reviewed did not include elderly subjects and excluded those with unstable health
  - The data do not answer whether a 6-mos heterologous boost is superior to a homologous boost in broadening the MN response

- Future research
  - Test specimens from these trials for MN potency against contemporary H5N1 isolates,
  - Assess the level of anti-H5 stalk domain antibody elicited by adjuvanted H5N1 vaccine
  - Explore the PD$_{50}$ of human serum from vaccinees against various H5N1 isolates in animal models of influenza