Influenza vaccines

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Current issues in influenza vaccinology

- Do the current vaccines work (enough)?
- How do they work (when they do)?
- New ways to manipulate and attenuate viruses
- Debates over gain-of-function research
- Cross reactive stalk/stem antibodies
- Novel viral antigens many be weakly antigenic
- Vaccine manufacture needs to speed up in pandemics
Background
• Seasonal flu induces heterotypic immunity to novel flu strains
• In animals, heterotypic immunity from flu is prevented by killed vaccines
• Effect of T cell immunity in children is currently unknown

Methods
• Compared influenza A virus-specific cellular and humoral responses of unvaccinated healthy children with cystic fibrosis children, vaccinated annually

Results
• Similar virus-specific CD4 T cell and antibody responses
• Age-dependent increase of the virus-specific CD8 T cells in normal children
• No such effect in vaccinated CF children

Conclusion
• Annual flu vaccination hampers virus-specific CD8 T cell responses
• Routine flu vaccines may leave children unprotected against novel outbreaks

Is the study design underpowered to find an effect in CF cases?
Increased Risk of Noninfluenza Respiratory Virus Infections Associated With Receipt of Inactivated Influenza Vaccine

Benjamin J. Cowling, Vicky J. Fang, Hiroshi Nishiura, Kwok-Hung Chan, Sophia Ng, Dennis K. M. Ip, Susan S. Chiu, Gabriel M. Leung, and J. S. Malik Peiris

We randomized 115 children to trivalent inactivated influenza vaccine (TIV) or placebo. Over the following 9 months, TIV recipients had an increased risk of virologically-confirmed non-influenza infections (relative risk: 4.40; 95% confidence interval: 1.31-14.8). Being protected against influenza, TIV recipients may lack temporary non-specific immunity that protected against other respiratory viruses.

Table 3. Incidence Rates of Respiratory Virus Detection by Reverse-Transcription Polymerase Chain Reaction and Multiplex Assay

<table>
<thead>
<tr>
<th>Variable</th>
<th>TIV (n = 69)</th>
<th>Placebo (n = 46)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Rate&lt;sup&gt;a&lt;/sup&gt; (95% CI)</td>
<td>No.</td>
</tr>
<tr>
<td>Any seasonal influenza</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seasonal influenza A (H1N1)</td>
<td>3</td>
<td>58 (19–180)</td>
<td>3</td>
</tr>
<tr>
<td>Seasonal influenza A (H3N2)</td>
<td>2</td>
<td>39 (10–160)</td>
<td>2</td>
</tr>
<tr>
<td>Seasonal influenza B</td>
<td>1</td>
<td>19 (3–140)</td>
<td>0</td>
</tr>
<tr>
<td>Pandemic influenza A (H1N1)</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Any noninfluenza virus&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20</td>
<td>390 (250–600)</td>
<td>3</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>12</td>
<td>230 (130–410)</td>
<td>2</td>
</tr>
<tr>
<td>Coxsackie/echovirus</td>
<td>8</td>
<td>160 (78–310)</td>
<td>0</td>
</tr>
<tr>
<td>Other respiratory virus&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5</td>
<td>97 (40–230)</td>
<td>1</td>
</tr>
<tr>
<td>ARI episode with specimen collected but no virus detected</td>
<td>19</td>
<td>369 (235–578)</td>
<td>14</td>
</tr>
<tr>
<td>ARI episode with no specimen collected</td>
<td>41</td>
<td>796 (586–1080)</td>
<td>28</td>
</tr>
</tbody>
</table>

<sup>a</sup> Rates are adjusted for age and sex using a generalized linear model.
<sup>b</sup> Includes infections due to respiratory viruses other than influenza A or B, including parainfluenza, respiratory syncytial virus, human metapneumovirus, coronavirus, enterovirus, rhinovirus, and other respiratory viruses.
<sup>c</sup> Includes Rhinovirus, Coxsackie/echovirus, and other respiratory viruses.
Microbes and mucosal immune responses

Epithelial cells
- Barrier role: tight junctions
- Mucociliary escalator
- Goblet cell metaplasia
- Sentinel role: PRRs for PAMPs
- Production of IFN-β/λ, cytokines, chemokines, antimicrobial peptides

Mesenchyme
Airway remodelling
- Fibroblasts
- Myofibroblasts
- Smooth muscle, AHR
- Angiogenesis

Interdigitating cDC

Professional APCs
- cDCs are specialised APCs in relation to T cells
- pDCs are major IFN-α/β-producing cells during viral infections
- Macrophages are phagocytic APCs
  M1: inflammatory and T-cell activation
  M2: patrolling and scavenging
  AAM: IL-13 production in atopy (M2 subtype)

The sentinel barrier
Epithelium with interdigitating cDCs
- IL-25, IL-33, TSLP
- and chemokines

Circle of lymphoid cells and pathways

Innate lymphoid cells
Group 1 ILCs (ILC1 and NK cells) produce IFN-γ
Group 2 ILCs (ILC2, NH cells) produce IL-5 and IL-13
Group 3 ILCs (including ILC3) produce IL-17 and IL-22

Th1 pathway
IFN-γ, TNF-β

Th2 pathway
IL-3, IL-4, IL-5, IL-9, IL-13

Immune homeostasis and remodelling
Th22, Treg
- IL-10, IL-22, TGF-β, IL-17

Cytotoxicity/cell killing
- Tc
- NK cells
- NKT cells

B cell
Ig and IgE

Neutrophil

Mast cell

Eosinophil

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Trevor T Hansel, Sebastian L Johnston*, Peter J Openshaw*
Lung tissue resident memory CD4 T cells
Retained locally regardless of Ag or inflammation.
Did not circulate or emigrate in parabiosis
Were protected from in vivo Ab labelling
Elevated CD69/CD11a

Protect against flu challenge whereas splenic CD4 T_{mem} recirculate to multiple tissues and fail to protect

*Journal of Immunology, 2011, 187: 5510–5514.*
Conclusion:
In seronegative volunteers challenged with H3N2 or H1N1, homotypic and heterotypic CD4 responses limit replication and severity of influenza responses.

But: are these cells actually those that protect, or a correlate of protective cells that are resident in the lung?
Background:
Role of T cells in heterosubtypic protection in humans is uncertain
The 2009 H1N1 pandemic: H1N1 virus in antibody-naive people

Methods:
Prospective study of 342 healthy adults
Pre-existing T cell responses to the pH1N1 virus epitopes

Results:
Symptom score inversely correlated with IFN-γ+ IL-2− CD8+ T cells
lung-homing cells with cytotoxic potential especially predictive

Conclusions
In the absence of cross-reactive neutralizing antibodies, CD8+ T cells cross-protect against symptomatic influenza
Vaccines for preventing influenza in the elderly


Background
- Flu vaccines have been used in the elderly for 40 years
- Recommended worldwide \( \geq 65 \) years
- Goal is to reduce complications among the vulnerable

Objectives
- To assess the effectiveness in the elderly

Search strategy
- Cochrane CENTRAL database, MEDLINE, EMBASE and Web of Science

Selection criteria
- RCTs, quasi-RCTs, cohort and case-control studies
- Laboratory confirmed cases or ILI

Main results
- 75 studies, 100 data sets
- “Due to the general low quality ... we were unable to reach clear conclusions”

Conclusions: No evidence of benefit of flu vaccines in the elderly
Rebuttal of Cochrane review of flu vaccines in the elderly (Jefferson et al. 2010)

- Jefferson failed to optimally separate vaccine benefits from background noise
- Re-analysis with stratification of vaccine types, study designs, populations and outcomes
- Corrected for virus circulation and antigenic match
- When flu is circulating, vaccine efficacy:
  - Influenza Like Illness: ~40%
  - Influenza: ~60%
  - Flu complications: ~30%

No benefit if flu is not circulating or if virus is mismatched
Current research gaps

- Is it possible to boost local mucosal immunity?
- Can T cell boosted vaccines reduce severity?
- Will T cell vaccines cross-protect?
- Might novel vaccines enhance disease?
- Can we induce effective cross-reactive antibodies?
- How can we extend the duration of immunity?
- Will resistance emerge?
- What are the risks, and benefits, of adjuvants?