Elderly Immunisation and Immunosenescence
Strategies for developing new influenza vaccines with enhanced protection in older adults

Janet E. McElhaney, MD, FRCPC, FACP
HSN Volunteer Association Chair in Healthy Aging
VP Research and Scientific Director
Health Sciences North Research Institute
Professor, Northern Ontario School of Medicine
Sudbury, Ontario, Canada
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Overview:

1) Influenza as a barometer of health in older people is the single most vaccine preventable disease and vaccination programs are cost-saving. *Why is influenza still a serious illness?*

2) Strain-specific antibody titres become poor predictors of vaccine failure with aging. How do we account for the effects of frailty on humoral and cell mediated immune response to influenza vaccination?

3) CD8 T cell responses show that greatest functional decline with aging. How can we recapitulate through vaccination, the ability of aged memory CD8 T cells to respond to natural influenza infection?
Laboratory-Confirmed Influenza Hospitalizations
Preliminary cumulative rates as of Apr 23, 2016

FluSurv-NET :: Entire Network :: 2015-16 Season

2015-2016
A/H1N1 pdm09

FluSurv-NET :: Entire Network :: 2014-15 Season

2014-2015
A/H3N2

FluSurv-NET :: Entire Network :: 2013-14 Season

2013-2014
A/H1N1 pdm09

FluSurv-NET :: Entire Network :: 2012-13 Season

2012-2013
A/H3N2

FluSurv-NET :: Entire Network :: 2011-12 Season

2011-2012
A/H3N2 + A/H1N1 pdm09

FluSurv-NET :: Entire Network :: 2009-10 Season

2009-2010
A/H1N1 pdm09
2017-18 Influenza Season

A/H3N2

Preliminary cumulative rates as of Apr 14, 2018

Age Selection
- Overall
- All Age Groups
  - 0-4 yr
  - 5-17 yr
  - 18-49 yr
  - 50-64 yr
  - 65+ yr
**Influenza A/H3N2 remains the greatest challenge to developing more effective vaccines in older adults**

**Incidence of serious outcomes of influenza**

- 90% of influenza deaths occur in older people
- For every influenza death, there are 3–4 influenza hospitalization

**Response to vaccination**

**CURRENT INFLUENZA VACCINE**

- Efficacy is 70–90% in preventing respiratory illness in healthy adults and only 30–40% in older people **particularly for H3N2 strains**
- BUT are cost-saving – mainly due to the prevention of A/H3N2 hospitalization

indicates a clear margin for improvement in protection against A/H3N2
Older adults have increasing susceptibility to pneumonia and influenza

**Older adults have increased prevalence of comorbid disease that fosters a risk of infections**

**Decrease in immunity** (Immunosenescence)

**Epigenetics**

**Microbiome**

**Comorbidities**

(Diabetes, COPD, heart failure)

**Functional status**

**Contributes to ageing process**

Baseline performance of basic activities of daily living is a major determinant of survival after infections

**Frailty Index > dynamic accumulation of biopsychosocial deficits**

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2. CMAJ August14;189:E1043-5, 2017 (Indian Residential School diets and current patterns of diabetes)
Vaccine-mediated resilience to influenza with aging

Frailty Index

Inflammaging & Multimorbidity

Andrew JID 2017
Catastrophic disability

- Defined as a loss of independence in ≥ 3 basic Activities of Daily Living
- 15% of older adults hospitalized with influenza experience catastrophic disability
- Dysregulated immune responses are the ‘geriatric giant’ of chronic diseases: influenza wakes the giant increasing the risk of catastrophic disability with:
  1. Strokes
  2. CHF
  3. Pneumonia and influenza
  4. Ischemic heart disease
  5. Cancer
  6. Hip fracture

2 Ferrucci et al. JAMA 1997;277:728.
Why do A/H3N2 strains have greatest impact in older adults?
Opportunities for developing new Influenza vaccines for older adults

• Antibody titers against influenza (hemagglutination inhibition assay) measures protection through sterilizing immunity

• Childhood exposure to different subtypes of influenza alters the antibody response to influenza vaccination later in life

• Age-related decline in the antibody response to influenza vaccination is an effect of repeat vaccination (not age)

• Frailty increases with age as we accumulate social, physical and cognitive deficits and contributes to “inflammaging”

• Frailty indices predict survival better than age and can be used as a single variable to measure of overall health status
Antibody responses as correlates of protection

**Log Titer for H3N2 Strain**

- A/H3N2
- $p=0.0001$
- ON Flu-
- ON Flu+

**Log Titer for H1N1 Strain**

- ON Flu-
- ON Flu+

**Log Titer for B Strain**

- ON Flu-
- ON Flu+

**Weeks post-vaccination**

**H3N2**-specific antibody responses as correlates of protection in older adults *may not predict vaccine failure*

**H1N1**-specific antibody responses as correlates of protection in older adults may be the ability to recall antibody responses from *childhood priming*

**Flu B**-specific immune responses as correlates of protection have *no shared epitopes* with Flu A
Targeting Immune Responses:
Developing more effective influenza vaccines for older adults

Killed Vaccines
New Vaccines

CTL

B

T_h

Age

T_h1
IFN-γ

T_h2 / T_reg
IL-4/IL-10

Vaccines
T cell correlates of protection: IFNγ:IL-10 ratio and iGrzB

Ex vivo challenge with A/H3N2

Mean IFNγ:IL-10 ratio (A/H3N2)

![Graph showing IFNγ:IL-10 ratio response to influenza predicts protection](image)

IFNγ:IL-10 ratio response to influenza predicts protection

**NOT** IFNγ alone in older adults


Mean iGrzB (A/H3N2)

![Graph showing Poor GrB responders to influenza vaccination predicts risk of influenza infection](image)

Poor GrB responders to influenza vaccination predicts ↑ risk of influenza infection


**AND**

illness severity correlates with IFNγ:IL-10 ratio & GrB (r= -.99)

(Shahid et al. Vaccine 28:6145-51, 2010)

**BUT**

can respond to influenza infection
Healthy Aging: The Balance

**Stimulates**
T cell responses

*but*

Do we press down on the gas pedal?

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**Suppresses**
T cell responses

*or*

Take our foot off the brake?

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IFNγ+IL-2− CD8 T cells (NP/M1) inversely correlate with pH1N1 illness symptoms in young adults.

Figure 4: Inverse correlation of crossreactive T cells and symptom score. Sridhar et al. Nat Med 19:1305-12, 2013.
**Figure 3:** T cell responses and illness severity.

IFN\(\gamma^+\) CD4 T cells (NP/M1) inversely correlate with A/H1N1 & A/H3N2 illness symptoms in young adults.

**Childhood priming** does not affect IFNγ or IL-10 responses to H1N1 or H3N2 challenge.

**Aging effect** is associated with a decline in IFNγ independent of H1N1 or H3N2 challenge.

**Aging effect on childhood priming** is associated with an increase in IL-10 response to H1N1 vs. H3N2 challenge.

**IFNγ:IL-10 ratio** is a correlate of protection when antibodies fail to provide sterilizing immunity.
Granzyme B: Inflammaging vs. Killing

>40% of aged GrzB⁺ CD8 T cells are Perf- in ex vivo response to influenza

Granzymes

CD8+ T cell
NK cell

Mac Mast Neut KC Chond

Inflammaging

Cleavage of IL-1α and extracellular matrix

Production of IL-6, IL-8, and GM-CSF
Loss of tissue structural integrity

Inflammation
Tissue injury and impaired tissue repair

Death of virus-infected cell

GrzB
Perforin
GrzB

McElhaney et al Vaccine 2060-7, 2012
Randomized trial of 4 Subunit Influenza Vaccines

Panel A: Granzyme B\(^+\) CD8\(^+\) cells

\%Granzyme B\(^+\) CD8\(^+\) >>> \%Granzyme B\(^+\) CD4\(^+\) cells

Panel B: Granzyme B\(^+\) CD4\(^+\) cells
Randomized trial of 4 Subunit Influenza Vaccines:
\[ \% \text{Perforin}^+ \text{ CD8}^+ = \% \text{Perforin}^+ \text{ Granzyme B}^+ \text{ CD8}^+ \]

PANEL A: Perforin $^+$ CD8$^+$ cells

PANEL B: Perforin $^+$ Granzyme B$^+$ CD8$^+$

![Bar chart showing % Positive for each vaccine group](chart_image)
bGrB activity correlates with frequency of late differentiated CD8⁺ T cell subsets

<table>
<thead>
<tr>
<th>CD8⁺ T cell subset</th>
<th>CD8⁺ T cell phenotype</th>
<th>Pearson Correlation (r)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CD8⁺ T cells</td>
<td>CD3⁺CD8⁺</td>
<td>0.601</td>
<td>.001</td>
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<tr>
<td>Late or terminally differentiated CD8⁺ T cells</td>
<td>CD8⁺CD57⁺</td>
<td>0.586</td>
<td>.001</td>
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<tr>
<td>Memory T cells</td>
<td>CD8⁺/CD45RA⁺CCR7⁻CD27⁻CD28⁻</td>
<td>0.553</td>
<td>.002</td>
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<tr>
<td>Memory T cells</td>
<td>CD8⁺/CD28⁺</td>
<td>-0.579</td>
<td>.001</td>
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<tr>
<td></td>
<td>CD8⁺/CD45RA⁻CCR7⁺CD27⁺CD28⁺</td>
<td>-0.476</td>
<td>.010</td>
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<tr>
<td></td>
<td>CD8⁺/CD45RA⁻CCR7⁻CD27⁺CD28⁺</td>
<td>-0.627</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Granzymes – Beneficial, Pathogenic, or Both?

Good
(apoptosis)

Bad
(extracellular, inflammation, autoantigens, anoikis)

Adjuvanted NP+M1 Influenza Vaccines

Cytomegalovirus
Age
Chronic Conditions
Correlate of protection: Granzyme B

**Influenza A/H3N2**

**Combined ’03-’04 and ’04-’05 Seasons**

**Geometric Mean**

**Granzyme B**

(U/mg protein)

Prior vs. No flu  P=0.02
No flu vs. Flu   P=0.004
SMWT, statins - significant at pre-vacc only
Error bar: std error

**Relative Vaccine Efficacy of FLUZONE® High-Dose**

**Benefit demonstrated across age groups, influenza types, comorbidities, and frailty-associated conditions**

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT¹</th>
<th>Similar to Vaccine Strains¹</th>
<th>Year 1³</th>
<th>Year 2³</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.2% more efficacious*</td>
<td>35.4% (95% CI: 12.5; 52.5)</td>
<td>45.3% (95% CI: 6.9; 68.6)</td>
<td>20.7% (95% CI: 4.4; 34.3)</td>
</tr>
<tr>
<td>65-74 Years of Age²</td>
<td>19.7% (95% CI: 0.4; 35.4)</td>
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<tr>
<td>75+ Years of Age²</td>
<td>32.4% (95% CI: 8.1; 50.6)</td>
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<tr>
<td>≥1 High-Risk Comorbidity²</td>
<td>22.1% (95% CI: 3.9; 37.0)</td>
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<tr>
<td>1 Frailty-Associated Condition²</td>
<td>27.5% (95% CI: 0.4; 47.4)</td>
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</tbody>
</table>

*against laboratory-confirmed influenza illness caused by any virus type or subtype in adults 65 years of age and older

**References:**
T-cell responses to H3N2 challenge following HD vs. SD influenza vaccination in older adults

bGrB activity in resting T cells

Dysregulated IFNγ and IL-10 responses are vaccine dose dependent

GLA-SE: Regulating Th1:Th2 response

IL-2/IL-6 restores the aged CD8⁺ T cell response to influenza

A. [Flow cytometry plots showing CD8⁺ tetramer⁺ T cells with different cytokine treatments: No cytokine, +IL-2, +IL-6, +IL-2+IL-6.]

B. [Bar graph showing the number of CD8⁺ tetramer⁺ T cells over days 0, +IL-2, +IL-6, +IL-2+IL-6.]

C. [Bar graph showing HO CD8⁺ tetramer⁺ T cells over days 0, +IL-2, +IL-6, +IL-2+IL-6.]

D. [Line graphs showing the number of HO CD8⁺ tetramer⁺ T cells over days 0, +IL-2+IL-6.]

Zhou et al Oncotarget. 7:39171-83, 2016
IL-2/IL-6 effect can be replicated with TLR3/4 ligand: CD8\(^+\) T cell response to influenza virus*

*unpublished

Zhou et al Oncotarget. 7:39171-83, 2016
Resilience of aging immune system: "Keeping your glass half full"

Why is influenza still a serious illness? *CD8+ CTL decline with aging. Dysregulated immune response to influenza challenge (but appears to be reversible).*

How can we develop more effective influenza vaccines?

- Vaccines that include M1 and NP
- TLR agonists stimulate mDC to produce IL-6, TNF-α, IL-1
- Suppress IL-10 production (Treg) upon influenza challenge