Adjuvanted vaccines for the elderly

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Role of Innate and adaptive immune response in adjuvant response

**Innate response (0 – 72h)**
- Granulocyte
- Macrophage
- Monocyte
- Cytokines
- Antigen

**Adaptive response (Day 1 to weeks)**
- T lymphocytes
- B lymphocytes
- APC

Stimulation of the local innate system
Local cytokine response
Recruitment of innate immune cells
Adaptive immune response

Site of infection/injection ➔ Lymph node ➔ Blood

Only few vaccine adjuvants have been evaluated in the Elderly

<table>
<thead>
<tr>
<th>Adjuvant name</th>
<th>Mechanism or receptor</th>
<th>Clinical phase or licensed product name</th>
</tr>
</thead>
<tbody>
<tr>
<td>dsRNA analogues (for example, poly(I:C))</td>
<td>TLR3</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Lipid A analogues (for example, MPL, RC529, GLA, E6020)</td>
<td>TLR4</td>
<td>Cervarix, Supervax, Pollinex Quattro, Melacine</td>
</tr>
<tr>
<td>Flagellin</td>
<td>TLR5</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Imidazoquinolines (for example, Imiquimod, R848)</td>
<td>TLR7 and TLR8</td>
<td>Aldara</td>
</tr>
<tr>
<td>CpG ODN</td>
<td>TLR9</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Saponins (for example, QS21)</td>
<td>Unknown</td>
<td>Phase 3</td>
</tr>
<tr>
<td>C-type lectin ligands (for example, TDB )</td>
<td>Mince, Naip3</td>
<td>Phase 1</td>
</tr>
<tr>
<td>CD1d ligands (for example, α-galactosylceramide)</td>
<td>CD1d</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Aluminum salts (for example, aluminum oxyhydroxide, aluminum phosphate)</td>
<td>Naip3, ITAM, Ag delivery</td>
<td>Numerous licensed products</td>
</tr>
<tr>
<td>Emulsions (for example, MF59, AS03, AF03, SE)</td>
<td>Immune cell recruitment, ASC, Ag uptake</td>
<td>Fluad, Pandemrix</td>
</tr>
<tr>
<td>Virosomes</td>
<td>Ag delivery</td>
<td>Epaxal, Inflexal V</td>
</tr>
<tr>
<td>AS01 (MPL, QS21, liposomes)</td>
<td>TLR4</td>
<td>Phase 3</td>
</tr>
<tr>
<td>AS02 (MPL, QS21, emulsion)</td>
<td>TLR4</td>
<td>Phase 3</td>
</tr>
<tr>
<td>AS04 (MPL, aluminum salt)</td>
<td>TLR4</td>
<td>Cervarix</td>
</tr>
<tr>
<td>AS15 (MPL, QS21, CpG, liposomes)</td>
<td>TLR4 and TLR9</td>
<td>Phase 3</td>
</tr>
<tr>
<td>GLA-SE (GLA, emulsion)</td>
<td>TLR4</td>
<td>Phase 1</td>
</tr>
<tr>
<td>IC31 (CpG, cationic peptide)</td>
<td>TLR9</td>
<td>Phase 1</td>
</tr>
<tr>
<td>CAF01 (TDB, cationic liposomes)</td>
<td>Mince, Ag delivery</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ISCOMs (saponin, phospholipid)</td>
<td>Unknown</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

Can Adjuvant help? Observed benefits of adjuvants in candidate or licensed vaccines

- Increased and persistent CD4 and antibody response\(^1\)
- Antigen dose sparing effect\(^2\)
- Increase breadth of the antibody response (MF59/AS03-adjuvanted flu)\(^3\)
- Evidence of cross-reactive T-cell response\(^5\)
- AS are being used in vaccines in populations with specific immune status, such as HIV+\(^7\) and other immunocompromised people\(^6\)

**WHAT IS THE EVIDENCE IN THE ELDERLY POPULATION?**

References:

1. Leroux-Roels et al. *Vaccine*, 2015 (HBs/AS01); Leroux-Roels et al., *Clin. Vaccine Immunol.* 2014 (F4/AS01); Roteli-Martins et al., *Hum Vaccin Immunother* 2012 (HPV/AS04)
Observation 1: limited efficacy of conventional non-adjuvanted Influenza vaccines in older adults

Estimated reduction in Influenza Illness\(^1\) Following Administration of Non-adjuvanted TIVs to Healthy Adults (<65 Years), Older Adults (≥60 Years) and Children (<16 Years)

- **Healthy adults** (<65 years of age)\(^2\):
  - Reduction in Influenza Illness: 70-90%

- **Older adults** (≥60 years of age)\(^3\):
  - Reduction in Influenza Illness: 40-60%

- **Children** (<16 years of age)\(^4\):
  - Reduction in Influenza Illness: 43-59%

  \(^{\text*}}\) **In children under two, the efficacy of inactivated vaccine was similar to placebo.**\(^4\)

Data shown are taken from different studies and definition of influenza illness endpoints can vary by study.

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1. Please refer to source references for more details;
2. CDC available at [http://www.cdc.gov/flu/professionals/vaccination/effectivenessqa.htm](http://www.cdc.gov/flu/professionals/vaccination/effectivenessqa.htm);
Observation 2: Herpes zoster incidence rate increases with age (regardless of geography)

Several studies have shown that the incidence of HZ increases substantially with age\textsuperscript{1,2}

HZ, herpes zoster; YOA, years of age

Impact on efficacy - Adjuvanted vs plain seasonal split flu

Number of participants infected and relative efficacy by influenza strain during the year 1 surveillance period in the year 1 efficacy cohort

<table>
<thead>
<tr>
<th>Participants infected</th>
<th>Relative efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS03-adjuvanted TIV (n=21,573)</td>
<td>Non-adjuvanted TIV (n=21,482)</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
</tr>
<tr>
<td>Influenza A or B, or both</td>
<td>274 (1.27%, 1.12 to 1.43)</td>
</tr>
<tr>
<td><strong>Exploratory analysis</strong></td>
<td></td>
</tr>
<tr>
<td>Influenza A</td>
<td>224 (1.04%, 0.91 to 1.18)</td>
</tr>
<tr>
<td>Influenza A H1N2</td>
<td>170 (0.79%, 0.67 to 0.92)</td>
</tr>
<tr>
<td>Influenza A H1N1</td>
<td>17 (0.08%, 0.05 to 0.13)</td>
</tr>
<tr>
<td><strong>Post-hoc analyses</strong></td>
<td></td>
</tr>
<tr>
<td>Influenza A H1N2</td>
<td>190 (0.88%, 0.76 to 1.01)</td>
</tr>
<tr>
<td>Influenza B Yamagata</td>
<td>12 (0.96%, 0.03 to 0.10)</td>
</tr>
<tr>
<td>Influenza B Victoria</td>
<td>37 (0.17%, 0.12 to 0.24)</td>
</tr>
</tbody>
</table>

Data are n (%). 95% CI or (95% CI). Excluding A H1N1 pdm09 strains. TIV= inactivated trivalent influenza vaccine. * Real-time PCR. †No subtype was identified with real-time PCR for 37 samples in the group given AS03-adjuvanted TIV and 53 samples in that given non-adjuvanted TIV; these samples were further analysed with multiplex RT-PCR.

N= 43,800 aged 65 years and older

Similar data with MF59-TIV with a reduced “pneumonia/influenza” hospitalizations by 23% over TIV*


Clinical outcomes during peak season in year 1 in the year 1 peak season efficacy cohort

<table>
<thead>
<tr>
<th>Relative efficacy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia or clinical influenza</td>
</tr>
<tr>
<td>AS03-adjuvanted TIV (n=21,394)</td>
</tr>
<tr>
<td>202 (0.94%, 0.82 to 1.08)</td>
</tr>
<tr>
<td>All-cause death</td>
</tr>
<tr>
<td>63 (0.29%, 0.23 to 0.38)</td>
</tr>
<tr>
<td>Admission to hospital because of respiratory diseases</td>
</tr>
<tr>
<td>84 (0.39%, 0.31 to 0.49)</td>
</tr>
<tr>
<td>Pneumonia only†</td>
</tr>
<tr>
<td>32 (0.15%, 0.10 to 0.21)</td>
</tr>
</tbody>
</table>

Data are n (%). 95% CI or (95% CI). TIV= inactivated trivalent influenza vaccine. * Descriptive estimates. †Post-hoc analysis with adjustment for regional differences in attack rates in the group given non-adjuvanted TIV.
Adjuvant (AS03) enhanced T cell response against seasonal split flu in individuals >65 YOA

Specific CD4^+ T cells expressing at least 2 markers per 10^6 CD4^+ T cells

<table>
<thead>
<tr>
<th></th>
<th>TIV/AS03 (≥65)</th>
<th>TIV (≥65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>1.64 (1.35-1.99; p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>1.70 (1.44-2.00; p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>180</td>
<td>1.40 (1.21-1.61; p&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

The level of T cell response in >65y approaches the one observed in younger adults

specific for the three (pooled) influenza vaccine strains

Couch et al, *BMC Infect Dis*, 2014; 14:425
Priming in the Elderly with MF59-adjuvanted H5N1 vaccine and boostability with heterovariant strain

Potential role of T cell induced by the adjuvanted vaccine in B cell “adaptibility”

Role of monocytes?

With adjuvant

Without adjuvant

“re-shaping” an optimized antibody repertoire

TCR affinity
Reactogenicity induced by adjuvanted Flu vaccine is generally of lower intensity in the Elderly than in younger adults.

If reactogenicity considers as a proxy for “innate activation”:

Due to lower innate stimulation by adjuvant

or

reduced fitness of innate effectors?

Some lessons from adjuvanted flu vaccine studies in the elderly

- Accumulating evidence that adjuvants - mainly o/w emulsions - can increase immunogenicity and efficacy of influenza vaccines in the elderly, across strains.

- Efficiency tends to be higher for pandemic vs seasonal strains -> highest benefit is when there is a limited established repertoire?

- A potential mechanism involving $T_{FH}$ may overcome this limitation by providing adaptability features to the established repertoire -> Increased breadth of antibody response? Role of other T cells?

- Activation of innate immunity by adjuvant may be reduced in the elderly (to be confirmed) but nevertheless sufficient to promote T/B-cell activation.
From one adjuvant to another....

Emulsions

AS01

MPL
Monophosphoryl Lipid A

LPS

Saponin QS-21

Phospholipid bilayer

Aqueous core

Liposome

AS01

Oil

Surfactant
GSK’s candidate Zoster vaccine antigen

VZV glycoprotein E (gE)

• Highly abundant VZV glycoprotein

• Central role in VZV infection – Essential for virus entry and cell–cell spread

• Expressed in skin lesions and ganglia during HZ episodes

• Target of both humoral and cellular responses
Results of the HZ/su Ph III efficacy studies

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>HZ/su group</th>
<th>Placebo group</th>
<th>VE (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HZ cases</td>
<td>Incidence (per 1000 person-yrs)</td>
<td>HZ cases</td>
</tr>
<tr>
<td>Overall (≥50)</td>
<td>6</td>
<td>0.3</td>
<td>210</td>
</tr>
<tr>
<td>50-59</td>
<td>3</td>
<td>0.3</td>
<td>87</td>
</tr>
<tr>
<td>60-69</td>
<td>2</td>
<td>0.3</td>
<td>75</td>
</tr>
<tr>
<td>≥70</td>
<td>1</td>
<td>0.2</td>
<td>48</td>
</tr>
</tbody>
</table>

*VE = % vaccine efficacy (Poisson method); CI, confidence interval; p-value = Two sided exact p-value conditional to number of cases, p-value for all comparisons <0.0001

- HZ/su efficacy appeared to be age-independent (even in people ≥70 years) and did not wane during the study period

- No imbalance in the incidence of safety endpoints observed between the HZ/su and placebo groups. Local and systemic reactions to HZ/su are common, large majority being mild-moderate and of short duration.

HZ risk correlates with a decline in VZV-specific T-cell levels

HZ, herpes zoster; VZV, varicella zoster virus

VZV primary infection establishes memory

Periodic boosting by exposure

HZ threshold

threshold correlating with increased risk of HZ disease

HZ, herpes zoster; VZV, varicella zoster virus

The ability of AS01 to improve cellular response in the elderly as the basis for its selection for the zoster program

- Immuno PoC study\(^1\). Open-label, randomized; N=155
- gE/AS01\(_B\) and/or VZV live attenuated (OKA) vaccine* administered separately or concomitantly
- 2 doses, Months 0, 2

![Graph showing cellular response over time](image)

- Older adults (50-70 years; N=45/group)
- Young adults (18-30 years; N=10/group)
- gE/AS01\(_B\) + OKA* (co-admin)
- gE/AS01\(_B\) alone
- OKA* alone

- Minimum release titer = \(10^{3.3}\) pfu/dose; actual titer of VZV used in this study: \(10^4\) pfu/dose

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\(^1\) Leroux-Roels G, et al., *J Infect Dis* 2012; 206: 1280-1290

Adjuvant dose selection study

Overall ages: AS01\textsubscript{B} induced higher CD4+ T cells than AS01E\textsuperscript{*} (also true for antibody levels)

AS01B contains 50µg of MPL and QS-21
AS01E contains 25µg of MPL and QS-21

*True for separate age strata although statistically significant only for the 60-69y.

Long-term persistence (6 years) of gE-specific T cells and antibodies

Comparable in the two age groups (60-69 and >70 years)

Phase II long-term follow-up:
- >60 yo elderly
- 50 μg gE/AS01ₐ

Chlibek et al. Vaccine 2015
Understanding the mode of action of AS01
The right model for the right question!

Hypothesis generation
Descriptive work
Mainly limited to blood signature

Mainly Descriptive work
Bridge blood signature to local response

Mechanistic work
Validate cellular and molecular mechanisms

IMPROVE
rational choice/design
MPL acts on DCs and QS-21 acts on monocytes, broadening the APC population in the LN

AS01
(MPL + QS-21)

Muscle/Injection site

Draining lymph node

Periphery

Muscle-derived migratory DC

monocytes derived DCs

Activated LN resident DCs

QS-21-activated monocyte

Monocyte

All three types of DCs and activated monocytes may ultimately cooperate to improve the quality of the Ag-specific T-cell response

AS01 increases the number of innate cells bearing antigen but does not increase antigen uptake intrinsically.

**Number of Ag+ cells in the LN**

Fluorescent gE + AS01

AS01 does not increase antigen uptake in APCs

**Quantity of antigen per cell**

Didierlaurent et al. *J. Immunol.*, 2014
Combination of MPL and QS-21 is critical for optimal gE-specific CD4+ T cell response

Immunization d0
Immunization d28
Analysis d58
Antigen: gE
Adjuvant: AS01/MPL/QS-21 i.m.

n=16

Dendouga et al, Vaccine 2012; 30:3126-35
• Understanding the mode of action of adjuvanted vaccines in older adults and potential differences with younger individuals will help to:
  - Define key elements of innate response involved and whether some should be preferentially targeted (monocytes, NK?)
  - Ability of adjuvant to genuinely prime de novo response or restore/boost quality/fitness of pre-existing pool of antigen-specific T and B cells
  - Extend use of adjuvants to target other diseases in the elderly population (Strep, Nosocomial, RSV…)- Zoster-related specificities?

• “Elderly prone” Adjuvants with specific features, targeting of specific innate cells? Need for new adjuvants?

• Combination with other vaccine delivery or other approaches (mTor)?
Vaccine responsiveness and adjuvants….

- BOTH properties antigen-specific memory response AND inflammatory status may condition vaccine responsiveness, in particular to adjuvanted vaccines.
- Adjuvants are likely dependent on “innate responsiveness/fitness” in the elderly considering their known mode of action.

> Some level of inflammation may be needed to overcome hypo-responsiveness
> (not enough with alum-based vaccine, achieved with AS01)

Or

> Baseline dysregulated pathways (inflammaging) should be modulated to alleviate hyporesponsiveness

From Alter and Sekaly, Vaccine 2015; 33supp2: B55-9
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