Controversies in the Prevention and Treatment of influenza

B. Salzberger
Infektiologie UKR
Regensburg
Prevention of Influenza

• What are the benefits of influenza vaccination in the elderly?
• How best to prevent influenza in the elderly?
  – Can we induce herd immunity by influenza vaccines?
Framework Influenza Vaccine Efficacy

• Endpoint: Influenza like-Illness (ILI), laboratory confirmed (clinical efficacy)
  – Difficult to measure, especially in pre-PCR times

• Serology as surrogate marker (serological efficacy)
  – Antibody titer in hemagglutinin-inhibition-Assay
  – Protection correlated to AIHA Titer, seen in experimental human infection, eg. AIHA 1:40 correlates with 50% reduction in ILI

Potter, Br Med Bull 1979
Claims

• Influenza vaccination in the elderly prevents
  – Influenza like illness (effectiveness 35%)
  – Influenza hospitalization (33%)
  – Influenza and pneumonia related deaths (47%)
  – All cause mortality (50%)

Vu, Vaccine 2002
Vaccination in the Elderly - Best evidence

- One larger placebo controlled randomized controlled trial from 1994 (n=1838)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vaccine</th>
<th>Risk/Rate-Ratio</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab. conf. Influenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all</td>
<td>16/927</td>
<td>38/911</td>
<td>0,42</td>
<td>58%</td>
</tr>
<tr>
<td>60-69y</td>
<td>12/649</td>
<td>29/645</td>
<td>0,41</td>
<td>59%</td>
</tr>
<tr>
<td>70 and more</td>
<td>4/278</td>
<td>9/256</td>
<td>0,43</td>
<td>57%</td>
</tr>
</tbody>
</table>

Seroprotection (AH3N2, AIHA 1:100)

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>all</td>
<td>5,9%</td>
<td>66,1%</td>
<td>11,2 (8,6-14,2)</td>
<td></td>
</tr>
<tr>
<td>60-69y</td>
<td>4,9%</td>
<td>66,5%</td>
<td>13,6 (9,6-19,2)</td>
<td></td>
</tr>
<tr>
<td>70 and more</td>
<td>8,3%</td>
<td>65,3%</td>
<td>7,9 (5,2-11,9)</td>
<td></td>
</tr>
</tbody>
</table>

Govaert, JAMA 1994
Accumulating evidence in the 1990s and later...

• Many cohort studies comparing outcomes of vaccinated and unvaccinated elder people
  – Within seasons with high viral circulation
  – Within seasons with good/bad match of vaccines

• Many cohort studies induce meta-analyses
  – Pre-1990s and post 1990 studies
  – Vaccine efficacy for all-cause mortality
    • In community living elderly >50%
    • In institutionalized elderly >68%

Simonsen; Lancet Inf Dis 2007
Influenza Vaccine and All cause mortality
US –scenario

Simonsen, Lancet
Inf Dis 2007

ESCMID Online Lecture Library
© by author
Influenza vaccine and Mortality - reality

Simonsen, Lancet Inf Dis 2007
Some simple fact checking....

- If 50% of all cause mortality is averted by influenza vaccine, influenza mortality must cause at least 50% of all cause mortality
- Clearly in contradiction to epidemiological data
  - Influenza related death are at most 10% of all winter deaths in the US

Simonsen, Arch Int Med 2005
Checkpoints for Case control studies

• Seasonality:
  – Death rates should differ most in or shortly after high viral circulation
    • In contrast, reduction of mortality in vaccinated people was most pronounced before the circulation of influenza in several studies

• Severity /Match:
  – Influenza effects should be more pronounced in severe seasons and good vaccine match

• Selection bias: vaccine uptake higher in healthy elderly
Better Designs for Case Control Studies?

• Test-negative design:
  – Outcome: influenza like illness with laboratory confirmation (positive test) vs. ILI with negative test (!)
  – Both groups show similar health care use
  – Outcome specific for influenza, relevant for evaluation of influenza effectiveness

– If you want to have a closer look at design of clinical studies: ESCMID course on clinical studies, 26-28th October 2016, Seville

Skowronski, Can Commun Dis Rep 2005
Rating Influenza Vaccination in the Elderly

• Serologic responses good, even in the very old (>85 yo)
• Clinically effective (in preventing ILI or worse)
• Mortality benefit in community dwelling elders low, if at all
• Some mortality benefit in institutionalized elderly people (less bias prone case-control studies)
Two Ladies...

Maria, 85yo, no chronic illness, still hikes in the Alps, albeit more slowly, works in the garden, cooks, 4 children, 7 grandchildren (7-40yo)

Hildegard, 95yo, no chronic illness, works in the garden, active in business, 2 children, 5 grandchildren 22-30yo
How best to protect?

• Influenza Vaccination in the elderly
  – What is the best vaccine?
  – Is it good enough – should we add other preventive measures – such as vaccination of friends and families?
How to make the Influenza vaccine more immunogenic?

- Intradermal vaccination – effect marginal
- Adjuvanted vaccine - more immunogenic (though in large trials superiority not clearly demonstrated), no data on clinical effectiveness
- High-dose vaccine – best data yet
High Dose vs SD Vaccine in the Elderly

- 2975 HD vs. 1276 SD pts., median age 73y, 67% one, 34% two comorbidities

<table>
<thead>
<tr>
<th></th>
<th>SD (&gt;75yo)</th>
<th>HD (&gt;75yo)</th>
<th>HAI-GMT-Ratio</th>
<th>Rate Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean AIHA -Titers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AH1N!</td>
<td>67 (62)</td>
<td>116 (104)</td>
<td>1,7</td>
<td>-</td>
</tr>
<tr>
<td>AH3N2</td>
<td>333 (339)</td>
<td>609 (533)</td>
<td>1,8</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>52 (64)</td>
<td>69 (68)</td>
<td>1,3</td>
<td>-</td>
</tr>
</tbody>
</table>

Seoprotection (AIHA 1:40)

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AH1N!</td>
<td>89,9%</td>
<td>76,8%</td>
<td>-</td>
</tr>
<tr>
<td>AH3N2</td>
<td>99,3%</td>
<td>96,5%</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>79,3%</td>
<td>67,6%</td>
<td>-</td>
</tr>
</tbody>
</table>

Falsey, J Inf Dis 2009
HD-Vaccine: Clinical effective?

- Randomized study with 32,000 elderly, 66% < 75 yo, 34% 75 yo and more
  - HD vs. SD vaccine: 23% Efficacy in preventing lab confirmed ILI, resp. Illness and related outcomes
  - Serologic and clinical efficacy in all age groups

- Case-control study
  - 900,000 pts. with HD, 130,000 pts with SD vaccine,
    50% 65-75 yo, 36% 75-85 yo, 13% > 85yo
  - ILI defined as consultation with rapid test and prescription of oseltamivir (HD 22% effective)
  - Influenza-hospitalization (HD 22% effective)

HD-vaccine: Is it clinically effective?
Herd Immunity for the Protection of Elderly?

- Young children central for influenza epidemiology—high rates of infection, high number of contact
- Does vaccination of young children/school children protect elderly patients
  - For pneumococcal infections clearly demonstrated
The Japanese Experience

- Introduction of Influenza vaccination for Schoolchildren in 1962, mandatory since 1972
- Coverage rates up to 85% in schoolchildren
- Growing concern of parents and doubt about efficacy led to termination of program in 1994

Reichert, NEJM 2001
The Japanese Experience

Reichert, NEJM 2001
Recommendations

- Influenza vaccination –is effective, does prevent respiratory illness (or worse)
  - Do not promise much more!
- Highdose vaccine –
  - best choice currently
  - modest higher efficacy, no concerns regarding safety
- Vaccination of children protects elderly – not generally accepted
What to do with the two Ladies...

High dose vaccine (unfortunatel not licensed in the EU)
Vaccinate 7yo grandson?

Same
Grandchildren are too old for herd protection criteria
If institutionalized: vaccinate staff!
Treatment of Influenza

• Are neuraminidase inhibitors effective at all?

• Are there cutoffs – when not to start or use neuraminidase inhibitors any longer?

• Is there a rationale for combination antiviral therapy?
Let's take a poll

- Neuraminidase inhibitors have clinical efficacy
- Neuraminidase inhibitors have efficacy in vitro, not in vivo
Efficacy of NIs in Influenza Complications

• Up to 2010 in all metaanalyses:
  – Use of NI prevents complications (lower resp. Infection, otitis media)

• Growing concern about data quality
  – Cochrane group went to original datasets
    • Endpoints not validated
    • Some adverse effects not properly reported

• Cochrane group (T. Jefferson) asked for complete original study data (not compilations)
Two new metaanalyses

• Oseltamivir/Zanamivir are effective in reducing time to symptom relief in children and adults (17h/24H)
• Oseltamivir/Zanamivir are effective in preventing infection after exposure

• No effect on complications (endpoints not validated, only low risk study participants)

Clinical Efficacy of NIs in Other Studies

- Clinical efficacy demonstrated in many cohorts
- Metaanalysis of 78 cohorts with approx. 30,000 pts. 2009-11
  - Median age 26y., 23% pregnant, 38% at least one comorbidity
  - 25% Pneumonia, 23% ICU
  - 36% untreated, 64% treated (92% oral oseltamivir, 8% other neuraminidase inhibit.)
- Over all reduction of mortality (OR 0.48), significant with start until day 4 of symptoms
- Reduction of mortality in pregnancy (OR 0.16-0.27)

Muthuri, Lancet Resp Med 2014
Survival and NI Therapy

Muthuri, Lancet Resp Med 2014
53 yo man in the ICU

- Progressive dyspnea, cough, fever for 4 days
- Family called ambulance, admission through ED
- 53yo man, CLL, allogeneic stem cell tx 1/2015, recurrent CLL therapy with donor lymphocytes
- Infection bacterial/viral? GvHD? Lung edema with cardiac failure
- CRP 150 mg/l (UN 3), PCT 0.27ng/ml (UN 0.2)
- Leukocytes 3800/mcl, 46% neutrophils
- Start Antibiotics, Steroids and noninvasive ventilation
53yo man, ICU 3.3.2016

• 3.3. Influenza A positiv; no other pathogens – start Oseltamivir
• 8.3 Influenza PCR positive
• 15.3. positive
• ..
• 19.4. positive (low titre) -
• 26.4. negative
Rules for using NIs

• If you have a patient with severe influenza (e.g., pneumonia) with replication – treat
• Treatment course 5 days, can be repeated
• There is no data on the maximum time, but 14 days seems sensible to most – All eminence base (R.G. Webster)

• What if there is still replication?
53yo man, ICU 3.3.2016

- 3.3. Influenza A positiv, B, RSV, Adenovirus negativ – start Oseltamivir
  - Sequence shows wild type virus
- 8.3 Influenza PCR positive
- 15.3. positive
- 5.4. positive
  - Sequence: H275Y mutation
- 19.4. positive
- 26.4. negative
Viral Turnover and Resistance

• Studies in experimental influenza infection: $10^{11}$ virus particles within 7 days infection
• Mutation rates of RNA-viruses are high - all single and dual mutants will be produced in one infection cycle
• Resistance to Oseltamivir with one nucleoside change....
• Use more drugs or raise the barrier to resistance!

Perelson JID 2012, 205 p1642
Combination antiviral therapy for Influenza

- Amantadine and Ribavirin more effective, reduction of resistance development in animal models
- Amantadine, Ribavirine and Oseltamivir currently in clinical trials
Conclusions

• Neuraminidase inhibitors have clinical efficacy – but the evidence for severe influenza is low

• Open questions about the optimal use of Nis:
  – Which patient to treat?
  – Cutoffs for starting and stopping therapy?

• There is a rationale for combination therapy – new strategies in development and clinicals studies
Other Controversies Worthy Studying

• Pathogenesis: Virus vs. Host Reaction
• Mandatory Vaccination of Health Care Workers
• Cause of Mortality: Viral or Bacterial Pneumonia
• What defines best immunity: T-cells or Antibodies?
• Does yearly vaccination yield additional benefit?