Influenza vaccines and Adjuvants

Bram Palache MSc, PhD

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GEIG, France

Speaker's background
Current positions

Solvay Biologicals, The Netherlands

- Global Scientific Communications and Public Affairs Director, Influenza Vaccines

- European Scientific Working group on Influenza (ESWI)
  - Non-voting member of the Executive Committee; treasurer; liaison with industry
- Asian Pacific Advisory Committee on Influenza (APACI)
  - Sponsoring member
- European Vaccine Manufacturers (EVM)
  - Member of Pandemic influenza working group
  - Member of Public Health working group
  - Member of Clinical Working group
- Influenza Vaccine Supply International Task Force (IVS-ITF)
  - Chair: policy, practice and communications subgroup

Vaccine adjuvants in historical perspective

- Vaccine adjuvant research and development has been an ongoing activity for more than a century
- Although many adjuvant systems have been developed and tested in preclinical models, few have actually proved useful for human vaccines
- The primary limitations for the use of new adjuvant systems with human vaccines revolve around safety issues
- …the safety barriers presented by regulatory and liability issues have continued to increase
- The development of successful vaccine adjuvants has been a constant balancing act between safety and immunogenicity, delivery and immunostimulation, and simplicity and complexity
- We appear to be at the beginning of a new era in which a variety of new adjuvants are being approved or are about to be approved for human vaccines

M.Singh: Vaccine adjuvants and delivery systems; Wiley, 2007

Adjuvants “danger hypothesis”

- “ tissue damage or toxicity as indusced by inflammatory cytokines is a necessary prerequisite for an effective immune response”
  - Matzinger P. The danger model: a renewed sense of self. Science 2002;296:301-305

Freeing vaccine adjuvants from dangerous immunological dogma

- Ideally, adjuvants should strongly stimulate B- and T- cell immunity while avoiding the excess innate immune system activation and inflammatory cytokine production that mediates adjuvant reactogenicity

N. Petrovsky; Expert Rev Vaccines 2008

Research approaches for vaccine adjuvants

- TLR4 Agonists
- CpG Oligodeoxynucleotides
- ISCOMS, Virosomes
- Poly(lactide-co-glycolde Microparticles
  - Delivery system
- Cytokines
- Polyphosphazenes
- Mucosal adjuvants

Vaccine Adjuvants and Delivery Systems: M. Singh editor. Wiley, 2007

R&D adjuvants for human influenza vaccines

- Complex, costly and long-term programs
- High-risk: safety, regulatory, liability
- Adjuvant needed for which vaccine?
  - Seasonal influenza
  - (Pre) pandemic influenza
- Need to define “added value” for adjuvanted vaccine (“vaccine profile”)
  - Increased immunogenicity
  - Increased cross-protection
  - Antigen sparing

- The current way of research for influenza vaccines leads to optimal influenza vaccines for mice and ferrets

  - Jean-Pierre Amorij; PhD thesis 2007.
    - The development of stable influenza vaccine powder formulations for new needle-free dosage forms.

Summary characteristics of globally available influenza vaccines "Golden standard"

- 60% - 90% efficacy in children and healthy adults*
- 50% - 60% efficacy in dwelling elderly*
- 30% - 40% efficacy in nursing home populations
- Excellent safety profile**
- Intramuscular administration
- Immunization by physician or nurse

New influenza vaccines should have an added value compared to the golden standard

*KL Nichol: Vaccine 2003;21:1769-75

**WHO, Wkly Epidemiol. Rec 2000;75281-188

MMWR

Morbidity and Mortality Weekly Report

Recommendations and Reports July 13, 2007 / Vol. 56 / No. RR-6

Prevention and Control of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007

A preventable disease not being prevented*

Vaccines do not protect: Immunization with vaccine protects

- What is needed to control influenza disease?
  - Insight in Disease Burden
  - Safe / Effective Vaccines / treatments ("tools")
  - Guidelines for the control of the disease (evidence based medicine ("policy"; economy, health structure and health priorities, politics)

Implementation of policy (behavior; influenced by environment)

*SR Mostow Am Rev Respir Dis 1986;134:1

Influenza vaccination benefits: Methodological debate

Mortality benefits of influenza vaccination in elderly people: an ongoing controversy

- "The remaining evidence base is currently insufficient to indicate the magnitude of the mortality benefit, if any, that elderly people derive from the vaccination program"

Simonsen L. et al; Lancet Inf 2007;7:658-66

Influenza vaccination benefits:
Methodological debate

Effectiveness of influenza vaccine in the community-dwelling elderly

- “During 10 seasons, influenza vaccination was associated with significant reductions in the risk of hospitalization for pneumonia or influenza and in the risk of death among community-dwelling elderly persons. Vaccine delivery to this high-priority group should be improved”

Nichol KL. et al; NEJM 2007;357:1373-1381

Limits of evidence based (preventive) medicines

Preventive medicine, like the rest of medicine, should be as scientific as possible, but we should not expect to find more than a few islands of firm ground, and for the rest we must learn to live with uncertainty and to be satisfied with best judgments

G. Rose. The Strategy of Preventive Medicine. Oxford medical Publications1992.
ISBN 0192621254

Geoffrey Rose
The strategy of preventive medicine

- Relative risk (and benefit) is only for researchers; decisions call for absolute measures

  - G. Rose. The Strategy of Preventive Medicine. Oxford medical Publications1992. ISBN 0192621254

Influenza vaccines:
Absolute Risk Reduction

- actual number of cases prevented is around 6 -14 / 100 people

- K.L.Nichol, ESWI bulletin 21, June 2007
  - www.eswi.org

Preventive medicine doctrine

- "…you do not treat people for hypertension because you can see that they do not get strokes, but you treat people for hypertension because the evidence says that treating people for hypertension reduces their risk of dying from strokes.."

G. Rose. The Strategy of Preventive Medicine. Oxford medical Publications1992. ISBN 0192621254

Analogy for influenza:

- ".. you do not vaccinate people against influenza because you can see that they do not get pneumonia or die, but you vaccinate people because the evidence says that vaccinating people against influenza reduces their risk of influenza-associated complications such as pneumonia and death.."

New Influenza Vaccines; Methodological and Vaccine needs

- Vacccines
  - Need for improved influenza vaccines
- Methodology
  - Need for consensus on methodology to assess vaccine efficacy / effectiveness
  - Need for head to head vaccine comparative randomized trials (including placebo?)
  - Need for “correlates of protection”

How to measure efficacy / effectiveness of influenza vaccines?

- **Clinical parameters**
  - Laboratory- confirmed influenza, Influenza-like illness (ILI), Hospitalization rates, Mortality rates
- Surrogate markers (correlates of protection)
  - Virus shedding
  - antibody titer levels
    - Systemic antibodies (HI-titer; Nt. abs)
    - Mucosal antibodies
  - Other immunological parameters
    - Cell Mediated Immunity (CMI)
    - Cytokines, granzymes, ……

Pandemic vaccines

- For methodological reasons, efficacy and effectiveness of pre- and pandemic vaccines cannot be measured before a real pandemic
- The pandemic vaccine strategy must be based on animal experiments and known-correlates of protection for seasonal influenza vaccines

> Preventive medicine, like the rest of medicine, should be as scientific as possible, but we should not expect to find more than a few islands of firm ground, and for the rest we must learn to live with uncertainty and to be satisfied with best judgments

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Adjuvants for (pandemic) influenza vaccines

- **POINTS TO CONSIDER:**

- **correlates of protection**
- **effectiveness**
- **safety issues (also upon challenge!!)**
- **availability**
- **ease of manufacturing**
- **ease of formulating**
- **stability**
- **separate storage possible**
- **IP rights**
- **cost / price**

Weakness of current seasonal vaccines

- Must be produced in an egg-based culture
  - yield may be a problem
  - appropriate egg-based viruses sometimes not available
- Late arrival is sometimes a problem
  - little ability to change or add strains after February decision
- Efficacy needs improvement in the elderly and probably young children
  - against influenza B lineages
- Non-injected delivery helpful, but not necessary
- Perception of safety concerns…

Strengths of current seasonal vaccines

- Efficacious in older children and most adults
- More efficacious in preventing severe outcomes in older individuals
- Safe and acceptable for annual administration
- Large enough quantities available just before influenza season

An “ideal” influenza vaccine

- Protection lasts for several years
- Close relation of antigens to circulating strains not necessary
- High efficacy (> 95%) in all population groups
- No (perceived) side-effects
- Same vaccine for all population groups
- Affordable for healthcare systems

ADJUVANTS AND FLU VACCINES

- **Seasonal flu-vaccine**
  - **Adjuvant desirable, particularly for specific target groups**
- **Pandemic flu-vaccine**
  - **Adjuvant necessary for adequate immune response (?) and production capacity**

Antigen sparing is achievable

Vaccine Type & Formulation	Dose
† Split H5N1, no adjuvant	2 x 90µg (Treanor et al, 2006)
Split H5N1, with alum	2 x 30-45µg (Bresson et al, 2006)
‡ Whole virus H5N1 (egg grown), with alum	2 x 10-15µg (Hehme et al, 2006; Lin et al, 2006; Tashiro et al, 2006 2 x 15µg (EPAR) 1 x 6µg (Vajo et al, 2007)
Subunit H5N3, with MF59	2 x 7.5µg* (Nicholson et al, 2001)
‡ Subunit H5N1, with MF59	2 x 7.5µg (commercial in confidence, March 2007; EPAR)
Vero cell whole virus H5N1 (wild type), no adjuvant	2 x 7.5µg* (presented, Vienna 2006)
Split H5N1 vaccine with AS	2 x 3.8µg* (Borowski et al, 2006)
Split H5N1 vaccine with novel adjuvant	2 x 1.9*–3.75µg (press release, 2007)**

† already licensed in the USA
‡ already licensed in Europe

* doses lower than this not evaluated so far in humans
** sanofi aventis R&D day meeting- 17 Septembre 2007

Source: IFPMA-IVS ITF, july 2008

Progress Towards Pandemic Vaccines
Current Market Authorization Status
MOCK-UP/PANDEMIC

Company	Strains	Regulatory status
GSK	H9N2 & H2N2	Submitted to EMEA (Dec. 05)
GSK	H5N1 (whole +alum)	**EMEA Approval (Mar. 07)**
GSK	H5N1 (split + AS03)	Received CHMP positive opinion (Feb. 08)
Novartis	H9N2 & H5N3 (SA+MF59)	Submitted to EMEA
Novartis	H5N1 (SA+MF59)	**EMEA approval (2007)**
CSL	H5N1 (Split + alum)	Submitted to TGA (Mid-07)
Baxter	H5N1 (whole virion cell culture non adjuvanted)	Submitted to EMEA Jan. 2008

Company	Strains	Regulatory status
sanofi pasteur	H5N1 (split non adjuvanted)	**FDA approval (Dec. 06)**
sanofi pasteur	H5N1 (split+alum)	Submitted to EMEA (May 07)
Sinovac	H5N1 (whole non adjuvanted)	**China SFDA approval (Apr. 08)**
BIKEN	H5N1 (whole +alum)	**MHLW approval (Oct. 07)**
KITASATO	H5N1 (whole +alum)	**MHLW approval (Oct. 07)**
Kaketsuken	H5N1 (whole +alum)	Submitted to MHLW (Apr. 08)
Denka Seiken	H5N1 (whole +alum)	Submitted to MHLW (Jan. 07)

IFPMA Influenza Vaccine Supply International Task Force

Progress Towards Pre-Pandemic Vaccines
Current Market Authorization Status

PRE-PANDEMIC

Company	Strains	Regulatory status
Novartis	H5N1 (SA+MF59)	Additional data requested by EMEA to be resubmitted within 2009.
GSK	H5N1 (split + AS03)	**EMEA approval (May 08)**
Sinovac	H5N1 (whole non adjuvanted)	**China SFDA approval (Apr. 08)**
BIKEN	H5N1 (whole +alum)	**MHLW approval (Oct. 07)**
KITASATO	H5N1 (whole +alum)	**MHLW approval (Oct. 07)**
Kaketsuken	H5N1 (whole +alum)	Submitted to MHLW (Apr. 08)
Denka Seiken	H5N1 (whole +alum)	Submitted to MHLW (Jan. 07)
Baxter	H5N1 (whole-virion cell culture non adjuvanted)	Submission planned 2008

Conclusions

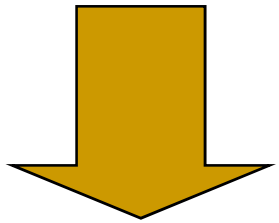
- Implementation of seasonal vaccination policy recommendation needs highest priority
- Adjuvanted- and non-adjuvanted vaccines provide protection only after actual immunization
- Desired characteristics of adjuvanted influenza vaccines need to be defined
- Needs for adjuvanted influenza vaccine may be different for seasonal and (pre) pandemic vaccines
- Adjuvanticity needs to be demonstrated for pre-defined objectives

Conclusions (cont'd)

- Efficacy of adjuvanted influenza vaccines should be demonstrated according to available European guidelines for licensing
- Safety of adjuvanted influenza vaccines need to be carefully established / monitored (annual administration……)
- Pandemic preparedness efforts have resulted in the development and licensing of adjuvanted (pre) pandemic vaccines

Objective of the global efforts for the control of influenza

- From the Control of Influenza



- Influenza under Control

SCIENTIFIC DEBATE AND MASS COMMUNICATION

Implication for health policy and practice?

The aim of this symposium is to gain more understanding of the interaction between science, mass media and public health:

- How does media publicity affect health-care consumers?
- What are the public health implications of media publicity about scientific debates on health issues?
- How can policymakers, opinion leaders, health-care professionals and scientists deal with media hypes?

ESWI conference Villamoura Sept 2008: Solvay satelite symposium

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