Adjuvant Development for IPV

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World Health Organization

Role of adjuvants in vaccine development

- Enable subunit antigens to induce protective immune response
- Achieve protective immunity with reduced number of doses
- Decrease the dose of antigen
- Permit immunisation by alternative routes
- Enhance responses in the young or old
- Increase the speed or duration of the response

Previous studies on adjuvants for IPV

- Water-in-mineral oil emulsions (1954)
  - 'Improved immune response observed' (not quantifiable..)
  - Not pursued since ID delivery adopted at time
  - Presents safety issues (abscess, nodules)
  - Major manufacturing challenges.
- Aluminium salts
  - enhancement on Neut titers (3-4x) by AlPO4 (1958)
  - AlOH > AlPO4 (later studies: was process optimised ?)

Brief review of adjuvants

- Aluminium salts
- Water-in-oil emulsions
- Oil-in-water emulsions
- TLR-agonists : MPL, CpG, poly-IC, imiquimod etc
- Saponins
- New candidates: eg VEE

Alum

- Aluminium hydroxide, oxy-hydroxide, phosphate, sulphate,..
- Particles with high surface (non-crystaline)
- Binds antigen and provides slow-release at site of injection
- Also acts as immunestimulant via NOD - upregulate MHCII, IL-4
- Can Not be frozen !!
- Cheap, no IP issues
- Manufacture and use can be complicated

o/w emulsions: eg MF59

In a licensed seasonal influenza vaccine (Fluad)

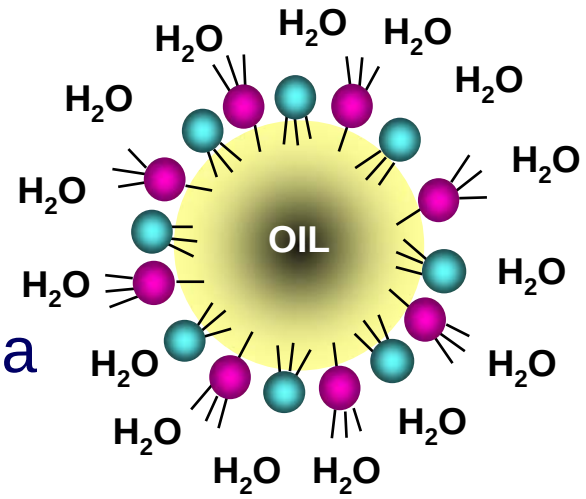
Approved for use in pandemic influenza

In phase 3 pediatric clinical trials (as AS02) for malaria

Off-patent in europe and most developing countries

Cheap and easy to produce (1-3 c per dose)

Strong dose-reduction effect seen with influenza and HepB



Other forms: AS03, AF3, Covaccine,…

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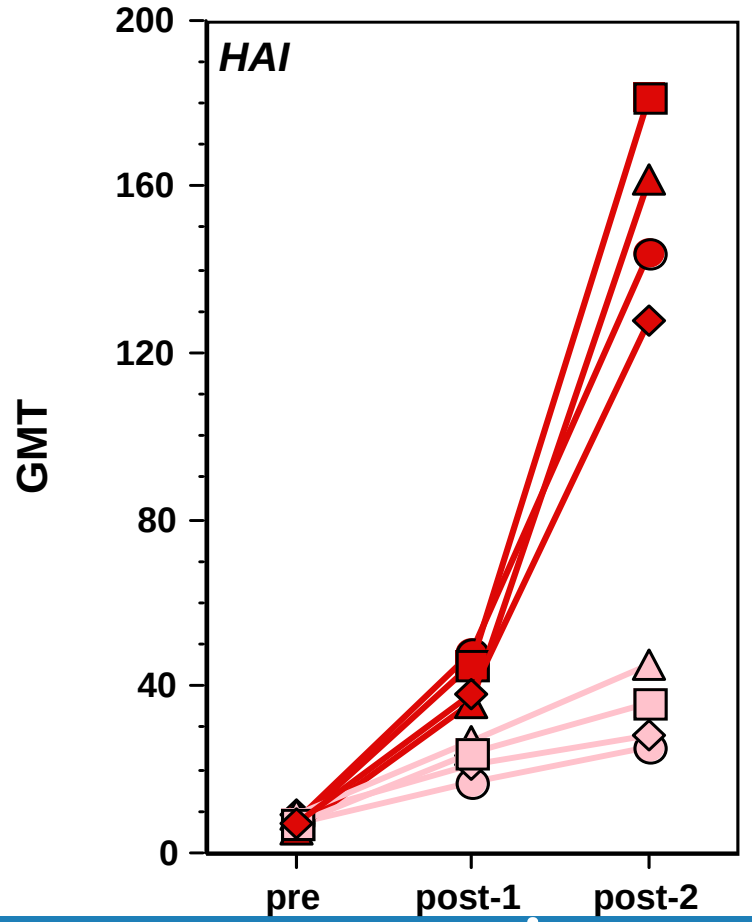
Pandemic Influenza: Addition of MF59 (Novartis) permits dose sparing

mg/dose	Plain	+ MF59
3.75		
7.5		
15		
30		

Pandemic H9N2 clinical trial: HAI Geometric Mean titers



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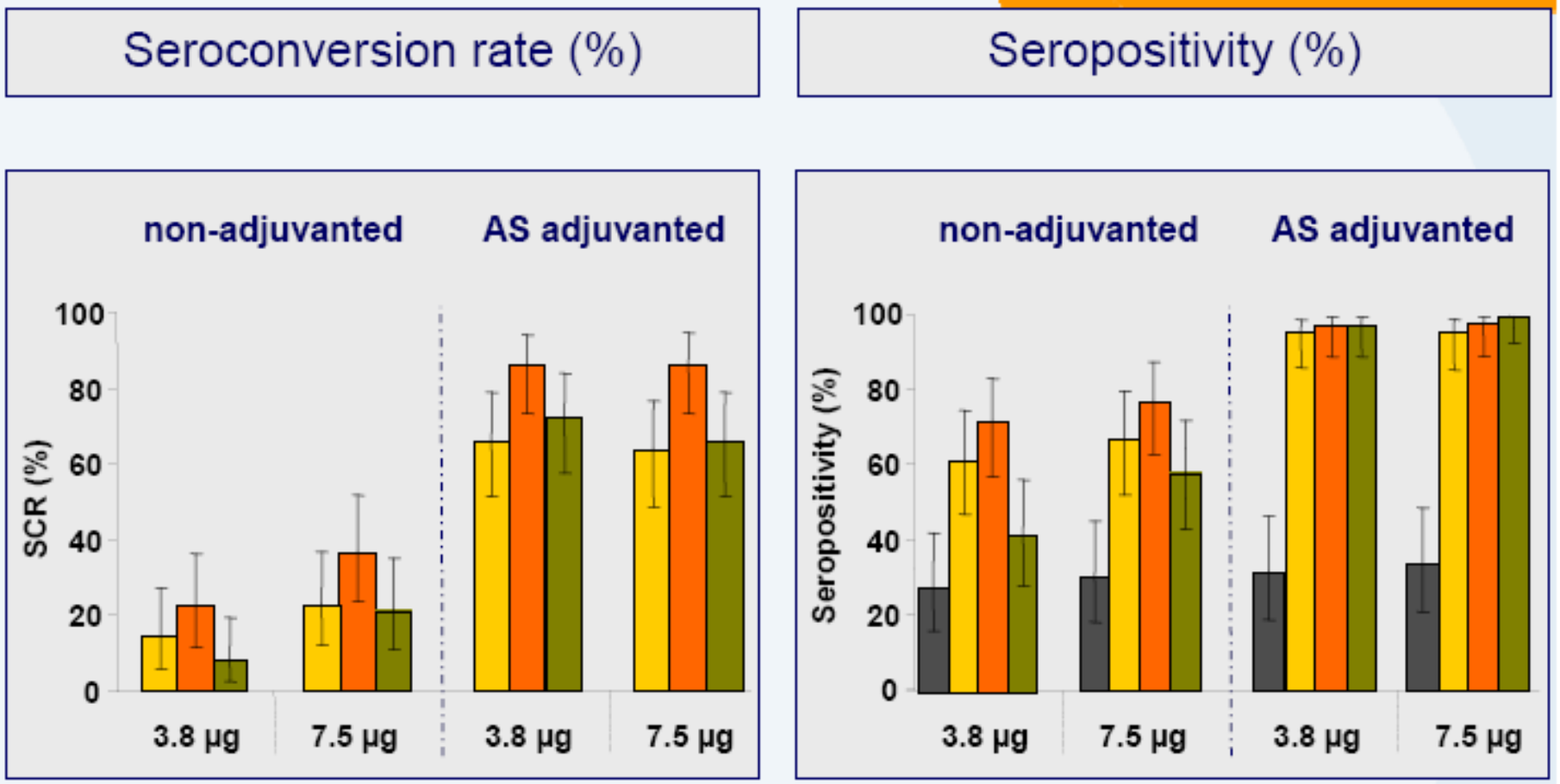
AS3 (GSK) permits dose reduction of pandemic influenza vaccine

Vaccinated cohort = 50 per group



Leroux-Roels et al. Broad Clade 2 Cross-Reactive Immunity Induced by an Adjuvanted Clade 1 rH5N1 Pandemic Influenza Vaccine. PlosOne, In press 2008

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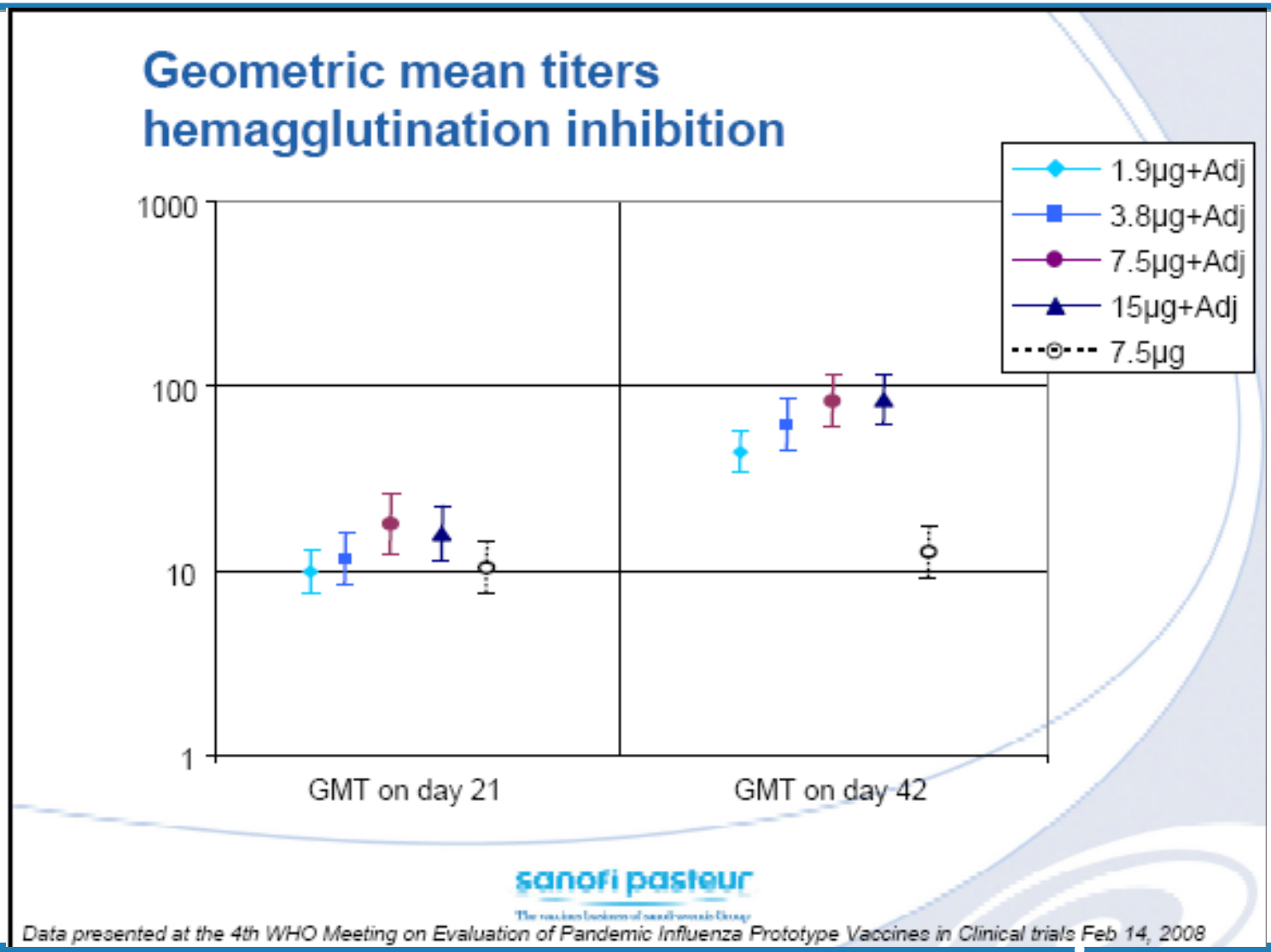
AF3 (Sanofi) permits dose-reduction of pandemic influenza vaccine (H5N1)



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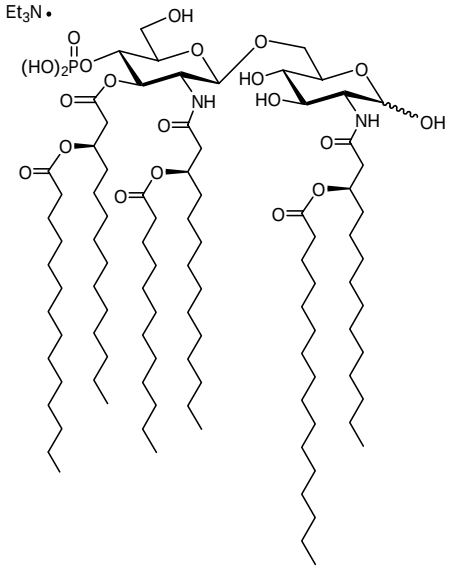
TLR agonists

- MPL (TLR-4 agonist)
  - In Cervarix (HPV) and Fendrix (HBV) adult
  - In phase 3 in infants (AS01 for malaria)
  - Extensive safety data
  - Non-proprietary forms now available: GLA, sMPLA
    - in phase 1 clinical trials USA
  - Cost may be significant (10c)
  - Benefit over o/w emulsion may only be Th1 response – marginal antibody increase.



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Other TLR agonists

- CpG (TLR-9)
  - Dynavax/Merck Heplisav trial: FDA stopped trial.
- Imiquimod.. (TLR 7/8)
  - Only used so far for cutaneous administration. Safety unknown.
- Poly I:C (TLR3)
  - Reproducible manufacture not yet achieved. IPV contains RNA.
- Flagellin (TLR-5), Pal3C (TLR2)
  - Experimental: efficacy, safety, heterogeneity.

Others (examples)

- Saponins (eg QS21)
  - Off-patent but currently single GMP supplier (Antigenics): cost!
  - Not yet in approved vaccine (but in pediatric trials: AS01)
  - Proprietary methods to overcome stability/toxicity
  - Good antibody and CMI responses
- Vit D3
  - Marginal effect on most antigens
- Venezuelan Equine Encephalitis (VEE) replicons
  - Induction of IgA following i.m. administration
  - Very strong adjuvant effect
  - Only preclinical data
    - Is IgA effect real
    - Is regulatory pathway feasible

IVR Proposal for dose-reduction of IPV

- Aluminum salts are safe (used in many pediatric vaccines) but are not known for permitting significant dose-reduction
- New adjuvants based on TLR agonists are likely to have a lengthy approval process and be costly
- Oil-in-water emulsions permit >30 fold dose-reduction for influenza vaccines.
  - MF59 patent has been revoked in the EU, no IP protection in much of the world.
  - MF59 is in a licensed vaccine for adults and has been tested in infants (but not babies). Regulatory pathway relatively simple.
  - MF59 type adjuvants will cost cents to produce (COG = 1-2c per dose) and can be easily produced in developing countries.

Studies underway

- Study being conducted at IDRI (Seattle) : APW from WHO
  - Collaborating center for Global Adjuvant Development Initiative
- Rat potency studies to identify dose-reduction potential of IPV with range of adjuvants
  - o/w emulsions: MF59, LCD, SE (+/- co-polymer and span)
  - lead o/w emulsion with TLR-4 agonist (GLA)
  - lead o/w emulsion with stabilising charged excipient
  - Comparison to: QS21, alum, alum-MPL, virosomes, niosomes
  - Adjuvant dose-studies: lead candidate identification
- Determination of neutralising titer at CDC.

Status of IDRI studies

- Contract, animals and protocols approved
- o/w emulsion production processes established and QC tests done
- Supply of tIPV by NVI
- First study with MF59 and SE should have been initiated early Oct but minor delay Starts Nov 3 – serology Dec 1.

Future Development

- Global Adjuvant Development Initiative
  - Establishing Adjuvant R&D center at University of Lausanne
    - Funding requested from Wellcome Trust
    - Collaboration with Swiss Vaccine Research Institute (SVRI)
  - 3 year program on IPV
    - Establishment of validated adjuvant production processes
    - Technology transfer of adjuvant production process to India
      - IPV and pandemic flu
    - Supply of GMP adjuvant for phase 1 IPV clinical study (adult) end 2009
    - Phase 1 Age-de-escalation
    - Phase II 2010-11 ? sIPV ?

Possible scenario for use ?

- Point-of-use mixing
  - No change to existing IPV manufacture or filling
  - No change to release
  - No requirement for new stability data (beyond 8hrs)
- One dose of IPV diluted into multi-dose vial of adjuvant