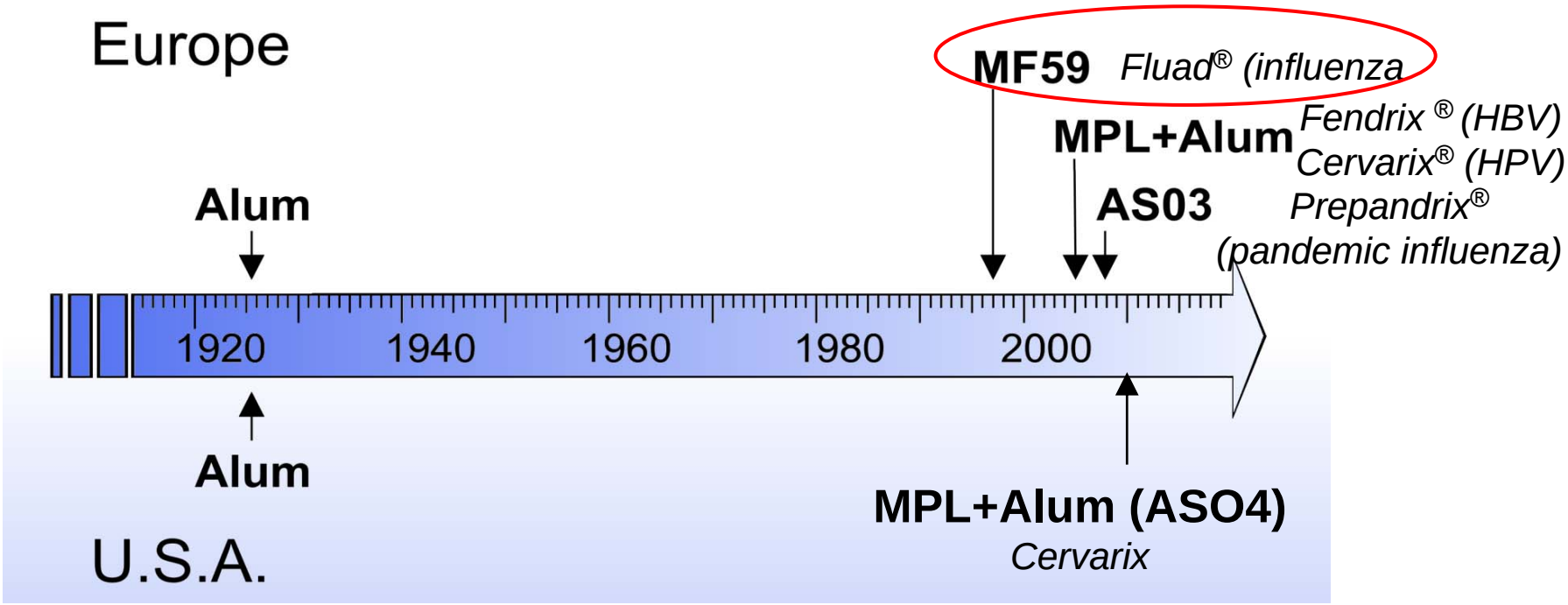
Adjuvants [Latin: 'adjuvare' – to help]: **What Do They Do?**

- Faster and higher antibody titers
- Increased breadth of response (overcome pathogen diversity)
- Induce long-lasting immune memory responses
- Less antigen needed
- Enhance immune responses in the elderly and young

But….

- Slow pace of development relative to current knowledge
- Few novel adjuvants in clinical testing -> safety concerns
- Mechanisms of action still uncertain

The Slow Pace of Adjuvant Development



- Many potent vaccine adjuvants have failed, due to safety concerns
- MF59 was first novel adjuvant in 70 years (Europe)
- Alum and MPL (AS04®) are the only adjuvants approved in US

MF59: an oil/water emulsion adjuvant

Composition

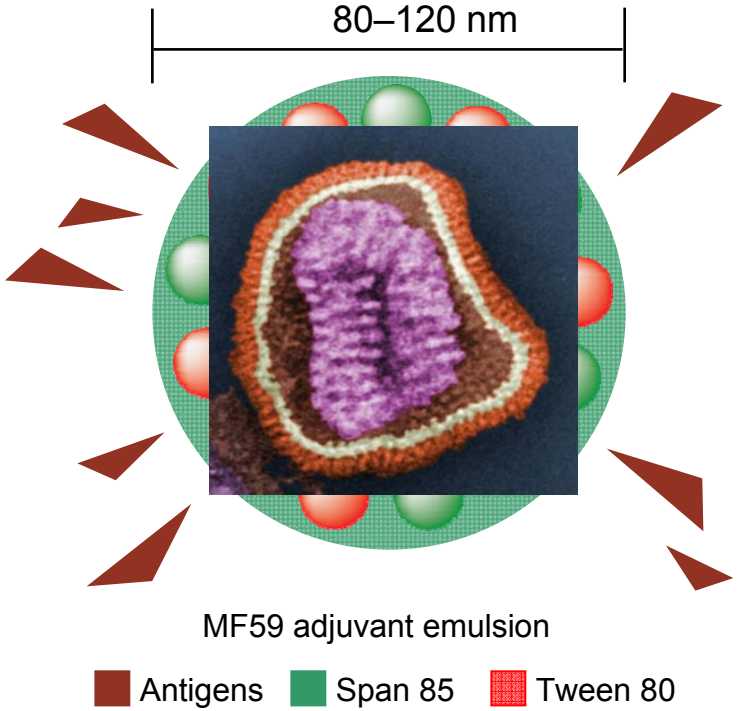
- Squalene oil (4.3% v/v)
- Span 85 (0.5% v/v)
- Tween 80 (0.5% v/v)
- 10 mM sodium citrate buffer

Characteristics:

- Viscosity close to water
- Filter sterilizable
- Stable for at least 2 years

Influenza vaccines

- Seasonal, Fluad
- Pandemic, Focetria®, Celtura®



FLUAD is licensed for use in adults >65 years of age; Focetria and Celtura are not licensed in Korea

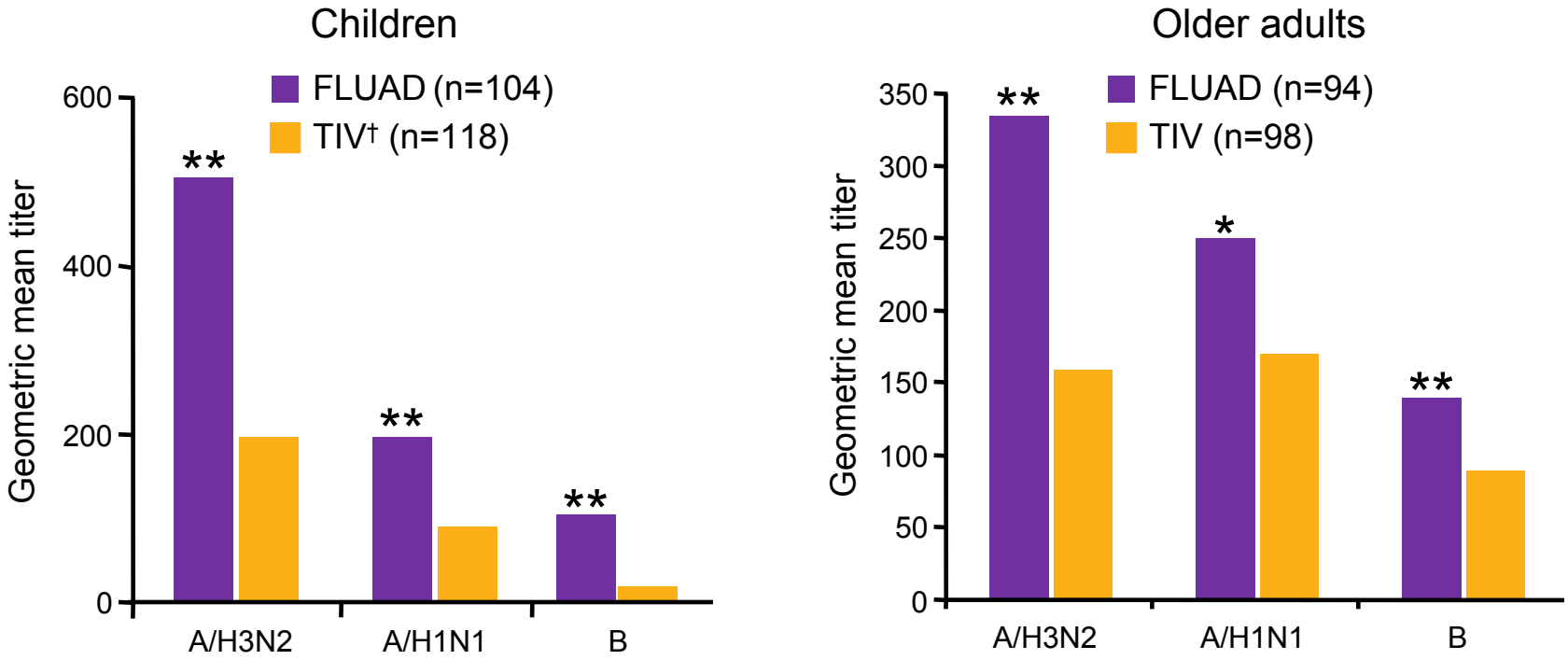
Podda A and Del Giudice G. *Exp Rev Vaccines* 2003; 2:197–204; O'Hagan D. *Exp Rev Vaccines* 2007; 6:699–710.

Local effects of MF59 after mouse IM injection

- Potent activator of innate immunity at the injection site
- Early recruitment of blood cells into the muscle
- MF59 is a weak inducer of cytokines in the serum, but chemokine secretion can be detected
- Increases antigen loaded cells in the draining lymph node

MF59-adjuvanted seasonal vaccine (Fluad) *Licensed in Europe for Children and Older adults*

HI assay, 3 weeks post-second vaccination

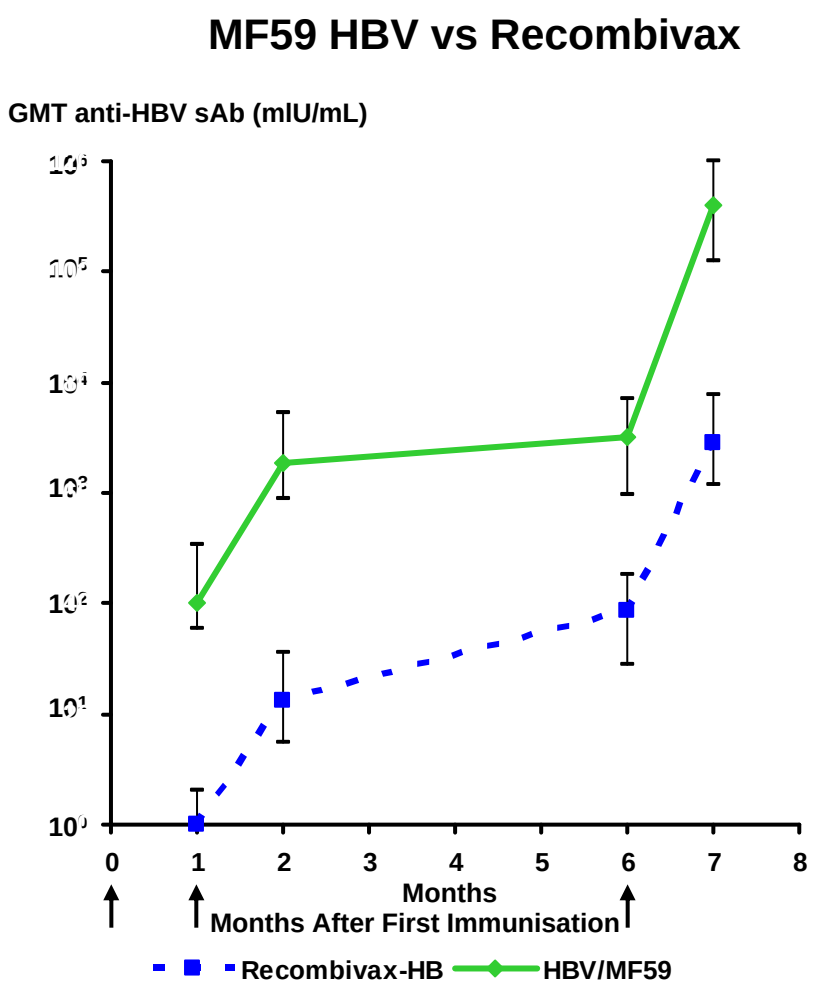


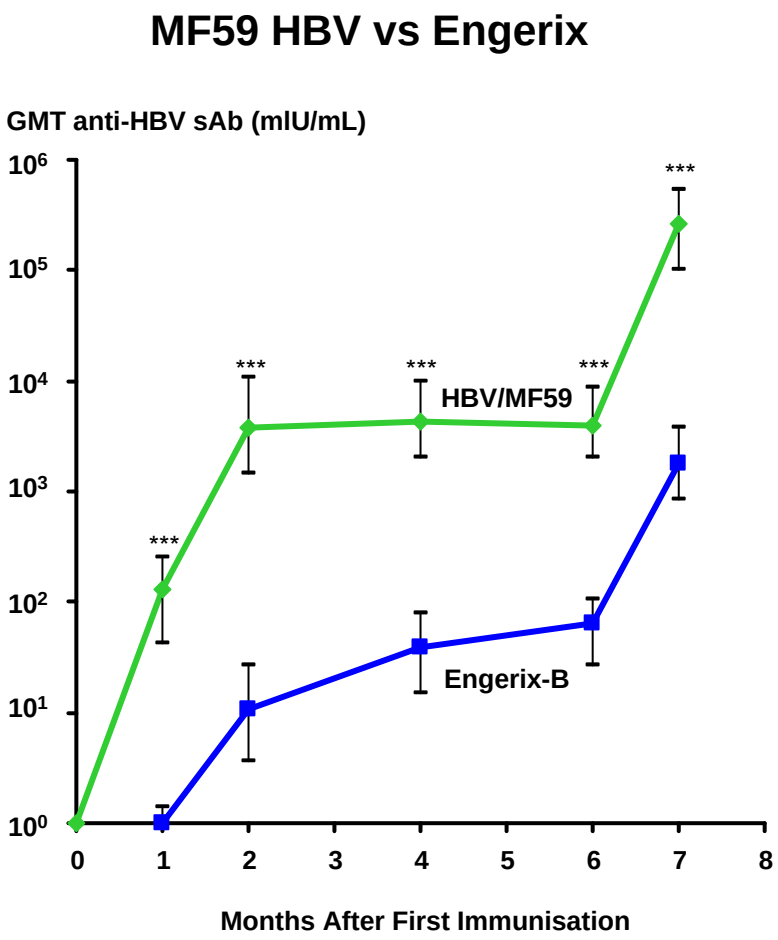
* *P*<0.01 *vs.* non-adjuvanted vaccine; ** *P*<0.001 *vs*. non-adjuvanted vaccine

FLUAD is licensed for use in adults ≥65 years of age; TIV, trivalent influenza vaccine;
† Vaxigrip®, Sanofi Pasteur.

De Donato S. *et al. Vaccine* 1999; 17:3094–3101; Vesikari I. *et al. PIDJ* 2009; 28:563–571.

MF59: Faster/Higher Anti-HBs Titers vs. Engerix-B® or Recombivax®



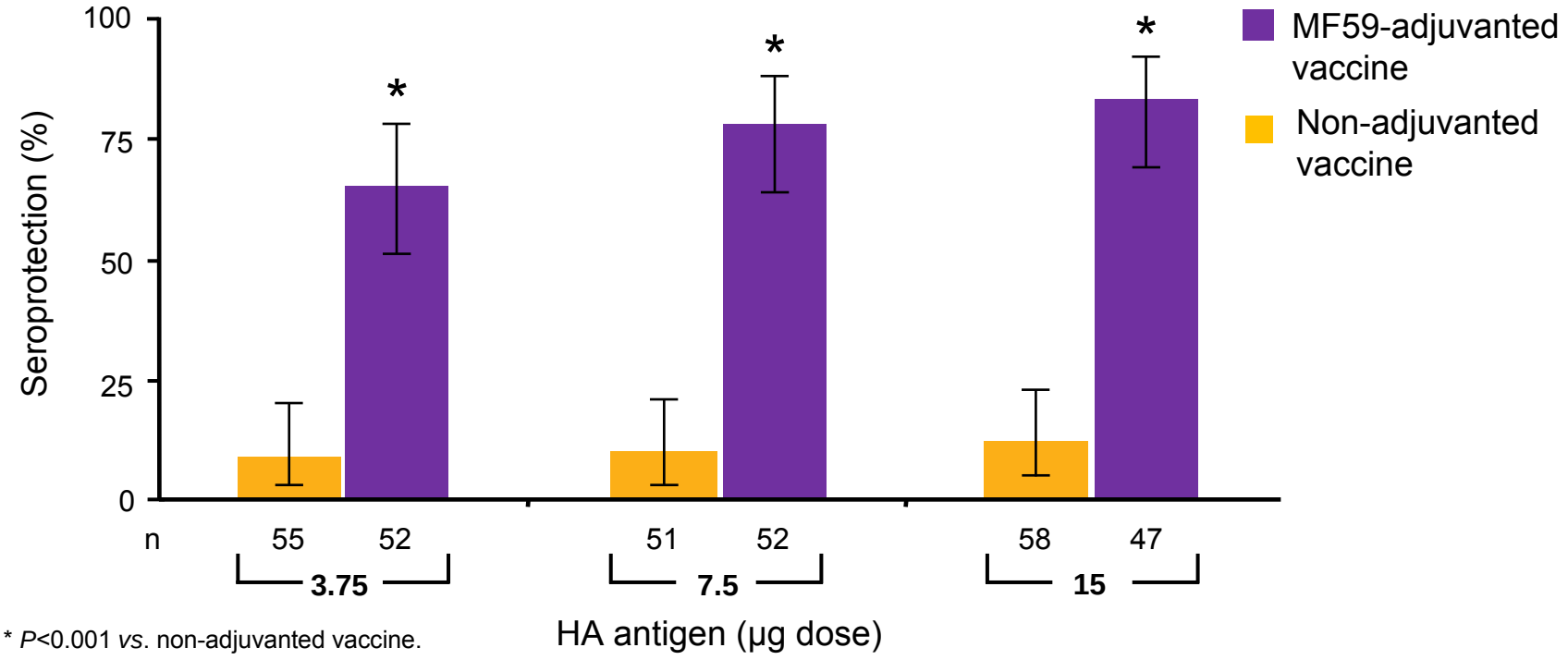


T.C. Heineman et al./Vaccine 17(1999) 2769-2778

Commun Dis Public Health 2003; 6(4): 320-4

Antigen Sparing: Critical for Pandemic Vaccines (MF59-adjuvanted H5N1 vaccine)

HI assay, 3 weeks post-second vaccination



Experimental bedside mixed MF59-adjuvanted H5N1 vaccine

HA, hemagglutinin.

Keitel W, *et al*. *Vaccine* 2010; 28:840–848.

Toll-like receptors (TLRs) are vaccine adjuvants (Generation 2 adjuvants)

- All TLRs are targets for vaccine adjuvants in pre-clinical models
  - Several TLR agonists are validated adjuvants in human

TLR	*Localization*	*Elicitor*	*Vaccine target*
TLR2	Plasma membrane	Triacyl lipopeptides (PAM3CSK4)	Lyme,Malaria, HIV
TLR3	Endosome	dsRNA (PolyI:C)	Flu
TLR4	Plasma membrane	**LPS (MPL; synthetic MPL)**	**MPL approved in EU for HBV and HPV vaccines (GSK), several trials ongoing**
TLR5	Plasma membrane	Flagellin	Phase 1 for flu (Vaxinnate)
TLR7	Endosome	ssRNA; imiquimod	Imiquimod cream used as adjuvant in cancer vaccines trials
TLR8	Endosome	ssRNA; resiquimod	Pre-clinical
TLR9	Endosome	**DNA; CpG oligonucleotides**	**CpG in trials for Anthrax, Malaria, HBV, influenza and cancer vaccines (Pfizer) ISS for HBV vaccine (Dynavax). IC31 in phase 1 for TB (Intercell)**
TLR10	Plasma membrane	Unknown	