Overview of Adjuvants:

Development, knowns and unknowns

Martin Friede Ph.D.

Initiative for Vaccine Research

World Health Organization

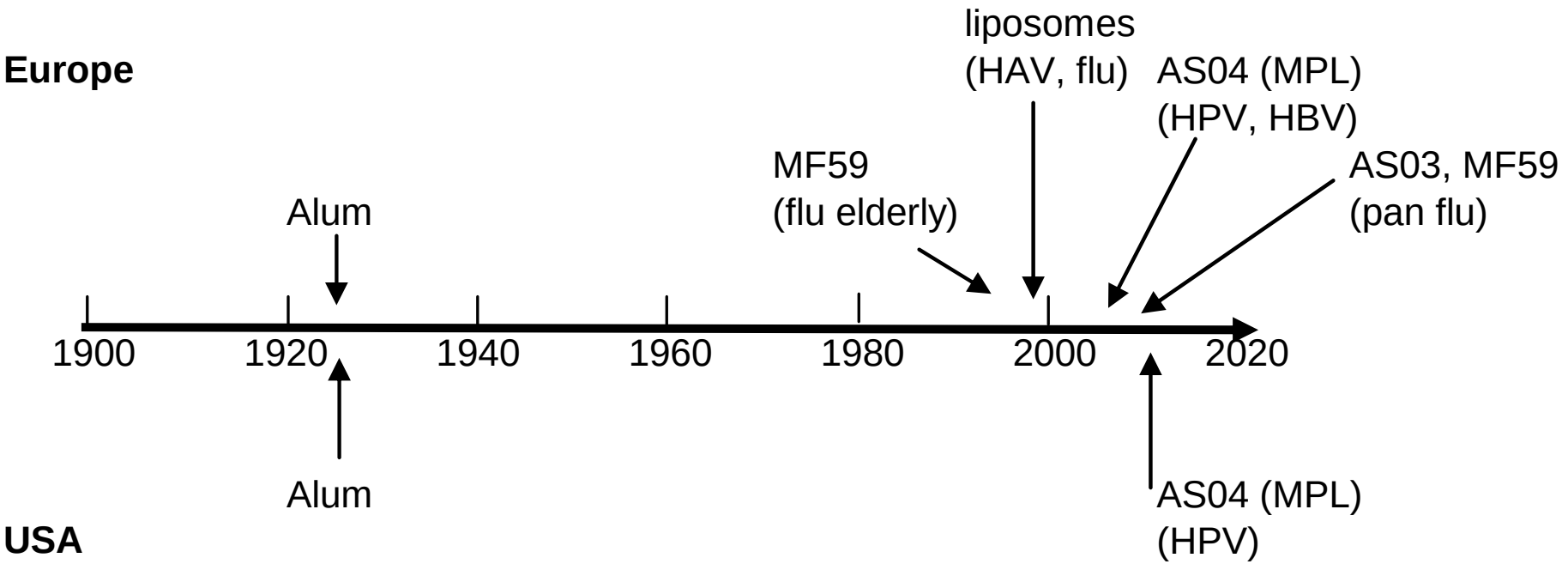
2009 – 2010 an excellent period for adjuvants…

- **October 2009: FDA Approves New Vaccine for Prevention of Cervical Cancer**
- First approval in the USA of a vaccine containing a 'novel' adjuvant.

Pandemic influenza (H1N1) website

- September 2009: Focetrea, Pandemrix approved.
  - H1N1 vaccines with oil-in-water emulsions (MF59, AS03)
- Population-wide use of adjuvanted H1N1 influenza vaccine began in Europe in October 2009.
- 2009-2010: Over 60 million doses of adjuvanted influenza vaccines distributed
  - Intense post-market surveillance
  - No serious safety signals observed

A century of darkness…



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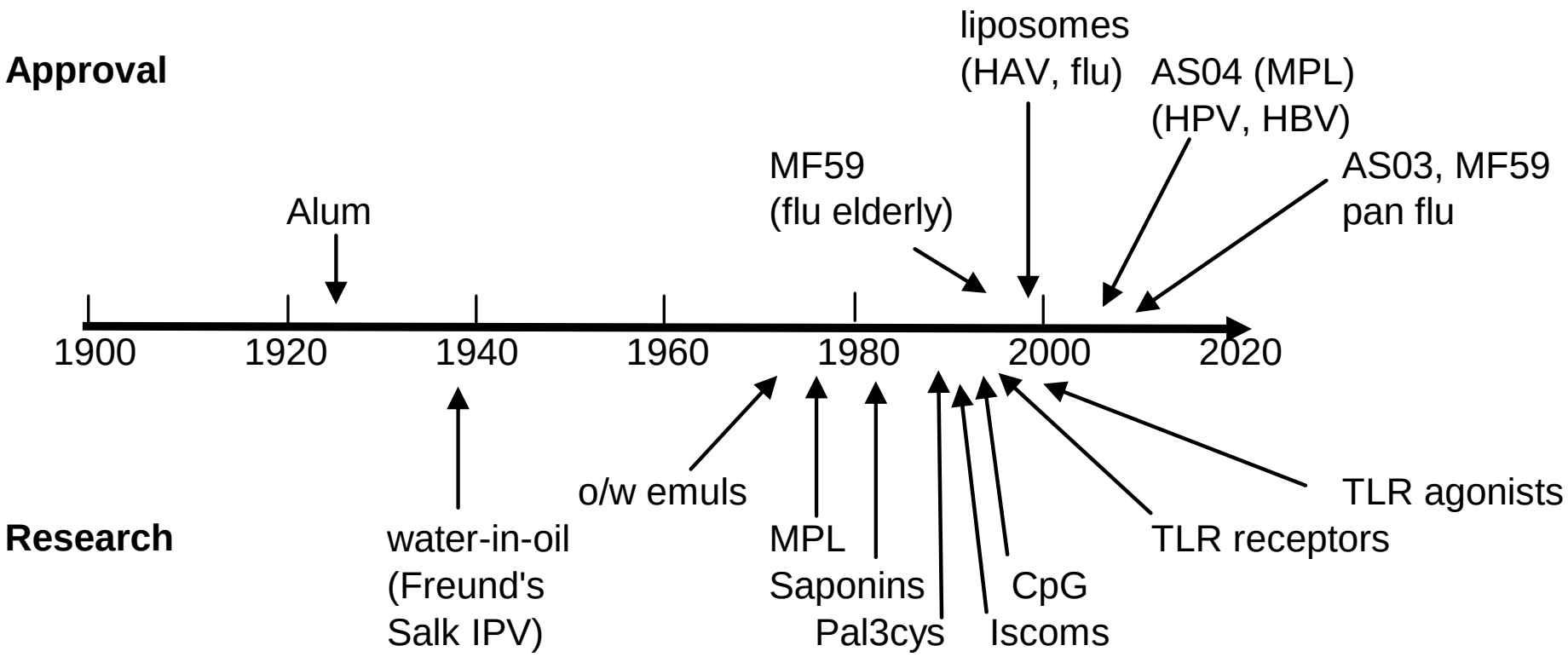
But not for lack of trying…



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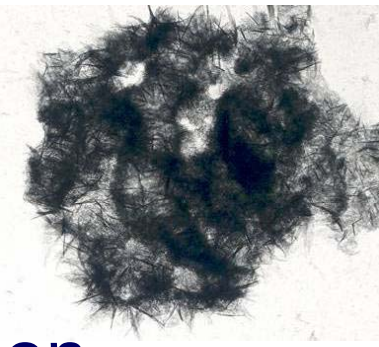
Many adjuvants in mid-late development

Class	component	phase 1	phase II	phase III	licensed
TLR3	Poly I:C	cancer			
TLR4	MPL	leish	herpes	malaria	HPV, HBV
	MPL		pneumonia	cancer	Allergy
	RC530	HIV			
	GLA	flu			
TLR5	flagellin	influenza			
TLR7	Imiquimod		cancer		
TLR8	Resiquimod		cancer		
TLR9	CpG, IC41	influenza	Allergy	HBV	
		TB	cancer		
Saponins	QS21	pneumonia	cancer	malaria	
	QS21	HIV	Alzheimer		
O/W emulsion	squalene	HIV	HBV, CMV		Seasonal flu
	tocopherol				Pandemic flu
W/O emulsion	squalene		malaria		
	mineral oil		cancer		
Polysaccharides	Inulin	HBV, flu			
Cationic liposomes	DDA	TB	influenza		
Virosomes		malaria			HAV, flu
poly-electrolytes	Polyoxidonium				influenza

A long and treacherous road to approval and acceptance

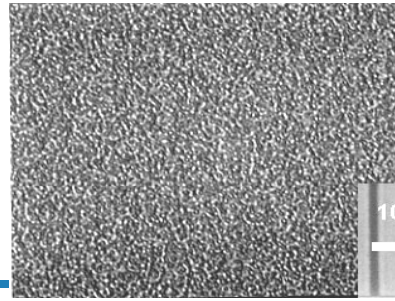
- Some examples…

Aluminium salts (Alum)



- Highly charged, large surface area, adsorbs antigen
- Used since 1920s in many vaccines:
  - DT, TT, Pertussis, HepB, HepA, S. pneu, Meningitis, JE,…
  - Different forms: Aluminium hydroxide gel, phosphate gel, ..
    - Different physical characteristics and adjuvant properties !!
- Mode of action: depot ? Nod-like-receptor ? Inflammasome ?
- Challenges
  - Role of antigen adsorption: good and bad – depends
  - Don’t freeze !
  - Poor CMI…

Water-in-oil (w/o) emulsions

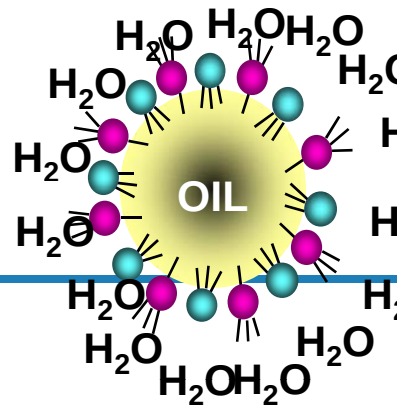


- 1960s: flu vaccine in UK based on water-in-mineral oil.
  - 60 cases of severe local reaction out of 1,000,000 doses given
  - Led to development of non-mineral-oil based adjuvants: Squalene
- Seppic ISA 720: 30% water 70% squalene
  - >70 completed clinical trials (mainly cancer vaccines, HIV,etc)
  - No product on market
  - Challenges:
    - Frequent local reactogenicity (abscess)
    - Formulation and scale up: not easy
    - Antigen instability in the emulsion

Long-term follow up on recipients of IFA

- 1953: 18,000 military recruits receive influenza vaccine adjuvanted with IFA (Salk et al.)
  - Some nodules observed. Not seen when Arlacel-A purified.
- 1964: 10-year follow-up (Beebe et al.)
  - Cysts in 0.1-0.6% of population. No other SAEs
- 1993: 35 year follow up (Page et al.)
  - No adverse correlations with 74 disease categories
  - Decreased mortality in 5 disease categories
- And yet… use restricted even in labs.

Oil-in-water emulsions



- Droplets of oil, in water, stabilised with surfactant
  - Squalene, squalane,..
  - Egg-yolk lecithin, tween 80,..
  - Developed in 1980s as vehicles for amphipathic adjuvants (MTP)
- MF59™ (Novartis): squalene in water with Tween + Span
  - Component of Fluad™ influenza vaccine for elderly
    - Approved in some EU countries since 1996
- AS03 (GSK): squalene + tocopherol
  - Component of Pandemrix influenza vaccine

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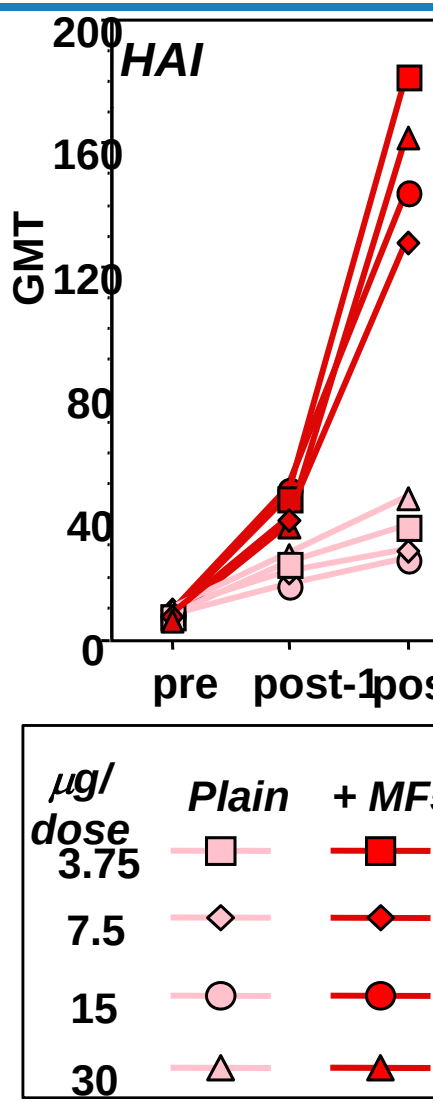
o/w emulsions and pandemic influenza

- Dose-sparing of antigen seen with o/w
  - 10-30 fold dose reduction for H5N1
    - MF59 (squalene), Novartis
    - AS03 (squalene + tocopherol), GSK
    - AF3 (squalene), Sanofi Pasteur
- Incorporated in 2009 H1N1 pandemic vaccine
  - 2-4 fold dose sparing
  - Increase global vaccine production capacity



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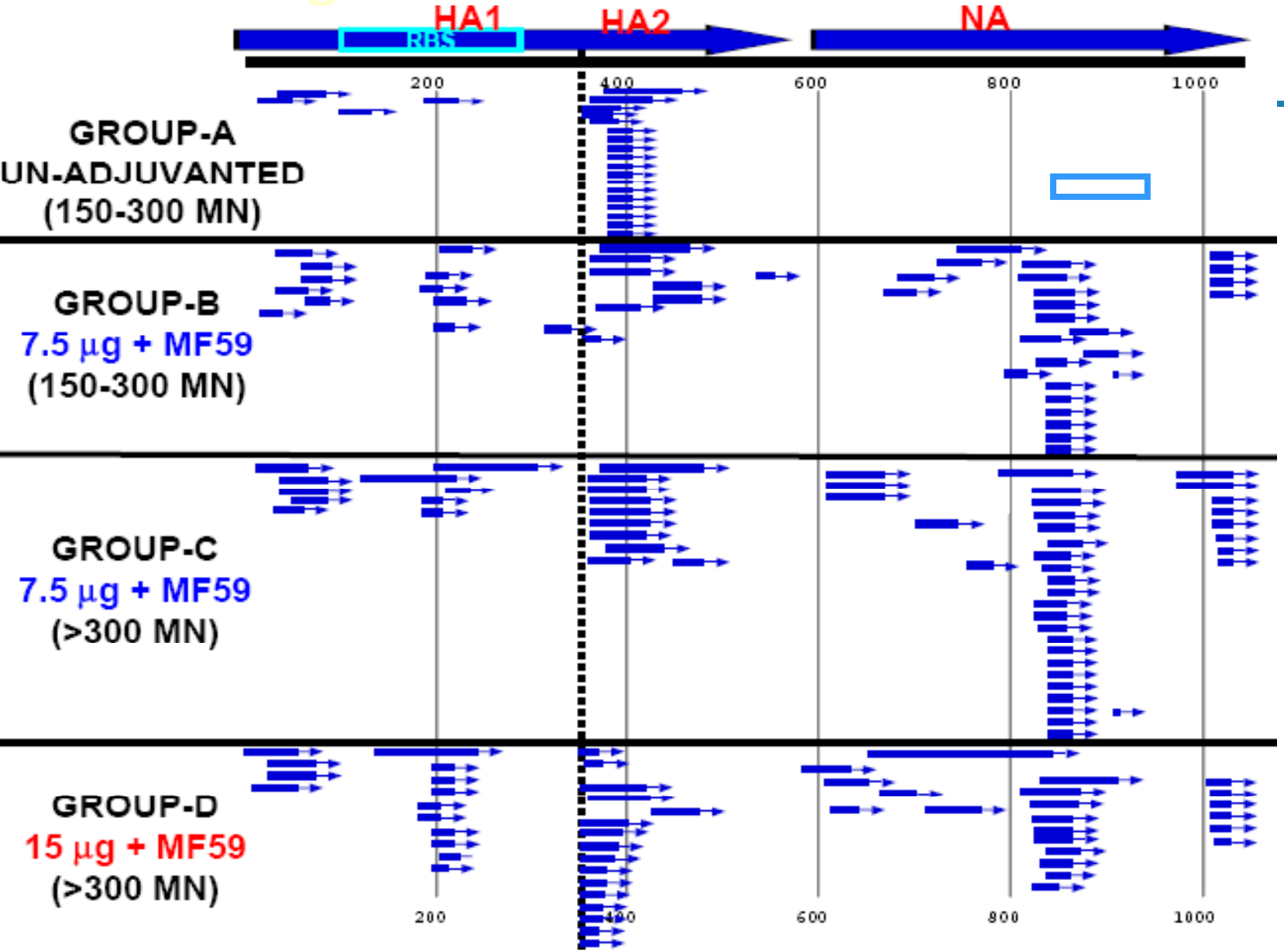
MF59 increases and changes the quality of protective antibodies against H5N1



Golding, H. et al. 201

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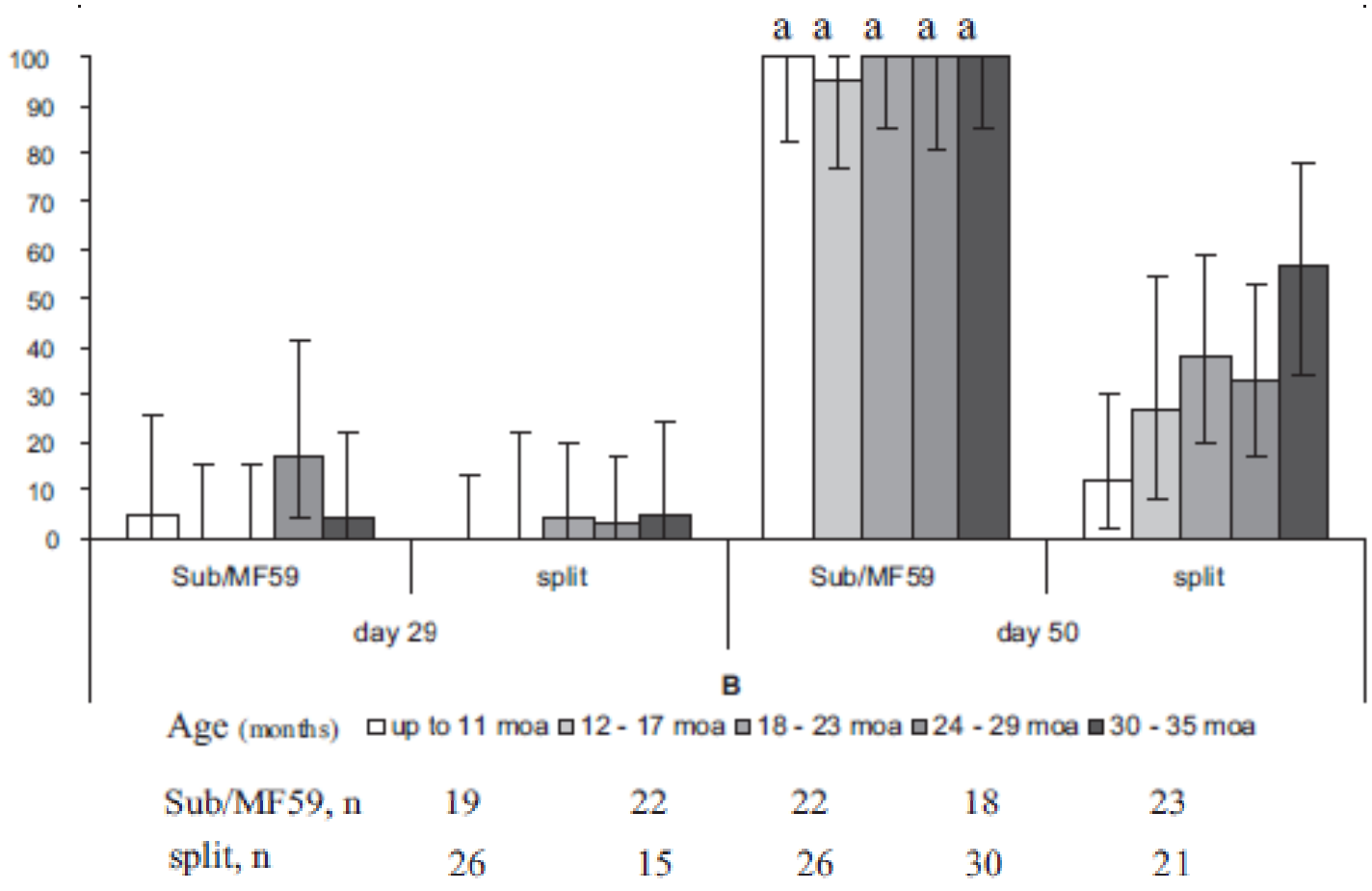
o/w emulsions for seasonal influenza: infants and children

- Potent immune enhancement in infants
- Example:
  HI>40 to B strain
  Split+MF59 vs Split



From Vesikari T et al., 2009

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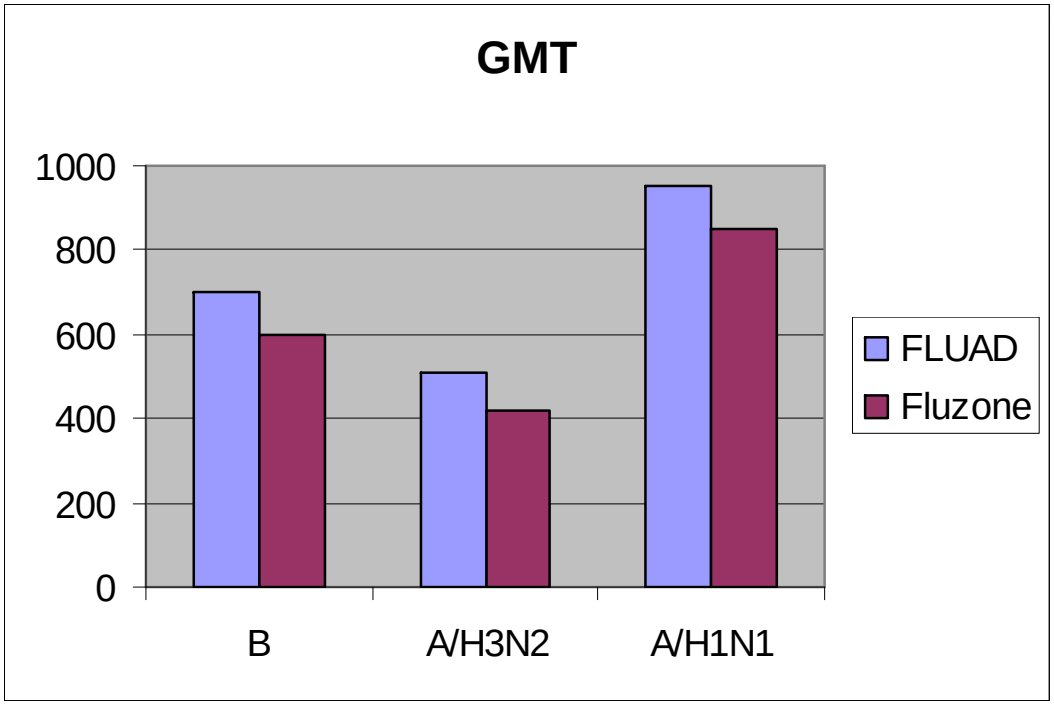
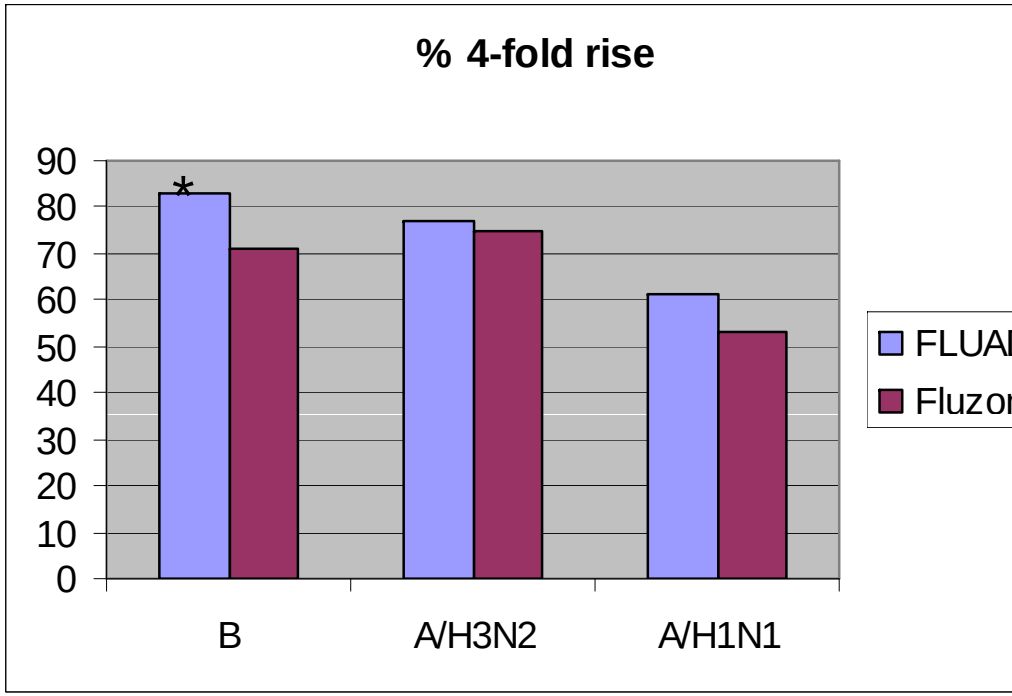
o/w emulsions for seasonal influenza: healthy adults





- Only modest effect
- FLUAD vs Fluzone in healthy adults

From Frey et al., 2003

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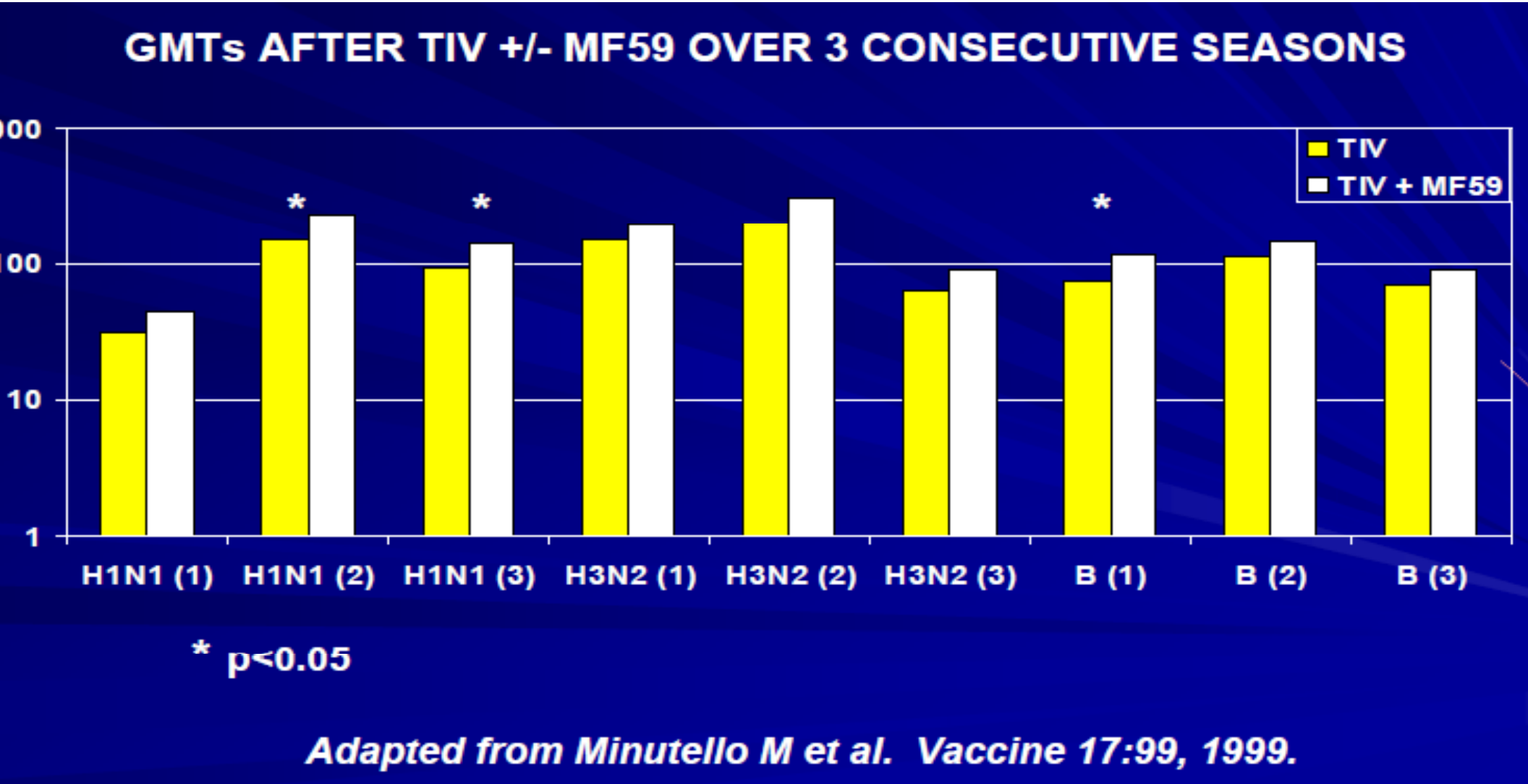
o/w emulsions for seasonal influenza: elderly adults

slide from W. Keitel



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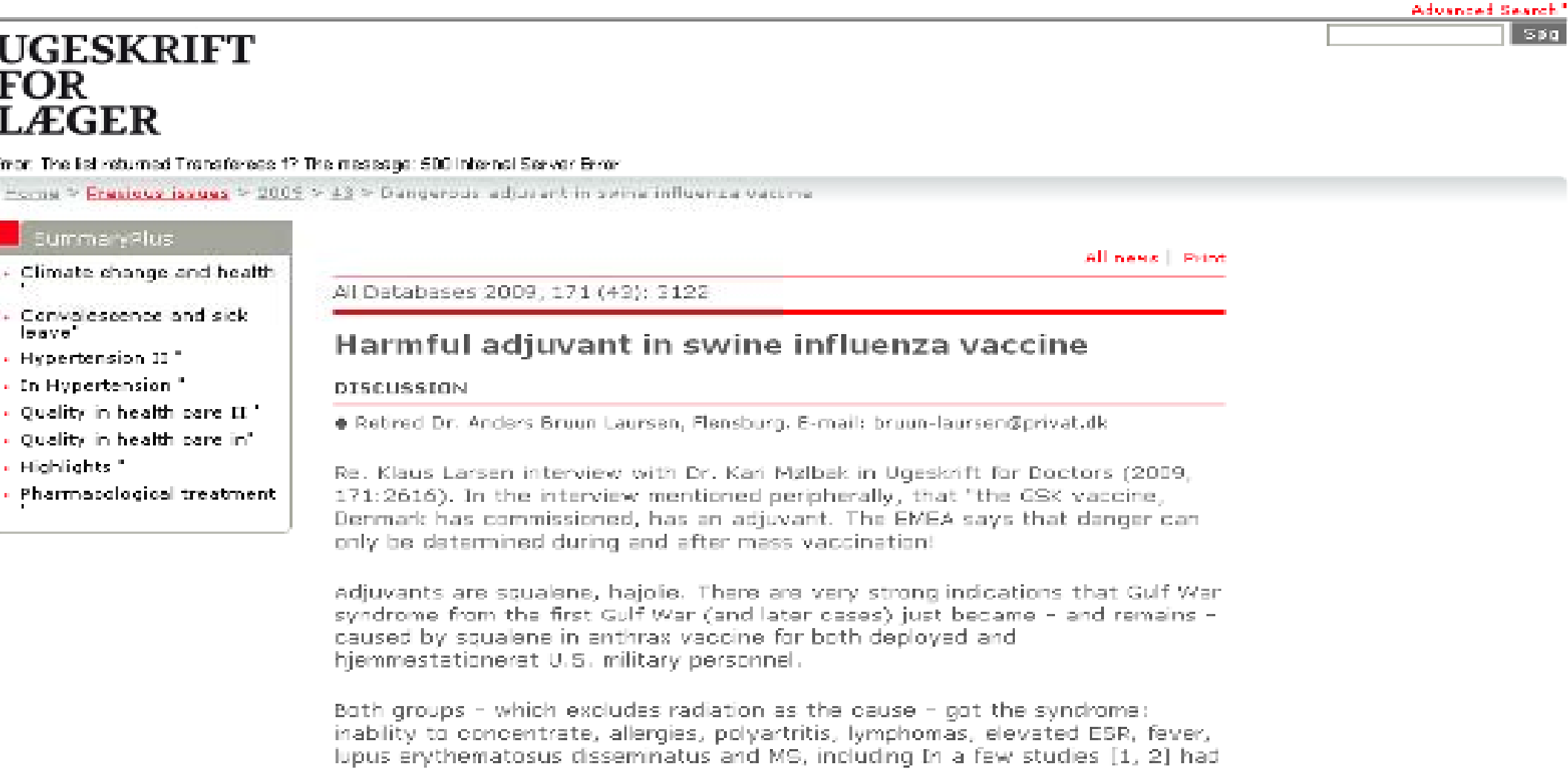
Public fears related to squalene in vaccine

Google: squalene adjuvant= 51,700 hits

Google: squalene adjuvant danger: 38,000 hits.



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Søg

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Forside > Previous issues > 2009 > 43 > Dangerous adjuvant in swine influenza vaccine

Summary Plus

- Climate change and health
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- Highlights
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All Databases 2009; 171 (43): 3122

Harmful adjuvant in swine influenza vaccine

DISCUSSION

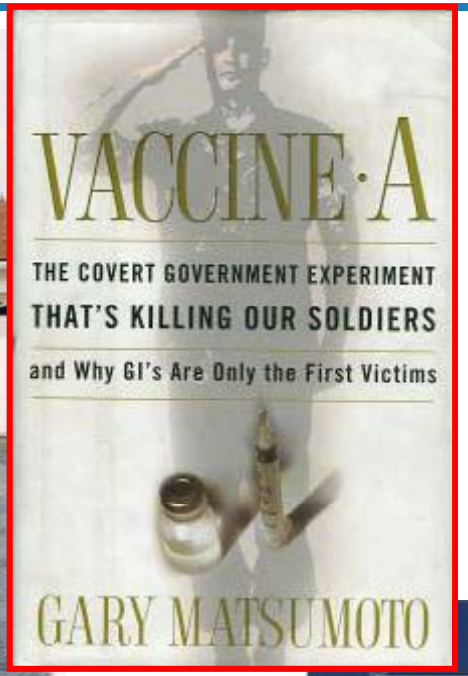
Retired Dr. Anders Braun Laursen, Flensburg. E-mail: braun-laursen@privat.dk

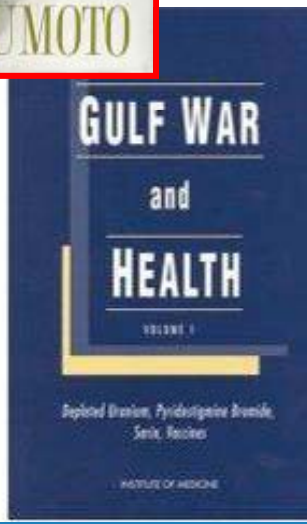
Re. Klaus Larsen interview with Dr. Kari Mølbak in Ugeskrift for Doctors (2009; 171:2616). In the interview mentioned peripherally, that 'the GSK vaccine, Denmark has commissioned, has an adjuvant. The EMEA says that danger can only be determined during and after mass vaccination!

Adjuvants are squalene, hajolie. There are very strong indications that Gulf War syndrome from the first Gulf War (and later cases) just became - and remains - caused by squalene in anthrax vaccine for both deployed and hjemmestationeret U.S. military personnel.

Both groups - which excludes radiation as the cause - got the syndrome: inability to concentrate, allergies, polyartritis, lymphomas, elevated ESR, fever, lupus erythematosus disseminatus and MS, including In a few studies [1, 2] had

The origins… a war in the gulf





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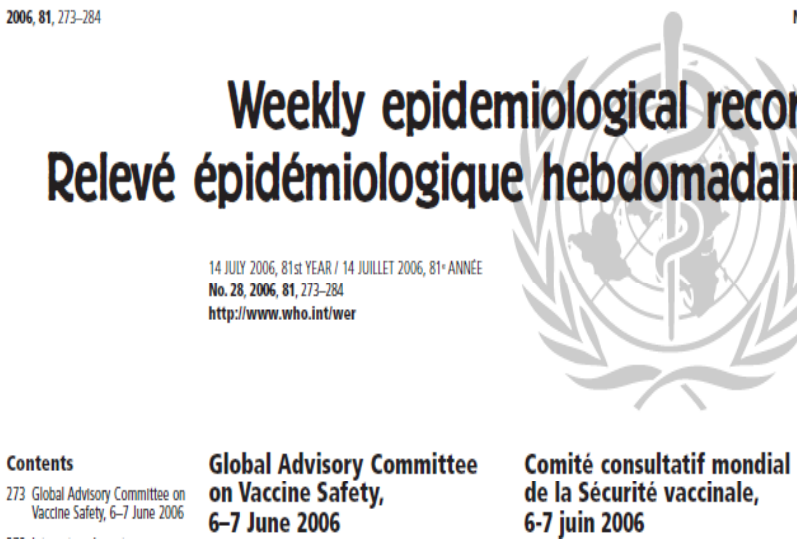
WHO consultations on safety of squalene

- June 2006..
  - The Committee concurred that fears of squalene in vaccine inducing pathological anti-squalene antibodies are unfounded.
- June 2009
  - To review known and theoretical safety concerns associated with using adjuvants in influenza vaccines
  - NO SIGNIFICANT SAFETY CONCERNS NOTED


2006, 81, 273–284

Weekly epidemiological recor
Relevé épidémiologique hebdomadair

14 JULY 2006, 81st YEAR / 14 JUILLET 2006, 81e ANNÉE
No. 28, 2006, 81, 273–284
http://www.who.int/wer

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Global Advisory Committee on Vaccine Safety, 6–7 June 2006

Comité consultatif mondial de la Sécurité vaccinale, 6-7 juin 2006

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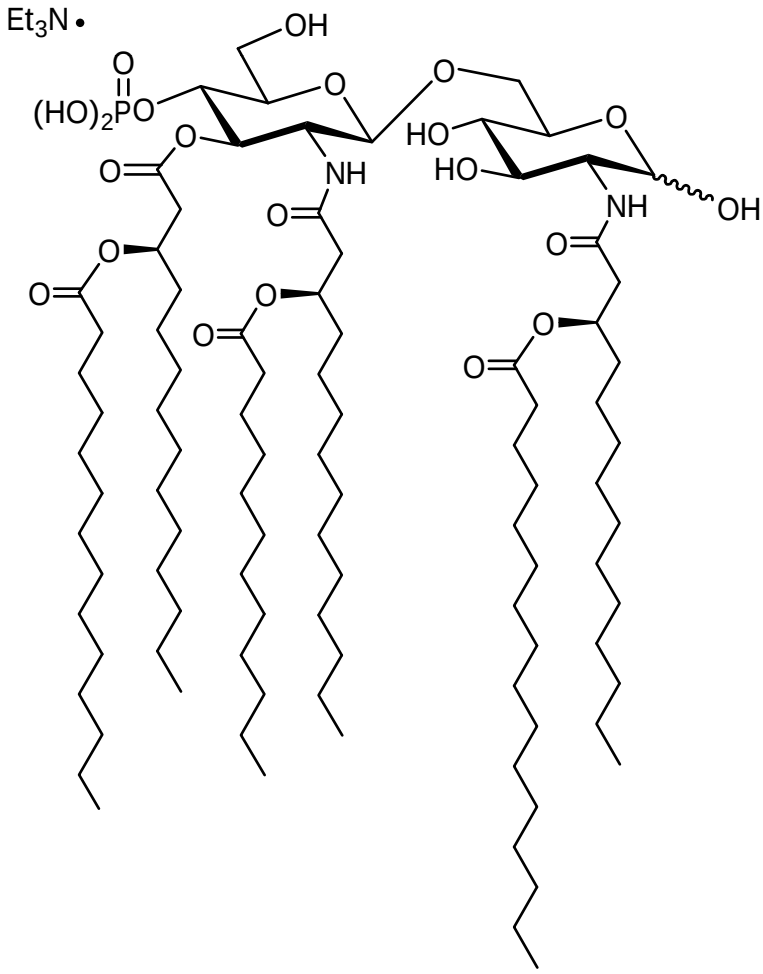
LPS-derived adjuvants

- MPL
  - Ribi, 1979, shows that partial hydrolysis eliminates toxicity but adjuvant effect retained
    - Monophosphoryl lipid A, MPL, MPLA, 3D-MPL
- Derived from Salmonella
  - Heterogenous
  - 4, 5, 6 acyl chains
- Combined with Alum = AS04 (GSK)
- Approved in
  - Cervarix (HPV vaccine),
  - Fendrix (HBV vaccine)
  - Pollinex Quatro (allergy)



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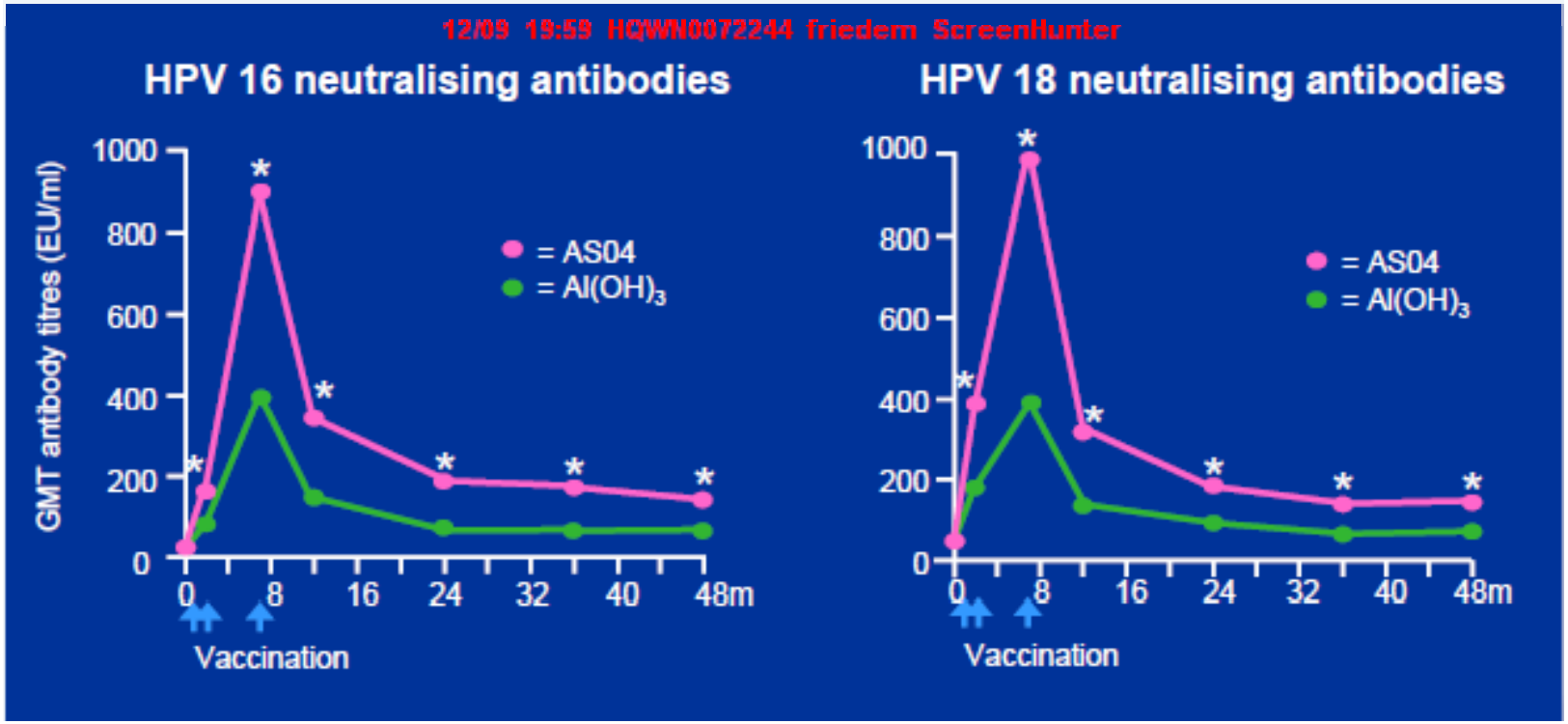
Monophosphoryl lipid A (MPL) in Cervarix



- MPL enhances the immune response

Giannini et al Vaccine 2006

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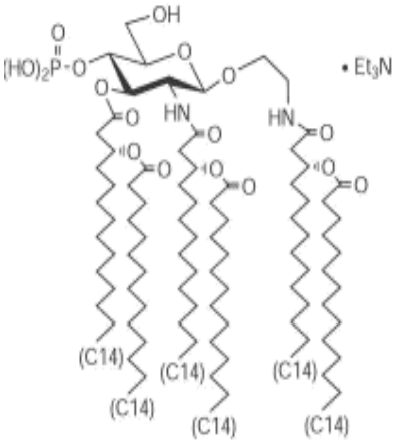
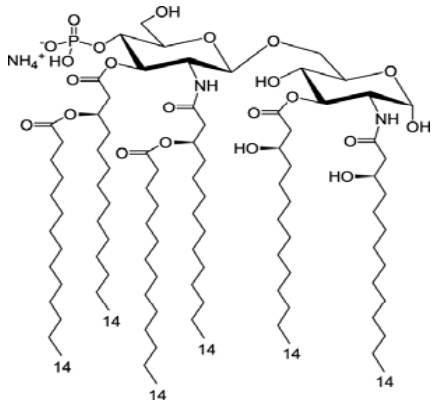
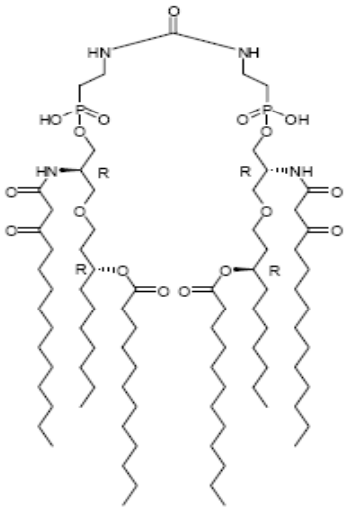
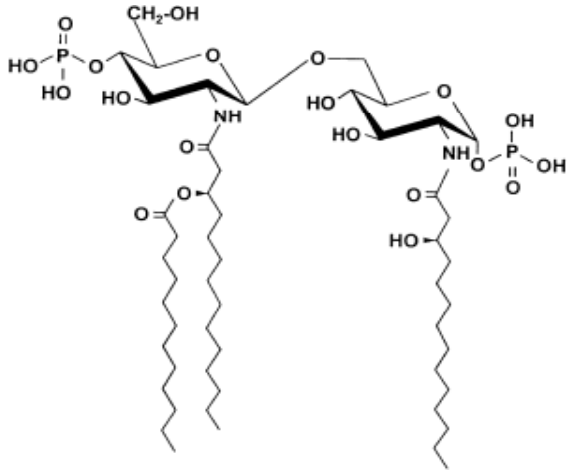
Other TLR-4 agonists

- RC-529 GLA E6020 OM-174









- MPL is heterogenous (4,5,6-acyl chains)
  - Humans TLR-4 recognises 6-acyl only. Mouse responds to all…
- Can not predict safety / efficacy of synthetic molecules…

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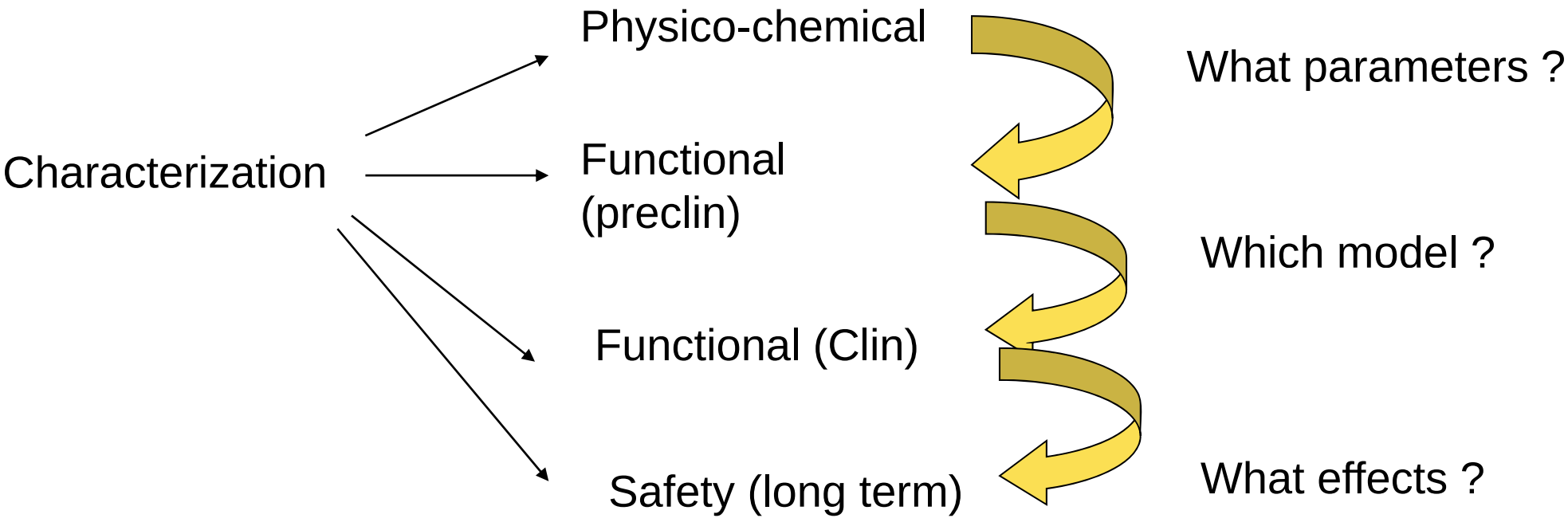
And others….

- Saponins: QS21 (AS01), Iscoms, Iscomatrix…
  - Act via inflammasome ? Stability and reactogenicity…
- TLR-3: recognizes double-stranded RNA
  - Poly I:C, Poly A:U
  - Challenge to manufacture reproducibly. Some candidates.
- TLR 5: recognizes bacterial flagellin
  - Recombinant influenza HA- flagellin candidate under development
- TLR 7,8: recognise G- or U-rich single-stranded RNA
  - Imidazoquinolines or guanosine analogues act as agonists
  - Imiquimod, R848, loxoribine,…
  - Formulation critical for effect – under development

The Critical Gaps in Knowledge



Effect of time, route, animal model, target age, read-out,….

- Selecting formulations to take into clinic is often….. roulette

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Knowns and Unknowns…

- "…There are known knowns, known unknowns and unknown unknowns.
- Each year some of the known unknowns become known knowns
- But equally each year we become aware of some more unknown unknowns so that they become known unknowns or even known knowns.
- Of course sometimes we realise that we do not know some of the known knowns as well as we thought we knew them…"

Conclusions

- Developing adjuvants is difficult, getting regulatory agencies to approve them more so, and getting the public to accept them even more so.
- Many adjuvants in the pipeline. Only a limited number of applicable disease targets.
- Risk management:
  - Using adjuvants in vaccines that don't require an adjuvant can be hazardous. Judicious selection of vaccine for first introduction of adjuvant.