

Developing Adjuvants for Public Use

A long and treacherous road

Martin Friede Ph.D.

Initiative for Vaccine Research



**World Health
Organization**

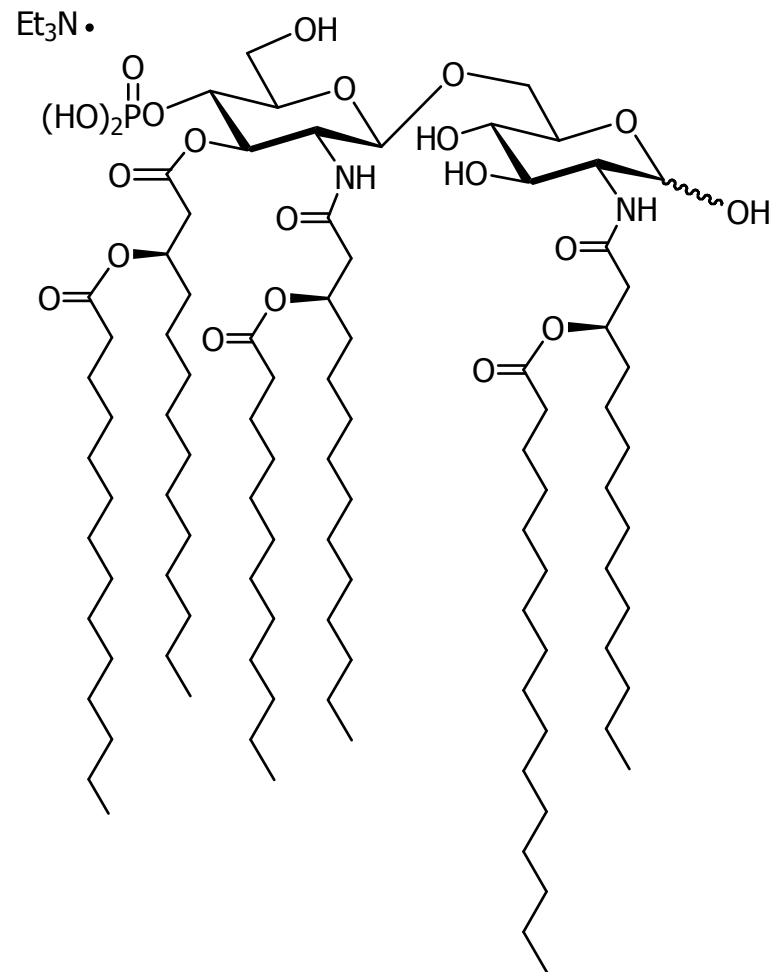
2009 – an excellent year for adjuvants



- **FDA Approves New Vaccine for Prevention of Cervical Cancer**
- The FDA today approved Cervarix, a new vaccine to prevent cervical cancer and precancerous lesions caused by human papillomavirus (HPV) types 16 and 18. The vaccine is approved for use in girls and women ages 10 years through 25 years
 - Oct. 16, 2009

Monophosphoryl lipid A (MPL)

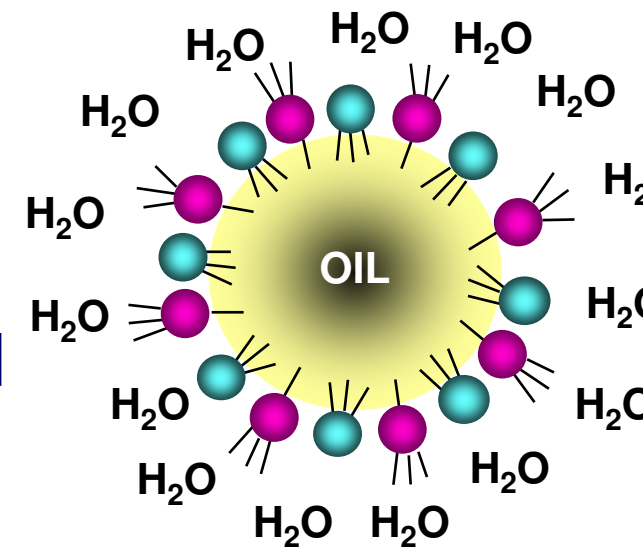
- Derived from LPS from *S. Minnesota* (Ribi, Corixa, GSK).
- TLR4 agonist,
- Used with Alum (AS04) or in emulsions (AS02) or liposomes (AS01).
- Licensed in Fendrix™ (HBV), Cervarix™ (HPV), Allergy (pollinex Quatro™).
- Synthetic variations now available, RC529, GLA, ..
- Issues: access, formulation



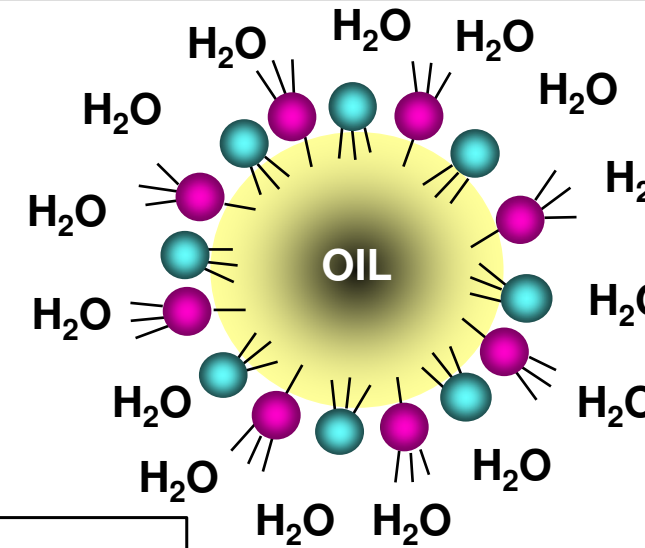
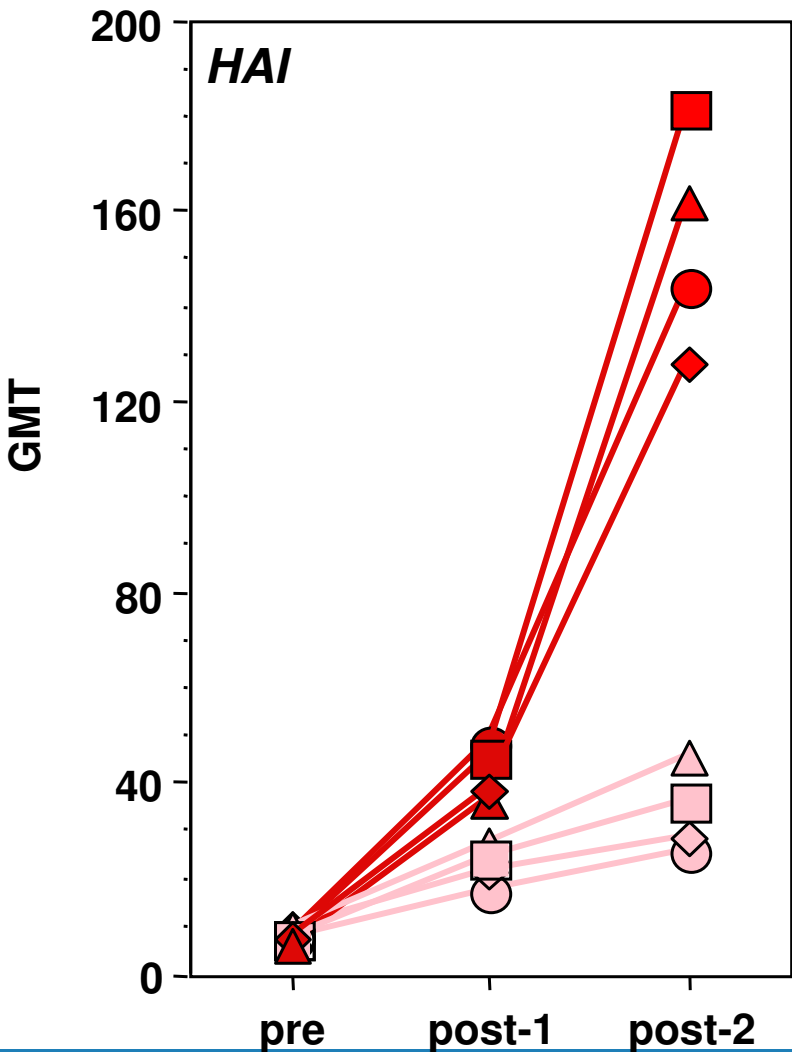
- Focetrea, Pandemrix approved.

- H1N1 vaccines with oil-in-water emulsions (MF59, AS03)
- September 2009

- Population-wide use of adjuvanted H1N1 influenza vaccine began in France in October 2009.

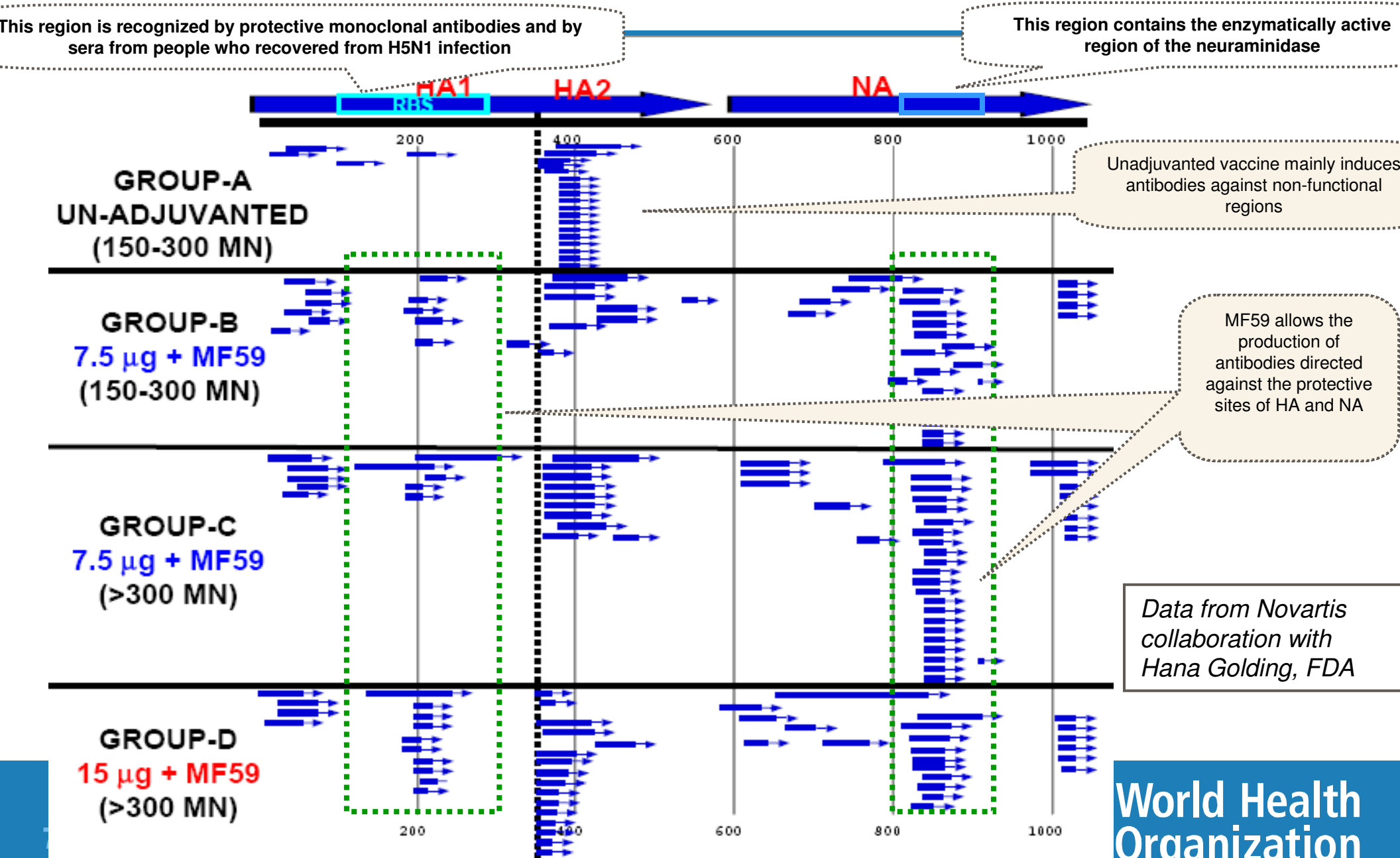


MF59 - o/w emulsion adjuvant



<i>µg/ dose</i>	<i>Plain</i>	<i>+ MF59</i>
3.75	□	■
7.5	◇	◆
15	○	●
30	△	▲

MF59 increases and changes the quality of protective antibodies against H5N1



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 influenza
	tocopherol				Pandemic influenza
W/O emulsion	squalene		malaria		
	mineral oil		cancer		
Polysaccharides	Inulin	HBV, flu			
Cationic liposomes	DDA	TB	influenza		
Virosomes		malaria			HAV, influenza
poly-electrolytes	Polyoxidonium				influenza



“They’re not going to equate my son with a lab rat,” says Asa. “It’s not right.”



BAD MEDICINE
Pamela Asa holds a jar of squalene, which she suspects was added to military vaccines and is causing autoimmune diseases.

fact that women made up a mere 6.8 percent of the U.S. force serving there).

Another startling fact pointed to the vaccination program. Many of Asa’s Gulf War–syndrome patients had never deployed to the Persian Gulf. They had never been exposed to petroleum fires, chemical-weapons fallout, pesticides, or the other suspected causes of Gulf War syndrome. But, she says, they did have one thing in common with the troops who were in theater: they had rolled up their sleeves and gotten their shots.

For Asa, all of this pointed to an adjuvant. Adjuvants are toxic substances which make vaccines more effective by stimulating an even stronger response from the immune system than a virus or bacterium might on its own. In the course of investigating the possible connection between her earlier patients’ breast implants and their illnesses, Asa says she came across a confidential Dow Corning document showing that the company had conducted research with silicone as a vaccine adjuvant in 1974. The term “adjuvant” comes from the Latin word *adjuvare*, “to aid.” But the quest for a safe, effective adjuvant has been like the medieval alchemist’s

ANITY FAIR

MAY 1999

Slide from C. Alving



GULF WAR

and

HEALTH

VOLUME 1

*Depleted Uranium, Pyridostigmine Bromide,
Sarin, Vaccines*

Carolyn E. Fulco, Catharyn T. Liverman, Harold C. Sox, *Editors*

Committee on Health Effects Associated with
Exposures During the Gulf War

Division of Health Promotion and Disease Prevention

INSTITUTE OF MEDICINE

2000

NATIONAL ACADEMY PRESS
Washington, D.C.

Future Research Directions Regarding Squalene

As squalene continues to be investigated for a number of clinical uses, ongoing toxicity studies will provide the additional information that is needed about its toxicity, both in animals and in humans. It will be important to examine the relevance of animal studies because of species differences in the absorption of squalene and the susceptibility of certain strains of animals to squalene's effects. In considering future research directions, the committee focused on squalene's potential use as a vaccine adjuvant. Research questions that remain to be addressed include the following:

- What types of immune responses does exogenous squalene evoke?
- Does the immune response differ with the route of administration or entry (i.e., oral, cutaneous, intramuscular)?
- How does the response vary according to the dose of squalene?
- Is the presence of antibodies to squalene abnormal, and if so, what is their functional significance?
- Could antibodies to squalene represent the consequences of, rather than the cause of, a pathological process?



American Journal of Pathology, Vol. 156, No. 6, June 2000
Copyright © American Society for Investigative Pathology

The Endogenous Adjuvant Squalene Can Induce a Chronic T-Cell-Mediated Arthritis in Rats



WHO consultation on safety of squalene

2006, 81, 273–284

No. 28

Weekly epidemiological record Relevé épidémiologique hebdomadaire

14 JULY 2006, 81st YEAR / 14 JUILLET 2006, 81^e ANNÉE

No. 28, 2006, 81, 273–284

<http://www.who.int/wer>

Contents

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

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

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



GACVS meeting June 2006

- The Committee concurred that fears of squalene in vaccine inducing pathological anti-squalene antibodies are unfounded.



Google search:

- squalene adjuvant: 51,700 hits
- squalene adjuvant danger: 38,000 hits.



<http://www.rense.com>

- **Million TIMES More Squalene
In H1N1 Vax Than Caused GWI !!**



<http://www.thenewamerican.com>

- **Risks of the Swine Flu Vaccine**
Experimental adjuvant squalene
implicated in autoimmune disorders
| Thursday, 03 September 2009 | Alex Newman



<http://euro-med.dk>

- Micropaleontologist Dr. Viera Scheibner conducted research into the adverse effects of adjuvants in vaccines and wrote:
Squalene “contributed to the cascade of reactions called “ Gulf War syndrome. GIs developed arthritis, fibromyalgia, lymphadenopathy,



Fox News: Sept 28 2009

- With the major manufacturers of the federally mandate vaccinations using such “ADJUVANTS” like “THIMERSOL” and even the DEADLY “SQUALENE” many long term health problems are going to occur...even some deaths.



<http://birdflu666.wordpress.com/>

- **Swine flu” vaccine has adjuvants that impair fertility**
- Daniel Solis from the Czech Republic has researched the side-effects of the adjuvant, squalene, and discovered it is known to destroy fertility as well as causing other forms of damage.
- A patent for a vaccine to impair fertility in animals contains squalene.



<http://www.novaccine.com/>

- Too dangerous for human use, Squalene is not licensed for use in the United States. Oil adjuvants like squalene have been ordinarily used to inflict diseases in animals – for experimentation and study. According to anthrax vaccine expert Gary Matsumoto and other reliable sources, the US ...**more**



<http://stanford.wellsphere.com/>

- **Cervarix: Squalene Adjuvant Approved in US**
- Despite data showing twice the rate of miscarriages in women who received Cervarix, FDA approved this new HPV vaccine from GlaxoSmithKline for the US market: the first-ever vaccine licensed in the US with a squalene-containing novel adjuvant, ASO3.



WHO Virtual Consultation on the Safety of Adjuvanted Influenza Vaccines (3 June 2009)

- To review known and theoretical safety concerns associated with using adjuvants in influenza vaccines
- Review clinical data on adjuvanted influenza vaccines:
 - MF59: > 30M doses in elderly. Trials in 26,000 individuals
 - AS02: Trials in 45,000 individuals
 - No safety signals detectable
- Challenge to detecting risk-association during large scale implementation of vaccination
- Risk groups: pregnant, very young, prior GBS,...
- **NO SIGNIFICANT SAFETY CONCERNS NOTED**



Incomplete Freund's Adjuvant: One of most potent adjuvants ever made

- Why is it not in routine use in humans ?
 - 1964-65: 900,000 people received influenza vaccine adjuvanted with IFA
 - 40 cases of nodules, of which 9 required surgery to remove
 - IFA induces tumors in male Swiss mice.
 - Not Balb/c or C57BL/6 mice
 - IFA is known as a potent agent for induction of autoimmune arthritis mice
- Based on the above, it is feared that IFA may cause cysts, cancer, or autoimmune arthritis in humans
 - Stuart-Harris, C.H. Adjuvant influenza vaccines. Bull WHO 41:617-621, 1969

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 Arlachel-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.



Reported SAEs in trials with novel adjuvants / formulations

- **Dynavax: HBsAg-CpG conjugate**
 - Wegener's granulomatosis reported in the Phase 3 trial (single case)
 - Clinical hold for use in healthy patients.
- **VAC19/HVTN042: lipo-peptide**
 - 1 case of myelitis (out of 125 volunteers)
 - Trial suspended
- **Berna (Crucell): intranasal influenza + cholera toxin**
 - Bell's Palsy observed in phase 4: potentially due to adjuvant-neurone interaction.
 - Vaccine withdrawn post marketing.



Need for improved non-clinical safety evaluation

- Current recommended preclin tox studies rarely flag safety issues
 - Exceptions include nasal delivery of LT
- But safety main reason for vaccine withdrawal / policy limitation
- Can we use preclinical models better ?
 - Documentation of potential disease enhancement (RSV, measles,...)
 - Disease specific
 - Documentation of relevance of non-specific immune effects
 - Adjuvant specific



Need for harmonization across clinical trials

- AEs may be rare, not noticeable in single trial
- Cumulative data requires harmonization of definition
- Challenges:
 - Each type of adjuvant carries its own specific AE profile
 - Toxicity can be dependent on the specific antigen
- Brighton Collaboration Working Group



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.

