佐劑在流感疫苗之效益評估

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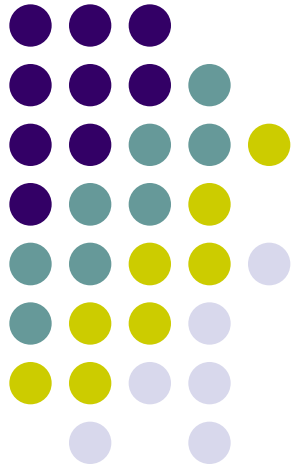


Outline of Presentation

- Introduction to Influenza vaccine and Adjuvants
- Aluminum Hydroxide: Historical perspective
- Aluminum adjuvants: Mechanism(s) of action
- Aluminum adjuvants: Safety profile
- Regulations and Conclusions of Al adjuvants

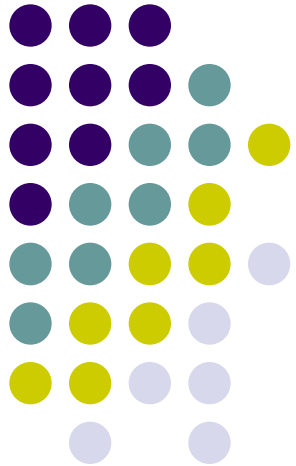
Adjuvant

- Compounds added to, or used in conjunction with, vaccine antigens to augment or potentiate (and possibly target) the specific immune response to an antigen
- An immunological vehicle for enhancing antigenicity

Rationale – Why Adjuvants are Needed

- Most vaccines based on non-living material lack the ability to stimulate a significant immune response, and thus, adjuvants are used to enhance immune responses to weak immunogens
- Induce long term persistence of protection
  - Higher levels of immune response
  - Improved immunological memory
- Improve adaptation to poorly responsive populations
  - Naïve children (and adults)
  - Adults >65 or immunosenescent
- Reduction in number of doses

Influenza vaccine



Real Objectives

- Why is this topic/ messaging so confusing
- Is vaccine really going to protect my patient?
- What are the real risks of influenza vaccination?
- Tamiflu for all?

Influenza vaccination

- 1918…. Only “effective therapy” was serum derived from recovered patients
- Suggested that antibody / immune response would help fight the virus
- Vaccine development against influenza started in 1930’s
- Routine vaccines available for the past 50 years

Efficacy of the vaccine

- Depends what you measure
- Most vaccines are 90+ % effective and the rest of the population is protected by

  "herd immunity"
- Healthy adults, 90% develop Ab to influenza
- Studies show influenza vaccine efficacy is 60-80% or 70-90% if a good seasonal match
- How do we measure efficacy: by antibody response or disease protection?

Case -1

- 78 yr old male admitted to CCU with a mild inferior MI
- It is influenza season; he has been vaccinated
- As part of screening “at risk exposed” ICU patients, he has NP swab
- He has no respiratory symptoms and no fever

Case-1

- The Naso-pharyngeal swab is positive for influenza virus
- His unvaccinated wife is admitted with ILI

- Is this a vaccine success or failure??

Case-1

- The patient is asymptomatic so clinically this is a success
- The positive culture makes him a public health case and by definition a failure
- He has a fatal brady-arrythmnia on day 3
- His death is recorded as an influenza death by definition.

Vaccine Efficacy

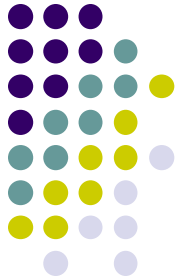
- Depends on the population you study
- The goal is reducing the burden of disease

- Thus our case is a vaccine success!

Nursing Home Patients

- Elderly, infirm and immunosuppressed respond poorly to vaccination so are protected by reducing the burden of diseases around them.
- Better effectiveness by vaccinating the heath care workers than the residents
- This is the key rationale to aggressively promote vaccination among HCW
- HCW's bring influenza into the hospital and don't acquire it there (2 outbreaks on a BMT unit).

Risk Factor Related to Influenza Vaccination



- Balance risks against not being vaccinated
- Local injection site irritation
- Transient fever (low grade) in 2-10%
- Whole –virus or split virus vaccines. Split type used in young children to reduce side effects
- Anaphylaxis to severe egg allergy (rare)
- Guillain-Barre rate is 1/100,000 and unrelated to vaccine

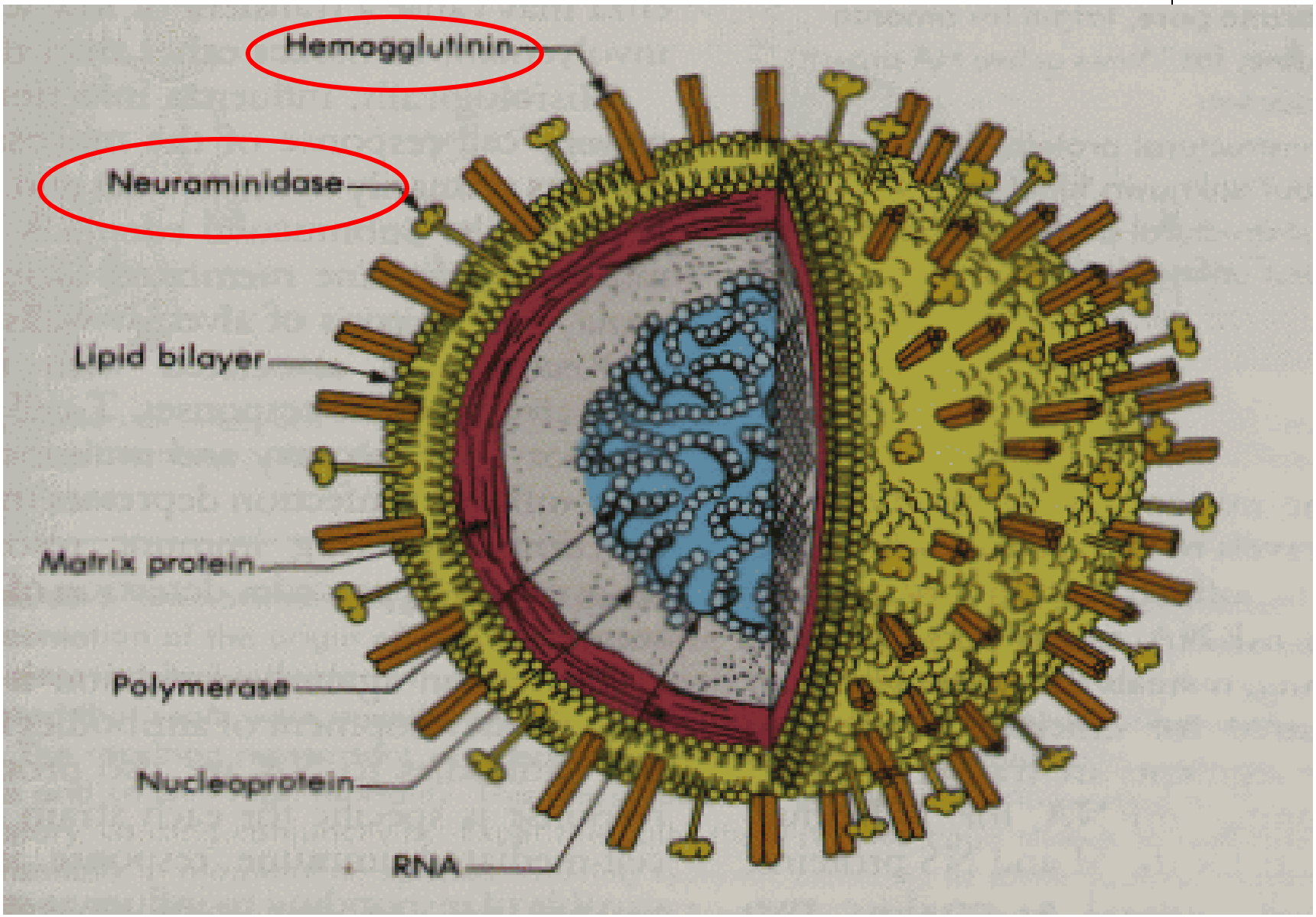
Vaccine Production

- Stock virus is injected into eggs, virions are harvested and then injected into more eggs , on average one vaccine dose equals the production from one egg
- Virus is inactivated and then packaged
- 50 million eggs have/will be used for HINI this year
- Preservative or adjuvant can be added
- In the summer, volunteer studies are performed for vaccine efficacy (Ab response)

Vaccine Production

- Because the same formula is used year to year the companies can bypass traditional phase 1-3 development and large formal clinical trials
- There is a lack of incentive to make a better vaccine i.e. one that may have alternative Ag to obviate annual vaccines or that uses non egg based production (costly research)
- Virus protection is actually cell mediated immunity. Why are we focusing on Ab?

Influenza Virus



Adjuvant

- Adjuvants are used to enhance the immune response
- Different adjuvants stimulate different parts of the immune system
- Alum, Freund’s, IL-10, VLP
- Oil-based (MF-59, AS03), used in Europe for years
- Not the routine in N America

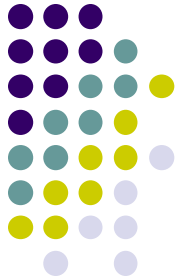
Adjuvants

- Long standing safety in European influenza program
- HINI initially shown to have low efficacy and may require boosting (2 doses)
- Canada chose to go with adjuvanted vaccine. This change slows testing and release in Canada
- Adjuvants not known to enhance auto-immunity. In fact active viral infection can induce autoimmunity

Vaccine Efficacy-HINI

- Single dose of unadjuvanted vaccine seems to provide adequate Ab response
- Adjuvant enables ¼ Ag dose to be used
- Thus 4 times the vaccine available.
- Canada has 50 M doses, 30 M doses needed for entire population, 20 million with adjuvant can vaccinate 40-80M people
- Same vaccine for pregnant and non-pregnant
- Highest pandemic mortality is in 3rd trimester pregnancy

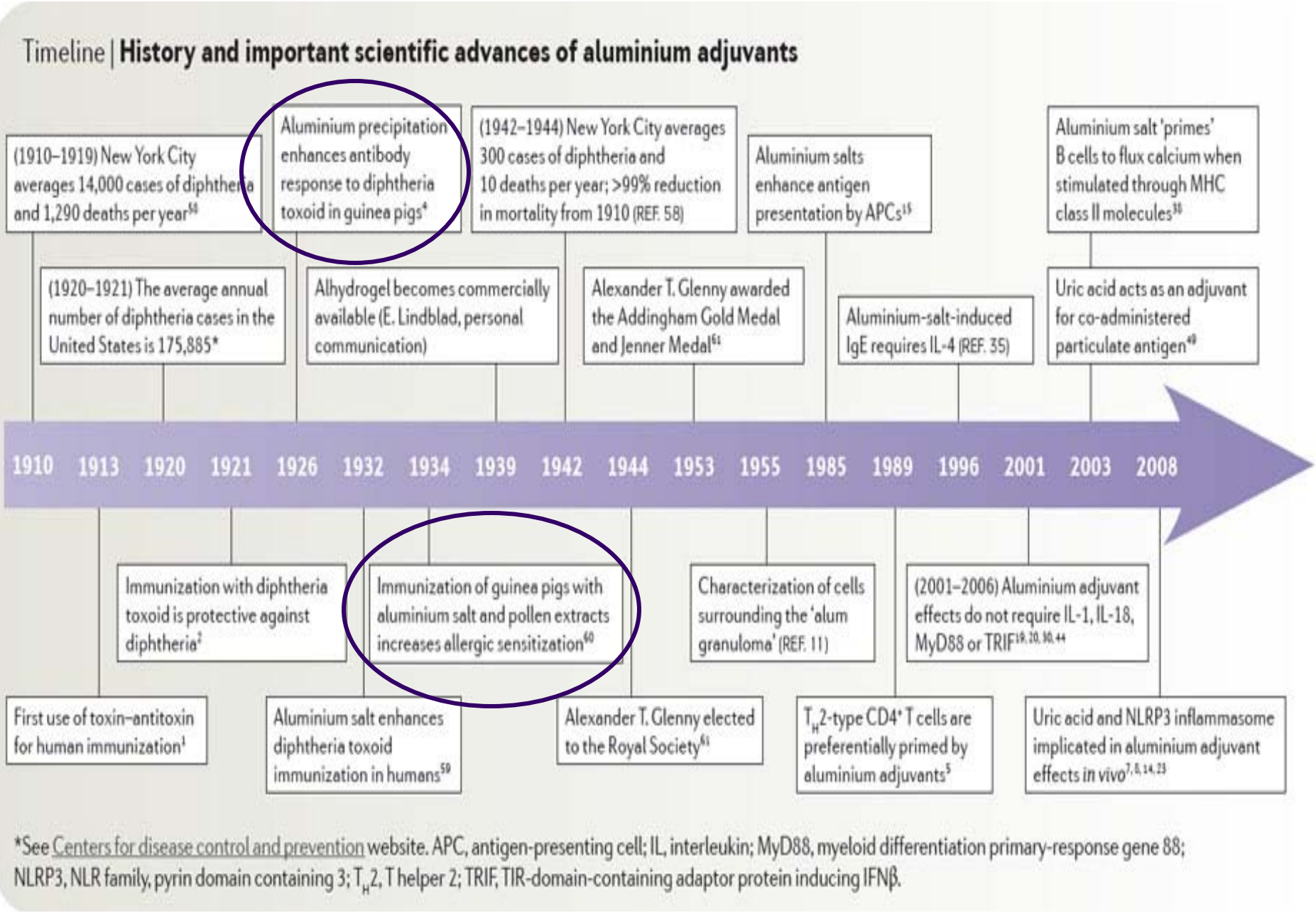
Preservatives- Thimerosal



- Multi-dose vials have in the past spread bacterial infection- trace or low dose thimerosal prevent bacterial contamination
- No evidence for mercury poisoning and studies have shown rapid excretion/metabolism in young children
- We can avoid preservatives with single dose vials
- Association with Autism is nonsense

Examples of Adjuvants

- Oil emulsions
  - MF59
  - AS03
- Microbial (natural and synthetic derivatives
  - Monophosporyl lipid A (MPL)
- Combination
  - AS04 (Aluminum hydroxide + MPL)
- Aluminum Salts
  - **Aluminum Hydroxide**
  - Aluminum Phosphate



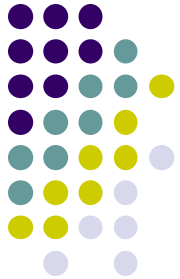
Philippa Marrack, Amy S. McKee & Michael W. Munks. Towards an understanding of the adjuvant action of aluminium. Nature Reviews. Immunology. Volume 9. April 2009.

Historical Perspective

- Aluminum salts are the most widely used adjuvants for human vaccines.
- 1926 - Glenny *et al* were the first researchers to demonstrate the adjuvant effect of aluminum compounds*
- 1932 – Aluminum salt found to enhance diphtheria toxoid immunization in humans
- 1934 – Immunization of guinea pigs with aluminum salt and pollen extracts was found to increase allergic sensitization
- 1938 – Sledge *et al* demonstrated that aluminum hydroxide-adsorbed allergen extracts improved stimulatory as well as reduced anaphylactic properties

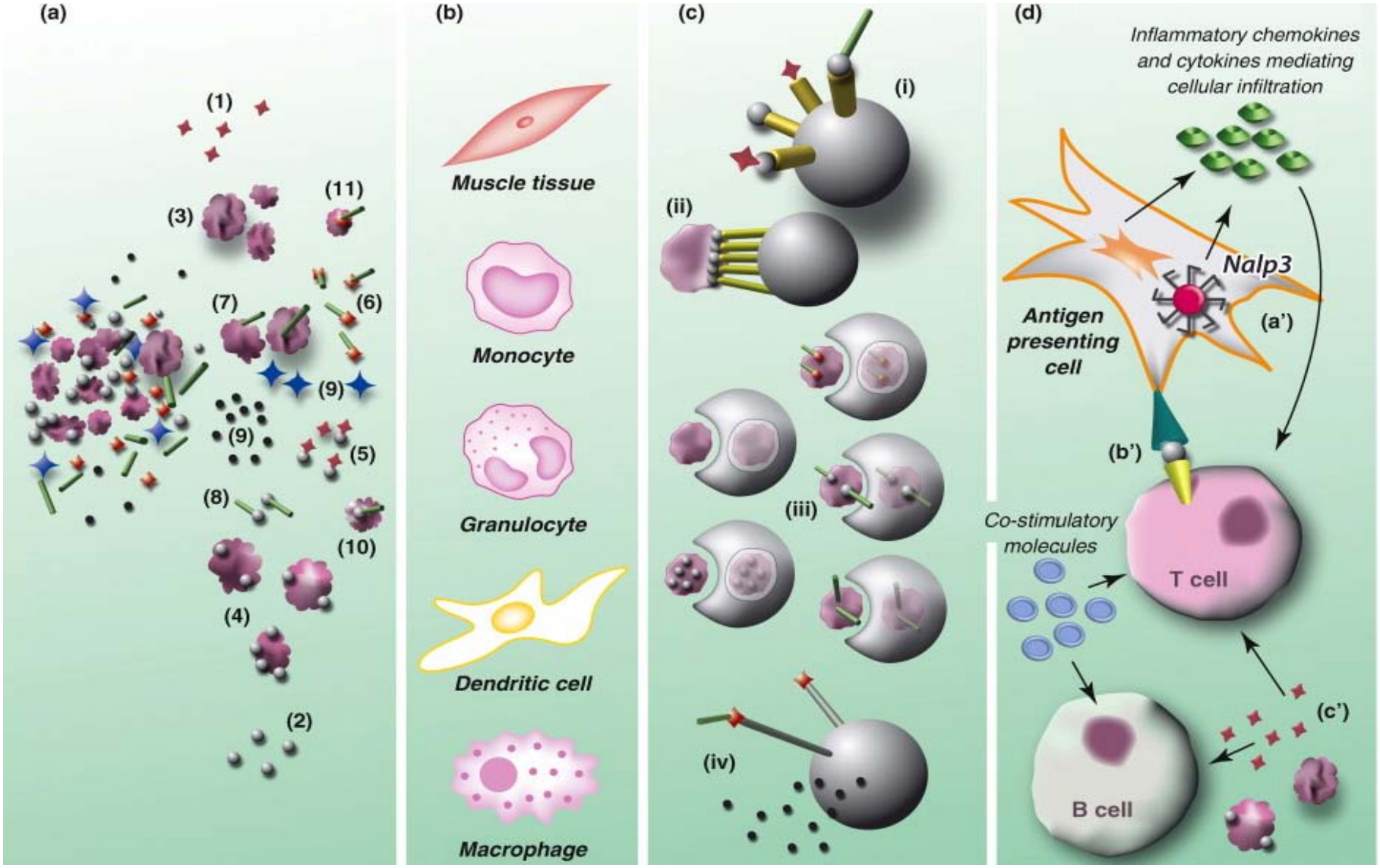
Philippa Marrack, Amy S. McKee & Michael W. Munks. Towards an understanding of the adjuvant action of aluminium. Nature Reviews. Immunology. Volume 9. April 2009.

Mechanisms of Immunopotentiation



- Aluminum adjuvants
  - Form a “depot” at the site of injection from which antigen is released slowly, leading to a prolonged exposure to antigen-presenting cells and lymphocytes
  - Promote antigen phagocytosis by antigen-presenting cells such as dendritic cells, macrophages, and B cells
  - Induce inflammation resulting in the recruitment of neutrophils, eosinophils, and macrophages
  - Boost Th2 type of immune response

The Aluminium Adjuvant Armoury and Innate and Adaptive Immunity.



Exley, Siesjö, Eriksson. The immunobiology of aluminum adjuvants: how do they really work?. Trends in Immunology, Volume 31, Issue 3, March 2010, Pages 103-109,)

Inflammation Process

- Particulate aluminum adjuvant is ingested by phagocytes
- Phagocytes release damage-associated molecular patterns (DAMPS) which increase activation of Nalp3 inflammasomes, and the production of IL-1beta, and thus induction of inflammation
- Recruitment, activation and maturation of immune complex cells follows
  - Inflammation mediates a link between the innate and adaptive immune response

Safety Profile

- There is a 70-year history of safe and effective use of aluminum salts in vaccines.
- Serious adverse effects attributable to aluminum adjuvants are rare.
- Not associated with immune complex disorders
- The aluminum adjuvants are not in themselves pyrogenic and there is no evidence of carcinogenicity or teratogenicity attributed to their use.

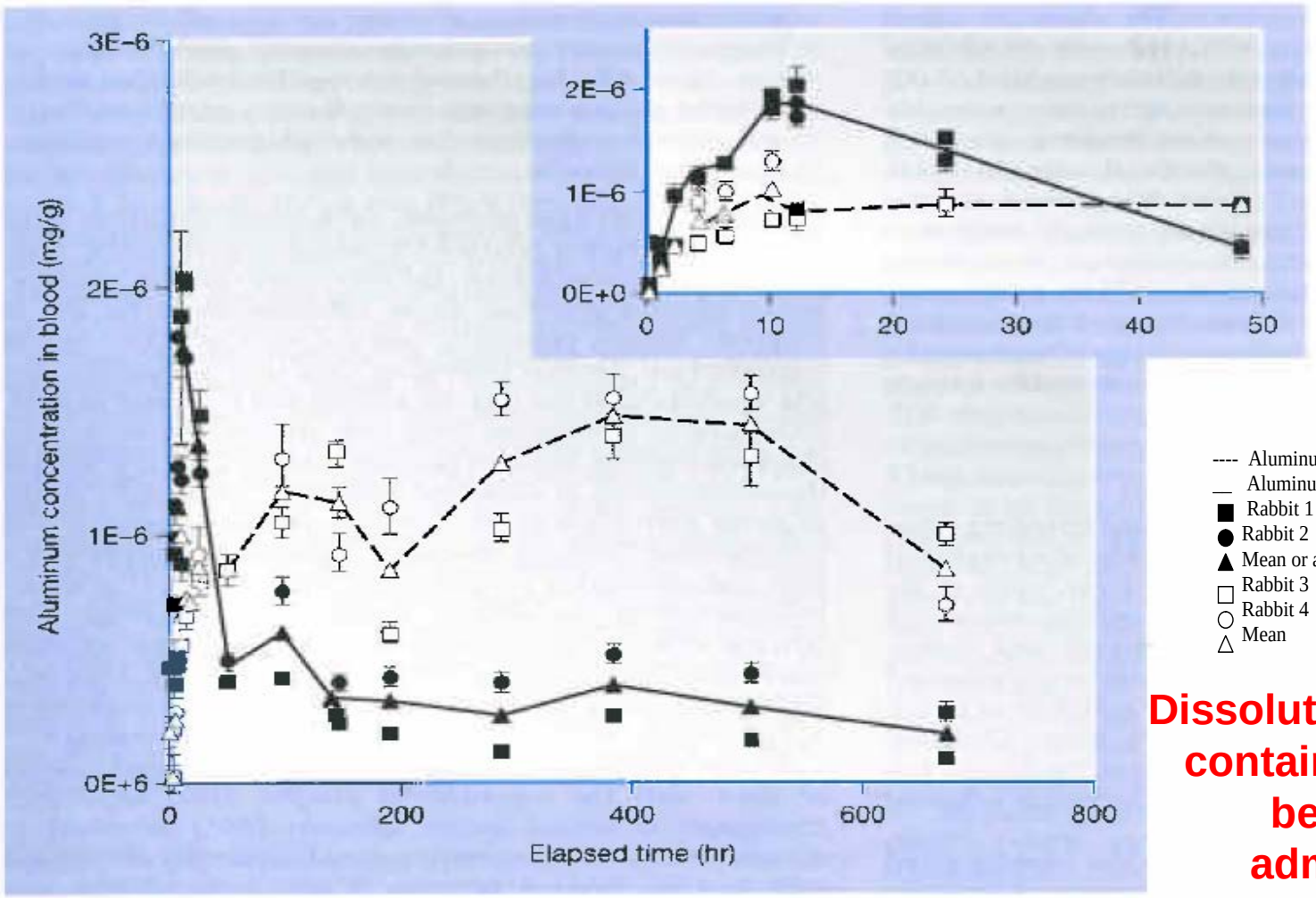
- Adverse reactions that have been reported with aluminum containing vaccines are generally local reactions including
  - Sterile abscesses
  - Erythema
  - Subcutaneous (SC) nodules
  - Granulomatous inflammation
  - Contact hypersensitivity

Strength of Evidence for Health Effects of Aluminum

Health Endpoint	Inhalation	Oral	Dermal	Injection
Acute toxicity				
Irritation	Strong	Limited	Limited	Strong
Mutagenicity	Limited	Limited		
Carcinogenicity	No clear evidence	No clear evidence		
Reproductive toxicity	Limited	Modest		No clear evidence
Neurological Toxicity	Limited	Modest		Modest
Bone Toxicity		No clear evidence		Modest
Metabolism		Limited		Limited

Krewski, Yokel, Nieboer, et al. Human Health Risk Assessment for Aluminum, Aluminum Oxide, and Aluminium Hydroxide. JJ *Toxicol Environ Health B Crit Rev.* 2007; 10(Suppl 1): 1–269

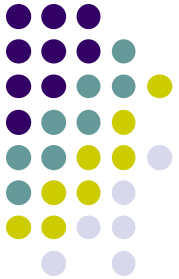
Blood Concentration Profile after IM Administration of ^{26}Al-labeled aluminum hydroxide adjuvant (See notes)



Dissolution of aluminum containing adjuvants begins upon administration

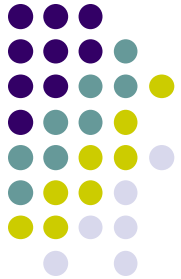
Plotkin, Oreinstein, Offit. Vaccines. Fifth Edition. 2008.

Limitations of Aluminum Adjuvants



- Despite, strong safety profile, there are limitations to aluminum adjuvants
  - Local Reactions
  - Production of IgE antibodies
  - Inability to elicit cell-mediated immunity

Regulations



- The aluminum content of a vaccine shall not exceed 0.85 mg of aluminum per dose.
- An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product.
- As with other ingredients in the final formulation, the adjuvant should be shown to be compatible with all components in the formulation.
- If appropriate, the manufacturer should demonstrate how much of each component is being adsorbed to the adjuvant

Conclusions

- Aluminum adjuvants have been administered safely to hundreds of millions of humans since 1932.

- Although there has been an increase in our knowledge of the biological events that are induced following the administration of aluminum salts, the mechanisms that are required for subsequent induction of the adaptive immune response requires further investigation

國光疫苗 vs 諾華疫苗

- 國光疫苗 (AdimFlu)
  - 抗原 15 mcg
  - 無佐劑
- 諾華疫苗 (Forcetria)
  - 抗原 7.5 mcg
  - 有佐劑 (MF59)

國光疫苗 VS 諾華疫苗:
18-60歲之抗體反應

	國光疫苗		諾華疫苗	
抗HA抗體	Total N=120	Seronegative at baseline N=98	Total N=132	Seronegative at baseline N=50
Seroprotective rate (day 22)	92.5%	92.9%	96%	98%
GMR (day 22 to day1)	32.6	41.4	18	65
Seroconversion or significant increase	93.3%	92.9%	88%	98%

國光疫苗 VS 諾華疫苗:
60歲以上之抗體反應

	國光疫苗		諾華疫苗	
抗HA抗體	Total N=53	Seronegative at baseline N=33	Total N=122	Seronegative at baseline N=27
Seroprotective rate (day 22)	75.5%	81.8%	72%	56%
GMR (day 22 to day1)	10.7	16.0	4	9.58
Seroconversion or significant increase	71.7%	81.8%	43%	56%

國光疫苗 VS 諾華疫苗:
18歲以下之抗體反應

3 weeks after 1st vaccination (n/N), %	國光疫苗 (1-3 y: 7.5 mcg, >3 y: 15 mcg)	諾華疫苗 (all 7.5 mcg with adjuvant)
1-<3 years	21/57 36.8%	29 Jan, 2010
3-<6 years	32/61 52.5%	15 Dec, 2009
6-<10 years	17/30 56.7%	15 Dec, 2009
10-<18 years	28/31 90.3%	15 Dec, 2009

國光疫苗 VS 諾華疫苗：
不良反應

Event	國光疫苗 N=292 (15 mcg=177, 30 mcg=115)	諾華疫苗 N=254 (7.5 mcg with adjuvant)
Redness	14.7%	Very common (10-100%)
Swelling	16.4%	Very common (10-100%)
Fever (>38.3)	0.7%	Common (1-10%)
Muscle aches/Myalgia	17.5%	Very common (10-100%)
Headache	13.4%	Very common (10-100%)
Nausea	4.8%	Common (1-10%)

懇請賜教