GSK's Adjuvanted Influenza Vaccines
The Taming of the Flu

JITMM, Bangkok, October 2008

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Annual Burden of Influenza in US:

25 million cases

31 million outpt visits

330,000 hospitalizations

41,000 deaths

Cost: $87 billion dollars

Health Outcomes in Thousands

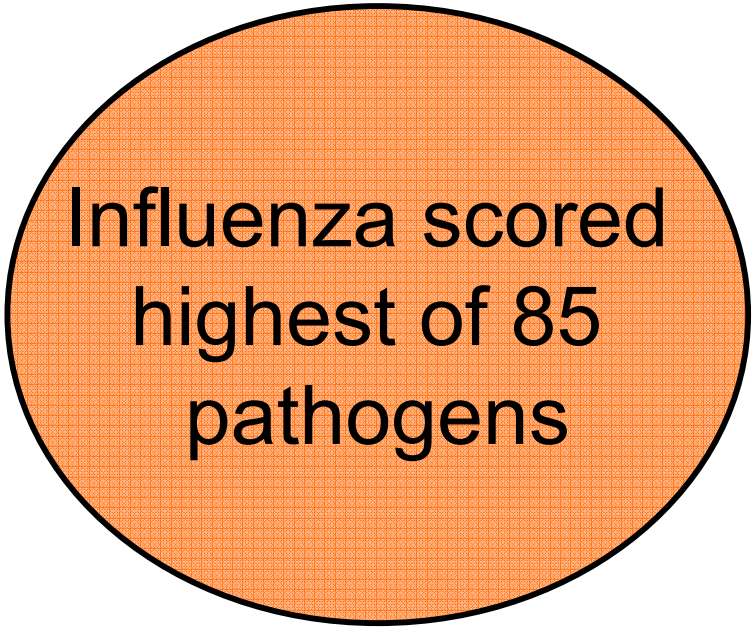
Age	Outpt visits	Hosp days	Productive days lost	Life years lost
<5	3728	280	5328	11
5-17	3718	22	6666	3
18-49	5270	305	10,178	36
50-64	4329	717	6,616	92
65+	14,309	1807	15,215	468
Total	31,354	3131	63,484	611

Molinari et al. Vaccine 2007; 25:5086-96

Prioritization of Infectious Diseases in Public Health: Robert Koch Institute

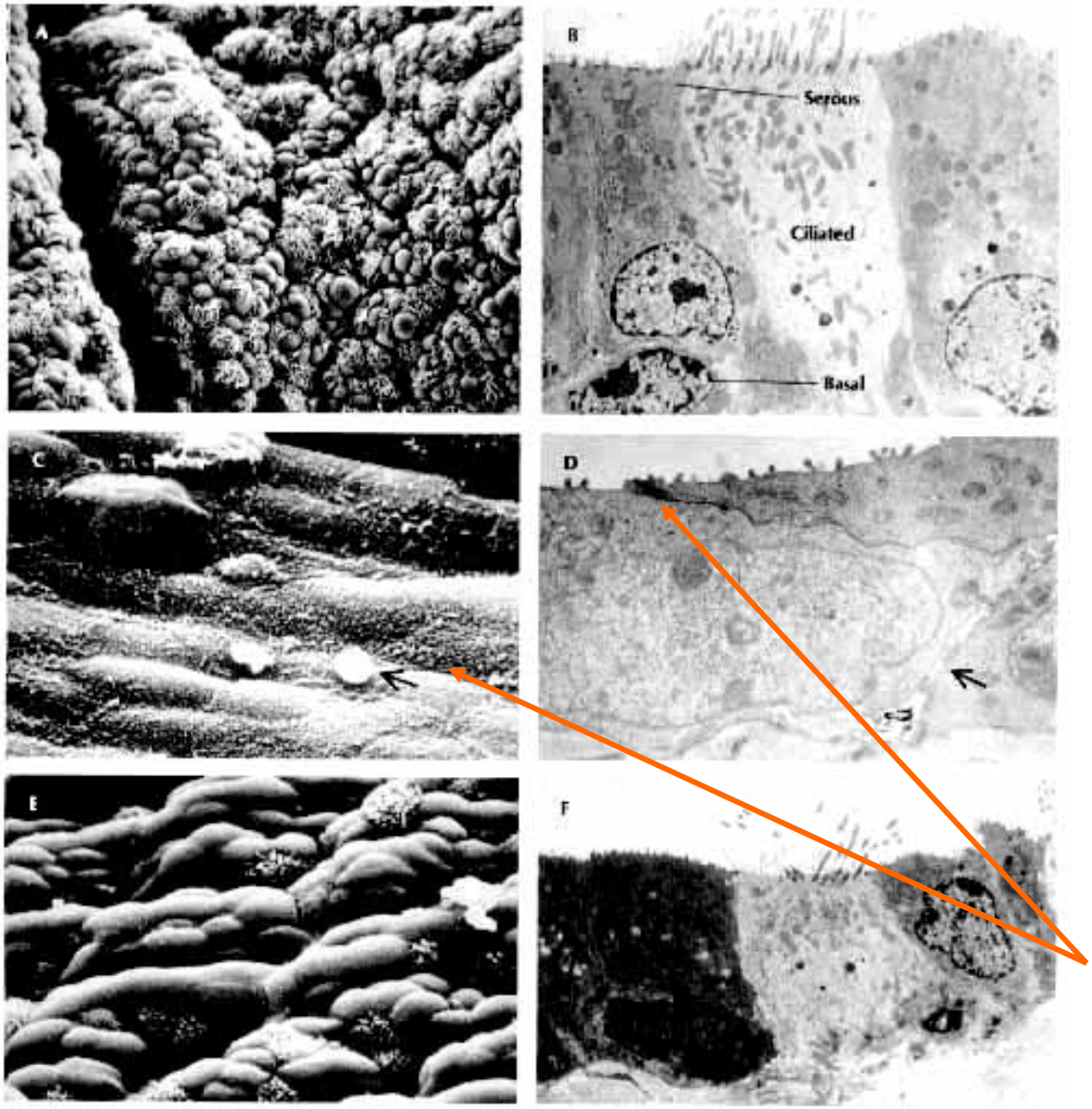
Scoring criteria

- Burden of disease
- Epidemiologic dynamic
- Information need
- Health gain opportunity

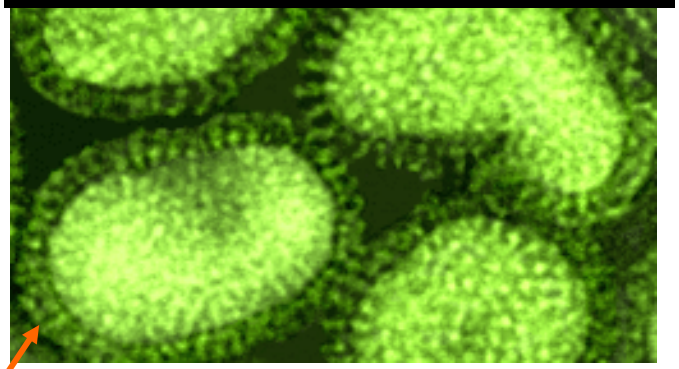


Eurosurveillance 2 Oct 2008

Influenza Virus: easily transmitted, destructive, mutable to escape immunity



Antibodies to HA & NA surface proteins are protective



Structural Diagram of the Influenza Virus

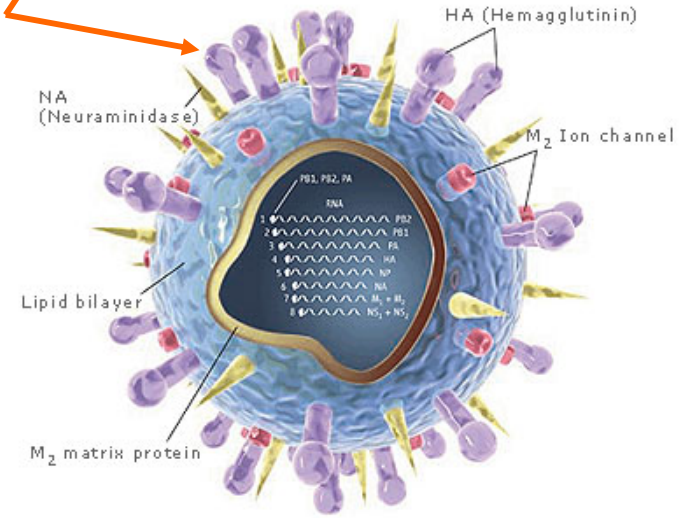


Illustration: Chris Bickel/Science. Reprinted with permission from Science Vol. 312, page 380 (21 April 2006) © 2006 by AAAS

2 diseases: based on virus surface proteins & extent of immunity to them

Interpandemic influenza

- A/H1N1
- A/H3N2
- B (2 lineages Victoria, Yamagata)

- Hemagglutinin drift

- Seasonal disease
- Disability and death of older adults

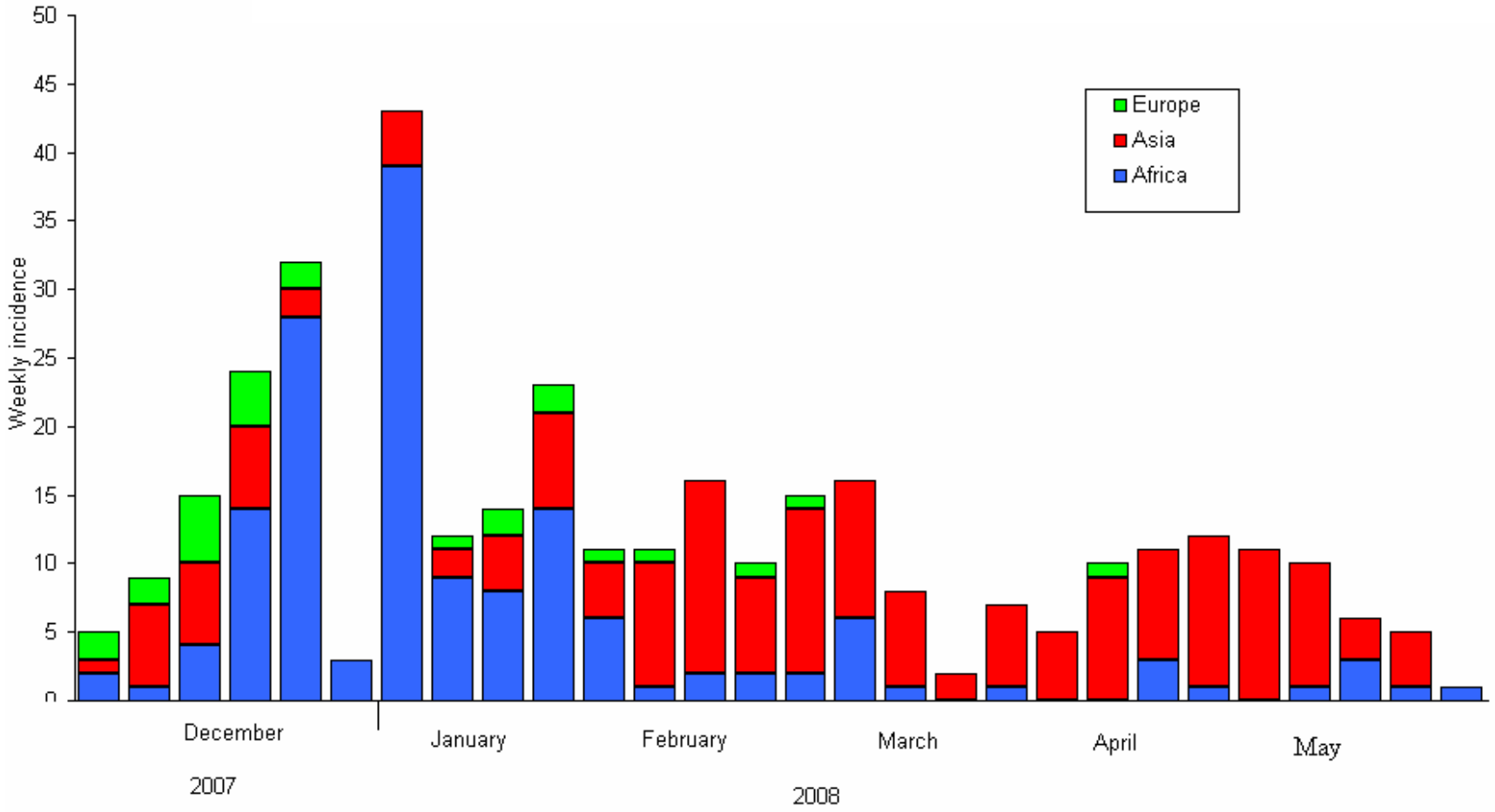
Pandemic influenza

- A/H1N1 (1918)
- A/H2N2 (1957)
- A/H3N2 (1968)
- H5N1 (when)?

- Hemagglutinin shift

- Rapid worldwide spread
- Increased deaths in all ages

HPAI Outbreaks in Domestic Poultry, Wild Birds in Asia, Europe, Africa



www.fao.org/avianflu/documents/AIDEnews_june08_no54

Number of Confirmed Human H5N1 Cases by Month, as of Jun 2008

WHO confirmed human cases, 2003-8:

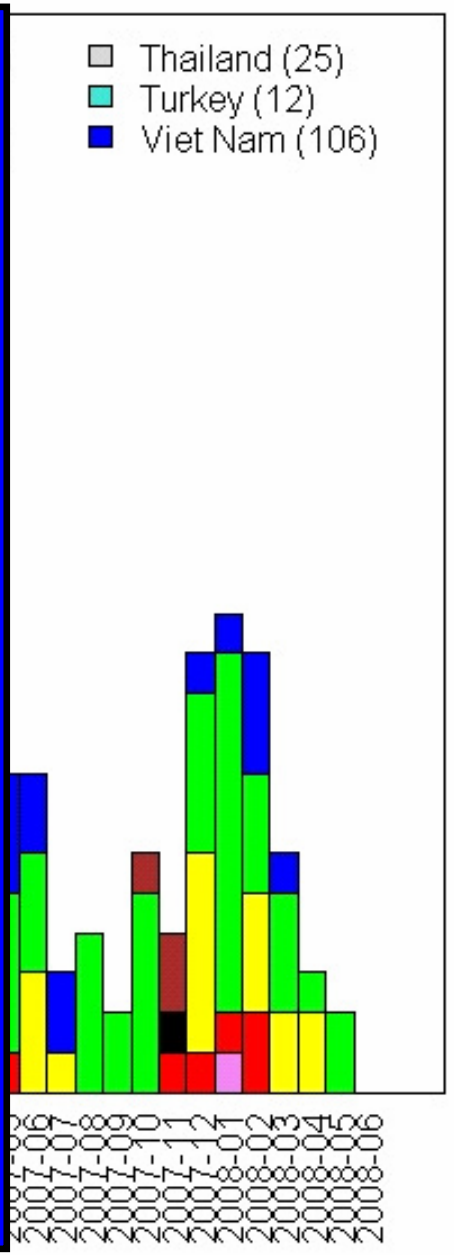
387 (245 fatal)

Cases in 2008, as of Sep:

36 (28 fatal)

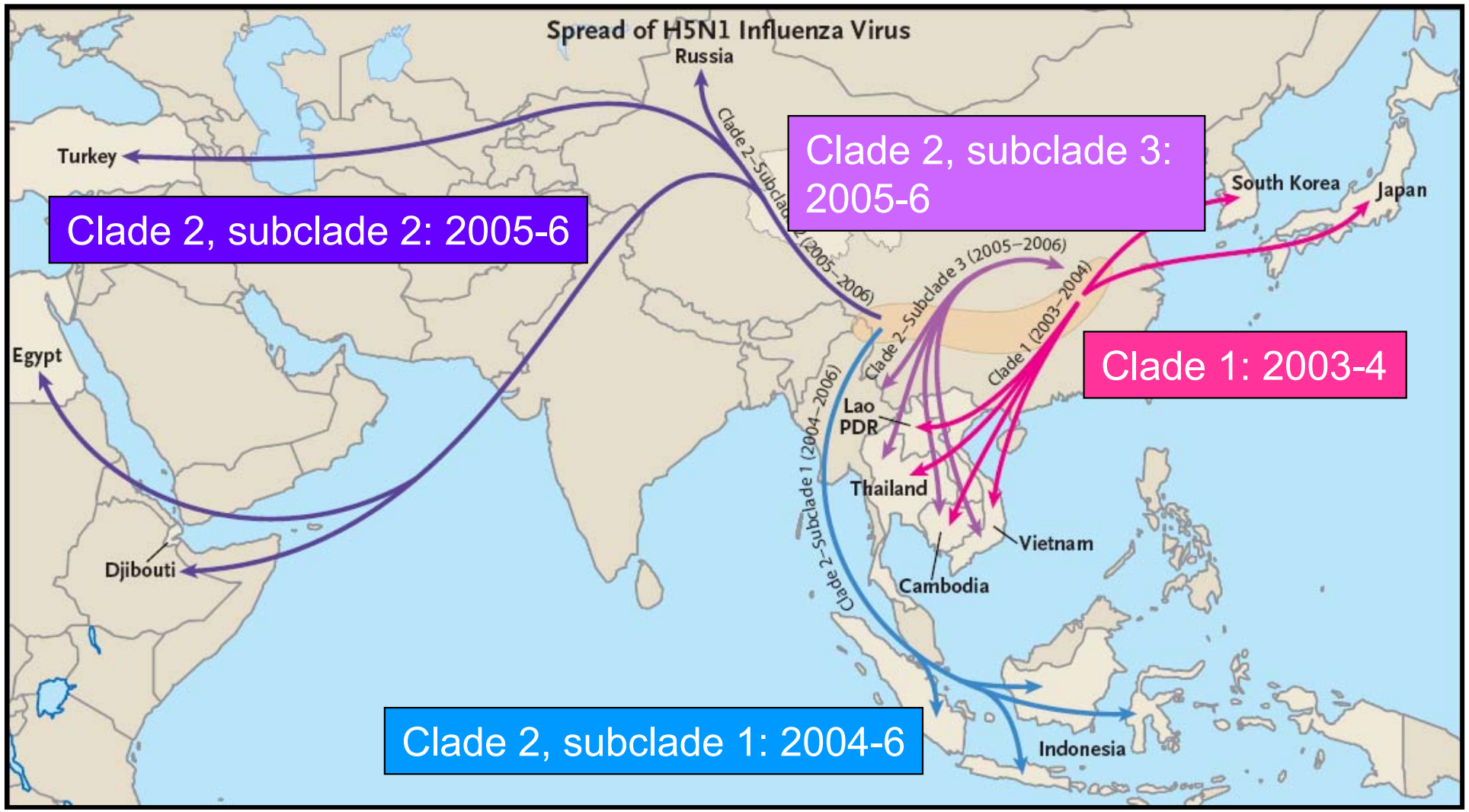
Indonesia	20
Egypt	7
Vietnam	5
China	3
Bangladesh	1

www.who.int/csr/disease/avian_influenza



www.fao.org/avianflu/documents/AIDEnews_june08_no54

Spread of Antigenically-Diverse H5N1



Webster and Govorkova, NEJM 2006; 355:21

Vaccination is the most important control measure

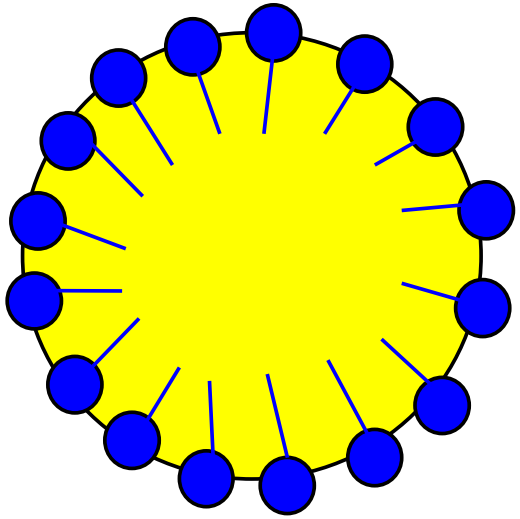
- Most vaccine is trivalent inactivated vaccine
- Annual production is ~560 million doses/yr

- Two problems w/ current vaccines:
  - Limited protection of older adults
  - Inadequate for a pandemic
    - Production takes too long
    - Poorly immunogenic against current H5N1 threat

GSK is using an oil in water emulsion adjuvant system to address those problems.

GSK's Oil in Water Adjuvant System

Antigen +



Surfactant

Naturally occurring oils: squalene and α-tocopherol

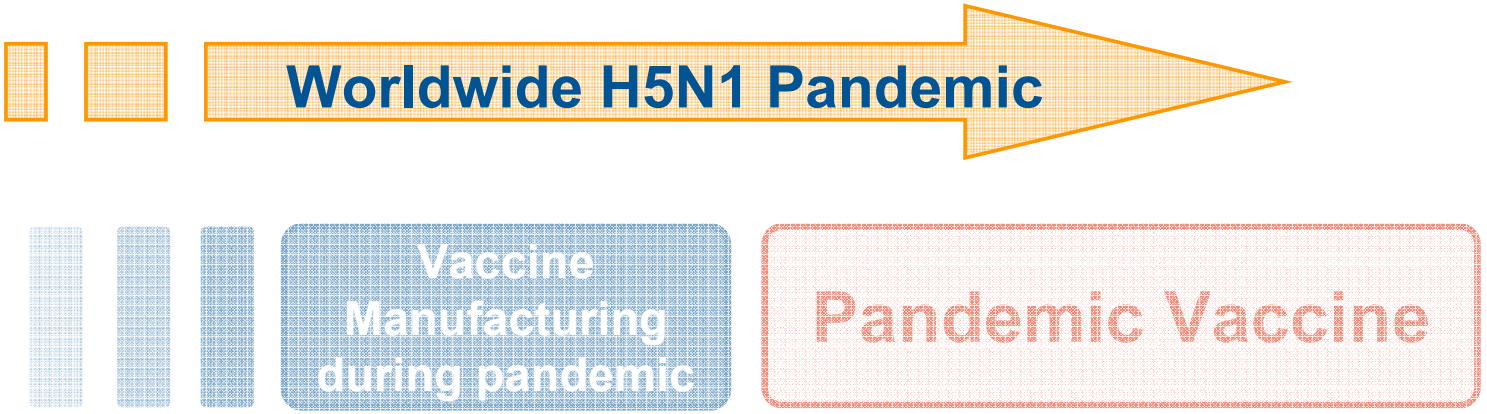
- Association of micelles of controlled size with Ag → promotes antigen presentation
  - Activates Th1 CD4 T-cell responses
  - Increases antibody responses
  - Generates increased memory

Vaccination against Influenza H5N1 (stockpiling)

Pre-pandemic influenza vaccines are a vital part of pandemic preparedness

Two major challenges for effective vaccine:

- *How to get enough vaccine doses (capacity)?*
- *How to induce protection as early as possible?*



Manufacturing before pandemic and stockpile

Pre-Pandemic Vaccine

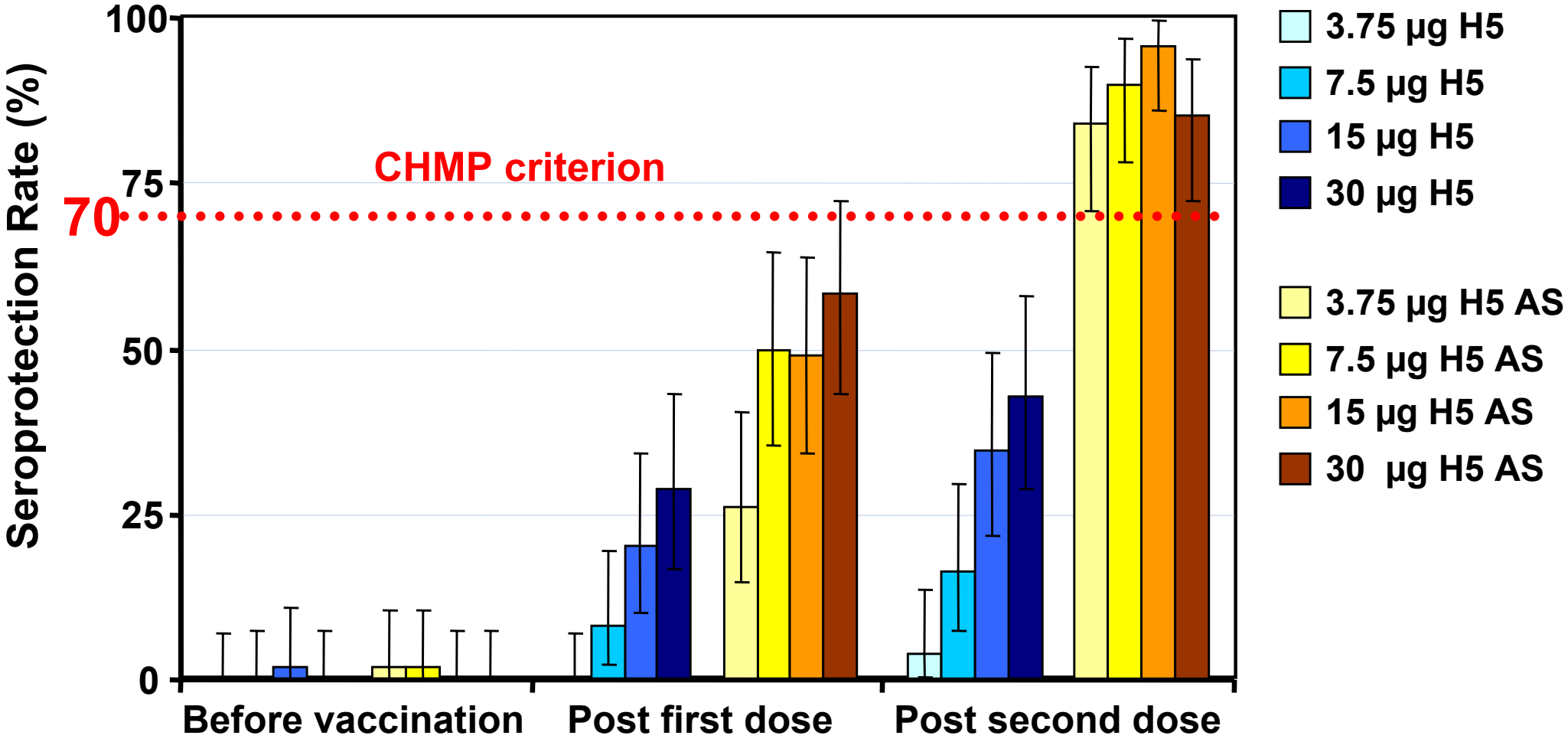
Dose Range - H5N1 Vaccine (A/Vietnam), With and Without Adjuvant System

- H5N1 split virus vaccine, A/Vietnam/1194/2004 (NIBRG-14) manufactured in Germany (*Fluarix* ™ process)
- 400 healthy adults aged 18-60 yrs
- Two doses given 21 days apart
- Key endpoint: immunogenicity

Vaccine composition								
µg H5N1 antigen	30	15	7.5	3.75	30	15	7.5	3.75
Adjuvant	/	/	/	/	AS	AS	AS	AS
Population: Healthy adults (18-60 yrs)								
Number	50	50	50	50	50	50	50	50

Leroux et al. Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial Lancet 2007; 370: 580-9.

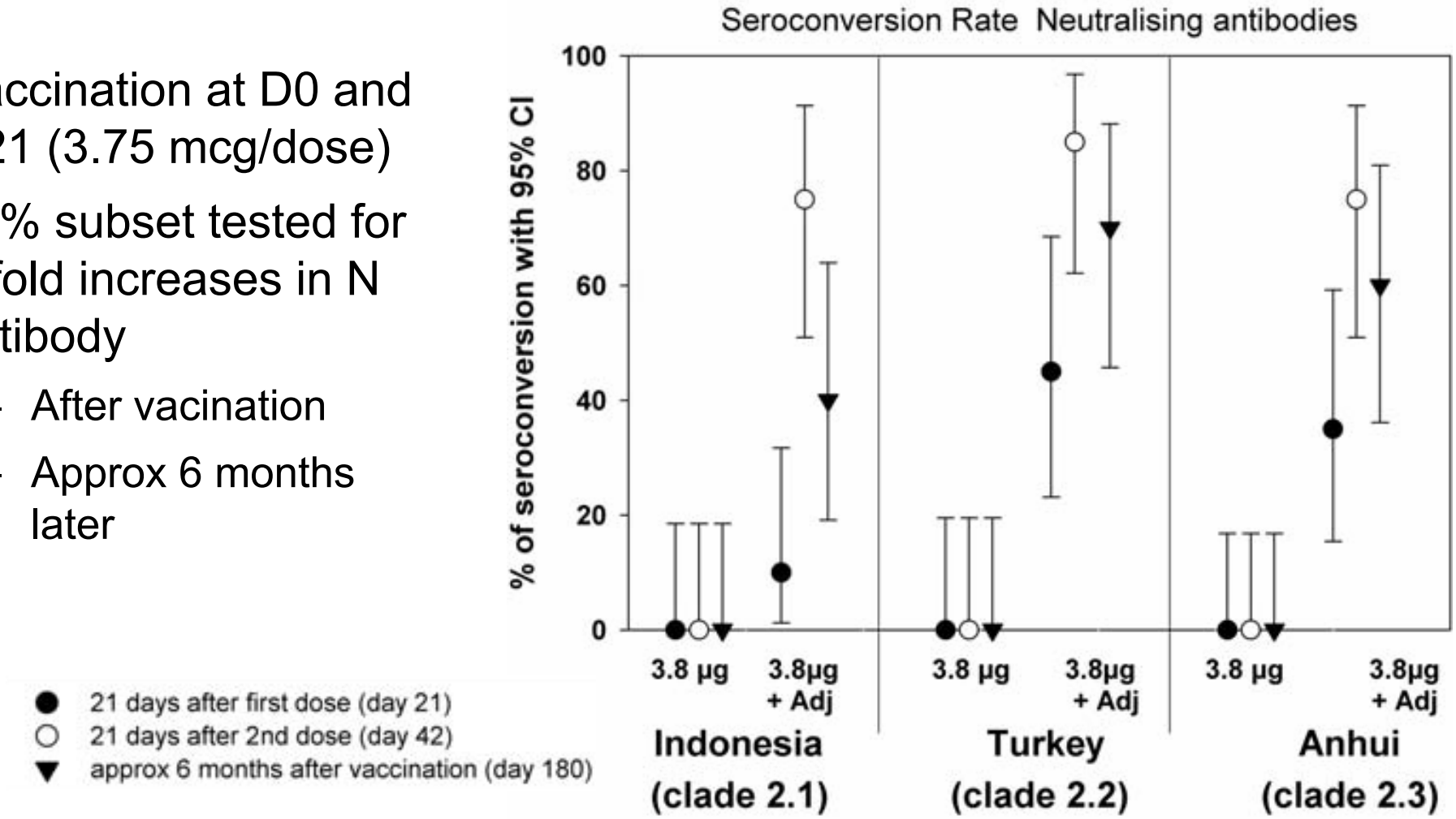
Adjuvanted H5N1 Vaccine Elicits HI Antibodies ≥1:40 in Most Recipients at a Dose of 3.75 µg



Leroux et al. Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial Lancet 2007; 370: 580-9.

Adjuvanted H5N1 Vaccine Elicits Cross-Reactive Immunity

- Vaccination at D0 and D21 (3.75 mcg/dose)
- 40% subset tested for 4-fold increases in N antibody
  - After vacination
  - Approx 6 months later



Leroux-Roels et al. Broad Clade 2 Cross-Reactive Immunity Induced by an Adjuvanted Clade 1 rH5N1 Pandemic Influenza Vaccine. PlosOne, 2008. 27;3(2):e1665.

Adjuvanted H5N1/Vietnam Vaccine Prevents Lethal H5N1/Indonesia Infection

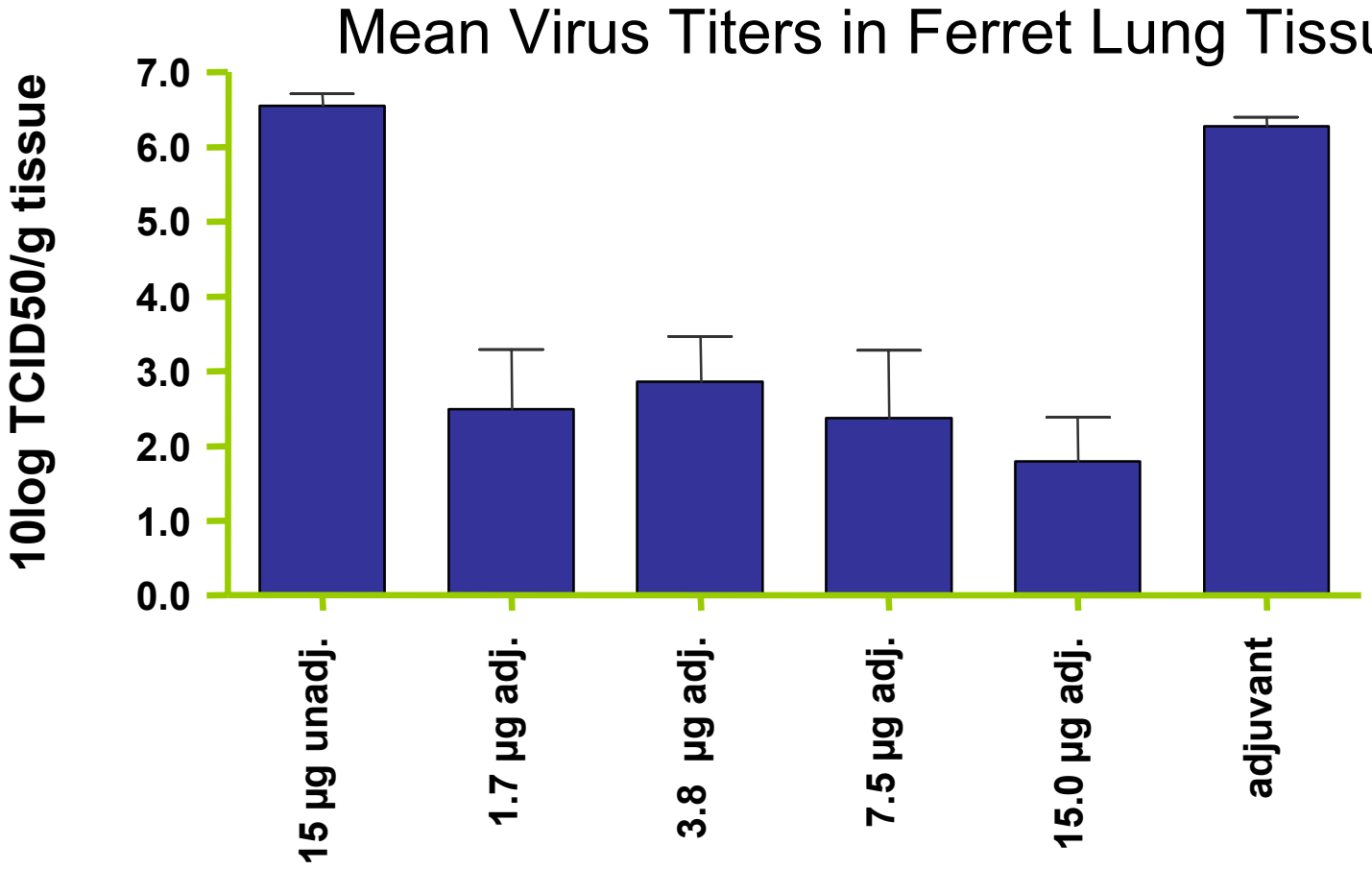
- Vaccination of **ferrets** at D0 and D21 (A/Vietnam, clade 1 vaccine)
- Heterologous challenge at D49 (A/Indonesia, clade 2 @ 10^5 $TCID_{50}$)
- Post challenge results at D5

	Dead	Alive	% survival	N ab ≥1:28
Pooled controls (15µg Antigen only or AS only)	12	0	**0**	**0/12**
1.7 µg H5N1 – AS	1	5	**83**	**4/6**
3.8 µg H5N1 – AS	0	6	**100**	**4/6**
7.5 µg H5N1 – AS	0	5	**100**	**3/5**
15 µg H5N1 – AS	0	6	**100**	**3/6**

Barras et al. Cross-Protection against Lethal H5N1 Challenge in Ferrets with an Adjuvanted Pandemic Influenza Vaccine. PLoS ONE. 2008 Jan 2;3(1):e1401

Adjuvanted H5N1 Vaccine Reduces Viral Load & Shedding – Heterologous Challenge

Vaccinated with Vietnam strain (Clade 1), challenged with Indonesia strain (Clade 2)

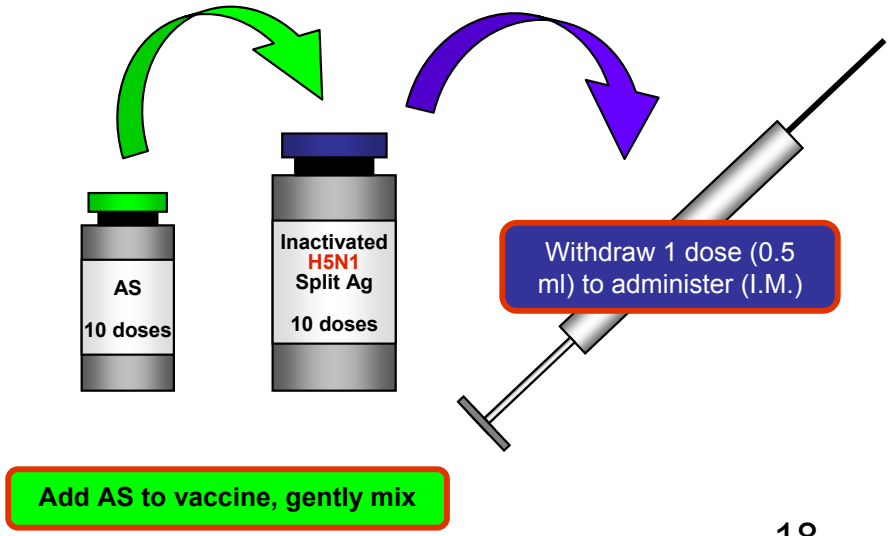


- All animals in control groups shed virus
- Only 30% animals in groups receiving AS-H5N1 shed virus

Barras et al. Cross-Protection against Lethal H5N1 Challenge in Ferrets with an Adjuvanted Pandemic Influenza Vaccine. PLoS ONE. 2008 Jan 2;3(1):e1401

GSK's Pre-Pandemic H5N1 Vaccine

- Split inactivated / AS vaccine
- Vaccine strain provided by NIBSC or other WHO reference laboratory, corresponding to WHO recommendations (A/ Vietnam/1194/2004 ⇨ A/Indonesia/5/2005)
- 3.75µg HA per dose
- Multidose vials (10 doses + preservative Thiomersal)
- Manufactured in Germany & Canada

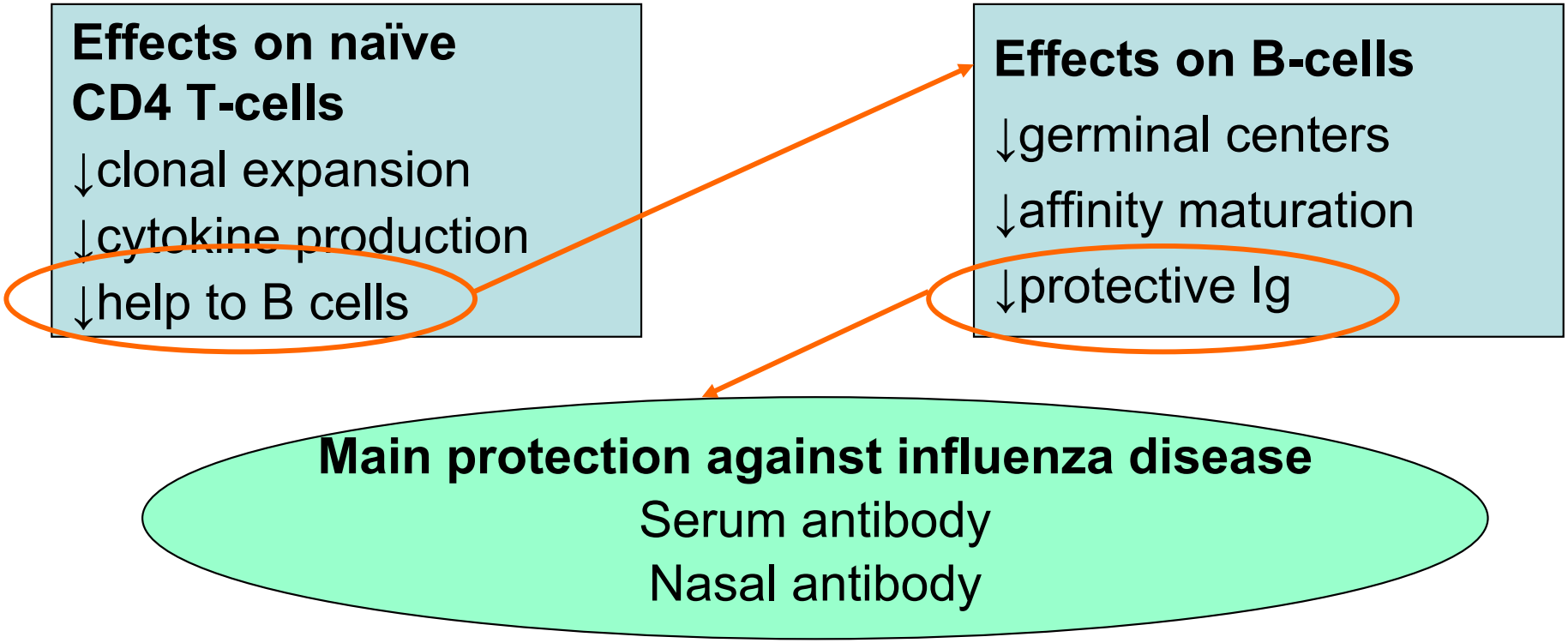


Vaccination against Seasonal Influenza (for adults age 65+)

Hypothesis to explain why 90% of influenza deaths are in adults age 65+ (despite vaccination)

Immunosenescence – w/ aging, gradual reduction immunity:

- Capacity to respond to infections
- Development of memory after vaccination



Haynes, Eaton. The effect of age on the cognate function of CD4+ T cells. Immuno Rev 2005; 205:220-28.

GSK2186877A, Candidate Seasonal Influenza Vaccine for Older Adults

Options to improve influenza vaccination:

- Change route of delivery
- Increase antigen in vaccine
- Use adjuvant

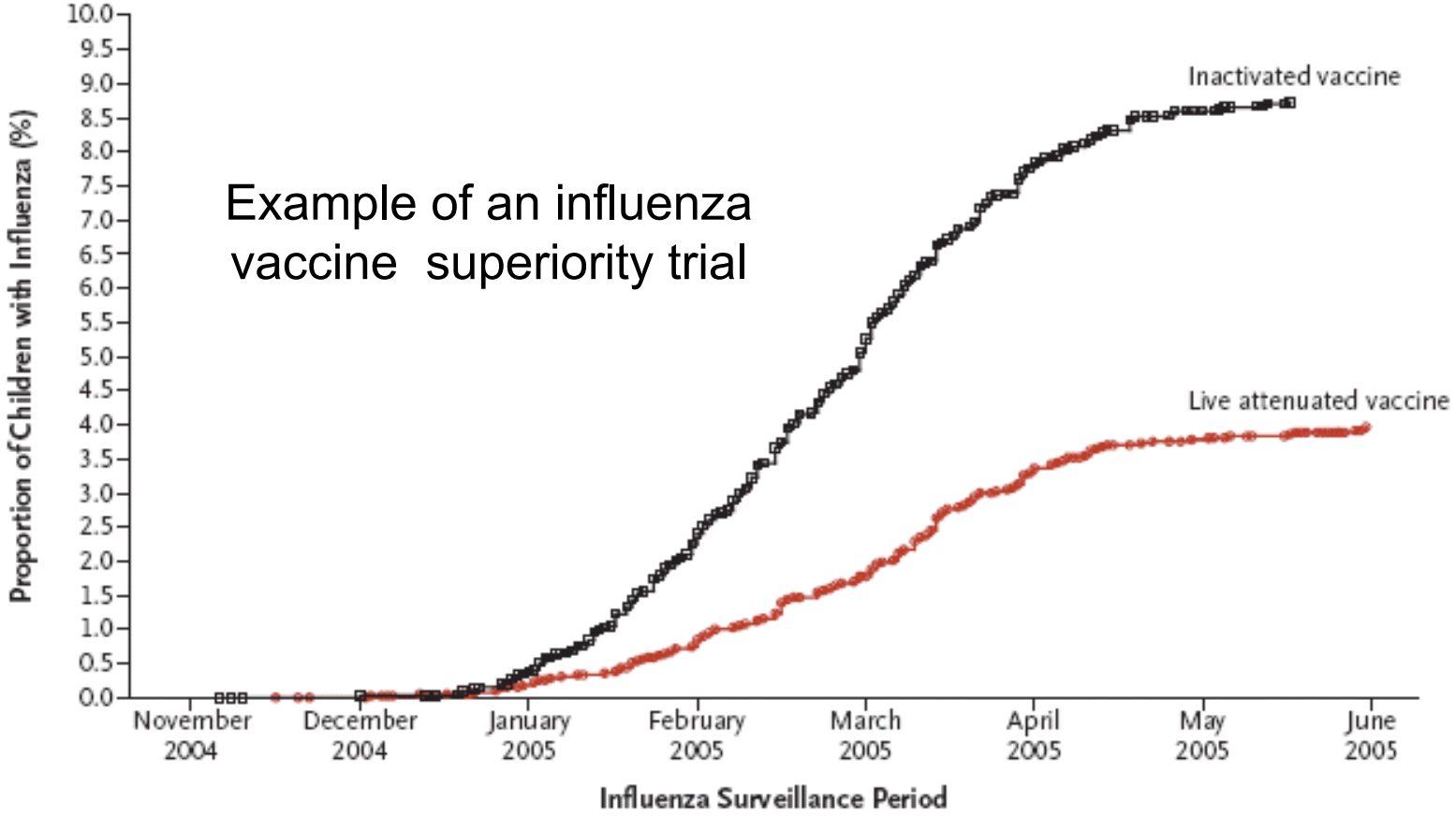
Select adjuvant based on capacity to:

- ↑ HI antibodies…..
- ↑ CD4+ T-cells…..
- …..to levels seen in adults 18 to 40 years of age

- Ag (3 strains in TIV) + adjuvant emulsion in pre-filled syringe
- Phase II trials in adults age 65+ showed candidate vaccine to be:
  - Well tolerated
  - More immunogenic than licensed inactivated flu vaccine

A better vaccine for older adults should deliver superior protection

(correlation of HI antibody responses with protection in older adults is uncertain)



55% reduction in AR of influenza during 2004-5 season w/ live vaccine: 8,352 children (age 6 to 59 months) randomized 1:1 vs TIV

Belshe et al. Live attenuated versus inactivated influenza vaccine in infants and young children. NEJM 2007; 356:686-96

Observer-blind superior efficacy trial with GSK2186877A in older adults

Enrolling now in 15 countries

- Randomized, blinded
  - GSK2186877A (TIV + adjuvant)
  - Fluarix (standard TIV)
- N=43,614 adults age 65+
- N Am, EU, Asia
- 2 seasons

- Main outcome measures:
  - RT-PCR confirmed influenza A or B disease
  - HI ab in a subset

Other outcome measures
- Culture confirmed disease
- Pneumonia, clinical influenza, congestive heart failure
- All-cause death
- Hospitalization
- Safety: numerous endpoints

Results available in 2010

NCT00753272
ClinicalTrials.gov

Recap: 2 Novel Vaccines Based on GSK's Emulsion Adjuvant System

Pre-Pandemic H5N1 Vaccine

- **Need:** stockpiling for vaccination before a pandemic
- **Design:** Induce lasting cross-reactive antibody and cell-mediated immunity against drifted H5N1 strains
- **Planned availability:** 2009 (EU 2008)

Seasonal Vaccine for Older Adults

- **Need:** reverse immuno-senescence, restore vaccine responses
- **Design:** Induce lasting cross-reactive antibody and cell-mediated immunity against (+/- drifted) seasonal strains
- **Planned availability:** 2011

Story Line

- Flu – a leading PH threat
  - Seasonal disease, disability and death of older adults
  - Pandemic disease, affects all
- Vaccination – most important control measure
- Two problems w/ current vaccines:
  - Limited protection of older adults
  - Inadequate for a pandemic
    - Production takes too long
    - Poorly immunogenic against current H5N1threat
- GSK has used an oil in water adjuvant system to deal with both problems