



# ***The GSK Adjuvant Experience***

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**Oral presentation  
New Cells for New Vaccines IV  
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# Presentation outline

- **Introduction**
- **Rationale for adjuvant selection**
- **Safety methodology for adjuvanted vaccines**
- **Pandemic influenza vaccine: The H5N1 case study for AS03-adjuvanted pandemic influenza vaccines**
- **Conclusions**

# Introduction

- Vaccines have made a tremendous impact on public health
- Challenges remain in addressing unmet needs
  - Population-specific
  - Disease-specific
- Immunological discoveries have led to further understanding of vaccine design
  - Increasing knowledge of the immune system
  - Pathogenesis of disease
  - Innovative technology
- A more tailored vaccine design can be achieved to formulate safe and effective vaccines with the appropriate selection of:
  - Antigens
  - Adjuvants and Adjuvant Systems
- A systematic approach to matching the right antigens and the right adjuvants can effectively tailor the immune response and achieve enhanced and sustained protection

**Why do we need adjuvants?**

# Infectious diseases require new strategies for the development of efficacious vaccines

## Linked to the target pathogen

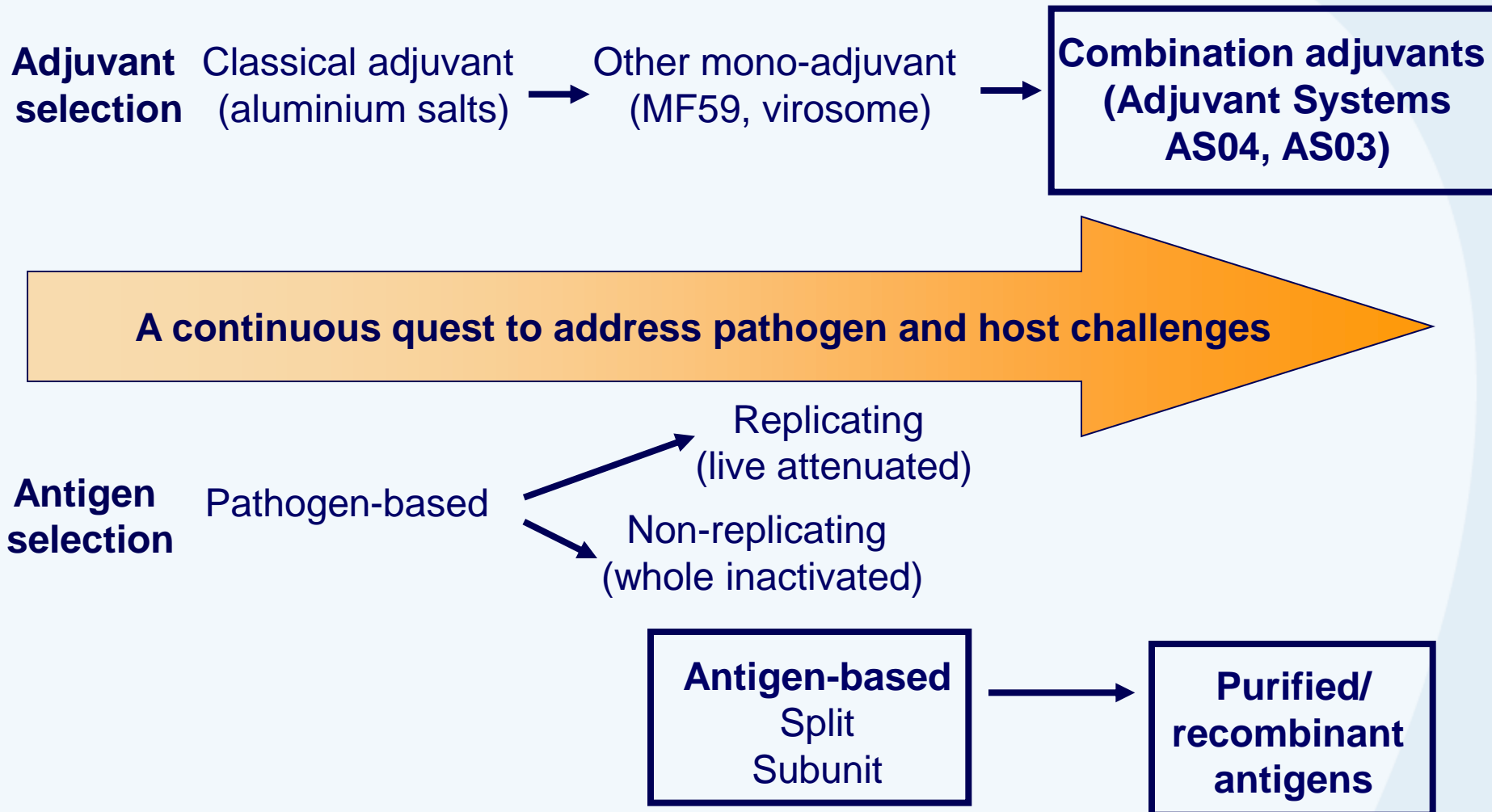
- **Highly variable and complex pathogens that have developed subtle mechanisms to evade or subvert immune defenses**
  - HCV, HIV, TB
- **Eukaryotic pathogens requiring complex, multistage immune responses**
  - Malaria
- **Pathogens where multiple strains or different subtypes occur**
  - Influenza, HPV
- **Pathogens inducing latency or localized to the infection site**
  - VZV, HSV, HPV
- **Pathogens rapidly appearing and infecting millions of people**
  - Pandemic influenza

# Unmet needs in immunization

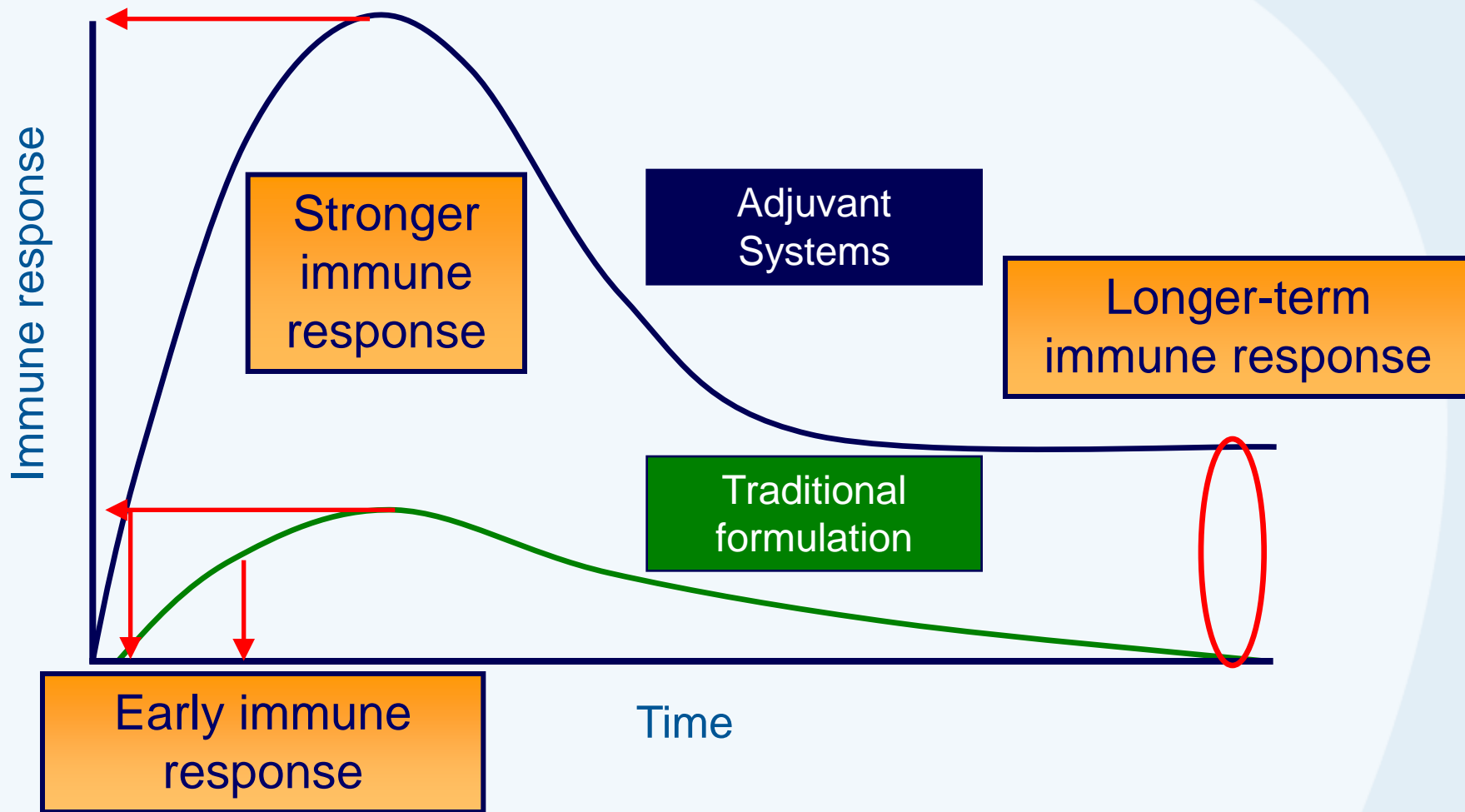
## Challenging Populations:

- **Adaptation to poorly responsive populations**
  - Naïve children (and adults)
  - The immunocompromised
  - The chronically ill
  - Adults >65 years of age or immunosenescent

# Vaccine development over time: towards a more tailored design

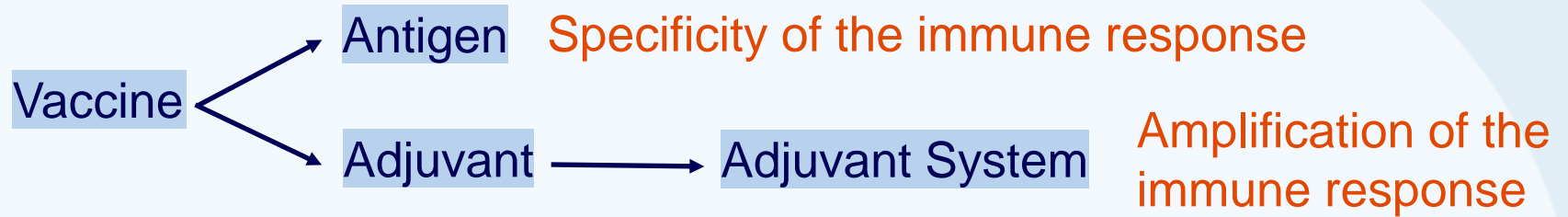


# Expected advantages of vaccines formulated with Adjuvant Systems over traditional formulations



# **Rationale for adjuvant selection**

# Adjuvant selection methodology



Example of Adjuvant System (AS) and its use in vaccines

| Adjuvant System | AS Composition                          |                      | Vaccine                           |
|-----------------|---|----------------------|-----------------------------------|
|                 | Adjuvants                               |                      |                                   |
| AS03            | Proprietary oil-in-water (o/w) emulsion | $\alpha$ -tocopherol | H5N1 pandemic influenza candidate |

*Goal is to select the antigen/adjuvant systems which induce a tailored immune response, delivering enhanced and sustained protection*

# **Safety methodology for adjuvanted vaccines**

# Safety development plan of adjuvanted Vaccines

- Follows the same general path as classical vaccines
- Preclinical safety assessment and the targeted population support and direct the clinical safety evaluation plan

Additionally.....

- Clinical program methodology standardized to allow for comparison and pooling of data
- Enhanced case reporting throughout entire study period for potentially immune-mediated diseases
- Testing of routine clinical safety labs in early (ph I&II) studies

# Model timing for safety evaluation

## IND-enabling phase, GLP for safety studies

Mechanism of action  
Local Tolerance  
Single Dose toxicity  
Repeated Dose Toxicity  
Safety Pharmacology (cardiovascular & respiratory)  
Genetic toxicology (adjuvants)

**Pre-Phase 1**

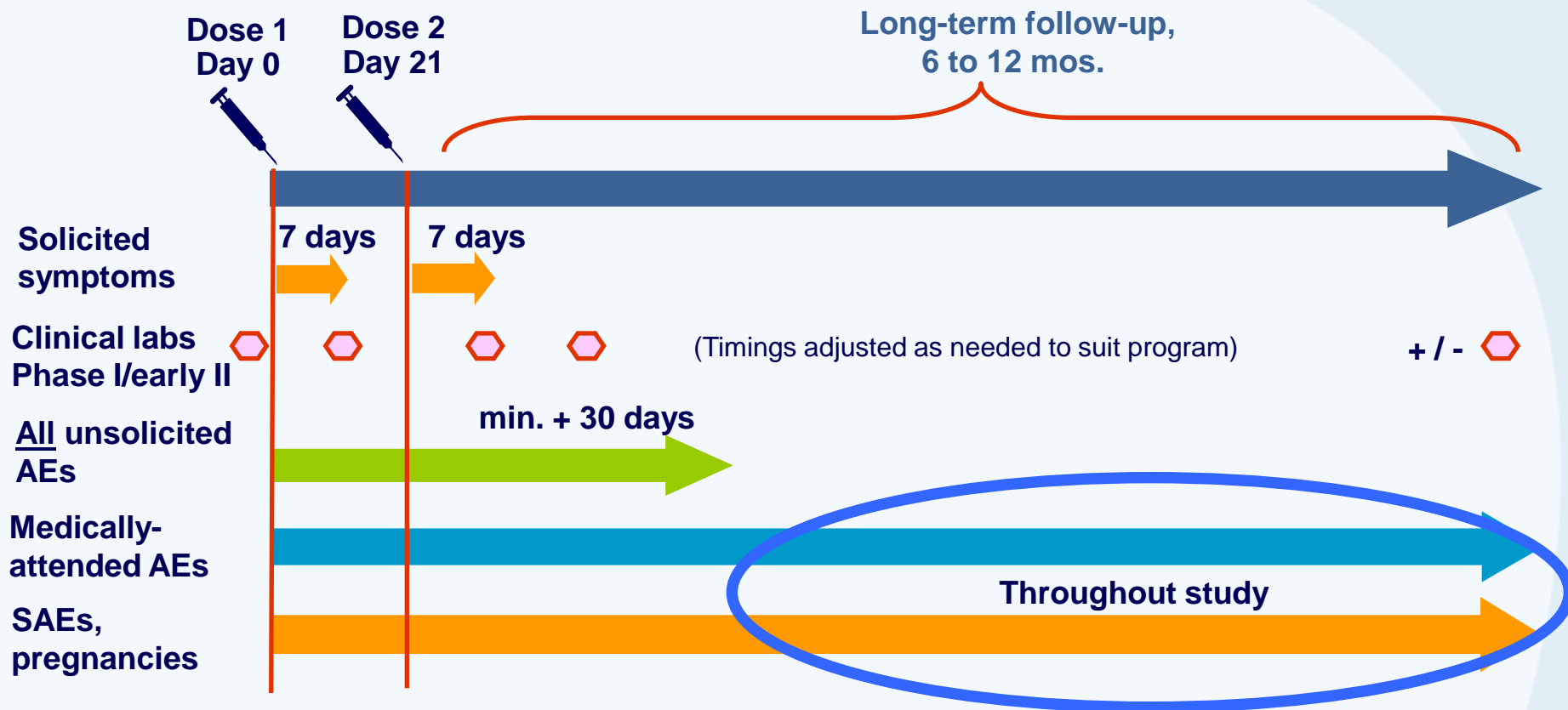
## In-Clinic phase, GLP for safety studies

Reproductive Toxicity studies  
Continued mechanism of action Studies

**Phase 1-3  
(PI-PIII)**

**Phase 4  
Post licensure  
Active follow-up**

# Reporting of Adverse Events PI-PIII clinical program



a) Medically-attended adverse events (MAEs) = any AE resulting in an unscheduled interaction with a healthcare provider.

b) Investigators invited to report SAEs they assess as related to test article indefinitely.

**Pandemic influenza vaccine:  
The H5N1 case study for AS03-  
adjuvanted pandemic influenza vaccines**

# The GSK vision for vaccines to address pandemic influenza

Using a proprietary  $\alpha$ -tocopherol containing o/w emulsion based adjuvant system, we are developing pandemic candidate vaccines to have the following characteristics:

- Safe – acceptable safety and reactogenicity profile
- Immunogenic – exceeds FDA immunogenicity criteria
- Antigen-sparing – provides more doses by stretching the available influenza virus manufacturing capacity
- Broad immune response – if an exact strain match is not needed, vaccine can be made and stockpiled before an emergency

# GSK's pandemic vaccines

- GSK is utilizing the  $\alpha$ -tocopherol containing o/w emulsion based Adjuvant System, AS03, with pandemic antigens made using licensed processes
  - “**D-Pan**” H5N1 antigen is manufactured in Dresden, Germany (*Fluarix*<sup>™</sup> process)
    - Safety data in adults and children 3-9 years of age<sup>1,2,3,4</sup>
    - Registered as *Pandemrix*<sup>™</sup> and *Prepandrix*<sup>™</sup> in Europe in May 2008
  - “**Q-Pan**” H5N1 antigen is manufactured in Quebec Province (*FluLaval*<sup>™</sup> process)
    - Safety data in adults<sup>5</sup>
    - Shown to be immunogenically equivalent to D-Pan when H5N1 antigen is mixed with AS03

Fluarix, Pandemrix, Prepandrix and FluLaval are a trademark of the GlaxoSmithKline Group of companies. FluLaval may be sold under different names elsewhere in the world e. g. Fluviral or Griplaval

<sup>1</sup>Rümke H et al. *Vaccine*. 2008;26:2378 <sup>2</sup>Leroux-Roels I et al. *Lancet*. 2007;370:580 <sup>3</sup>Moris P et al. *ISRV*. 2009 <sup>4</sup>Schwarz TF et al. *Vaccine*. 2009;doi:10.1016 <sup>5</sup>Langley L. et al. *ESWI* 2008, Villamoura, Portugal.

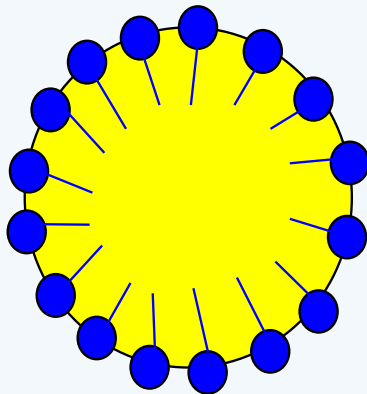
# The AS03 Adjuvant System is a tocopherol based o/w emulsion

## AS03 Adjuvant System

Squalene

DL- $\alpha$ -tocopherol

Polysorbate 80 (Tween 80)



Surfactant (Polysorbate 80)



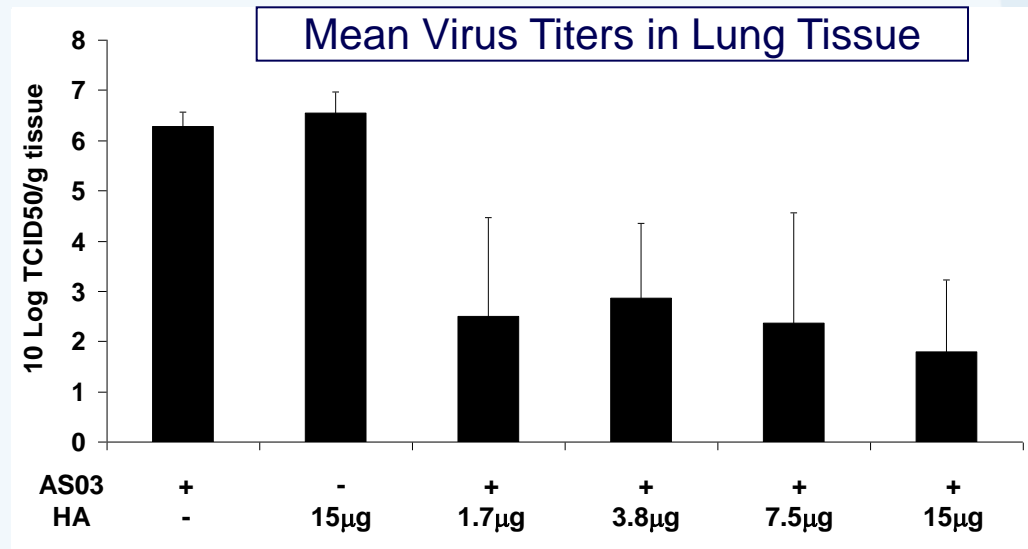
Oil (squalene and DL- $\alpha$ -tocopherol)

# H5N1/AS03 protects ferrets against heterologous intra-tracheal challenge

- Immunizations at D0 and D21 with inactivated split A/Vietnam/1194/04 (H5N1, NIBRG-14, clade 1), vaccine with or without AS03
- Challenge at D49 (wild-type virus A/Indonesia/5/05, clade 2,  $10^5$  TCID<sub>50</sub>)
- Results 5 days after challenge

| Vaccine  |      | Alive | Survival (%) |
|----------|------|-------|--------------|
| HA* (μg) | AS03 |       |              |
| 15       | -    | 0/6   | 0            |
| -        | +    | 0/6   | 0            |
| 1.7      | +    | 5/6   | 83           |
| 3.8      | +    | 6/6   | 100          |
| 7.5      | +    | 5/5   | 100          |
| 15       | +    | 6/6   | 100          |

\* HA: haemagglutinin



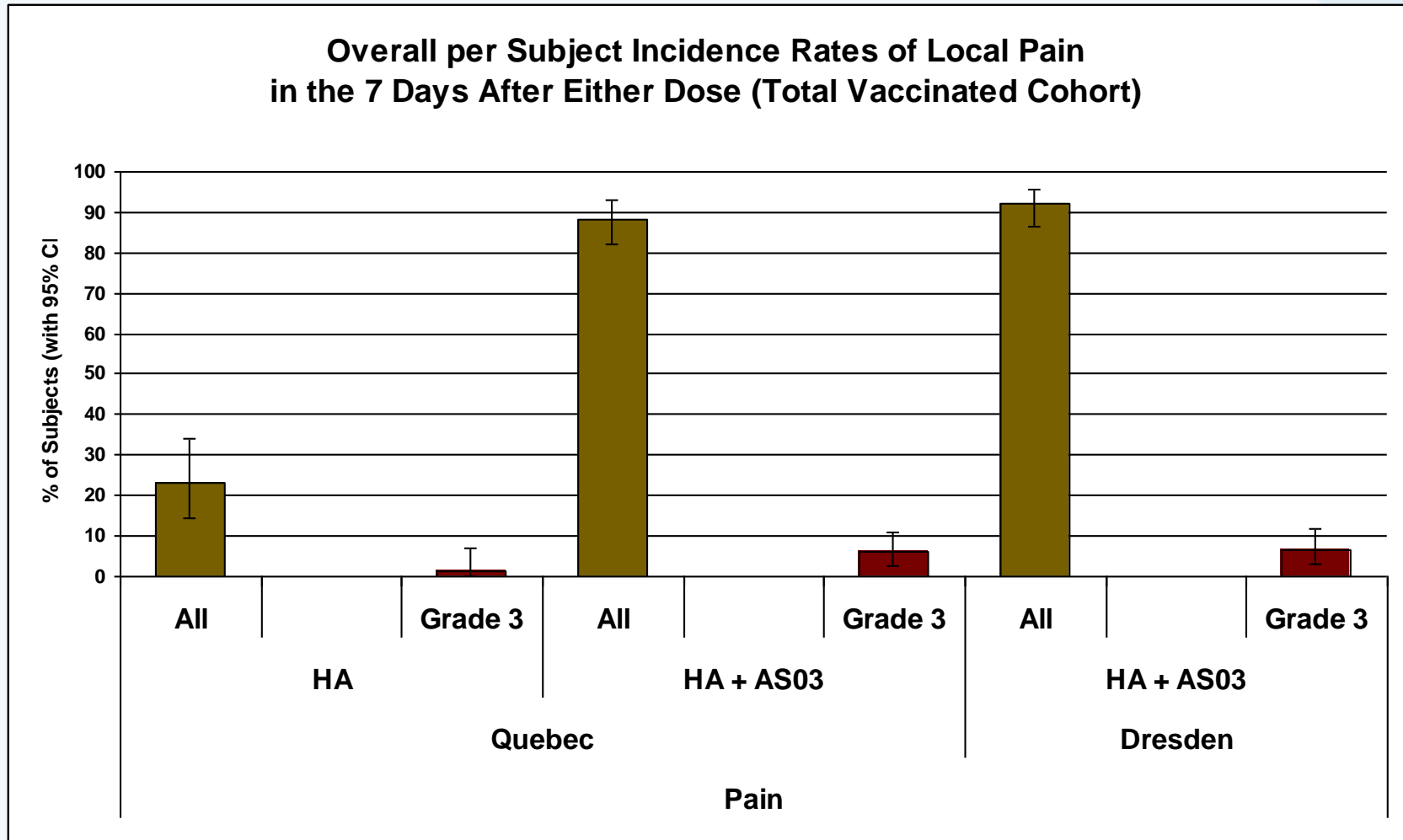
# **Phase II study in adults comparing 2 series of H5N1 vaccine antigen**

# Phase II study in adults with 2 series of H5N1 vaccine antigen

- Study NCT00510874
- 680 adults (18-64 years)
- Dosing on study days 0 and 21
- 3.75µg of hemagglutinin (HA) with or without AS03
  - A/Indonesia/5/05 (clade 2.1)
  - D-Pan and Q-Pan H5N1 antigens
- Primary endpoint = Day 42 homologous HI antibody response (or titers)

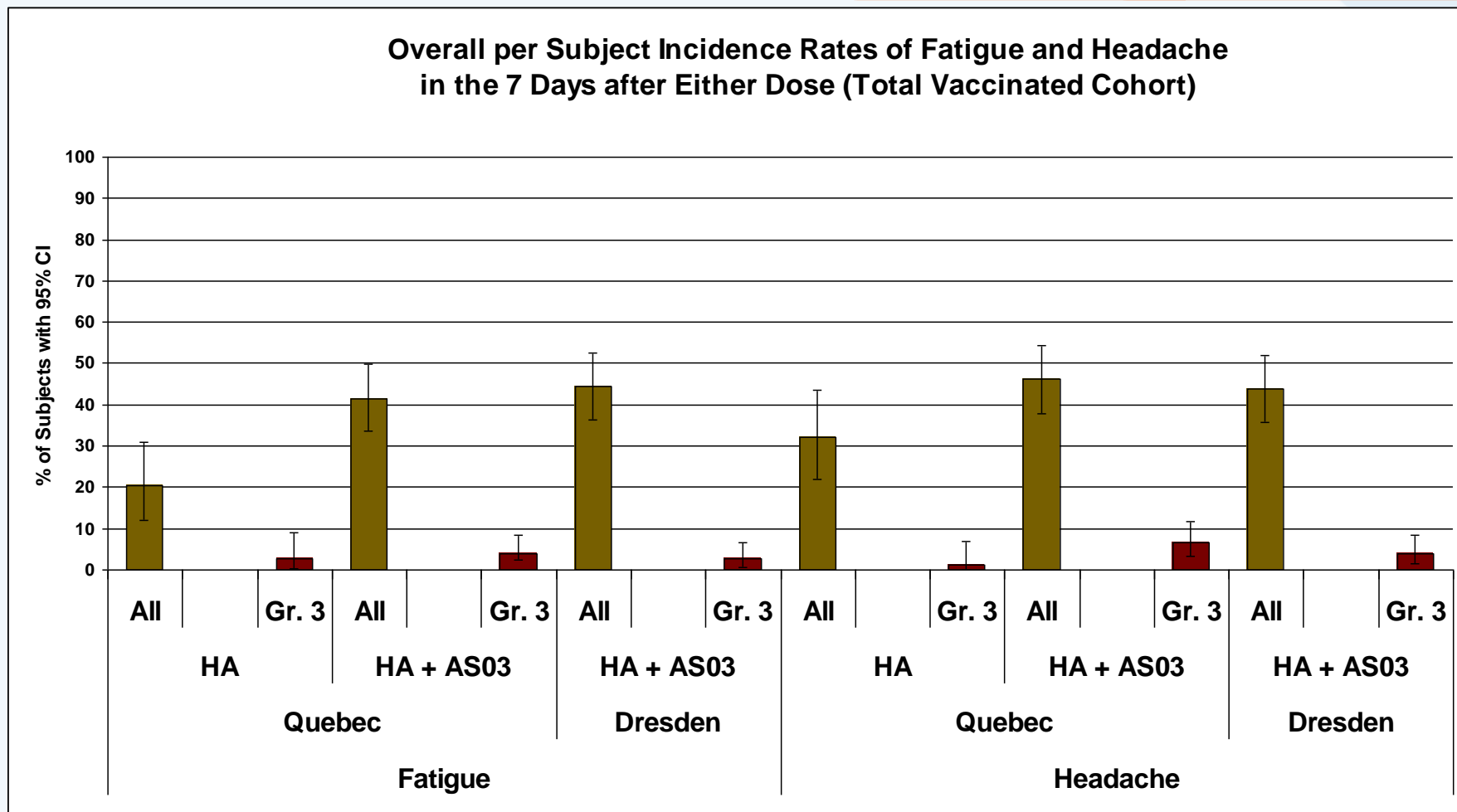
# Acceptable reactogenicity profile

## Local injection site pain



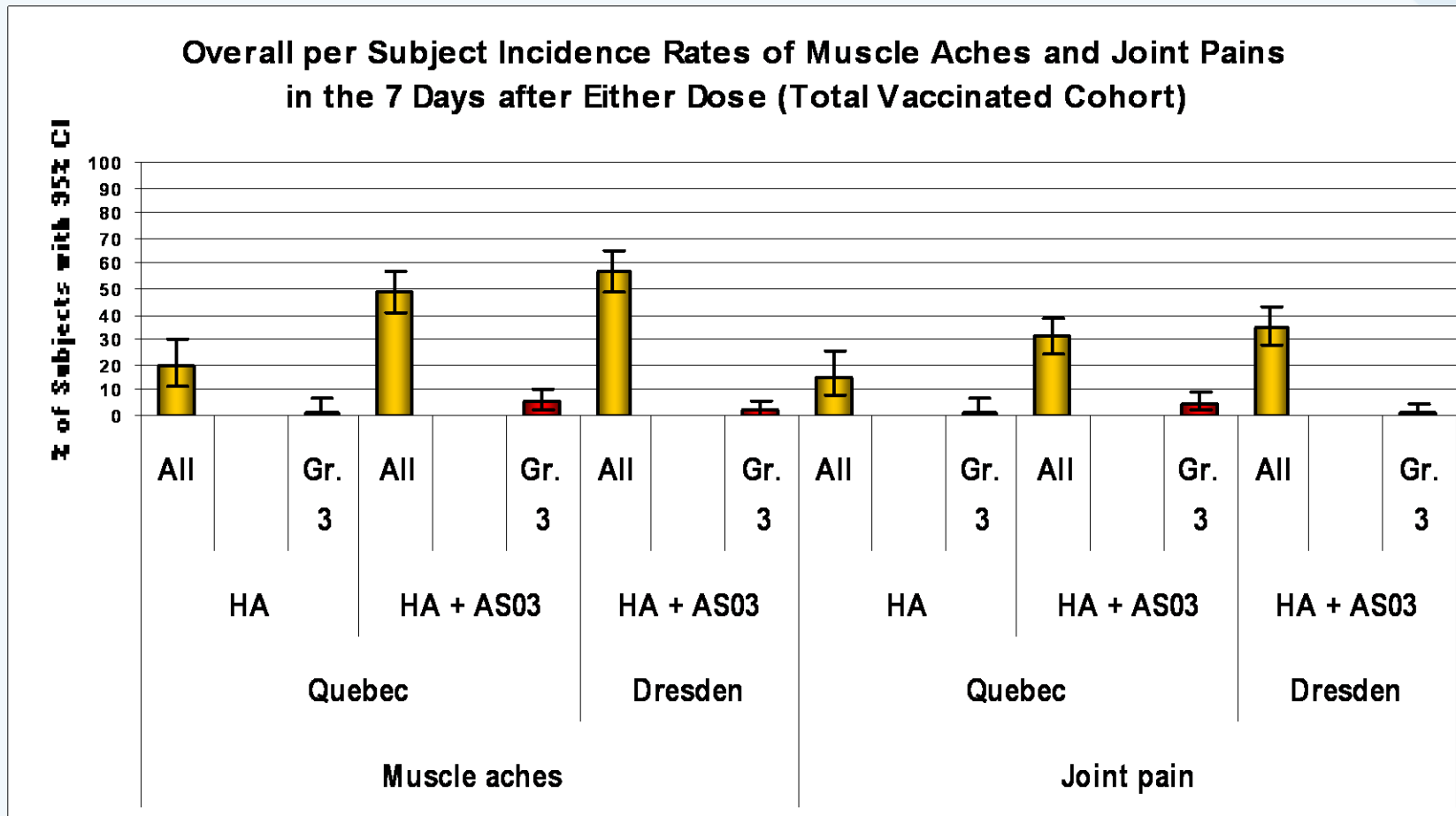
# Acceptable reactogenicity profile

## General solicited symptoms

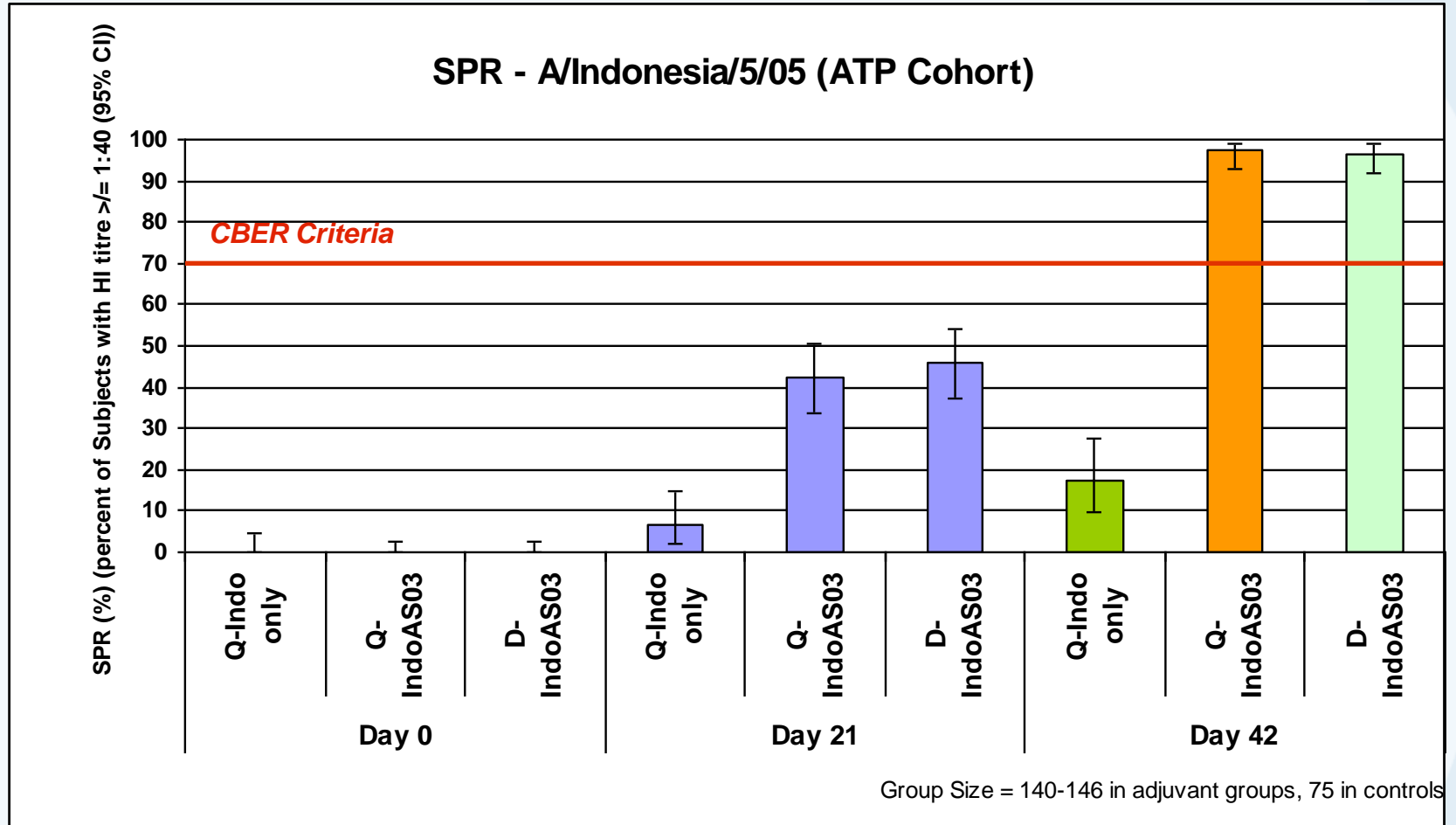


# Acceptable reactogenicity profile

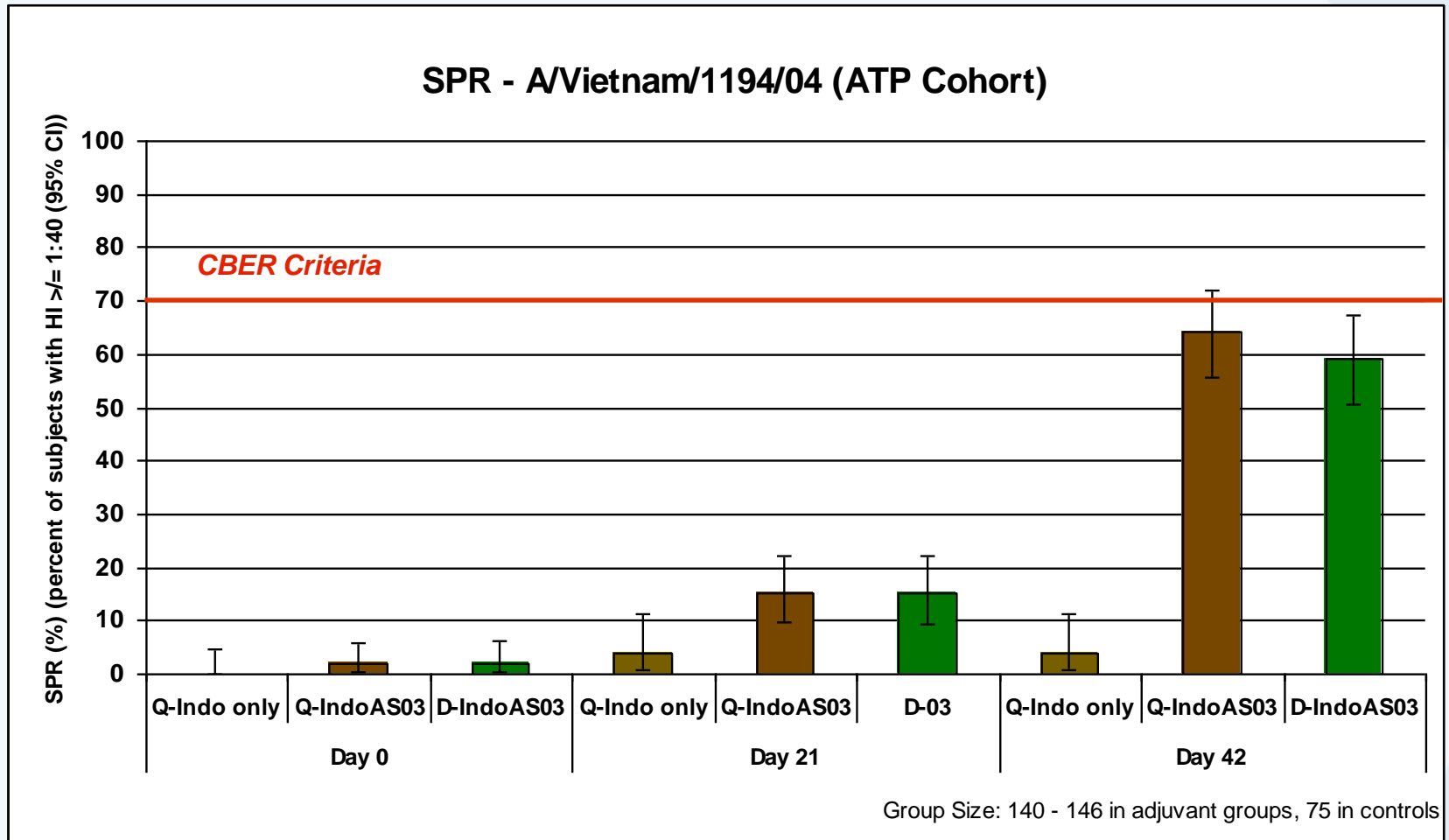
## General solicited symptoms



# Seroprotection rate (SPR) with ATP cohort



# Broad cross-clade immunogenicity against drifted variants



# Pandemic vaccine conclusion

- The AS03-adjuvanted H5N1 pandemic influenza vaccine has shown that the formulation of the antigen with the appropriate adjuvant system is able to fulfill the needs of a pandemic vaccine
- EU has approved the AS03-adjuvanted pandemic vaccines for H5N1 and H1N1

# **Conclusions: Adjuvant Experience**

# Conclusions

## Key concepts

- Novel Adjuvant Systems offer new strategies to protect against infectious diseases
- New adjuvants need to induce a response:
  - Tailored to the pathogens or pathogenesis of disease
  - Tailored to the target populations
- More than one adjuvant can be combined in Adjuvant Systems to obtain the desired immune response
- Only the right match of selected antigens and adjuvants can induce effective immune responses to enable enhanced and sustained protection

**‘One size does not fit all’**

# Acknowledgements

## GSK Biologicals:

All those involved in many departments including Research, Development, Manufacturing, Regulatory and Clinical.

## Collaborators:

All those who have supported our work in the many fields critical for the development of a vaccine including investigators, volunteers and health care personnel.