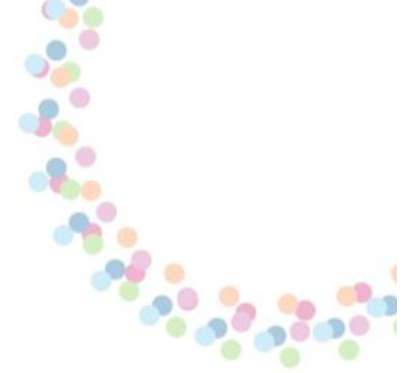




Experience with GSK's H5N1 and H1N1 Influenza Vaccine

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MBBS, M Med (Public Health), Dip (Fam Med)
Head of Medical Affairs,
Elderly Franchise & Influenza Portfolio
GSK Biologicals, Asia Pacific*



Outline

- Overview of clinical/preclinical data of GSK's AS03_A-adjuvanted H5N1 vaccine
- Flexible prime-boost vaccination strategy using GSK's AS03_A-adjuvanted H5N1 vaccine
- Safety
- Real life demonstration of high vaccine effectiveness of GSK's AS03_A-adjuvanted pandemic H1N1 influenza in all age groups – Canada and Germany

GSK's AS03_A-Adjuvanted H5N1 Influenza Vaccine Has Received Market Authorisation

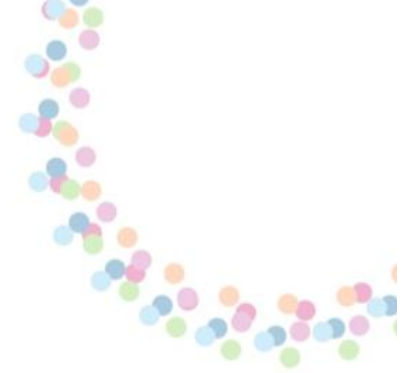


- Europe
- Switzerland
- Norway
- Iceland
- Singapore
- Hong Kong
- Malaysia
- South Korea

Therapeutic indications

- Active immunization against H5N1 subtype of influenza A virus
- Indication is based on immunogenicity data from healthy subjects aged 18–60 years following administration of two doses of vaccine prepared from A/Indonesia/05/2005 PR8-IBCDC-RG2 (H5N1)
- GSK's AS03_A-adjuvanted H5N1 influenza vaccine should be used in accordance with official guidance

The AS03 Adjuvant System is Designed to Produce a Highly Targeted Immune Response

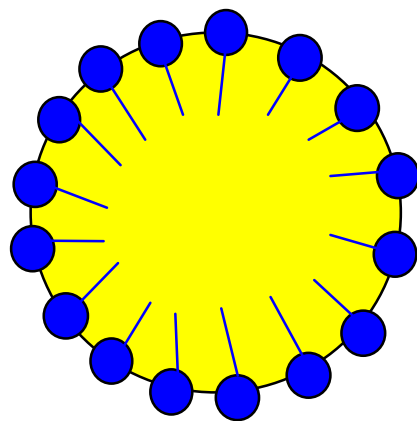
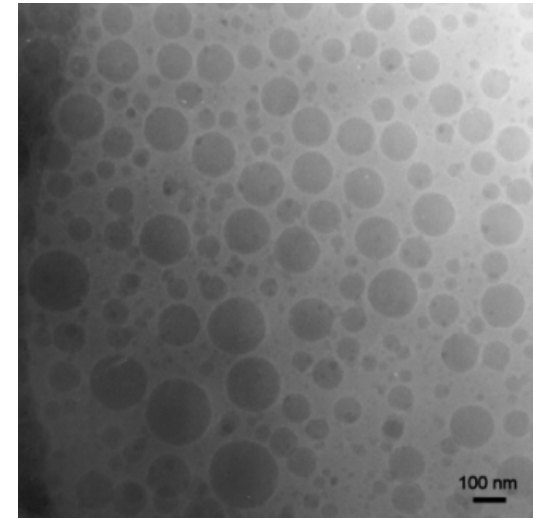


The AS03 Adjuvant System is a vitamin E-based, oil-in-water emulsion

DL- α -tocopherol

Squalene

Polysorbate 80 (Tween™ 80)




Surfactant (Polysorbate 80)



Oil (squalene and DL- α -tocopherol)

GSK's AS03_A-Adjuvanted H5N1 Influenza Vaccine Displays Several of the Essential Characteristics for a Prepandemic Influenza Vaccine



<i>Essential characteristics</i>	<i>Available data for GSK's AS03_A-adjuvanted H5N1 influenza vaccine</i>
Be available before the onset of a pandemic and produced and stockpiled in advance	- GSK's AS03 _A -adjuvanted H5N1 influenza vaccine is available and is licensed in several countries
Have a favourable safety profile	- Rumke et al. Vaccine 2008 - Chu et al. Vaccine 2009 - Diez-Domingo et al. Ped Inf Dis J 2010
Immunogenic at low antigen content, 3.75 µg in adults (1.9 µg in children)	- Leroux-Roels et al. Lancet 2007 - Baras et al. PlosOne 2008 - Diez-Domingo et al. Ped Inf Dis J 2010
Induce a broad, cross-clade immune response (human and ferrets) and protection (ferrets) against drifted strains	- Leroux-Roels et al. Lancet 2007 - Leroux-Roels et al. PlosOne 2008 - Baras et al. PlosOne 2008
Persistence of immune response	- Leroux-Roels et al. PlosOne 2008
Be produced on a large scale	- Chu et al. Vaccine 2009
Have flexibility of the interval between doses	- Leroux-Roels et al. Vaccine 2010

Outline

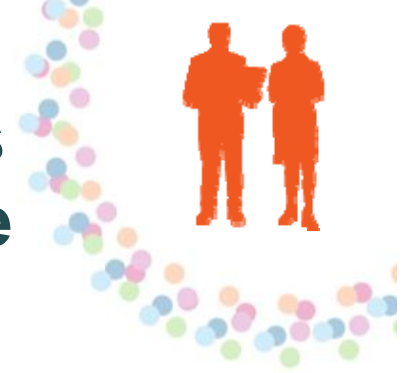


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**Immunogenicity
of GSK's AS03_A-
Adjuvanted H5N1
Influenza Vaccine
in the Adult
Population**

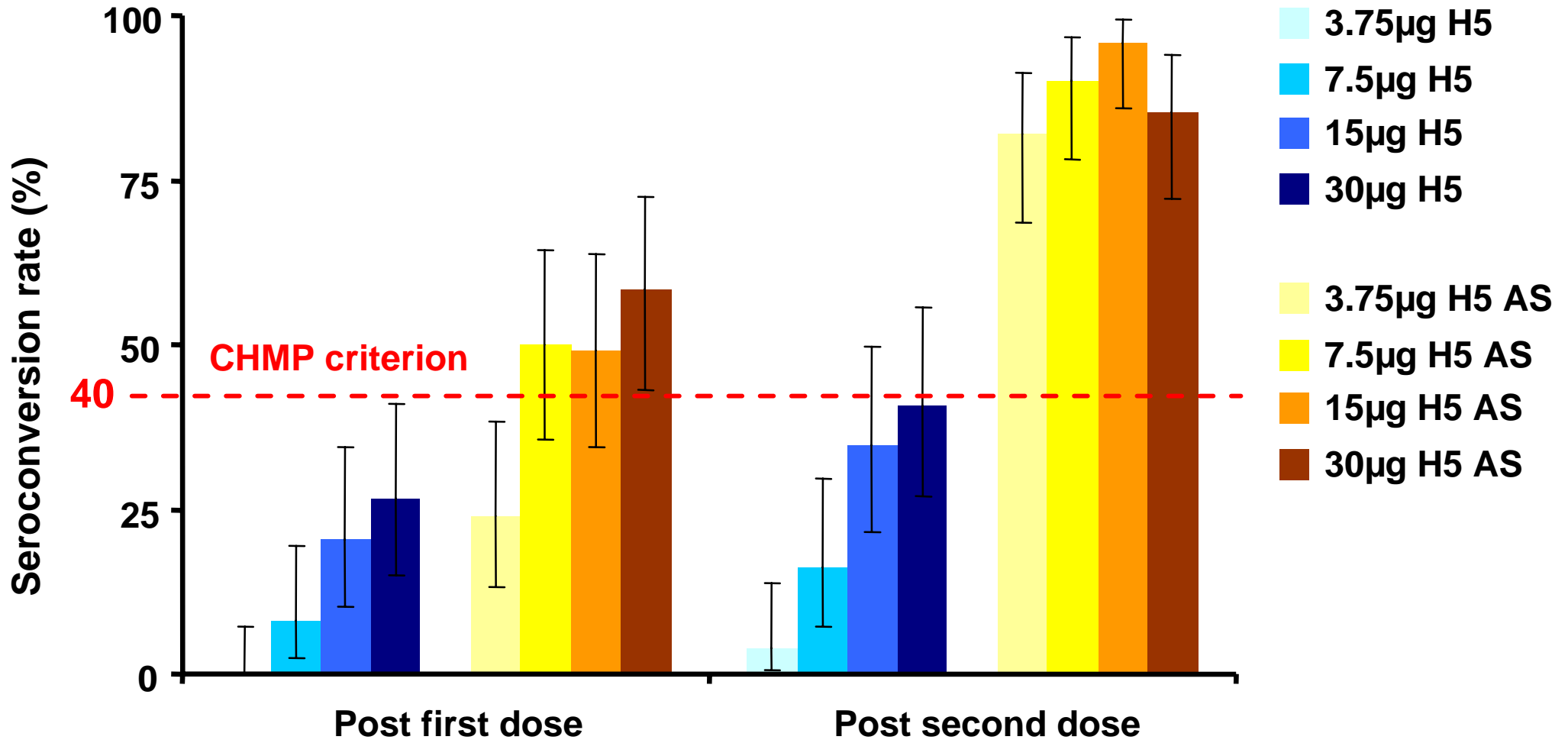


GSK's AS03_A-Adjuvanted H5N1 Influenza Vaccine Meets All Three CHMP Criteria in Adults at a Very Low Antigen Dose of 3.75 μ g Per Dose



HI Seroconversion rate

Two immunizations at day 0 and day 21 (H5N1 A/Vietnam/1194/04 split virus/AS03_A)



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.

Persistence of Cross-Reactive Neutralizing Antibodies Demonstrated

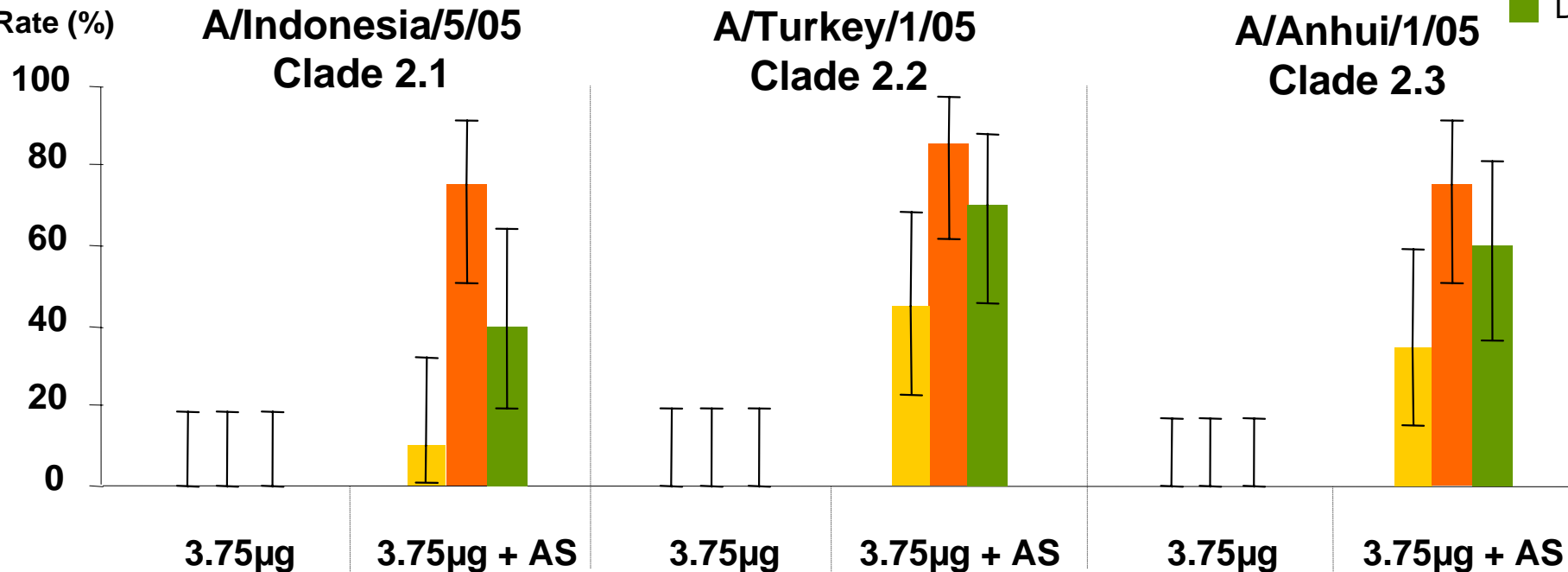


Vaccinated with 2 doses 3.75 μ g H5N1 A/Vietnam/1194/04 influenza vaccine

NT Seroconversion rate

Seroconversion
Rate (%)

Day 21
Day 42
Day 180



- Persistent cross-neutralizing antibodies with high seroconversion rate at month 6 (40% clade 2.1, 70% clade 2.2 and 60% clade 2.3).
- No cross-reactive neutralising antibodies seen with non-adjuvanted vaccine.

The Ferret Model



A surrogate for clinical testing with live potentially pandemic influenza virus:

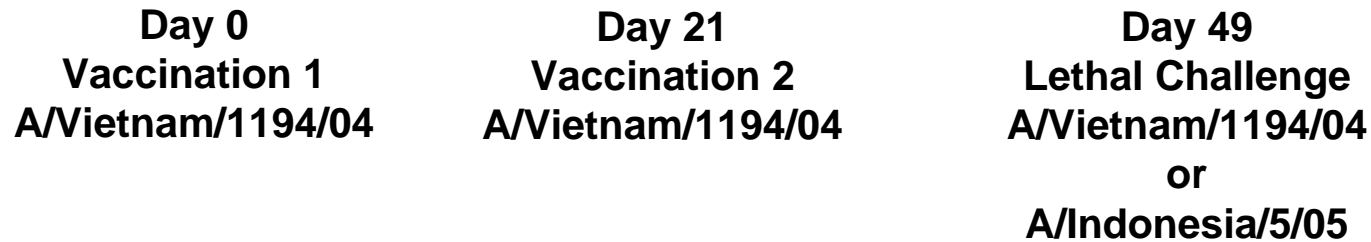
- Homologous challenge (A/Vietnam/1194/04)
- Heterologous challenge (A/Indonesia/5/05)



Survival against Lethal H5N1 Challenge in Animal (Ferret) Model



Study start



Group	Survival Homologous challenge ¹ (Wild-type virus A/Vietnam1194/04, 10 ⁵ pfu, TCID ₅₀)	Survival Heterologous challenge ² (Wild-type virus A/Indonesia/5/05, 10 ⁵ pfu, TCID ₅₀)
Controls*	1/11 (9%)	0/12(0%)
H5N1 Vaccine – AS	6/6 (100%) (5µg H5N1-AS03) 4/5 (80%) (1.7µg H5N1-AS03)	6/6 (100%) (3.75µg H5N1-AS03) 5/6 (83%) (1.7µg H5N1-AS03)

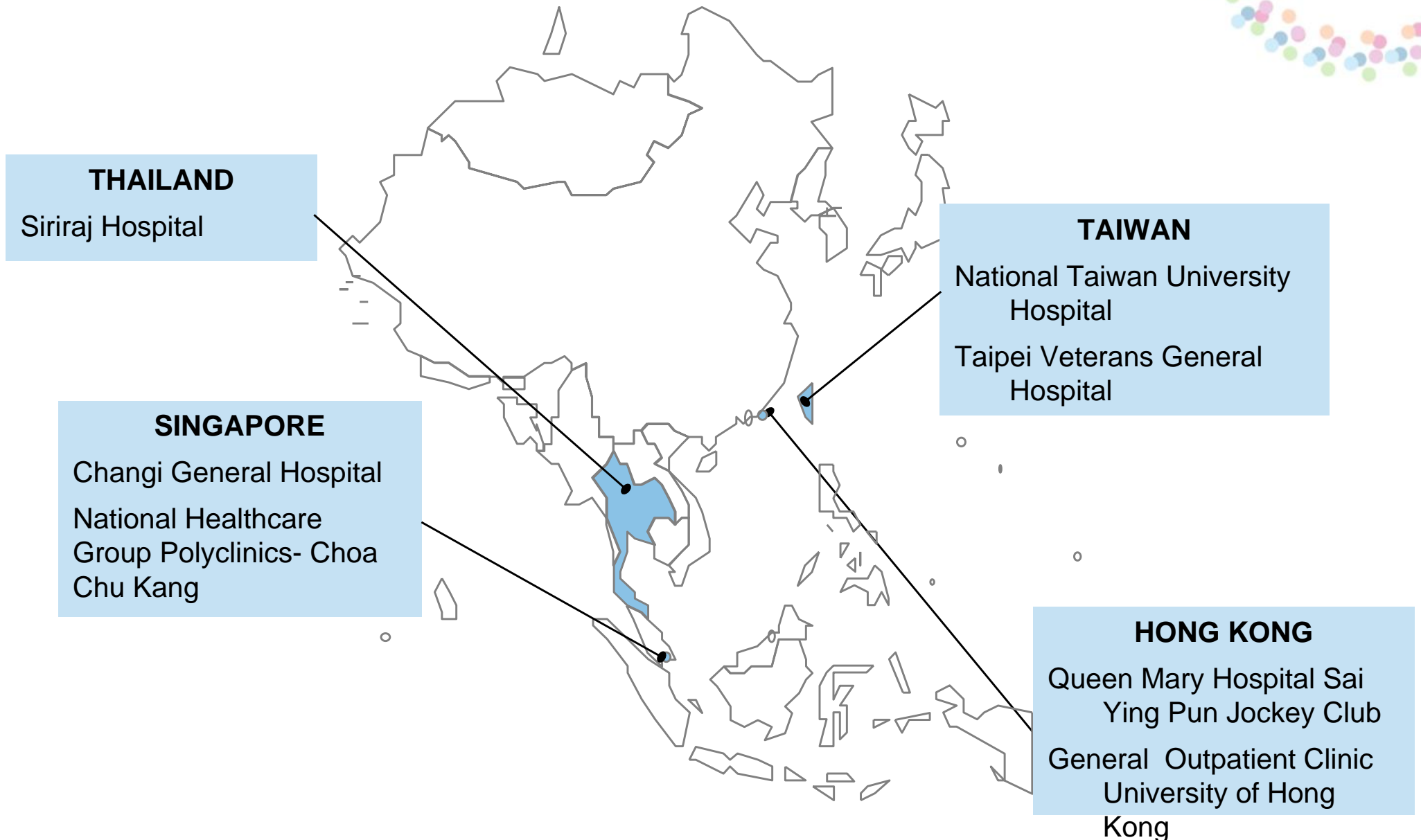
*Control in homologous study = saline OR adjuvant only
Control in heterologous study = antigen OR adjuvant only

1. Benoît Baras et al. Abstract for Options for the Control of Influenza VI June 17–23, 2007 - Toronto, Canada
2. Benoit Baras et al. Cross-protection against Lethal H5N1 Challenge in Ferrets with an Adjuvanted Pandemic Influenza Vaccine. PLOS one January 2008, Issue 1, e1401.

**Safety and
Immunogenicity
of GSK's AS03_A-
adjuvanted H5N1
Influenza Vaccine
in the Asian
Population**



Study Sites for Phase III Study in a Large Population of Asian Adults (H5N1-002)



Daniel Wai-Sing Chu et al. Immunogenicity and tolerability of an AS03A-adjuvanted prepandemic influenza vaccine: A Phase III study in a large population of Asian adults. Vaccine 27 (2009) 7428–7435

NCT 00449670

Study Design for Phase III Study in a Large Population of Asian Adults



Study population

- 1206 healthy adult volunteers; 18-60 years old (mean age: 33.6 yrs)

Objectives

- To evaluate the safety of the AS adjuvanted formulation containing 3.75 μg H5N1 haemagglutinin
- To evaluate the immune response against clade 1 and clade 2 strains

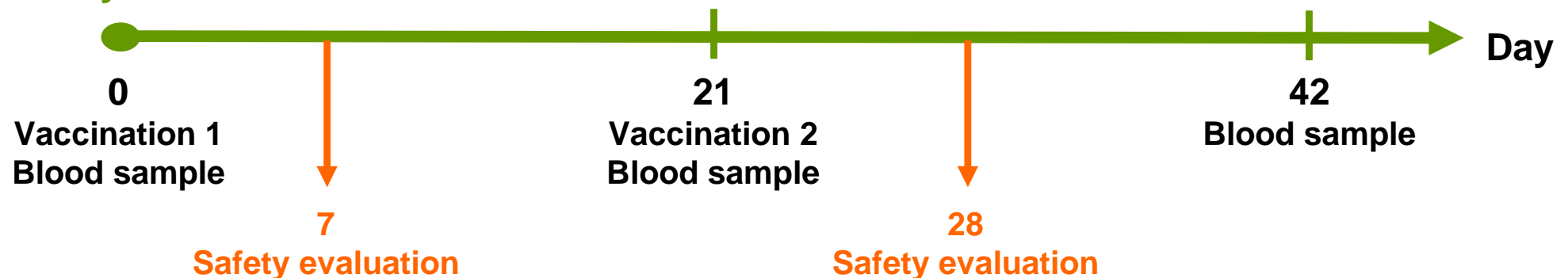
Vaccine composition

- split virion prepandemic influenza candidate vaccine (A/Vietnam/1194/04)

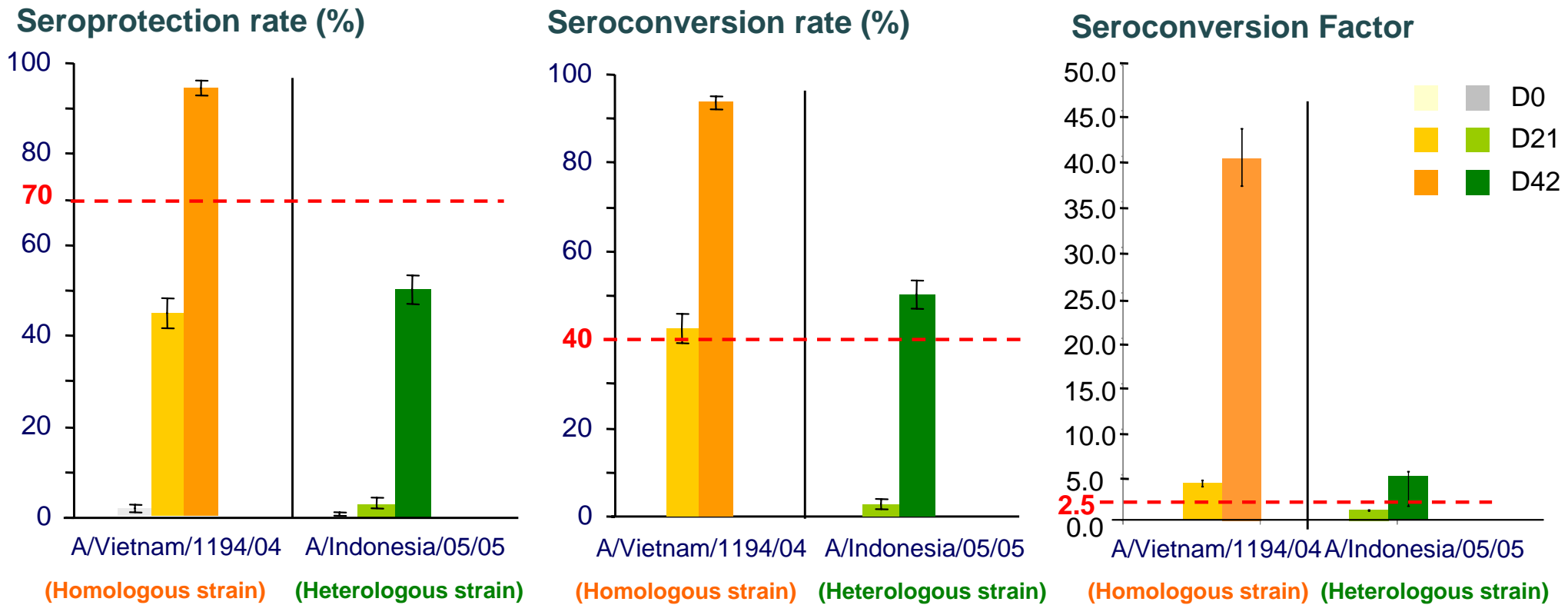
Study design

- 2 vaccine doses administered 21 days apart
- 3.75 μg H5N1 haemagglutinin with (N=961) or without (N=245) AS adjuvant system
- 2 lots of HA antigen & 2 lots of AS adjuvant system tested

Study start



Cross-Reactive Immunity of GSK's AS03_A-Adjuvanted H5N1 Vaccine in the Asian Population



1. Daniel Wai-Sing Chu et al. Immunogenicity and tolerability of an AS03A-adjuvanted prepandemic influenza vaccine: A Phase III study in a large population of Asian adults. *Vaccine* 27 (2009) 7428–7435

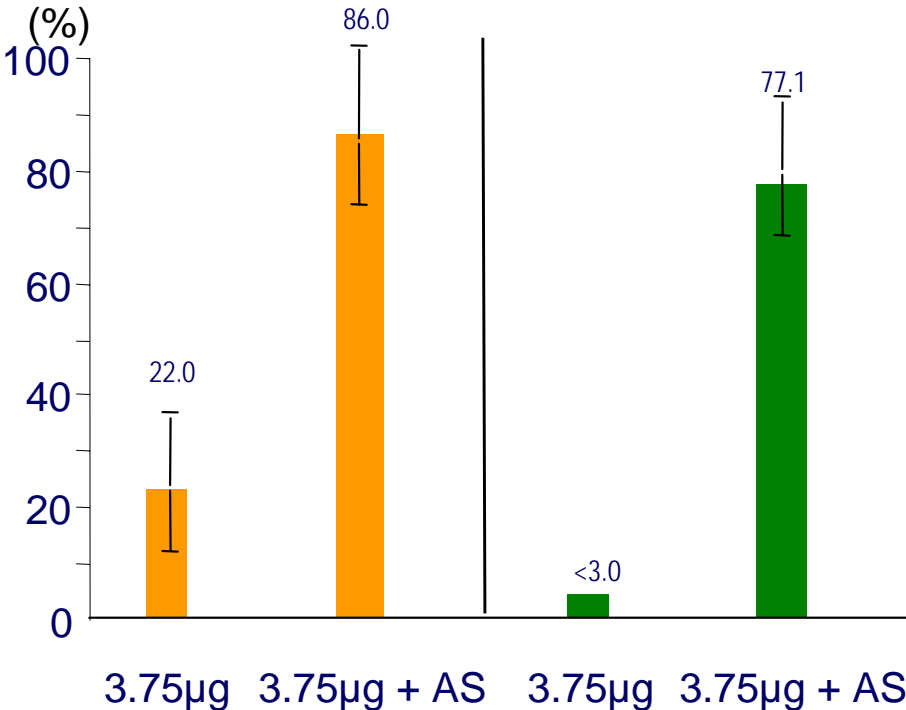


Neutralizing Antibody Seroconversion Rates in Europe and Asia–Day 42

Study H5N1-007 (Europe)^{1,2}

A/Vietnam/1194/04
(Homologous strain)

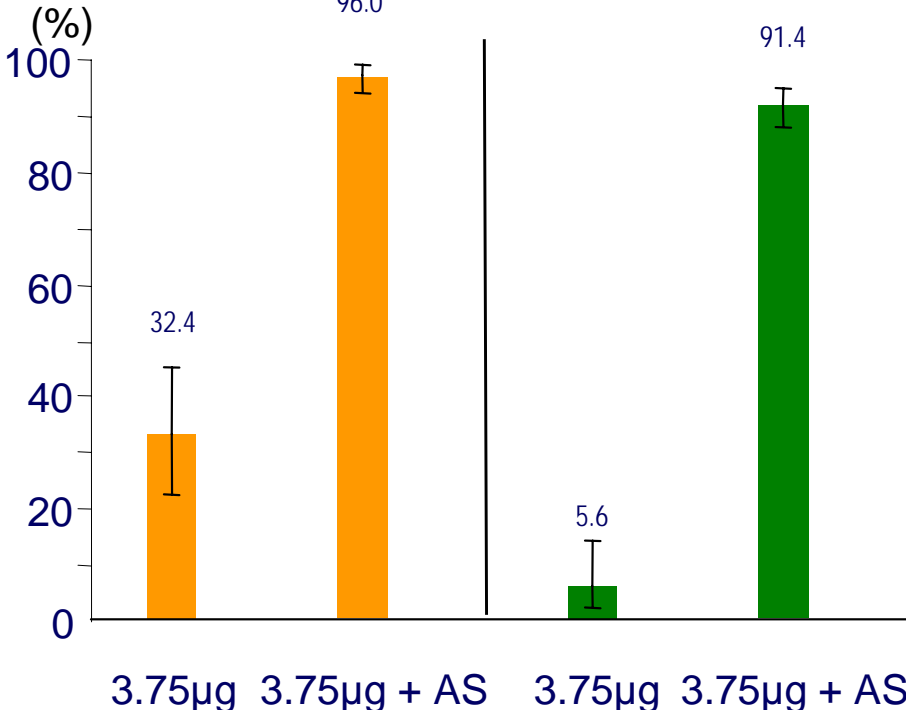
A/Indonesia/05/05
(Heterologous strain)



Study H5N1-002 (Asia)³

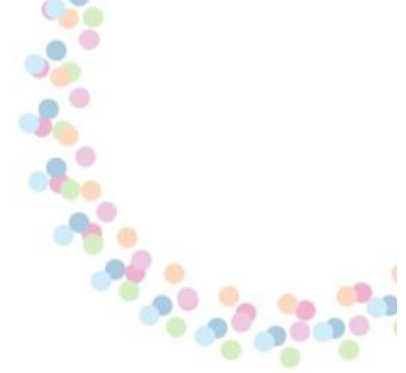
A/Vietnam/1194/04
(Homologous strain)

A/Indonesia/05/05
(Heterologous strain)



● A marked heterologous immune response was demonstrated for neutralising antibody

1. Leroux-Roels I, et al. PLoS ONE 2008;3(2):e1665. doi:10.1371/journal.pone.0001665
2. Leroux-Roels I et al, Lancet 2007;370:58
3. Daniel Wai-Sing Chu et al. Immunogenicity and tolerability of an AS03A-adjuvanted prepandemic influenza vaccine: A Phase III study in a large population of Asian adults. Vaccine 27 (2009) 7428–7435



Outline

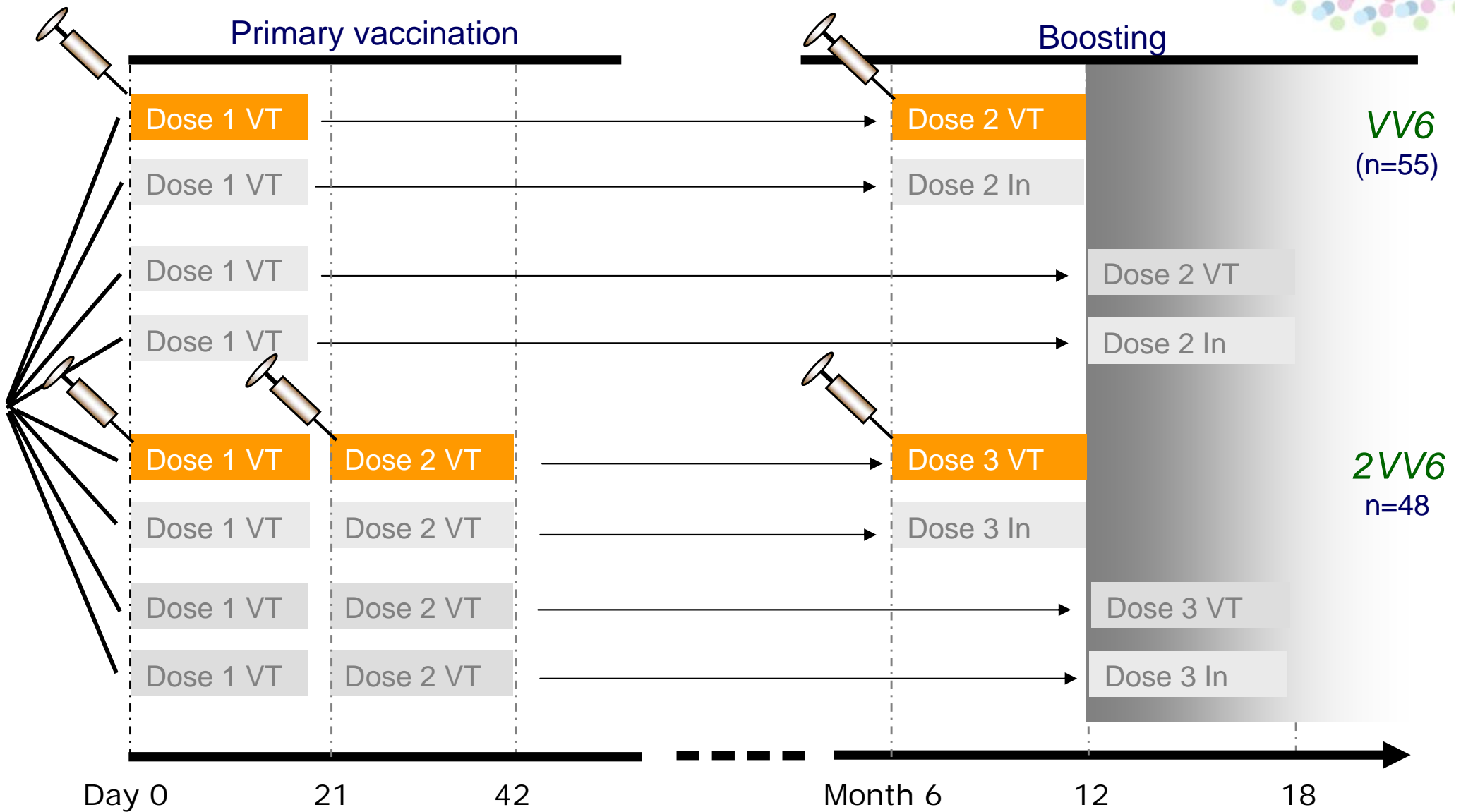
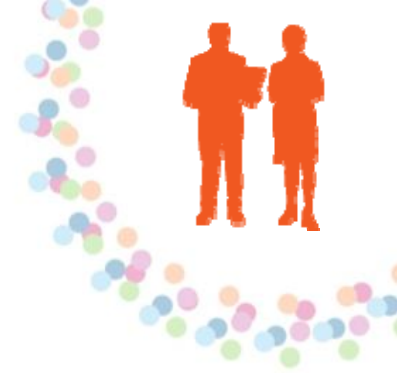
- Overview of clinical/preclinical data of GSK's AS03_A-adjuvanted H5N1 vaccine

- Flexible prime-boost vaccination strategy using GSK's AS03_A-adjuvanted H5N1 vaccine

- Safety

- Real life demonstration of high vaccine effectiveness of GSK's AS03_A-adjuvanted pandemic H1N1 influenza in all age groups – Canada and Germany

GSK's AS03_A-Adjuvanted H5N1 Vaccine Allows for a Highly Flexible Prime-Boost Vaccination Strategy (H5N1-012): Homologous Booster

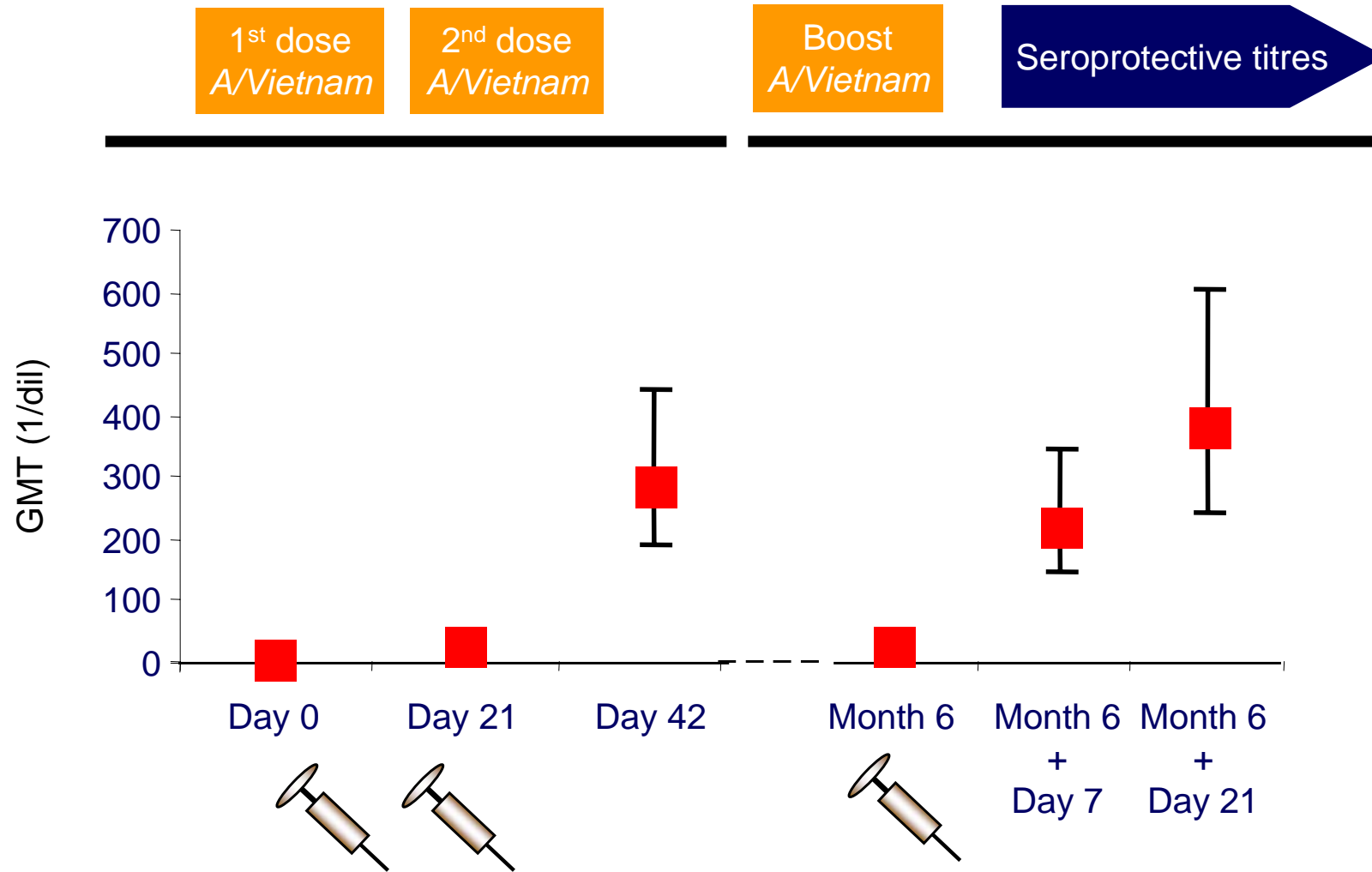


Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. Vaccine 2009; 27: 6284-6290.

GSK's AS03_A-Adjuvanted H5N1 Vaccine and the Highly Flexible Prime-Boost Vaccination Strategy



Results – GMTs against A/Vietnam

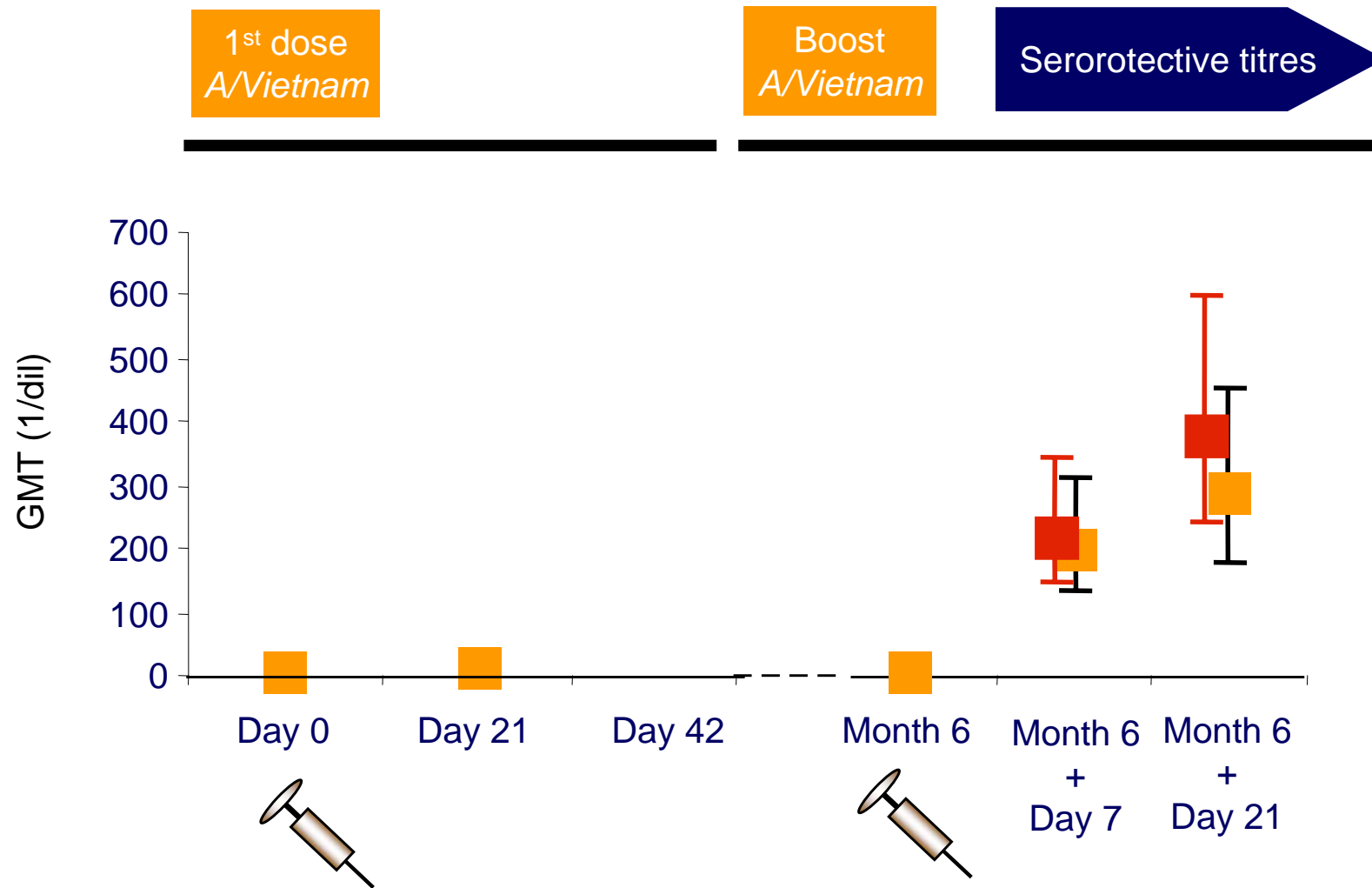


Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. Vaccine 2009; 27: 6284-6290.

GSK's AS03_A-Adjuvanted H5N1 Vaccine and the Highly Flexible Prime-Boost Vaccination Strategy

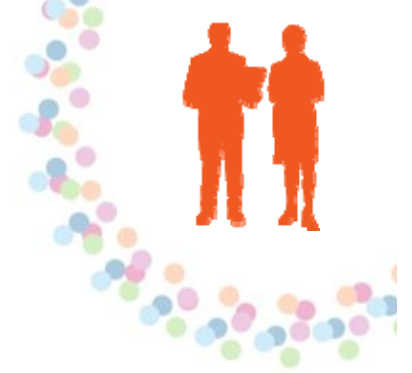


Results – GMTs against A/Vietnam



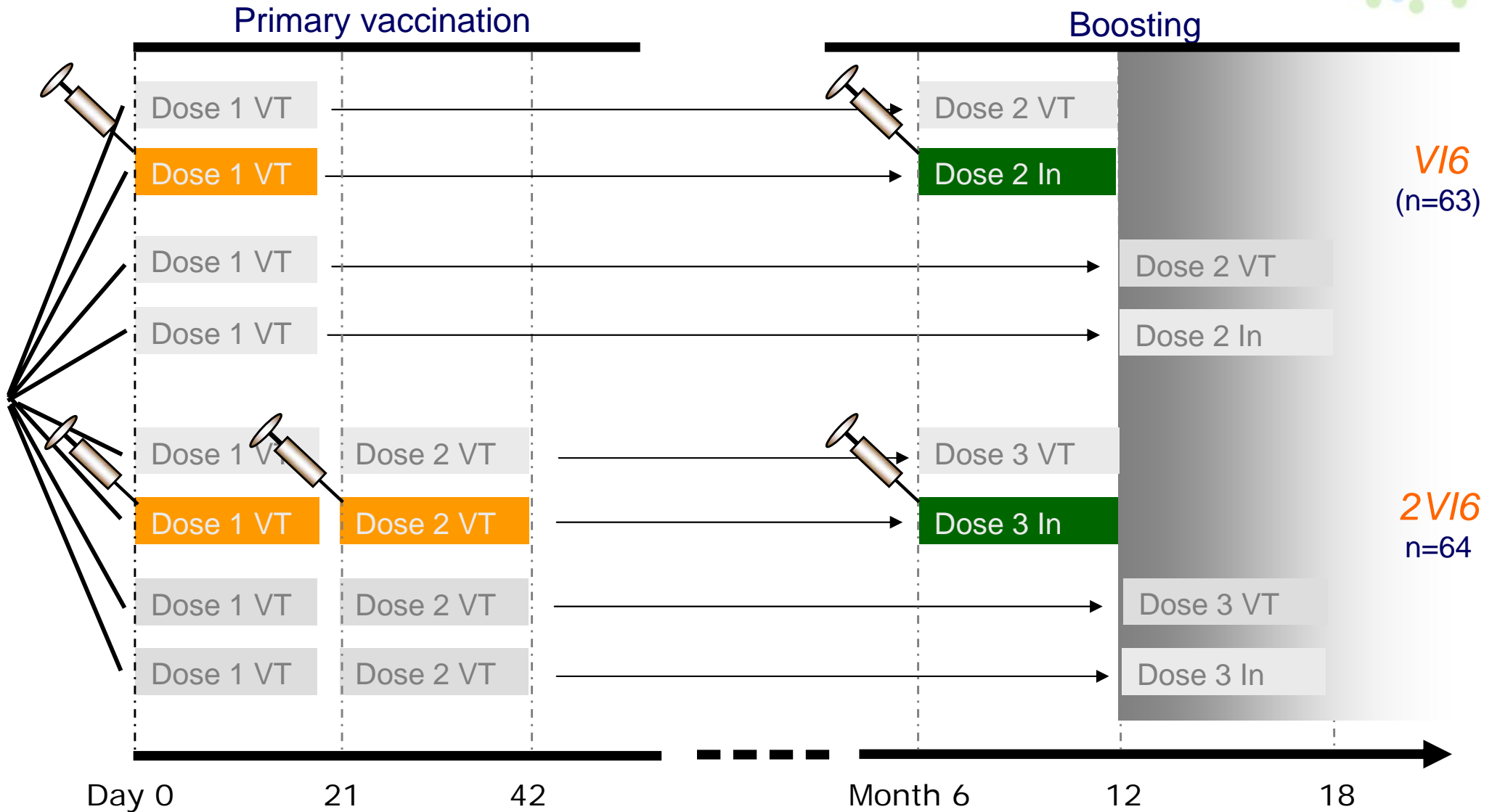
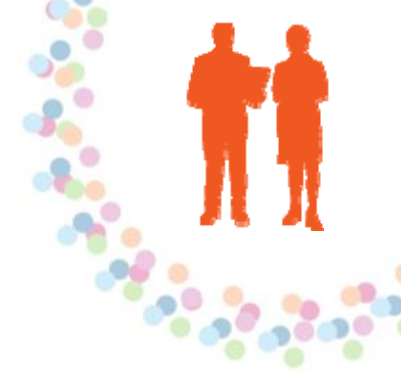
Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. *Vaccine* 2009; 27: 6284-6290.

GSK's AS03_A-Adjuvanted H5N1 Vaccine and the Highly Flexible Prime-Boost Vaccination Strategy (H5N1-012)



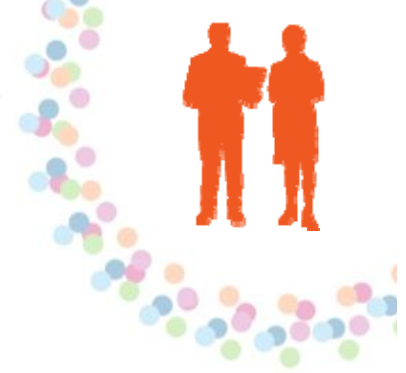
- Regardless of the primary vaccination schedule, 1-dose booster vaccination induced a high immune response
- Similar GMT levels were reached 21 days after the 2-dose primary vaccination and 21 days after booster vaccination

GSK's AS03_A-Adjuvanted H5N1 Vaccine and the Highly Flexible Prime-Boost Vaccination Strategy (H5N1-012): Heterologous Booster

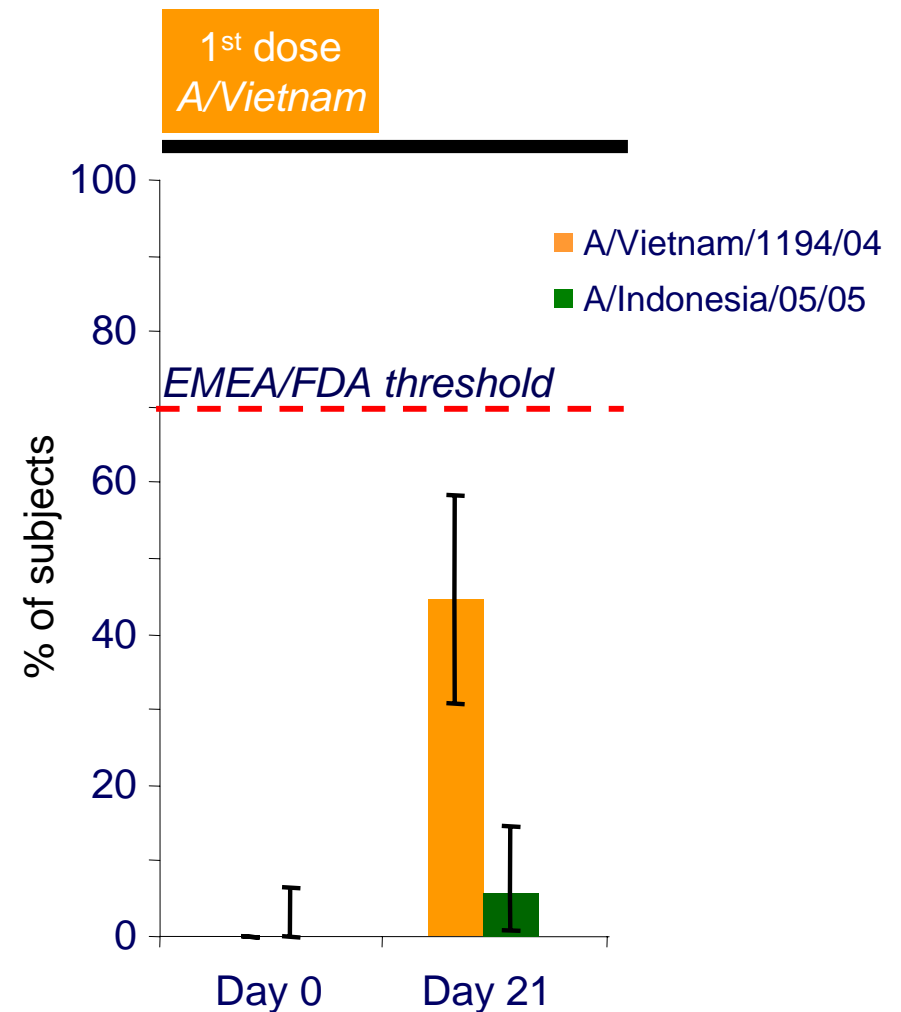
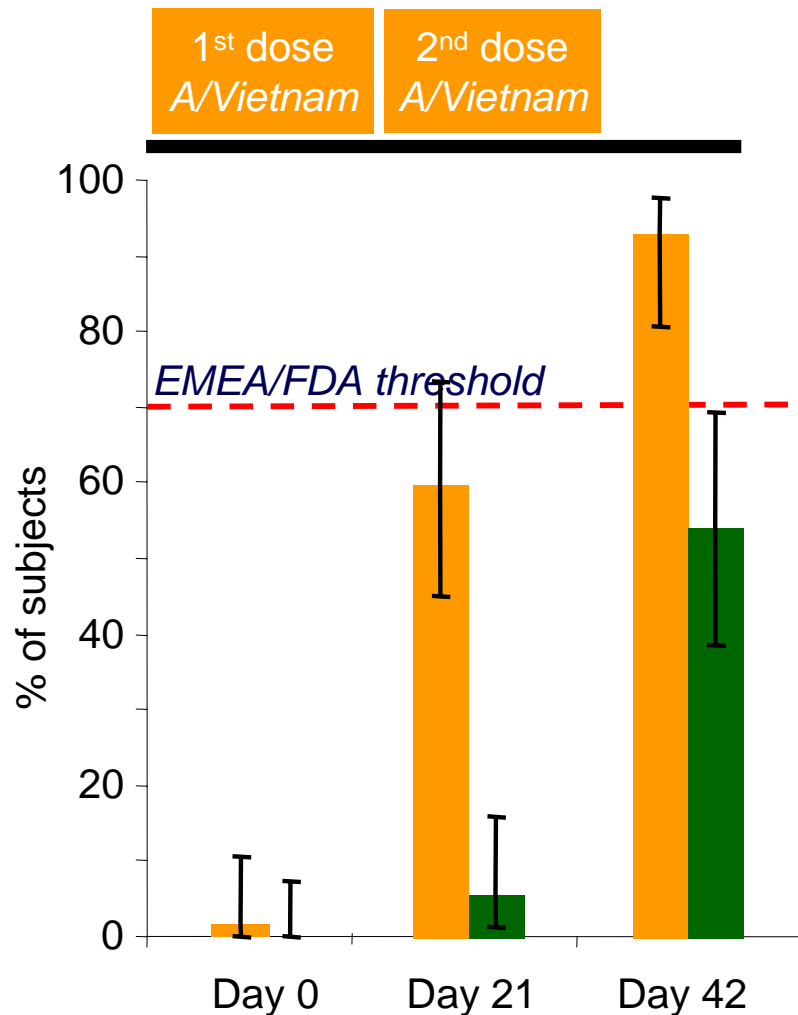


Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. *Vaccine* 2009; 27: 6284-6290.

GSK's AS03_A-Adjuvanted H5N1 Vaccine and the Highly Flexible Prime-Boost Vaccination Strategy: Heterologous Booster



Results – Seroprotection Rate after Primary Vaccination

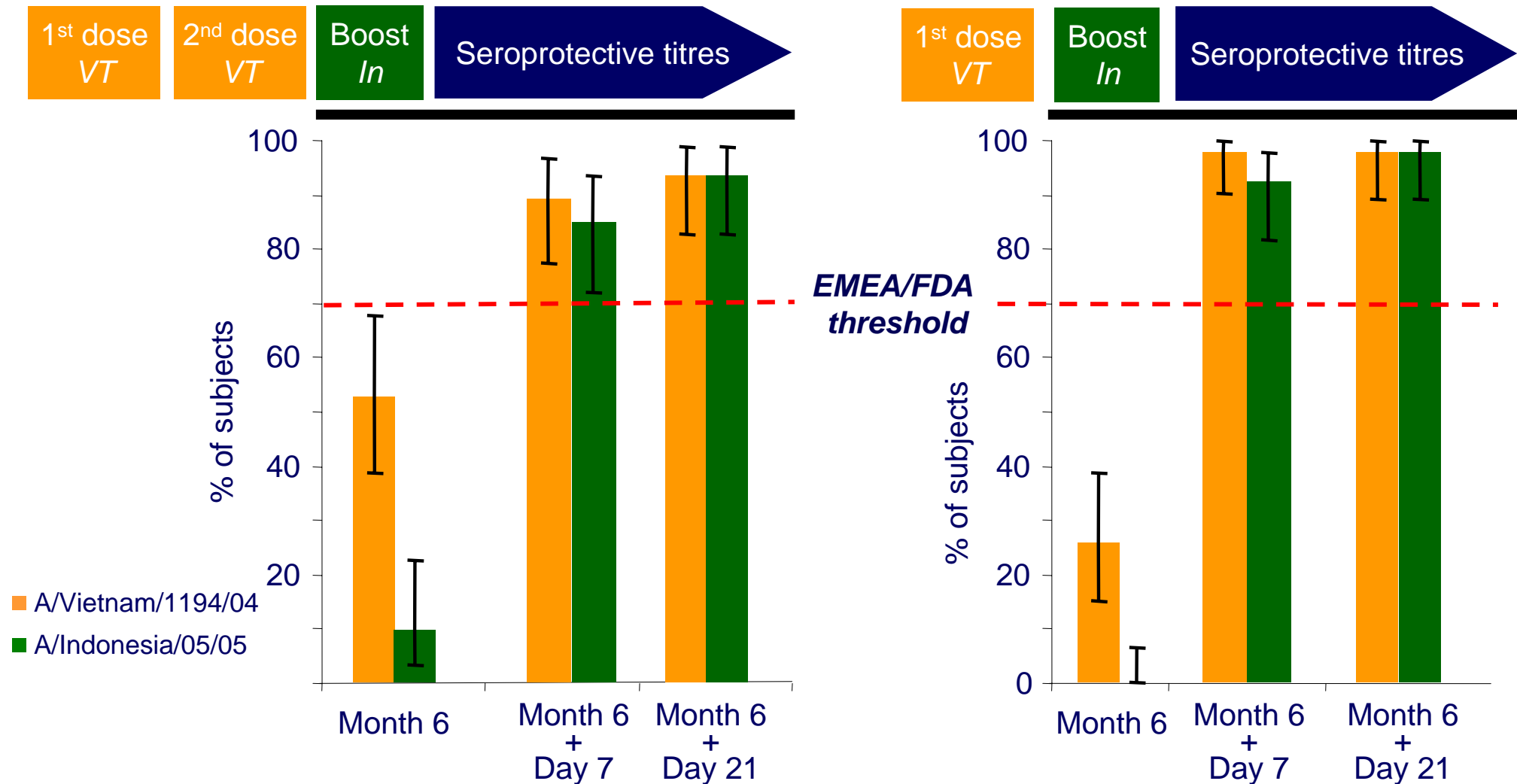


Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. Vaccine 2009; 27: 6284-6290.

Using Combination of Different H5N1 Vaccine Strain gives Good Immunogenicity for Both Strains

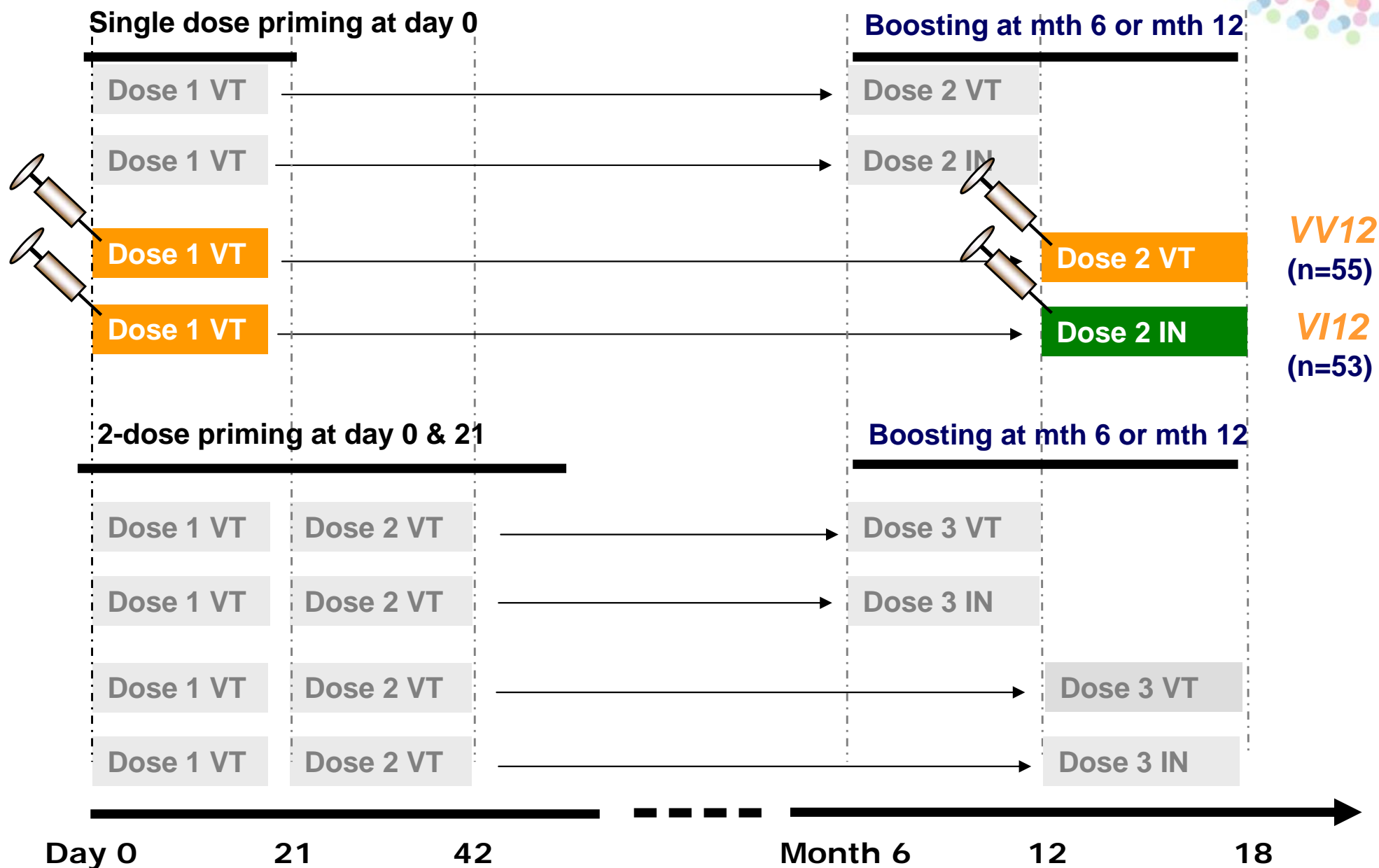


Results – Post-boosting Seroprotection Rate

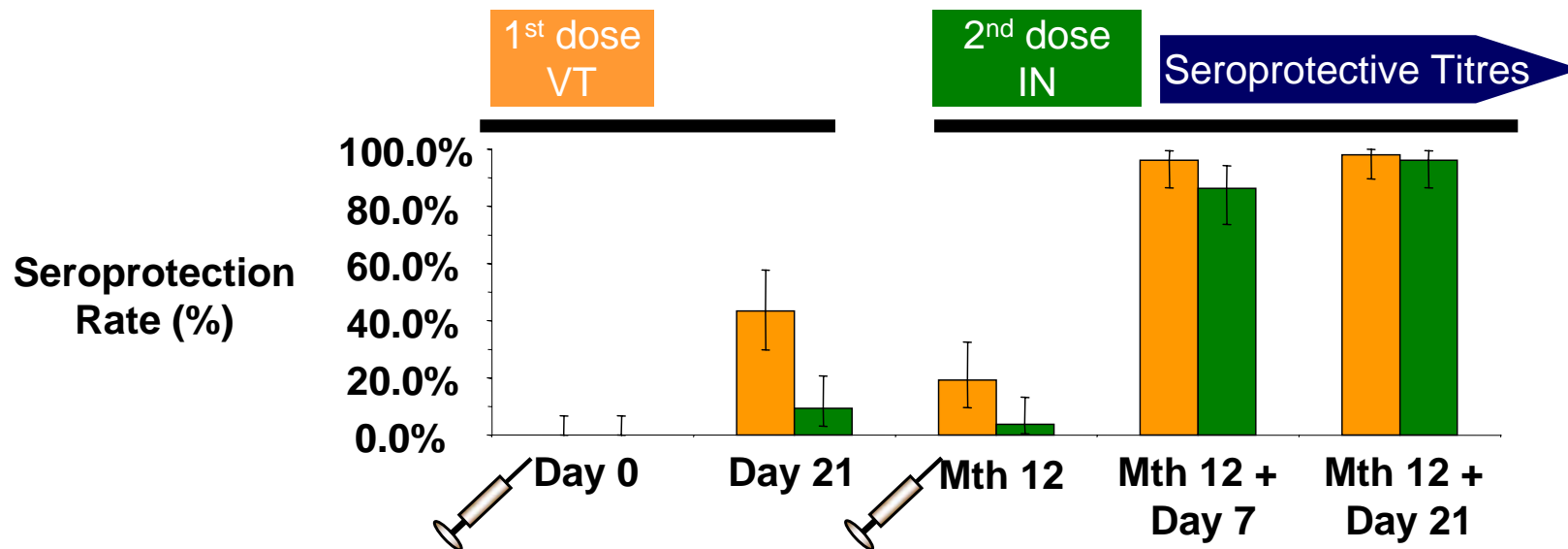
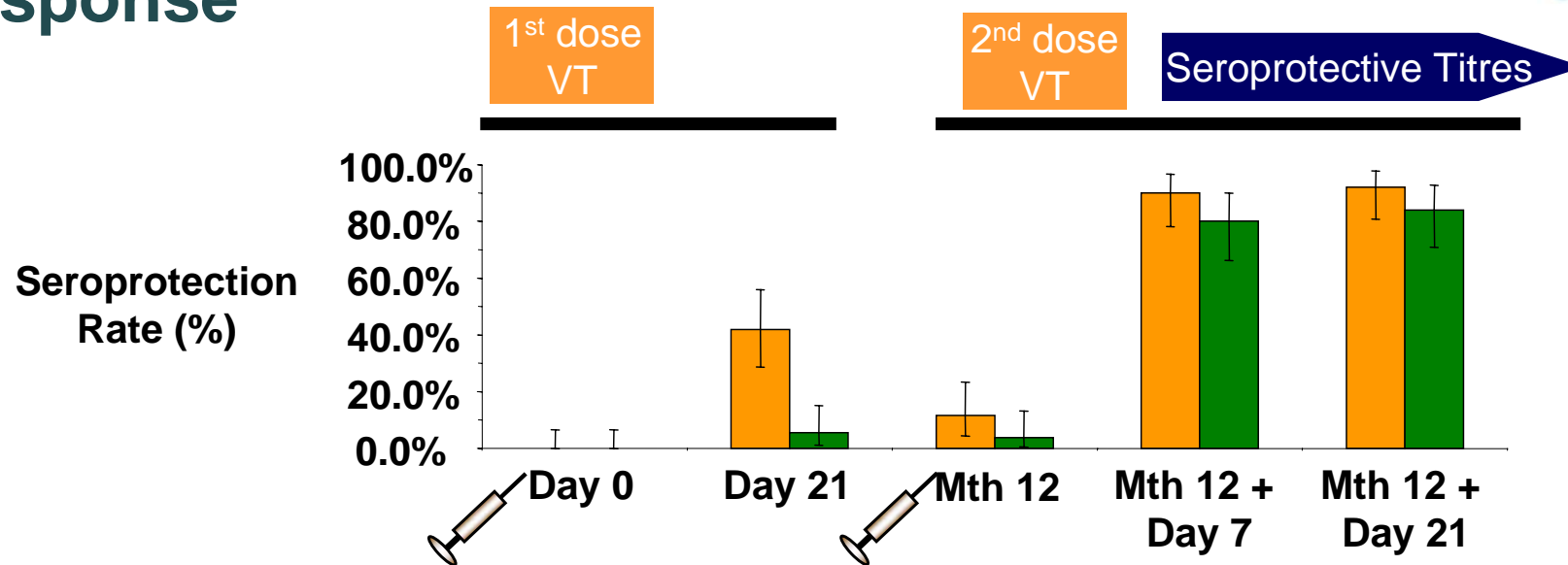


Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. *Vaccine* 2009; 27: 6284-6290.

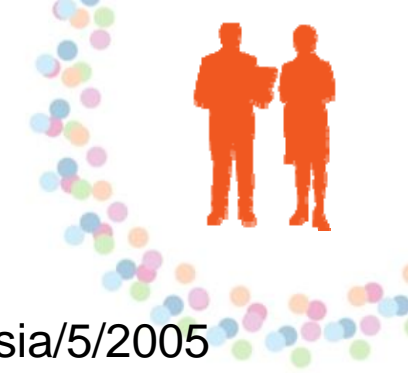
Vaccination Strategy Using a Combination of Vietnam and Indonesia Strains



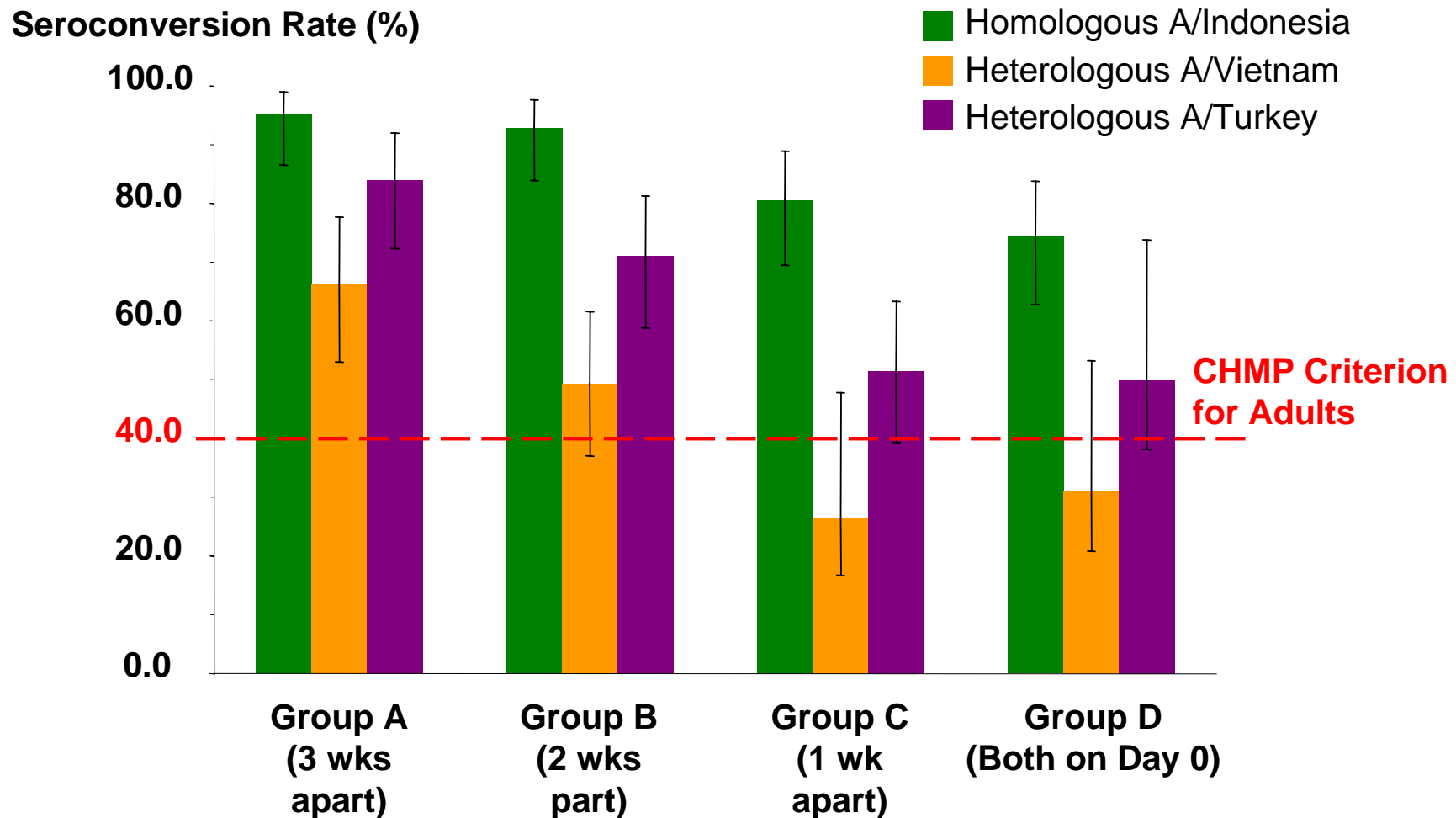
2 Doses Primary Vaccination Given 12 mths Apart Induced Rapid and Strong Cross-Clade Immune Response



Flu Q-PAN-009: HI Seroconversion Rates (Day 21 After Dose 2)



Adults vaccinated with 2 doses 3.75 µg AS03-adjuvanted H5N1 A/Indonesia/5/2005
prepandemic vaccine

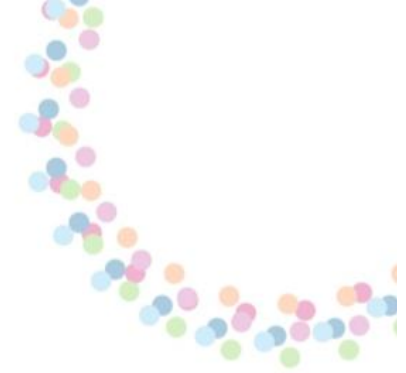


Conclusion and Practical Implications



- Administration flexibility :
adaptable to local pre-pandemic vaccination policies
- Stockpiles of GSK AS03-adjuvanted vaccines derived from different H5N1 strains may be compatible with each other
- Potential for reducing the logistic stress on vaccination programme delivery during the crucial first months of pandemic

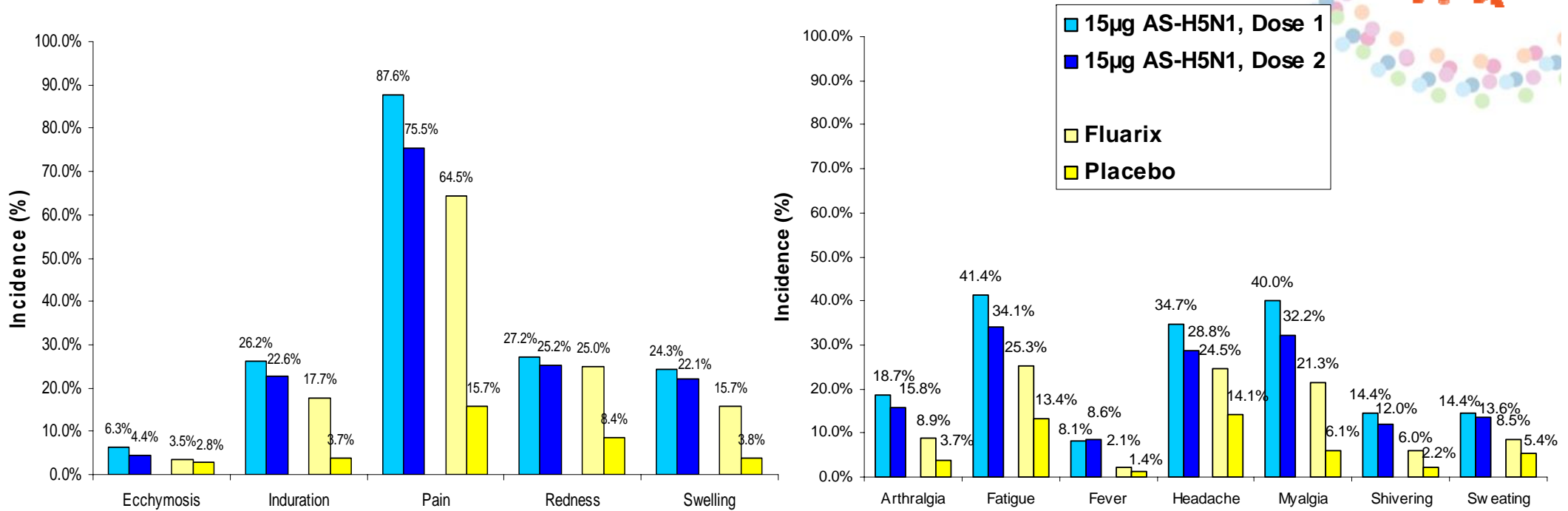
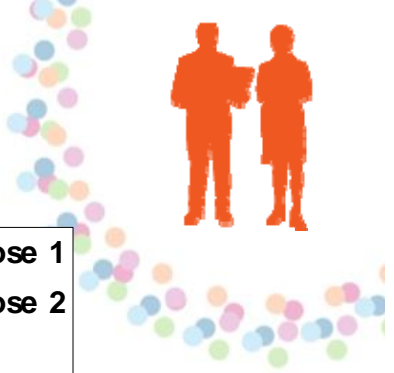
GSK's AS03_A-adjuvanted H5N1 vaccine is a step forward in the prevention of possible H5N1 pandemics and has the potential to reduce the overall burden of disease in countries where both H5N1 and H1N1 influenza virus strains are epidemic



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Safety Demonstrated in Studies in Asia & Europe



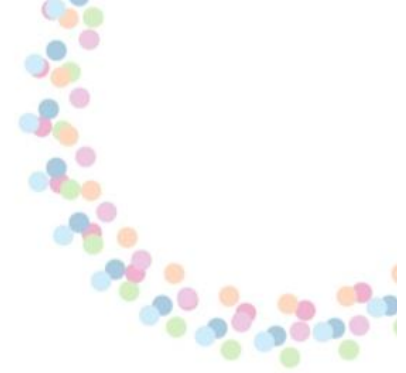
Safety Data:

- Safety study of 5071 adults using 15 µg H5N1 + AS vaccine, compared to seasonal flu + placebo¹
- Overall, large clinical trials in over 6700 subjects (both adults and children aged 3–9 yrs) vaccinated^{1–3}

Key Conclusions:

- Higher incidence of local and general symptoms in adjuvanted group vs non-adjuvanted vaccine
- Overall reactogenicity profile was clinically acceptable with no safety concerns
- Most symptoms were mild or moderate and transient (mostly resolved within 3 days)
- No serious adverse events were reported

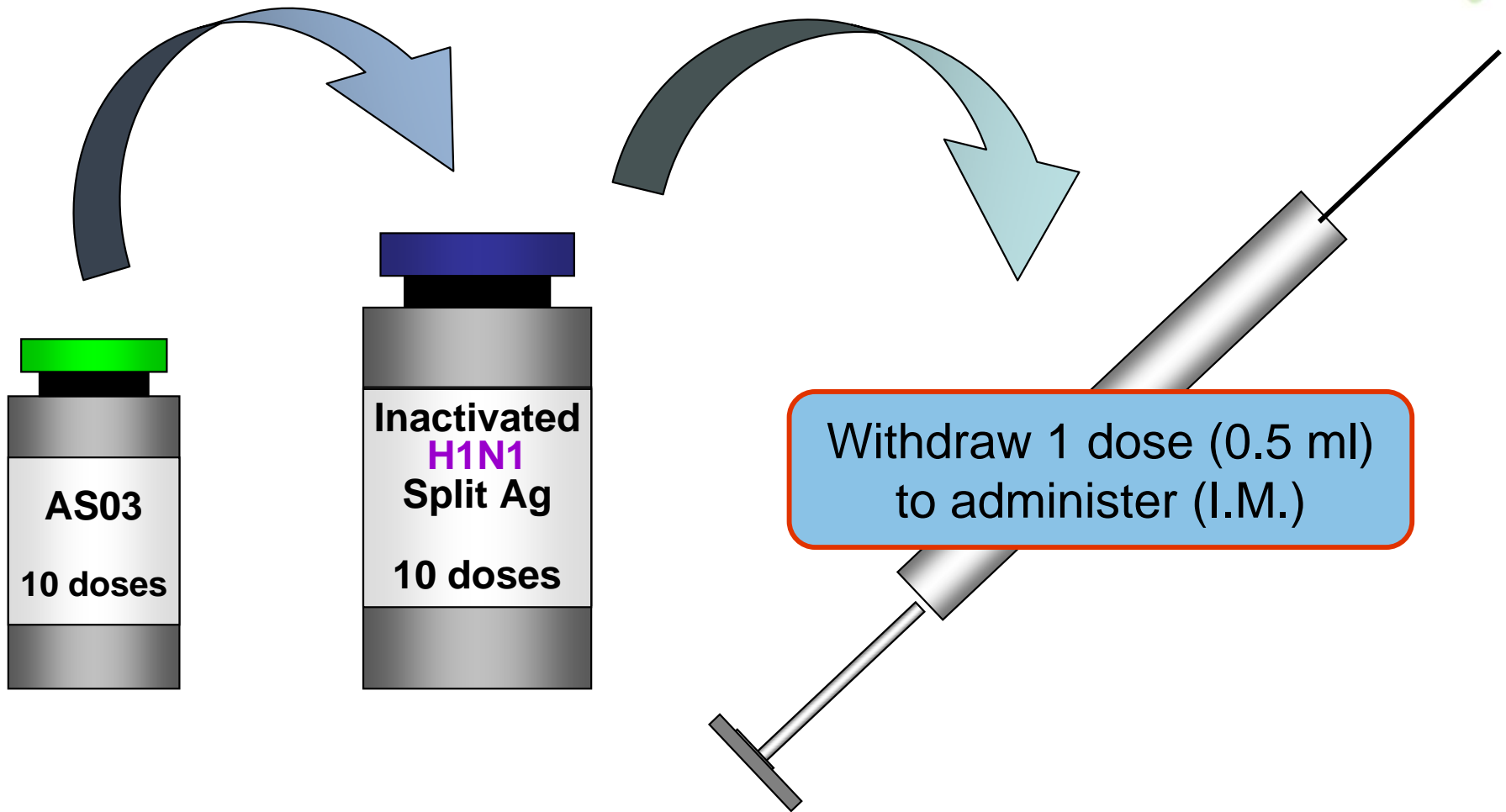
1. Daniel Wai-Sing Chu et al. *Vaccine* 27 (2009) 7428–7435
 2. Leroux-Roels I, et al. *Lancet* 2007;370:58
 3. Rumke H, et al. *Vaccine* (2008) 26, 2378–2388



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GSK is Using the Twin-Vial Antigen-Adjuvant Vaccine, Permitting Flexible Supply



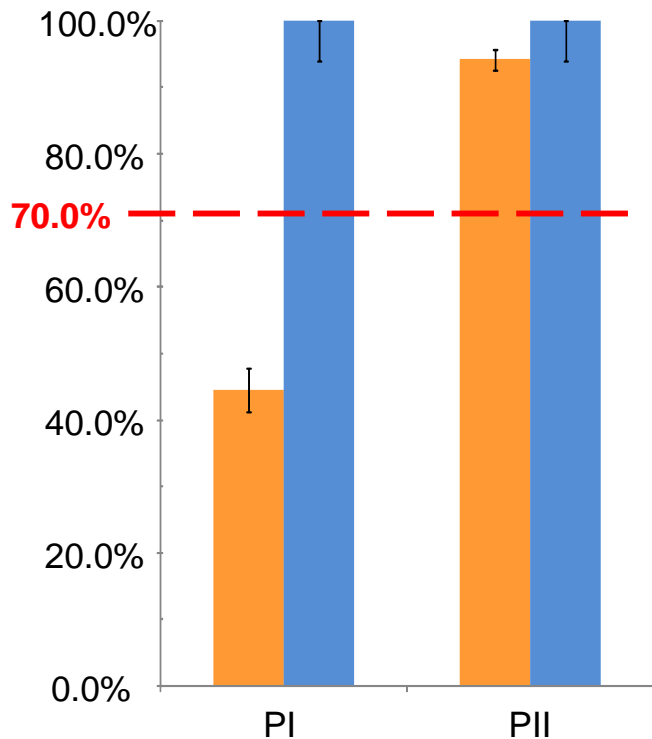
Add AS03 to antigen, shake well

Comparing GSK's AS03_A-Adjuvanted Vaccines— H5N1 versus H1N1

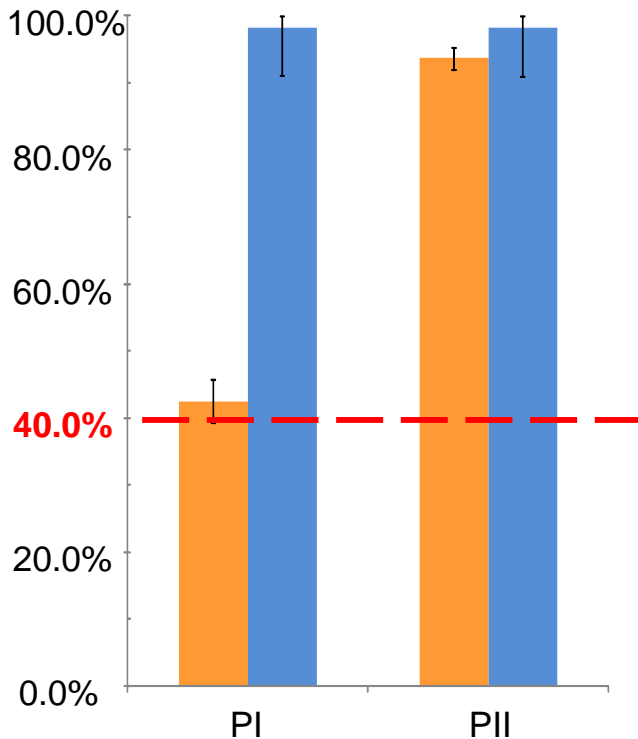


■ 3.75 µg H5N1 + AS03_A¹
■ 3.75 µg H1N1 + AS03_A²

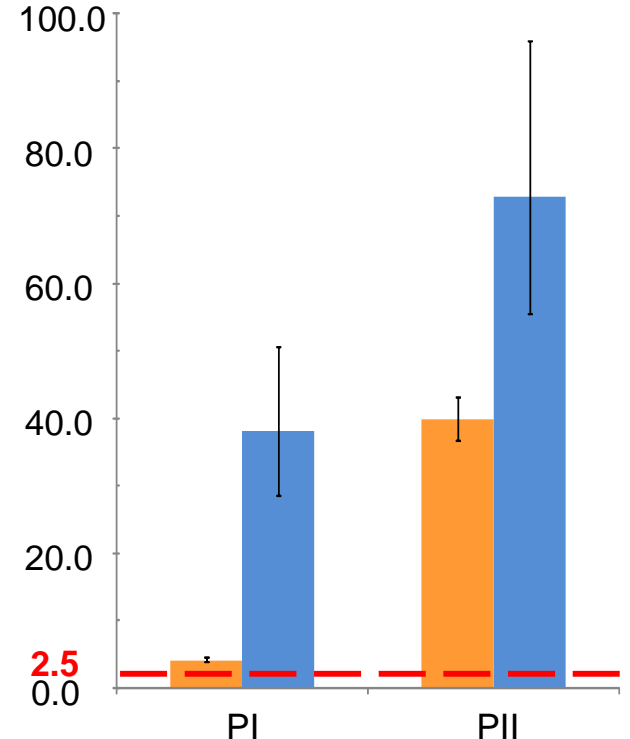
Seroprotection Rate



Seroconversion Rate



Seroconversion Factor



--- CHMP criterion

1. Daniel Wai-Sing Chu et al. Immunogenicity and tolerability of an AS03A-adjuvanted prepandemic influenza vaccine: A Phase III study in a large population of Asian adults. *Vaccine* 27 (2009) 7428–7435
 2. <http://download.gsk-clinicalstudyregister.com/files/a03ddc51-96cb-42c1-ac85-bd45e71f6a94>

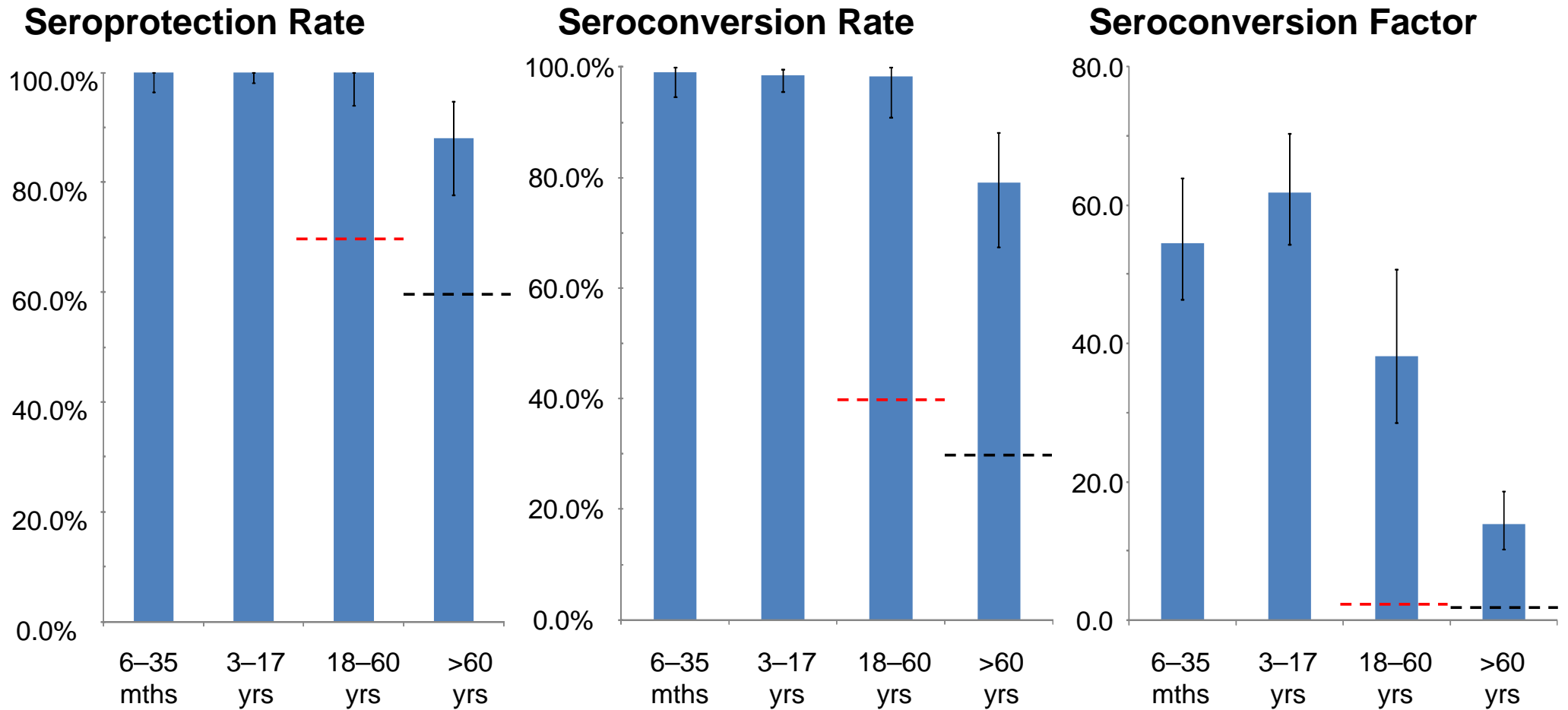
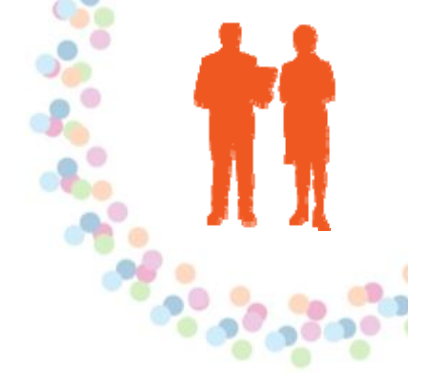
H1N1 Clinical Studies



- GSK's adjuvanted H1N1 vaccines are very immunogenic in all populations including the elderly and very young
- GSK's adjuvanted H1N1 vaccines showed an acceptable safety profile in all populations
- GSK's adjuvanted vaccines from the two manufacturing sites are clinically equivalent



GSK Pandemic H1N1 Vaccine Clinical Data



-----CHMP Criteria for adults (aged 18-60yrs)

-----CHMP Criteria for elderly (aged >60yrs)

Canada: Effectiveness of GSK's AS03-Adjuvanted Pandemic H1N1 2009 Vaccine



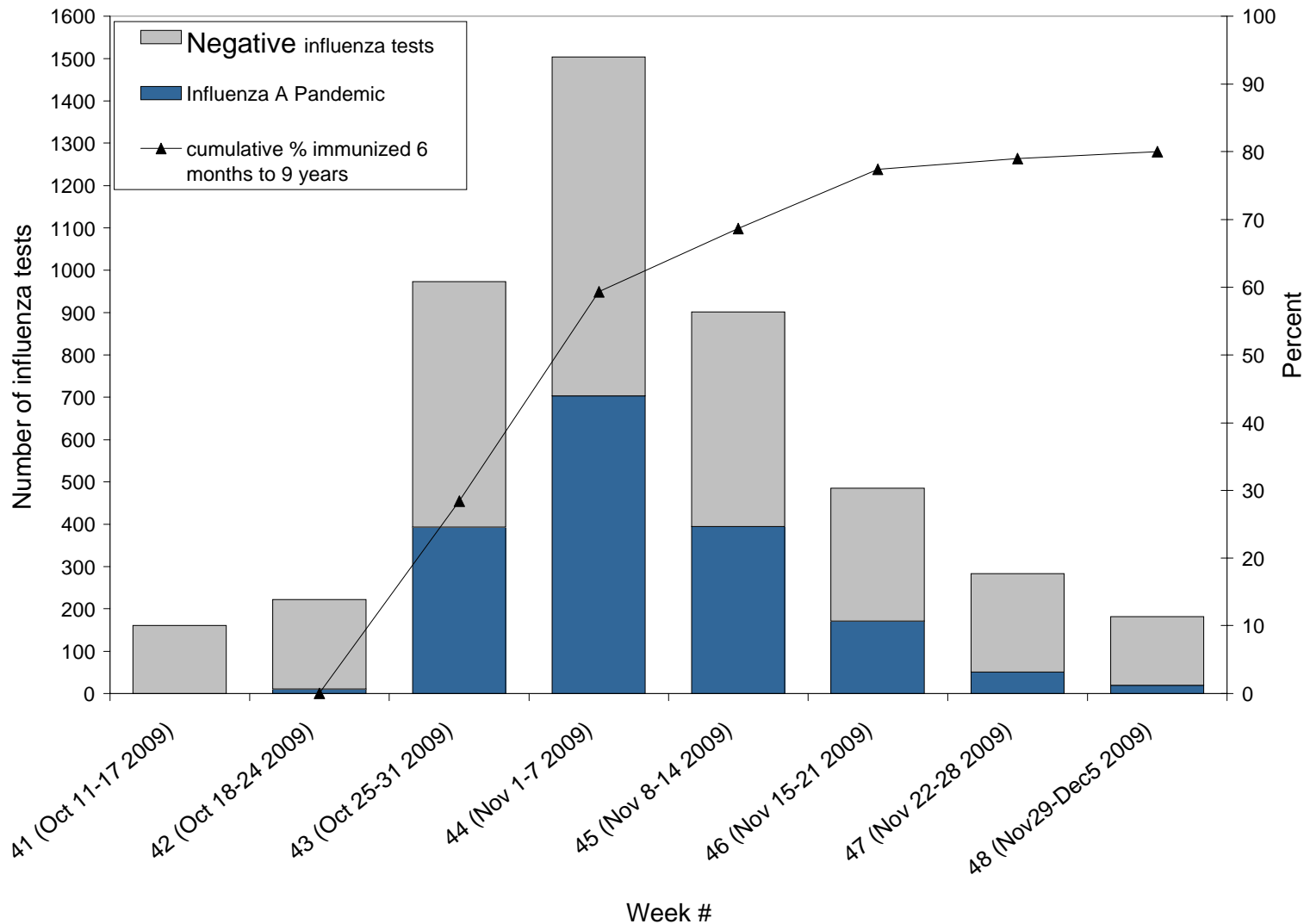
Community based case-control vaccine effectiveness review of children < 10 years with influenza-like illness who were tested for H1N1 infection at the central provincial laboratory.

- Children 36 months to <10 years
 - Well: received a single dose of 0.25 ml of GSK's AS03-adjuvanted pandemic H1N1 vaccine (1.9 μ g HA).
 - Chronic medical conditions: received 2 doses, 21 days apart.
- Children 6 months to 35 months received two doses, 21 days apart.

Canada: Effectiveness of GSK's AS03-Adjuvanted Pandemic H1N1 2009 Vaccine



Number of positive pandemic influenza specimens and percent of immunized children 6 months to 9 years with H1N1 vaccine, New Brunswick



- Van Buynder PG, et al. Protective effect of single dose adjuvanted pandemic influenza vaccine in children. *Influenza and Other Respiratory Viruses* 2010; 4(4): 171-178.

Canada: Effectiveness of GSK's AS03-Adjuvanted Pandemic H1N1 2009 Vaccine



Conclusion

As stated by Van Buynder PG et al.

(New Brunswick Department of Health, Office of the Chief Medical Officer of Health, New Brunswick, Canada):

“If vaccination was designated to be effective after 14 days, none of the vaccinated child had laboratory confirmed influenza as compared to 38% of controls. The vaccine effectiveness of 100% was statistically significant for children <10 years and <5 years of age considered separately.

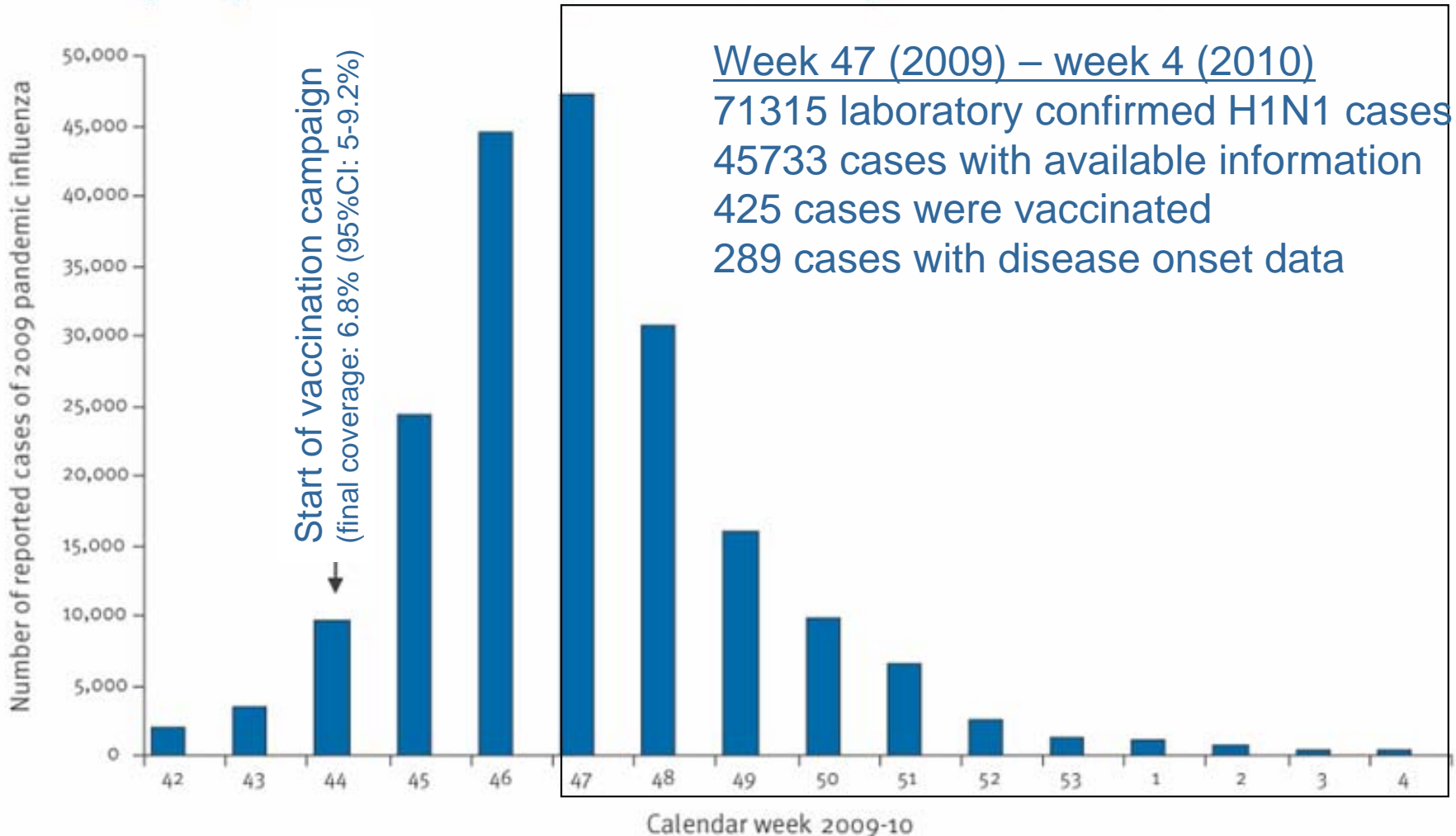
If vaccination was considered effective after 10 days, vaccine effectiveness dropped to 96% overall, but was statistically significant and over 90% in all age subgroups, including <36 months.”

- *Van Buynder PG, et al. Protective effect of single dose adjuvanted pandemic influenza vaccine in children. Influenza and Other Respiratory Viruses 2010; 4(4): 171-178.*

Germany: Effectiveness of GSK's AS03-Adjuvanted Pandemic H1N1 2009 Vaccine

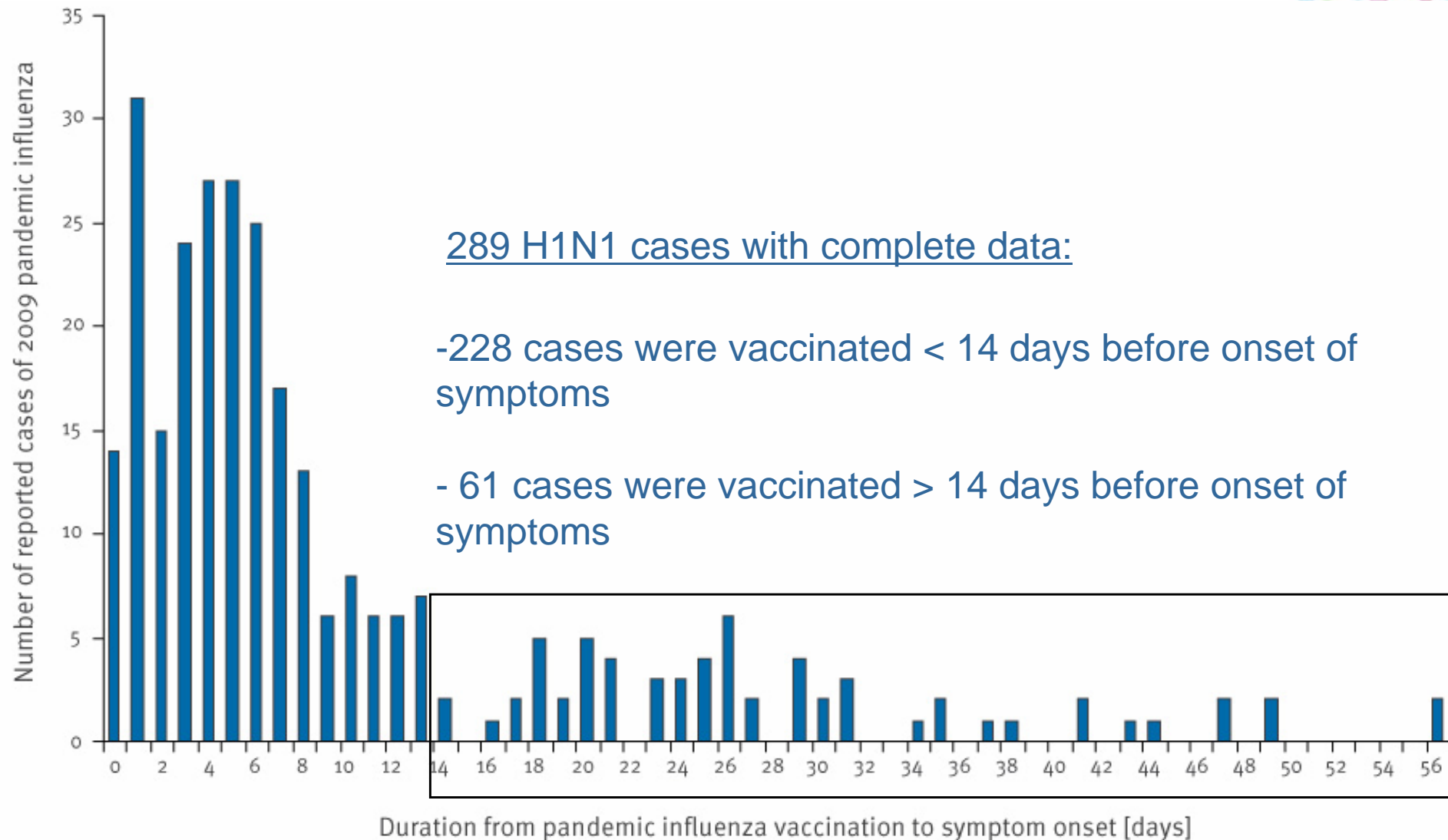


Number of reported pandemic influenza cases by calendar week, Germany, week 42, 2009 - week 4, 2010



O. Wichmann, P. Stöcker, G. Poggensee, et al. Pandemic influenza A(H1N1) 2009 breakthrough infections and estimates of vaccine effectiveness in Germany 2009-2010. *Euro Surveill* 2010.

Germany: Effectiveness of GSK's AS03-Adjuvanted Pandemic H1N1 2009 Vaccine



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Age	H1N1 cases	H1N1 cases with vaccination status		Vaccine failures ^A	Expansion factor ^B	Vaccine failures ^C	Proportion H1N1 cases ^D	Proportion vaccinated (95% CI) ^E	VE (95% CI)
		Not vaccinated	vaccinated						
14-59 y	37 756	23 853	219	35	1.52 (219/144)	53.2	0.0022	0.064 (0.044-0.093)	96.8% (95.2-97.9)
≥ 60 y	430	923	25	7	1.92 (25/13)	13.4	0.0141	0.079 (0.047-0.131)	83.3% (71.0-90.5)

A: Cases with disease >14 days after vaccination

B: (Total vaccinated cases/vaccinated cases with information on date of vaccination and symptom onset)

C: After applying expansion factors

D: With vaccine failure among H1N1 cases with available vaccination status

E: In the general population

Conclusion

As stated by Wichmann O et al. (Robert Koch Institute, Berlin, Germany):

- “Excellent VE in persons 14 to 59 years: 96.8% (95% CI 95.2-97.9)”
- “Moderately high VE in persons ≥60 years: 83.3% (95% CI: 71-90.5)”



Thank You