GRADE and Policy Options for Influenza A (H5N1) Vaccine

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Policy Question

- Should licensed influenza A (H5N1) vaccine be recommended to adults with increased risk of exposure during the inter-pandemic time period?

Influenza A (H5N1)

DEFINE OUTCOMES OF INTEREST

Define Outcomes of Interest

- Work group enumerated all possible outcomes of interest (independent of whether data were available)
- Each member independently scored outcomes using numerical scale
  - Critical to decision making (7-9)
  - Important, not critical (4-6)
  - Low importance (1-3)
- Rankings summarized

Safety Outcomes

Outcome	Importance
Any vaccine-related serious adverse event	Critical
Anaphylaxis or immediate hypersensitivity	Critical
Narcolepsy	Critical
Guillain-Barré syndrome	Critical
Other serious neurologic outcomes (e.g., encephalitis, transverse myelitis, Bell's palsy, acute disseminated encephalomyelitis , other acute demylinating diseases)	Critical
Mortality	Critical
General symptoms (fatigue, headache, joint pain, muscle aches, chills, malaise, nausea, shivering, sweating)	Important
Syncope	Important
Fever	Important
Injection site reactions (pain, tenderness, redness, swelling)	Low

Immunogenicity Outcomes

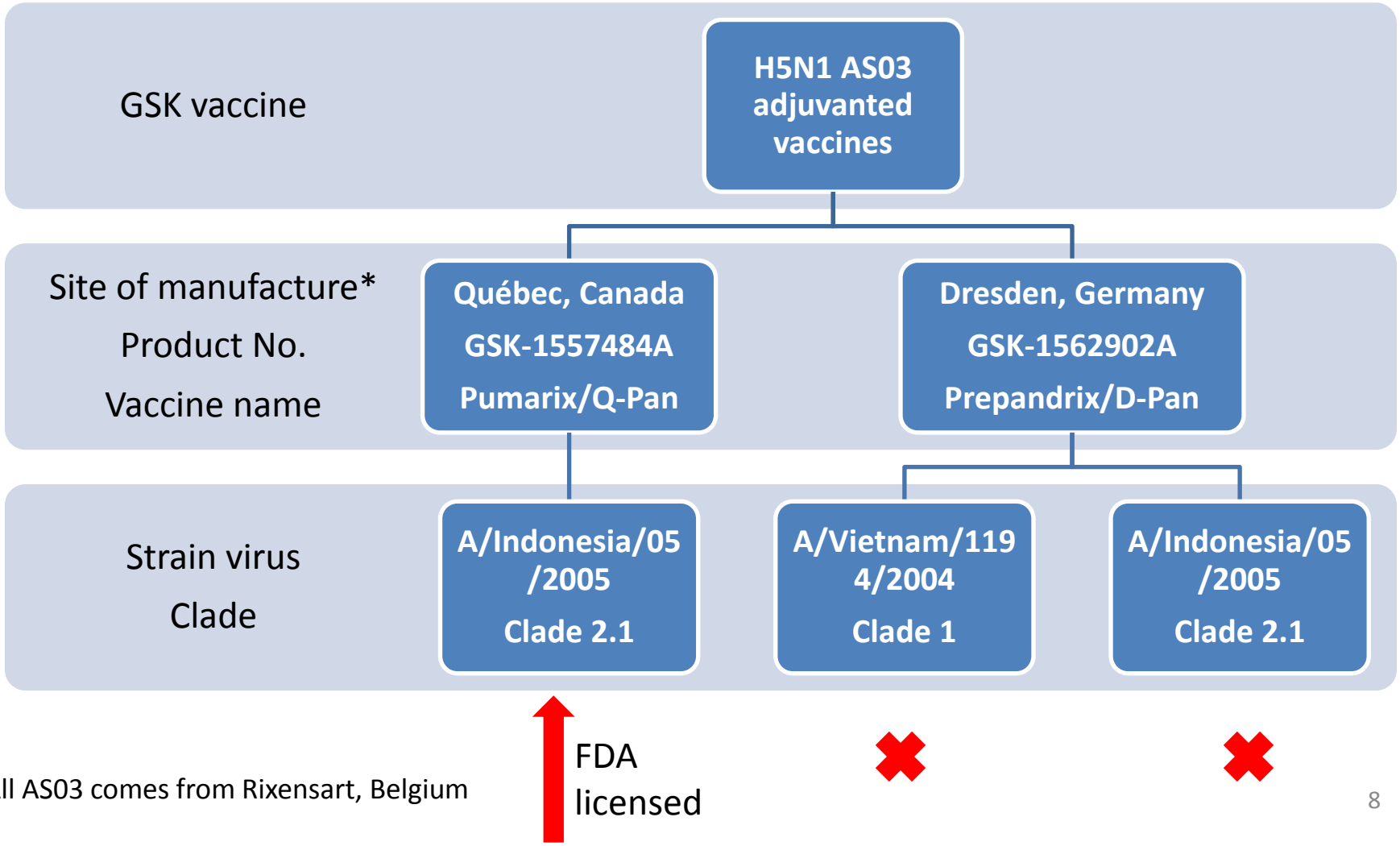
Outcome			Definition	Importance
21-day	homologous	seroprotection	% of subjects achieving ≥1:40 HI ab titer to A/Indonesia/05/2005	Critical
		seroconversion	% of subjects achieving seroconversion to A/Indonesia/05/2005	Critical
	heterologous	seroprotection	% of subjects achieving ≥1:40 HI ab titer to currently circulating strains and strains in vaccine development	Important
		seroconversion	% of subjects achieving seroconversion to currently circulating strains and strains in vaccine development	Important
6-month	homologous	seroprotection	% of subjects achieving ≥1:40 HI ab titer to A/Indonesia/05/2005	Important
		seroconversion	% of subjects achieving seroconversion to A/Indonesia/05/2005	Important
	heterologous	seroprotection	% of subjects achieving ≥1:40 HI ab titer to currently circulating strains and strains in vaccine development	Important
		seroconversion	% of subjects achieving seroconversion to currently circulating strains and strains in vaccine development	Important

*Seroconversion = % of subjects with a pre-vaccination HI titer <10 and a post-vaccination titer ≥40 or with a pre-vaccination HI titer (Day 0) ≥10 and a fold-increase (post/pre) ≥4.

Influenza A (H5N1)

DEFINE DATA TO REVIEW

GSK H5N1 Vaccines



*All AS03 comes from Rixensart, Belgium

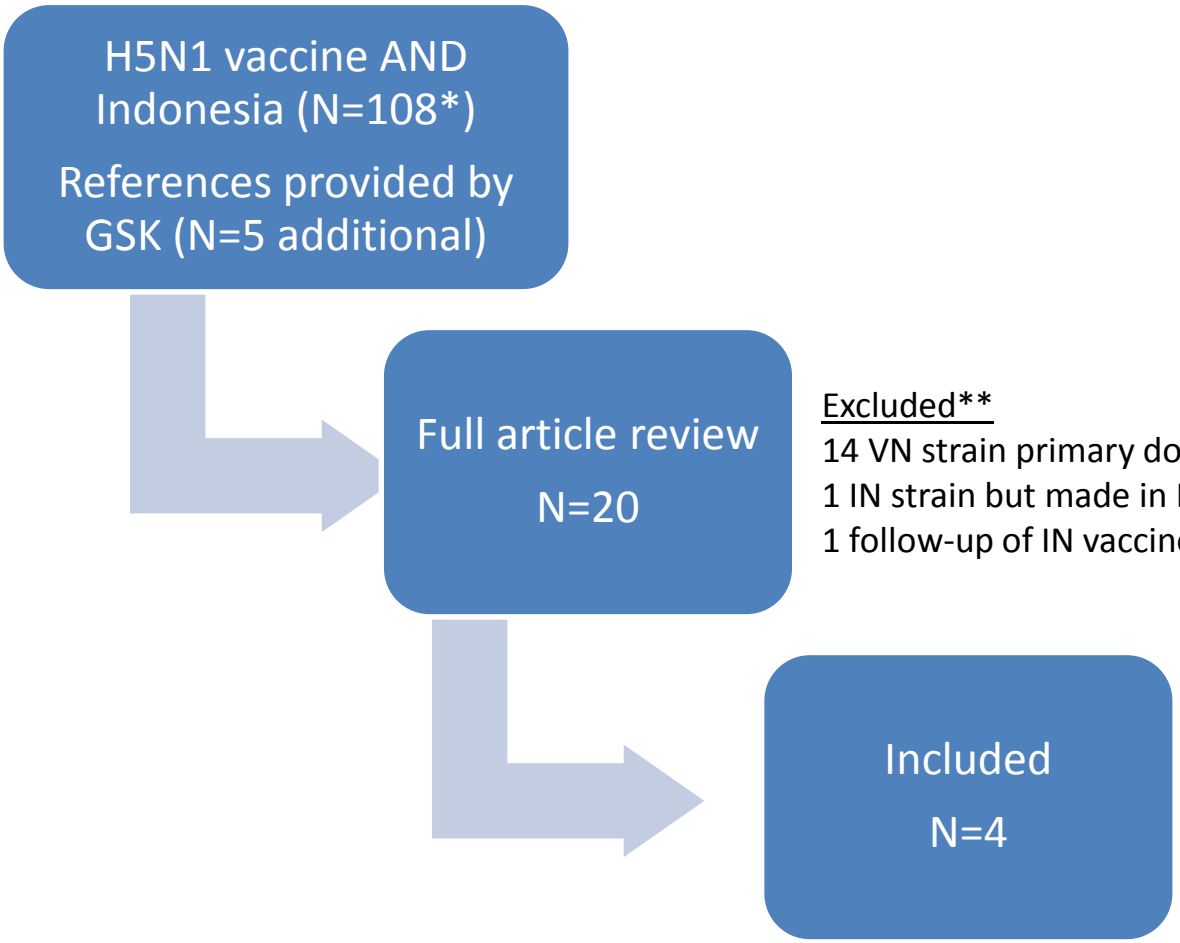
Other GSK Influenza Vaccines

Vaccine	Description	Manufacturer Location	Haemagglutinin (HA) per 0.5 mL dose	Adjuvant
Seasonal Vaccines				
FluLaval®	U.S.-licensed seasonal influenza vaccine (trivalent, inactivated, split virion)	Québec, Canada	15 µg HA	None
FluLaval® Quadrivalent	U.S.-licensed seasonal influenza vaccine (inactivated, split virion)	Québec, Canada	15 µg HA	None
Fluarix®	U.S.-licensed seasonal influenza vaccine (trivalent, inactivated, split virion)	Dresden, Germany	15 µg HA	None
2009 Pandemic Vaccines				
Arepanrix™	GSK's H1N1 AS03-adjuvanted pandemic vaccine	Québec, Canada	3.75 µg HA	$AS03_A$
Pandemrix™	GSK's H1N1 AS03-adjuvanted pandemic vaccine	Dresden, Germany	3.75 µg HA	$AS03_A$

Why Not Use Data from These Vaccines?

- Difficult to extrapolate the data
  - Manufacturing process (Québec vs. Dresden)
  - Antigen content (3.75µg vs. 15µg)
  - Adjuvant (none vs. AS03)
- Avian H5 hemaggultinin (HA) less immunogenic than those of human influenza viruses

Literature Review



*Medline, Embase and Web of Science databases as of April 24, 2014

**VN = Vietnam, IN = Indonesia, TUR = Turkey

Studies Considered

Paper	Design	Arms	Ages (yr)	Setting	Outcomes
Langley (2010)*	Phase 1/2 Randomized (no placebo) Observer blinded	1. Nonadjuvanted 2. $AS03_A$ Quebec 3. $AS03_A$ Dresden 4. $AS03_B$ Quebec 5. $AS03_B$ Dresden	18-64	United States, Canada	Safety, Immunogenicity
Langley (2011)*	Phase III Randomized Placebo-controlled Observer-blinded	1. Vaccine, 18-64yr 2. Placebo, 18-64yr 3. Vaccine, ≥65yr 4. Placebo, ≥65yr	≥18	North America	Safety, Immunogenicity
Laskos (2011)	Phase II Randomized (no placebo) Open-label	1. Vaccine days 0/21 2. Vaccine days 0/14 3. Vaccine days 0/7 4. Vaccine days 0/0	18-64	Canada	Safety, Immunogenicity
Nagai (2011)	Phase II Open-label No comparison group	1. Vaccine, 20-40yrs 2. Vaccine, 41-64yrs	20-64	Japan	Safety, Immunogenicity

Red = Q-pan

*Data from these studies used in FDA's Summary Basis of Regulatory Action.

Review of Data

- Reviewed data from all four papers
  - Each study had a different question
    - Dosing of vaccine or adjuvant
    - Vaccine yes/no
    - Timing of vaccine
    - Descriptive only
- Only one study designed to answer our question (vaccine yes/no)
  - Data from other studies are not presented but are included as extra slides

Outcomes Available

Outcome			Importance	Langley 2011
Harms				
Any vaccine-related SAE			Critical	✓
Anaphylaxis, immediate hypersensitivity			Critical	-
Narcolepsy			Critical	-
Guillain-Barré syndrome			Critical	-
Other serious neurologic outcomes			Critical	-
Mortality			Critical	✓
General symptoms (listed individually)			Important	✓
Syncope			Important	✓
Fever			Important	✓
Benefits				
21-day	homologous	seroprotection	Critical	✓
		seroconversion	Critical	✓
	heterologous	seroprotection	Important	-
		seroconversion	Important	-
6-month	homologous	seroprotection	Important	✓
		seroconversion	Important	✓
	heterologous	seroprotection	Important	-
		seroconversion	Important	-

Influenza A (H5N1)

GRADE, SAFETY OUTCOMES (HARMS)

Safety Outcomes (Critical)

Study Design (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect		Quality
					RR [95% CI]	Risk Difference with Q-Pan [95% CI]	
Any vaccine-related SAE							
RCT (1)	Not Serious	Not Serious	Not Serious	Serious*	Not estimable	Not estimable	2 (Mod.)
	Q-Pan = 0/3422 (0%); placebo = 0/1139 (0%)						
Mortality							
RCT (1)	Not Serious	Not Serious	Not Serious	Not Serious	0.19 [0.06-0.65]	5 fewer per 1000 [2-6 fewer]	1 (High)
	Q-Pan = 4/3422 (0.1%); placebo = 7/1139 (0.6%)						

*Imprecision downgraded for sample size too small to detect rare SAE (e.g., neurologic)

Safety Outcomes (Important)

Slide 1 of 3

Study Design (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect		Quality
					RR [95% CI]	Risk Difference with Q-Pan [95% CI]	
Fatigue							
RCT (1)	Not Serious	Not Serious	Not Serious	Not Serious	1.51 [1.34-1.70]	115 more per 1000 [77-158 more]	1 (High)
	Q-Pan = 1148/3375 (34.0%); placebo = 253/1123 (22.5%)						
Headache							
RCT (1)	Not Serious	Not Serious	Not Serious	Not Serious	1.55 [1.38-1.74]	124 more per 1000 [86-167 more]	1 (High)
	Q-Pan = 1179/3375 (34.9%); placebo = 253/1123 (22.5%)						
Joint Pain							
RCT (1)	Not Serious	Not Serious	Not Serious	Not Serious	2.09 [1.76-2.47]	132 more per 1000 [92-178 more]	1 (High)
	Q-Pan = 853/3375 (25.3%); placebo = 136/1123 (12.1%)						

Safety Outcomes (Important)

Slide 2 of 3

Study Design (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect		Quality
					RR [95% CI]	Risk Difference with Q-Pan [95% CI]	
Muscle Aches							
RCT (1)	Not Serious	Not Serious	Not Serious	Not Serious	2.20 [1.95-2.48]	247 more per 1000 [195-304 more]	1 (High)
	Q-Pan = 1526/3375 (45.2%); placebo = 231/1123 (20.6%)						
Shivering							
RCT (1)	Not Serious	Not Serious	Not Serious	Not Serious	1.72 [1.42-2.09]	70 more per 1000 [41-106 more]	1 (High)
	Q-Pan = 563/3375 (16.7%); placebo = 109/1123 (9.7%)						
Sweating							
RCT (1)	Not Serious	Not Serious	Not Serious	Serious*	1.11 [0.90-1.35]	11 more per 1000 [10 fewer-34 more]	2 (Mod.)
	Q-Pan = 362/3375 (10.7%); placebo = 109/1123 (9.7%)						

*Imprecision downgraded for confidence interval that includes 1.

Safety Outcomes (Important)

Slide 3 of 3

Study Design (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect		Quality
					RR [95% CI]	Risk Difference with Q-Pan [95% CI]	
Syncope							
RCT (1)	Not Serious	Not Serious	Not Serious	Very Serious	1.00 [0.04-24.51]	Not Estimable	3 (Low)
	Q-Pan = 1/3422 (0.03%); placebo = 0/1139 (0%)						
Fever							
RCT (1)	Not Serious	Not Serious	Not Serious	Serious*	1.37 [0.96-1.93]	13 more per 1000 [1 fewer-31 more]	2 (Moderate)
	Q-Pan = 156/3375 (4.6%); placebo = 38/1123 (3.4%)						

*Imprecision downgraded for wide confidence interval.

Influenza A (H5N1)

GRADE, IMMUNOGENICITY OUTCOMES (BENEFITS)

Immunogenicity Outcomes (Critical)

Study Design (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect		Quality
					RR [95% CI]	Risk Difference with Q-Pan [95% CI]	
21-day Homologus Seroprotection							
RCT (1)	Not Serious	Not Serious	Not Serious	Not Serious	53.11 [13.44-209.82]	898 more per 1000 [214-1000 more]	1 (High)
	Q-Pan = 1801/1967 (91.6%); placebo = 2/116 (1.7%)						
21-day Homologus Seroconversion							
RCT (1)	Not Serious	Not Serious	Not Serious	Not Serious	50.72 [12.84-200.39]	857 more per 1000 [204-1000 more]	1 (High)
	Q-Pan = 1720/1967 (87.4%); placebo = 2/116 (1.7%)						

Immunogenicity Outcomes (Important)

Study Design (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect		Quality
					RR [95% CI]	Risk Difference with Q-Pan [95% CI]	
6-month homologus seroprotection							
RCT (1)	Not Serious	Not Serious	Not Serious	Serious*	34.92 [5.00-243.92]	606 more/1000 [71-1000 more]	2 (Mod.)
	Q-Pan = 285/457 (62.4%); placebo = 1/56 (1.8%)						
6-month homologus seroconversion							
RCT (1)	Not Serious	Not Serious	Not Serious	Serious*	34.80 [4.98-243.07]	604 more/1000 [71-1000 more]	2 (Mod.)
	Q-Pan = 284/457 (62.1%); placebo = 1/56 (1.8%)						

*Imprecision downgraded for small sample size and wide confidence interval.

Evidence Table, Harms

Comparison: Q-Pan vs. placebo

Outcome	Importance	Study Design (# studies)	Findings (risk among vaccinated)	Evidence Type	Overall Evidence Type*
Any vaccine-related SAE	Critical	RCT (1)	No difference	2 (Mod.)	2 (Mod.)
Mortality	Critical	RCT (1)	Decreased risk	1 (High)	
Anaphylaxis, immediate hypersensitivity	Critical	None			
Narcolepsy	Critical	None			
Guillain-Barré syndrome	Critical	None			
Other serious neurologic outcomes	Critical	None			
Fatigue	Important	RCT (1)	Increased risk	1 (High)	
Headache	Important	RCT (1)	Increased risk	1 (High)	
Joint pain	Important	RCT (1)	Increased risk	1 (High)	
Muscle aches	Important	RCT (1)	Increased risk	1 (High)	
Shivering	Important	RCT (1)	Increased risk	1 (High)	
Sweating	Important	RCT (1)	No difference	2 (Mod.)	
Syncope	Important	RCT (1)	No difference	3 (Low)	
Fever	Important	RCT (1)	No difference	2 (Mod.)	

*Overall Evidence Type based on critical outcomes for which data are available.

Evidence Table, Benefits

Comparison: Q-Pan vs. placebo

Outcome			Importance	Study Design (# studies)	Findings	Evidence Type	Overall Evidence Type*
21 Day	Homologous	Seroprotection	Critical	RCT (1)	Increased response in vaccinated	1 (High)	1 (High)
		Seroconversion	Critical	RCT (1)		1 (High)	
	Heterologous	Seroprotection	Important	None			
		Seroconversion	Important	None			
6 Month	Homologous	Seroprotection	Important	RCT (1)	Increased response in vaccinated	2 (Mod.)	
		Seroconversion	Important	RCT (1)		2 (Mod.)	
	Heterologous	Seroprotection	Important	None			
		Seroconversion	Important	None			

*Overall Evidence Type based on critical outcomes

Considerations For Formulating Recommendations

Key Factor	Comments
Balance between benefits and harms	• Evidence based on a single study. • Benefit may not be generalizable (Clade evolution). • Data absent on 4 of 6 critical harms, resulting in uncertainty about balance of benefits vs. harms. • No data on efficacy. • Low exposure risk. • Zero transmission risk.
Evidence type	• Evidence Type 2 (Moderate) for safety. • Evidence Type 1 (High) immunogenicity.
Values and preferences	• No data on how target group values the outcome. • Potential recipients are few in number (<3,000).
Health economic analyses	• Not relevant as vaccine is paid for by U.S. government

DRAFT Recommendation for Influenza A (H5N1) Vaccine

- Category B
  - Adults aged ≥18 years with increased risk of occupational exposure during the inter-pandemic period may receive adjuvanted influenza A (H5N1) vaccine for protection against infection with influenza A (H5N1)*
- Intervention: Q-Pan, 2 doses administered 21 days apart
- Occupational exposure defined as follows
  - Laboratory workers who have contact or works with live influenza A (H5N1) virus or clinical samples from suspected cases
  - Experimental animal study workers who have contact with or care for influenza A (H5N1)-inoculated or infected animals, secretions or products
  - Public health responders investigating or managing suspected or confirmed human case(s) of influenza A (H5N1) infection
  - Public health responders investigating suspected or confirmed avian case(s) of influenza A (H5N1) infection
  - Others who work in locations where exposure to influenza A (H5N1) virus could occur

*H5N1 is used herein to denote any H5 subtypes with the A/goose/Guangdong/96 lineage H5

Influenza A (H5N1)

EXTRA SLIDES: DATA FROM FOUR PAPERS

Outcomes by Paper

Outcome			Importance	Langley 2010	Langley 2011	Laskok 2011	Nagai 2011
Harms							
Any vaccine-related SAE			Critical	✓	✓	✓	✓
Anaphylaxis, immediate hypersensitivity			Critical	-	-	-	-
Narcolepsy			Critical	-	-	-	-
Guillain-Barré syndrome			Critical	-	-	-	-
Other serious neurologic outcomes			Critical	-	-	-	-
Mortality			Critical	-	✓	✓	-
General symptoms (listed individually)			Important	✓	✓	✓	✓
Syncope			Important	-	✓	✓	-
Fever			Important	✓	✓	✓	✓
Benefits							
21-day	homologous	seroprotection	Critical	✓	✓	✓	✓
		seroconversion	Critical	✓	✓	✓	✓
	heterologous	seroprotection	Important	✓	-	✓	✓
		seroconversion	Important	✓	-	✓	✓
6-month	homologous	seroprotection	Important	✓	✓	✓	✓
		seroconversion	Important	✓	✓	✓	✓
	heterologous	seroprotection	Important	✓	-	-	✓
		seroconversion	Important	✓	-	✓	✓

Influenza A (H5N1)

DATA ON SAFETY (HARMS)

Safety: Any Vaccine-Related SAE* (Critical)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo	0/3424	0/1139	Not estimable
Langley 2010			
Q-Pan vs. nonadjuvanted	0/152	0/78	Not estimable
Q-Pan vs. AS03A Dresden	0/152	0/151	Not estimable
Q-Pan vs. AS03B Quebec	0/152	0/151	Not estimable
Q-Pan vs. AS03B Dresden	0/152	0/148	Not estimable
Lasko 2011			
Q-Pan vs. vaccine days 0/14	0/78	0/78	Not estimable
Q-Pan vs. vaccine days 0/7	0/78	0/78	Not estimable
Q-Pan vs. vaccine days 0/0	0/78	0/78	Not estimable
Nagai 2010	0/100		

*Langley 2011: Up to 6 months and study end (one year)
Langley 2010, Lasko, Nagai: Up to 6 months

Safety: Mortality* (Critical)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo	4/3424 (0.1%)	7/1139 (0.6%)	0.19 (0.06-0.65)
Langley 2010			
Q-Pan vs. nonadjuvanted			
Q-Pan vs. AS03A Dresden			
Q-Pan vs. AS03B Quebec			
Q-Pan vs. AS03B Dresden			
Lasko 2011			
Q-Pan vs. vaccine days 0/14	0/78	0/78	Not estimable
Q-Pan vs. vaccine days 0/7	0/78	1/78 (1.3%)	0.33 (0.01-8.06)
Q-Pan vs. vaccine days 0/0	0/78	0/78	Not estimable
Nagai 2010			

*Up to study end day

Safety: Fatigue* (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo	1148/3375 (34%)	253/1123 (23%)	1.51 (1.34-1.70)
Langley 2010			
Q-Pan vs. nonadjuvanted	64/152 (42%)	16/78 (21%)	2.05 (1.28-3.30)
Q-Pan vs. AS03A Dresden	64/152 (42%)	67/151 (44%)	0.95 (0.73-1.23)
Q-Pan vs. AS03B Quebec	64/152 (42%)	50/151 (33%)	1.27 (0.95-1.71)
Q-Pan vs. AS03B Dresden	64/152 (42%)	69/148 (47%)	0.90 (0.70-1.16)
Lasko 2011			
Q-Pan vs. vaccine days 0/14	23/76 (30%)	30/77 (39%)	0.78 (0.50-1.21)
Q-Pan vs. vaccine days 0/7	23/76 (30%)	22/77 (29%)	1.07 (0.66-1.75)
Q-Pan vs. vaccine days 0/0	23/76 (30%)	27/77 (35%)	0.86 (0.55-1.36)
Nagai 2010	71/100 (71%)		

*Within 7 days after any vaccination

Safety: Headache* (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo	1179/3375 (35%)	253/1123 (23%)	1.55 (1.38-1.74)
Langley 2010			
Q-Pan vs. nonadjuvanted	71/152 (47%)	25/78 (32%)	1.46 (1.01-2.10)
Q-Pan vs. AS03A Dresden	71/152 (47%)	66/151 (44%)	1.07 (0.83-1.37)
Q-Pan vs. AS03B Quebec	71/152 (47%)	61/151 (40%)	1.16 (0.89-1.50)
Q-Pan vs. AS03B Dresden	71/152 (47%)	61/148 (41%)	1.13 (0.88-1.46)
Lasko 2011			
Q-Pan vs. vaccine days 0/14	30/76 (39%)	28/77 (36%)	1.09 (0.72-1.63)
Q-Pan vs. vaccine days 0/7	30/76 (39%)	24/77 (31%)	1.28 (0.83-1.98)
Q-Pan vs. vaccine days 0/0	30/76 (39%)	20/77 (26%)	1.52 (0.95-2.43)
Nagai 2010	51/100 (51%)		

*Within 7 days after any vaccination

Safety: Joint Pain* (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo	853/3375 (25%)	136/1123 (12%)	2.09 (1.79-2.47)
Langley 2010			
Q-Pan vs. nonadjuvanted	49/152 (32%)	12/78 (15%)	2.10 (1.19-3.70)
Q-Pan vs. AS03A Dresden	49/152 (32%)	53/151 (35%)	0.92 (0.67-1.26)
Q-Pan vs. AS03B Quebec	49/152 (32%)	36/151 (24%)	1.35 (0.94-1.95)
Q-Pan vs. AS03B Dresden	49/152 (32%)	39/148 (26%)	1.22 (0.86-1.74)
Lasko 2011			
Q-Pan vs. vaccine days 0/14	20/76 (26%)	23/77 (30%)	0.88 (0.53-1.47)
Q-Pan vs. vaccine days 0/7	20/76 (26%)	22/77 (29%)	0.93 (0.56-1.56)
Q-Pan vs. vaccine days 0/0	20/76 (26%)	11/77 (14%)	1.84 (0.95-3.58)
Nagai 2010	34/100 (34%)		

*Within 7 days after any vaccination

Safety: Muscle Aches* (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo	1526/3375 (45%)	231/1123	2.20 (1.95-2.48)
Langley 2010			
Q-Pan vs. nonadjuvanted	74/152 (49%)	15/78 (19%)	2.53 (1.56-4.10)
Q-Pan vs. AS03A Dresden	74/152 (49%)	86/151 (57%)	0.85 (0.69-1.06)
Q-Pan vs. AS03B Quebec	74/152 (49%)	64/151 (42%)	1.15 (0.90-1.47)
Q-Pan vs. AS03B Dresden	74/152 (49%)	63/148 (43%)	1.14 (0.89-1.47)
Lasko 2011			
Q-Pan vs. vaccine days 0/14	49/76 (64%)	43/77 (56%)	1.15 (0.89-1.50)
Q-Pan vs. vaccine days 0/7	49/76 (64%)	40/77 (52%)	1.26 (0.96-1.65)
Q-Pan vs. vaccine days 0/0	49/76 (64%)	40/77 (52%)	1.24 (0.95-1.63)
Nagai 2010	70/100 (70%)		

*Within 7 days after any vaccination

Safety: Shivering* (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo	563/3375 (17%)	109/1123 (9.7%)	1.72 (1.42-2.09)
Langley 2010			
Q-Pan vs. nonadjuvanted	18/152 (35%)	4/78 (9.0%)	2.31 (0.81-6.59)
Q-Pan vs. AS03A Dresden	18/152 (35%)	27/151 (18%)	0.66 (0.38-1.15)
Q-Pan vs. AS03B Quebec	18/152 (35%)	21/151 (14%)	0.85 (0.47-1.53)
Q-Pan vs. AS03B Dresden	18/152 (35%)	17/148 (11%)	1.03 (0.55-1.92)
Lasko 2011			
Q-Pan vs. vaccine days 0/14	10/76 (13%)	13/77 (17%)	0.78 (0.36-1.67)
Q-Pan vs. vaccine days 0/7	10/76 (13%)	13/77 (17%)	0.79 (0.37-1.69)
Q-Pan vs. vaccine days 0/0	10/76 (13%)	10/77 (13%)	1.01 (0.45-2.29)
Nagai 2010	20/100 (20%)		

*Within 7 days after any vaccination

Safety: Sweating* (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo	362/3375 (11%)	109/1123 (9.7%)	1.11 (0.90-1.35)
Langley 2010			
Q-Pan vs. nonadjuvanted	23/152 (15%)	6/78 (7.7%)	1.97 (0.84-4.63)
Q-Pan vs. AS03A Dresden	23/152 (15%)	24/151 (16%)	0.95 (0.56-1.61)
Q-Pan vs. AS03B Quebec	23/152 (15%)	12/151 (7.9%)	1.90 (0.98-3.69)
Q-Pan vs. AS03B Dresden	23/152 (15%)	21/148 (14%)	1.07 (0.62-1.84)
Lasko 2011			
Q-Pan vs. vaccine days 0/14	15/76 (20%)	11/77 (14%)	1.38 (0.68-2.81)
Q-Pan vs. vaccine days 0/7	15/76 (20%)	8/77 (10%)	1.92 (0.87-4.27)
Q-Pan vs. vaccine days 0/0	15/76 (20%)	5/77 (6.5%)	3.04 (1.16-7.95)
Nagai 2010	21/100 (21%)		

*Within 7 days after any vaccination

Safety: Syncope* (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011 Q-Pan vs. placebo	 1/3422 (0.03%)	 0/1139	 1.00 (0.04-24.51)
Langley 2010 Q-Pan vs. nonadjuvanted Q-Pan vs. AS03A Dresden Q-Pan vs. AS03B Quebec Q-Pan vs. AS03B Dresden			
Lasko 2011 Q-Pan vs. vaccine days 0/14 Q-Pan vs. vaccine days 0/7 Q-Pan vs. vaccine days 0/0	 0/78 0/78 0/78	 0/78 1/78 (1.3%) 0/78	 Not estimable 0.33 (0.01-8.06) Not estimable
Nagai 2010			

*Langley: up to day 20 and day 84
Lasko: within 51-day period after primary vaccination

Safety: Fever* (T≥38^{O}C/100.4^{O}F) (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo	156/3375 (4.6%)	38/1123 (3.4%)	1.37 (0.96-1.93)
Langley 2010			
Q-Pan vs. nonadjuvanted	4/152 (2.6%)	0/78	4.65 (0.25-85.23)
Q-Pan vs. AS03A Dresden	4/152 (2.6%)	12/151 (7.9%)	0.33 (0.11-1.00)
Q-Pan vs. AS03B Quebec	4/152 (2.6%)	3/151 (2.0%)	1.32 (0.30-5.82)
Q-Pan vs. AS03B Dresden	4/152 (2.6%)	11/148 (7.4%)	0.35 (0.12-1.09)
Lasko 2011			
Q-Pan vs. vaccine days 0/14	2/76 (2.6%)	4/77 (5.2%)	0.51 (0.10-2.68)
Q-Pan vs. vaccine days 0/7	2/76 (2.6%)	1/77 (1.3%)	2.05 (0.19-22.17)
Q-Pan vs. vaccine days 0/0	2/76 (2.6%)	1/77 (1.3%)	2.03 (1.19-21.88)
Nagai 2010	11/100 (11%)		

*Within 7 days after any vaccination

Influenza A (H5N1)

DATA ON IMMUNOGENICITY (BENEFITS)

Immunogenicity: 21-day homologous seroprotection (Critical)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo	1801/1967 (92%)	2/116 (1.7%)	53.11 (13.44-209.82)
Langley 2010			
Q-Pan vs. nonadjuvanted	140/144 (97%)	13/75 (17%)	5.61 (3.42-9.20)
Q-Pan vs. AS03A Dresden	140/144 (97%)	135/140 (96%)	1.01 (0.97-1.05)
Q-Pan vs. AS03B Quebec	140/144 (97%)	131/146 (90%)	1.08 (1.02-1.15)
Q-Pan vs. AS03B Dresden	140/144 (97%)	131/142 (92%)	1.05 (1.00-1.11)
Lasko 2011			
Q-Pan vs. vaccine days 0/14	59/62 (95%)	64/69 (93%)	1.03 (0.94-1.12)
Q-Pan vs. vaccine days 0/7	59/62 (95%)	59/72 (82%)	1.16 (1.03-1.31)
Q-Pan vs. vaccine days 0/0	59/62 (95%)	57/74 (77%)	1.24 (1.08-1.42)
Nagai 2010	91/100 (91%)		

Immunogenicity: 21-day homologous seroconversion (Critical)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo	1720/1967 (87%)	2/116 (1.7%)	50.72 (12.584-200.39)
Langley 2010			
Q-Pan vs. nonadjuvanted	140/144 (97%)	13/75 (17%)	5.61 (3.42-9.20)
Q-Pan vs. AS03A Dresden	140/144 (97%)	135/140 (96%)	1.01 (0.97-1.05)
Q-Pan vs. AS03B Quebec	140/144 (97%	131/146 (90%)	1.08 (1.02-1.15)
Q-Pan vs. AS03B Dresden	140/144 (97%)	131/142 (92%)	1.05 (1.00-1.11)
Lasko 2011			
Q-Pan vs. vaccine days 0/14	59/62 (95%)	63/78 (81%)	1.18 (1.04-1.33)
Q-Pan vs. vaccine days 0/7	59/62 (95%)	57/73 (78%)	1.22 (1.07-1.39)
Q-Pan vs. vaccine days 0/0	59/62 (95%)	55/74 (74%)	1.28 (1.11-1.48)
Nagai 2010	91/100 (91%)		

Immunogenicity: 21-day heterologous seroprotection (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo			
Langley 2010			
Q-Pan vs. nonadjuvanted (VIET)	92/144 (64%)	3/78 (3.8%)	15.97 (5.23-48.73)
Q-Pan vs. AS03A Dresden (VIET)	92/144 (64%)	83/140 (59%)	1.08 (0.90-1.30)
Q-Pan vs. AS03B Quebec (VIET)	92/144 (64%)	88/146 (60%)	1.06 (0.89-1.27)
Q-Pan vs. AS03B Dresden (VIET)	92/144 (64%)	80/138 (58%)	1.10 (0.91-1.33)
Lasko 2011			
Q-Pan vs. vaccine days 0/14 (VIET)	42/62 (68%)	34/69 (49%)	1.37 (1.02-1.85)
Q-Pan vs. vaccine days 0/7 (VIET)	42/62 (68%)	22/72 (31%)	2.22 (1.50-3.27)
Q-Pan vs. vaccine days 0/0 (VIET)	42/62 (68%)	27/74 (36%)	1.86 (1.31-2.62)
Q-Pan vs. vaccine days 0/14 (TUR)	58/62 (94%)	55/69 (80%)	1.17 (1.02-1.37)
Q-Pan vs. vaccine days 0/7 (TUR)	58/62 (94%)	44/72 (61%)	1.53 (1.26-1.86)
Q-Pan vs. vaccine days 0/0 (TUR)	58/62 (94%	43/74 (58%)	1.61 (1.31-1.97)
Nagai 2010			
VIET	30/100 (30%)		
TUR	56/100 (56%)		

Immunogenicity: 21-day heterologous seroconversion (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo			
Langley 2010			
Q-Pan vs. nonadjuvanted (VIET)	89/144 (62%)	1/75 (1.3%)	46.35 (6.59-326.16)
Q-Pan vs. AS03A Dresden (VIET)	89/144 (62%)	79/140 (56%)	1.10 (0.90-1.33)
Q-Pan vs. AS03B Quebec (VIET)	89/144 (62%)	86/146 (59%)	1.05 (0.87-1.26)
Q-Pan vs. AS03B Dresden (VIET)	89/144 (62%)	76/138 (55%)	1.12 (0.92-1.37)
Lasko 2011			
Q-Pan vs. vaccine days 0/14 (VIET)	41/62 (66%)	35/78 (45%)	1.47 (1.09-2.00)
Q-Pan vs. vaccine days 0/7 (VIET)	41/62 (66%)	16/73 (22%)	3.02 (1.89-4.82)
Q-Pan vs. vaccine days 0/0 (VIET)	41/62 (66%)	19/74 (26%)	2.58 (1.68-3.95)
Q-Pan vs. vaccine days 0/14 (TUR)	52/62 (84%)	51/78 (65%)	1.28 (1.06-1.56)
Q-Pan vs. vaccine days 0/7 (TUR)	52/62 (84%)	41/73 (56%)	1.49 (1.19-1.88)
Q-Pan vs. vaccine days 0/0 (TUR)	52/62 (84%)	39/74 (53%)	1.59 (1.25-2.03)
Nagai 2010			
VIET	26/100 (26%)		
TUR	54/100 (54%)		

Immunogenicity: 6-month homologous seroprotection (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo	285/457 (62%)	1/56 (1.8%)	34.92 (5.00-243.92)
Langley 2010			
Q-Pan vs. nonadjuvanted	77/144 (53%)	2/75	20.05 (5.07-79.37)
Q-Pan vs. AS03A Dresden	77/144 (53%)	68/140	1.10 (0.88-1.38)
Q-Pan vs. AS03B Quebec	77/144 (53%	66/146	1.18 (0.94-1.50)
Q-Pan vs. AS03B Dresden	77/144 (53%)	63/142	1.21 (0.95-1.53)
Lasko 2011			
Q-Pan vs. vaccine days 0/14	46/65 (71%)	43/68 (63%)	1.12 (0.88-1.42)
Q-Pan vs. vaccine days 0/7	46/65 (71%)	31/71 (44%)	1.62 (1.19-2.20)
Q-Pan vs. vaccine days 0/0	46/65 (71%)	41/73 (56%)	1.26 (0.698-1.63)
Nagai 2010	67/99 (68%)		

Immunogenicity: 6-month homologous seroconversion (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo	284/457 (62%)	1/56 (1.8%)	34.80 (4.98-243.07)
Langley 2010			
Q-Pan vs. nonadjuvanted	77/144 (53%)	2/75 (2.7%)	20.05 (5.07-79.37)
Q-Pan vs. AS03A Dresden	77/144 (53%)	67/140 (48%)	1.12 (0.89-1.41)
Q-Pan vs. AS03B Quebec	77/144 (53%)	66/146 (45%)	1.18 (0.94-1.50)
Q-Pan vs. AS03B Dresden	77/144 (53%)	62/140 (44%)	1.21 (0.95-1.54)
Lasko 2011			
Q-Pan vs. vaccine days 0/14	45/65 (69%)	42/68 (62%)	1.12 (0.88-1.44)
Q-Pan vs. vaccine days 0/7	45/65 (69%)	29/71 (41%)	1.69 (1.23-2.34)
Q-Pan vs. vaccine days 0/0	45/65 (69%)	38/73 (52%)	1.33 (1.01-1.75)
Nagai 2010	67/99 (68%)		

Immunogenicity: 6-month heterologous seroprotection (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo			
Langley 2010			
Q-Pan vs. nonadjuvanted (VIET)	15/141 (11%)	1/74 (1.4%)	7.87 (1.06-58.44)
Q-Pan vs. AS03A Dresden (VIET)	15/141 (11%)	26/142 (18%)	0.58 (0.32-1.05)
Q-Pan vs. AS03B Quebec (VIET)	15/141 (11%)	19/145 (13%)	0.81 (0.43-1.53)
Q-Pan vs. AS03B Dresden (VIET)	15/141 (11%)	15/138 (11%)	0.98 (0.50-1.92)
Lasko 2011			
Q-Pan vs. vaccine days 0/14			
Q-Pan vs. vaccine days 0/7			
Q-Pan vs. vaccine days 0/0			
Nagai 2010			
VIET	15/99 (15%)		
TUR	50/99 (51%)		

Immunogenicity: 6-month heterologous seroconversion (Important)

Study	Q-Pan	Other	Risk Ratio (95% CI)
Langley 2011			
Q-Pan vs. placebo			
Langley 2010			
Q-Pan vs. nonadjuvanted (VIET)	13/141 (9.2%)	0/74	14.26 (0.86-236.58)
Q-Pan vs. AS03A Dresden (VIET)	13/141 (9.2%)	15/142 (11%)	0.87 (0.43-1.77)
Q-Pan vs. AS03B Quebec (VIET)	13/141 (9.2%)	15/145 (10%)	0.89 (0.44-1.80)
Q-Pan vs. AS03B Dresden (VIET)	13/141 (9.2%)	12/138 (8.7)	1.06 (0.50-2.24)
Lasko 2011			
Q-Pan vs. vaccine days 0/14 (TUR)	30/65 (46%)	22/68 (32%)	1.43 (0.93-2.20)
Q-Pan vs. vaccine days 0/7 (TUR)	30/65 (46%)	14/71 (20%)	2.34 (1.37-4.01)
Q-Pan vs. vaccine days 0/0 (TUR)	30/65 (46%)	18/73 (25%)	1.87 (1.16-3.02)
Nagai 2010			
VIET	12/99 (12%)		
TUR	48/99 (48%)		