DE GRUYTER OPEN
ASIAN BIOMEDICINE
DOI 10.1515/abm-2018-0008 — Asian Biomed (Res Rev News) 2017; 11(4): 359–64

Brief communication

Open access

Reactogenicity and safety of AS03$_B$-adjuvanted H5N1 influenza vaccine in children: an open-label, one-way, crossover trial

Patricia Izurieta[1,*], Pope Kosalaraksa[2], Louise Frenette[3], Mamadou Dramé[4], Bruce L. Innis[5,#], David W Vaughn[5], Anne Schuind[5]

Abstract

Background: Human cases of highly pathogenic avian-origin influenza A/H5N1 infection continue to be reported to the World Health Organization, and recent outbreaks of human cases of other zoonotic influenza strains highlight the continued need for strategies to mitigate influenza pandemic potential.

Methods: A Phase II–III randomized, placebo-controlled, observer-blind trial was conducted to assess the immunogenicity, reactogenicity, and safety of two 1.9 μg hemagglutinin doses of AS03$_B$-adjuvanted H5N1 (AS03$_B$-H5N1; A/Indonesia) vaccine in children (6 months to <18 years old) of Thailand, the United States, and Canada (Year 1, published elsewhere). After database lock in Year 1, the trial was unblinded, and children who had been randomized to receive placebo and continued to fulfill the eligibility criteria were invited to participate in an open-label, one-way, crossover safety extension phase, in which they received AS03$_B$-H5N1 vaccine. Here we report the safety analysis in Year 2.

Results: A total of 155 children were vaccinated in Year 2. The most frequent solicited adverse event (AE) during 7 days post vaccination was injection site pain. Irritability or fussiness was reported in about one-third of younger children (aged <6 years) during 7 days post vaccination and was the most common solicited general AE in this age group. Postvaccination temperature (≥38°C) was reported in 4 (5.1%) children. The most common solicited general AEs in older children (aged ≥6 years) were muscle aches, headache, and fatigue. The AS03$_B$-H5N1 vaccine had a clinically acceptable safety profile up to 385 days post vaccination.

Conclusions: Safety in the crossover phase was acceptable and consistent with that observed in vaccine recipients in the randomized, blinded phase of the study.

Clinical trial registration: ClinicalTrials.gov: NCT01310413.

Keywords: AS03$_B$ adjuvanted, children, H5N1, influenza, pandemic, safety, vaccine

***Correspondence to: Patricia Izurieta,** GSK, Rue Fleming 20, Wavre 1300, Belgium. e-mail: patricia.s.izurieta@gsk.com
[1] GSK, Rue Fleming 20, Wavre 1300, Belgium
[2] Department of Pediatrics, Khon Kaen University, Khon Kaen 40002, Thailand
[3] Q&T Research, Sherbrooke, QC J1J 2G2, Canada
[4] GSK, King of Prussia, PA 19406, USA
[5] Vaccines Discovery and Development, GSK, King of Prussia, PA 19406, USA
[#] Present address: PATH, 455 Massachusetts Ave NW, Suite 1000, Washington, DC 20001-2621, USA

Human cases of avian-origin influenza A infections are regularly reported in Asia, with most infections occurring in people who are in direct or indirect contact with poultry [1]. Human cases of highly pathogenic H5N1 infection continue to be reported to the World Health Organization, and in 2014, there were 52 human cases of H5N1, down from a peak of 115 cases in 2006 [2]. More recent outbreaks of human cases of other zoonotic influenza strains, such as H7N9, H9N2, and H10N8, highlight the continued need for strategies to mitigate influenza viruses with pandemic potential [1].

As part of a global pandemic preparedness program, GSK has developed 2 vaccines against the avian-origin H5N1 influenza viruses with pandemic potential, A/Indonesia/5/2005 and A/Vietnam/1194/2004. The vaccines are formulated with an oil-in-water adjuvant system, AS03, containing 11.86 mg of α-tocopherol for use in adults ($AS03_A$) and 5.93 mg of α-tocopherol for use in children ($AS03_B$). The vaccines, which are manufactured in Dresden, Germany, and Québec, Canada, have been shown to provide strong, durable, cross-clade immune responses with a clinically acceptable safety profile in adults [3–6]. In a Phase III study of $AS03_A$-adjuvanted H5N1 ($AS03_A$-H5N1) pandemic influenza vaccination in populations in Taiwan, Thailand, Singapore, and Hong Kong, the vaccine was found to be immunogenic and well tolerated [7]. A 4-year follow-up study showed that the vaccine was immunogenic and cross-reactive when given according to various prime-boost schedules, which is key to providing adequate and rapid vaccine coverage in the event of the emergence and rapid spread of a pandemic strain [8].

Because children are vulnerable to influenza viruses and are important for viral transmission, they represent a target population for vaccination in the event of an influenza outbreak [9, 10]. Therefore, to improve our understanding of pandemic influenza vaccines in this vulnerable group, the clinical trial program for AS03-adjuvanted avian-origin H5N1 influenza vaccines included large pediatric studies [11–13]. A Phase II–III randomized, placebo-controlled, observer-blind trial was conducted to assess the immunogenicity, reactogenicity, and safety of two 1.9 μg hemagglutinin (HA) doses of Québec-manufactured $AS03_B$-adjuvanted H5N1 ($AS03_B$-H5N1; A/Indonesia) vaccine in children aged from 6 months to <18 years recruited in Thailand, the United States (US), and Canada [14]. The study demonstrated robust hemagglutination inhibition antibody responses and a clinically acceptable safety profile [14].

After completion of the safety follow-up and database lock in Year 1, the trial was unblinded, and children who had been randomized to receive placebo and continued to fulfill the eligibility criteria were invited to participate in an open-label, one-way, crossover safety phase, in which they received $AS03_B$-H5N1 vaccine (Year 2). The rationale for the crossover study was to ensure that, according to ethical practice, children in the placebo group had the opportunity to receive active vaccine. A further objective was to increase the safety data for $AS03_B$-H5N1 vaccine. Here we report the safety analysis in Year 2.

Methods

The primary study was a Phase II–III randomized, placebo-controlled, observer-blind trial that assessed the immunogenicity, reactogenicity, and safety of a 2-dose primary series of $AS03_B$-H5N1 (A/Indonesia/5/2005) vaccine in children aged 6 months to <18 years. The study was conducted in Thailand, the US, and Canada (www.ClinicalTrials.gov, NCT01310413).

After the database lock and unbinding at the end of Year 1, an open, one-way, crossover safety phase was conducted, in which eligible children allocated to receive placebo in Year 1 were invited to receive $AS03_B$-H5N1 vaccine in Year 2. The randomized phase ended in October 2012, and the first child was enrolled in Year 2 on 1 November 2012. The most recent study visit/contact was on 26 January 2014, and the data lock point was 23 April 2014. The Year 2 outcomes were reactogenicity during the 7-day postvaccination period and safety from Day 0 to Day 385 after vaccination.

All protocols and study documents were approved by independent and local ethics committees including the institutional review board of Khon Kaen University (approval No. HE531398), Chesapeake Research Review (protocol no. 114464), and Comité central d'ethique de la recherche du ministre de la Santé et des Services sociaux (approval no. CCER 10-11–10) in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice Guidelines, the contemporary revision of the Declaration of Helsinki, and regulatory requirements. Informed consent was obtained for study participants before the start of Year 1 and again in Year 2. Parents or legal guardians provided informed written consent; children aged from 9 to <18 years provided their assent according to local standards. Children aged ≤18 years in Year 2 provided informed written consent.

The inclusion and exclusion criteria for the crossover study were the same as those previously reported for Year 1 apart from age range (i.e. children were about 1 year older in Year 2) [9]. In Year 2, eligible children received 2 doses of vaccine 21 days apart, containing 1.9 μg HA of H5N1 A/Indonesia/5/2005 adjuvanted with $AS03_B$ (lot number H5N1 vaccine, DFLPA606A; lot number AS03 adjuvant, AA03A209C).

Definitions and methods for assessing reactogenicity and safety were as previously described [14]. In brief, solicited injection site symptoms and solicited general symptoms were recorded during each 7-day postvaccination period and unsolicited adverse events (AEs) from Day 0 to Day 42 (21 days after each vaccination) were recorded on diary cards; medically attended adverse events (MAEs), serious adverse events (SAEs), and potential immune-mediated diseases (pIMDs) were recorded from Day 0 to Day 385.

For medically attended events, the investigator reviewed available documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) relative to the event and recorded relevant information as applicable on the participant's electronic case report form. The assessment of an SAE or pIMD and its severity was based on the investigator's clinical judgment. Pain at the injection site was assessed and scored as follows: 0 (no pain), 1 (minor reaction to touch in children aged <6 years and pain on touching the site in children aged ≥6 years), 2 (cries/protests on touch in children aged <6 years and pain on moving the limb, which interfered with normal activities in children aged ≥6 years), or 3 (cries when limb was moved/spontaneously painful in children aged <6 years and significant pain at rest in children aged ≥6 years). Unsolicited events were coded using the Medical Dictionary for Regulatory Activities, and investigators provided causality assessments.

The reactogenicity data are provided as the overall frequency of solicited events pooled for each postvaccination period with 95% confidence intervals (CI). Unsolicited AEs, SAEs, and MAEs were tabulated with 95% CIs. Safety was assessed in the total vaccinated cohort (TVC), which included all children who received at least one dose of vaccine in Year 2. Reactogenicity was assessed in the TVC participants with data available (i.e. those who returned the diary cards).

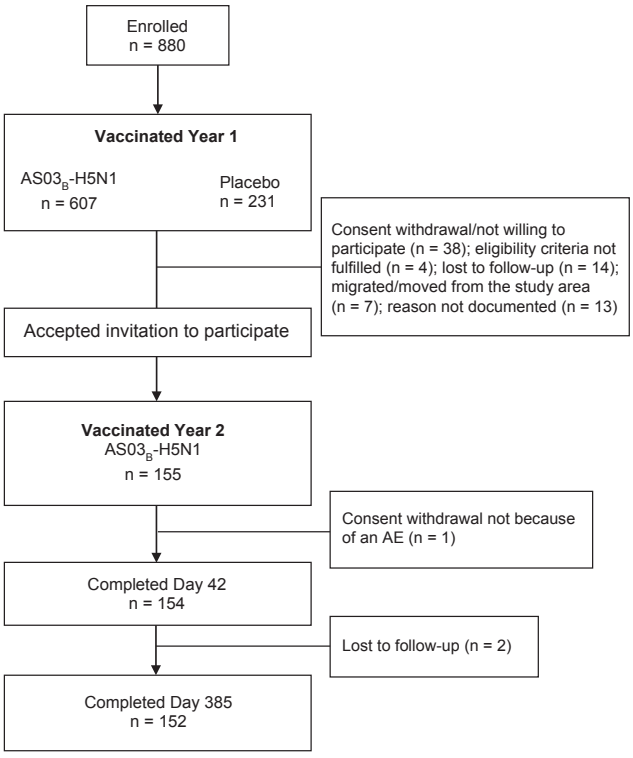

Figure 1. Participant flow diagram
AE = adverse event, AS03$_B$-H5N1 = AS03$_B$-adjuvanted H5N1

Results

Of 231 children who received a placebo in Year 1, 155 participants accepted the invitation to participate in Year 2 and received at least one dose of AS03$_B$-H5N1 vaccine (**Figure 1**). Among them, 154 received 2 doses of the vaccine and 1 participant received one dose of the vaccine.

Of eligible children who did not participate in Year 2, the reasons were consent withdrawal or not willing to participate (n = 39), eligibility criteria not fulfilled (n = 4), lost to follow-up (n = 14), migrated or moved from the study area (n = 6), and reason not documented (n = 13). The age of children at baseline in Year 2 TVC varied between 19 and 226 months. In the TVC, 47.7% were of Southeast Asian ancestry, 38.7% were white of European ancestry, and 11.0% were African or African American. Three children were withdrawn because of consent withdrawal not related to safety (n = 1) and loss to follow-up (n = 2).

During the 7-day postvaccination period, the most commonly reported solicited injection site symptom was pain, which was reported in 111 (72.1%) children. Grade 3 injection site pain was reported in 8 (5.2%) children. Redness and swelling were reported by 6 (3.9%) and 5 (3.2%) children, respectively, with no Grade 3 redness or swelling (>100 mm) being reported. In children aged <6 years (n = 79), the most frequent solicited general symptom was irritability or fussiness (n = 28; 35.4%). The incidence of fever (temperature ≥38.0°C) was observed in 4 (5.1%) children, with Grade 3 fever (≥39.0°C) in 2 (2.5%) children.

In children aged ≥ 6 years (n = 75), the most common solicited general events were muscle aches (n = 34; 45.3%), headache (n = 24; 32.0%), and fatigue (n = 18; 24.0%). The incidence of fever (temperature ≥38.0°C) was observed in 1 (1.3%) child, and there were no reports of Grade 3 fever. Reactogenicity is given in **Table 1**.

The rate of unsolicited AEs reported up to Day 42 was 26.5% (n = 41; 95% CI 19.7, 34.1), which were most frequently nasopharyngitis (n = 10; 6.5%; 95% CI 3.1, 11.5), cough (n = 9; 5.8%; 95% CI 2.7, 10.7), and vomiting and

Table 1. Solicited injection site and general AEs in the TVC

Solicited symptom	TVC† (N = 154)							
	All events				Grade 3			
	n			% (95% CI)	n			% (95% CI)
Injection site								
Pain	111			72.1 (64.3, 79.0)	8			5.2 (2.3, 10.0)
Redness	6			3.9 (1.4, 8.3)	0			0.0 (0.0, 2.4)
Swelling	5			3.2 (1.1, 7.4)	0			0.0 (0.0, 2.4)
	<6 years (n = 79)				6–<18 years (n = 75)			
	All events		Grade 3		All events		Grade 3	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
General								
Drowsiness	23	29.1 (19.4, 40.4)	1	1.3 (0.0, 6.9)	–		–	
Irritability/fussiness	28	35.4 (25.0, 47.0)	1	1.3 (0.0, 6.9)	–		–	
Loss of appetite	18	22.8 (14.1, 33.6)	0	0.0 (0.0, 4.6)	–		–	
Increased temperature	4	5.1 (1.4, 12.5)	2	2.5 (0.3, 8.8)‡	1	1.3 (0.0, 7.2)	0	0.0 (0.0, 4.8)‡
Fatigue	–		–		18	24.0 (14.9, 35.3)	1	1.3 (0.0, 7.2)
Gastrointestinal disorder	–		–		7	9.3 (3.8, 18.3)	0	0.0 (0.0, 4.8)
Headache	–		–		24	32.0 (21.7, 43.8)	1	1.3 (0.0, 7.2)
Increased sweating	–		–		5	6.7 (2.2, 14.9)	0	0.0 (0.0, 4.8)
Joint pain	–		–		14	18.7 (10.6, 29.3)	0	0.0 (0.0, 4.8)
Muscle aches	–		–		34	45.3 (33.8, 57.3)	0	0.0 (0.0, 4.8)
Shivering (chills)	–		–		7	9.3 (3.8, 18.3)	2	2.7 (0.3, 9.3)

Grade 3 redness or swelling >100 mm

†Includes all children who received at least one dose of vaccine for whom diary cards of solicited events were available, ‡≥39°C

AE, adverse event; CI, confidence interval; n, number of participants reporting the event at least once; N, number of participants with one or more vaccine dose; TVC, total vaccinated cohort

Table 2. Summary of unsolicited AEs in the TVC

AE type	TVC (N = 155)	
	n	% (95% CI)
Days 0–42		
≥1 AE(s)	41	26.5 (19.7, 34.1)
≥1 Grade 3 AE(s)	3	1.9 (0.4, 5.6)
≥1 AE(s) causally related to vaccination†	3	1.9 (0.4, 5.6)
Days 0–385		
≥1 MAE(s)	36	23.2 (16.8, 30.7)
≥1 SAE(s)	2	1.3 (0.2, 4.6)
≥1 pIMD	0	–

†Causal relationship with vaccination based on the medical assessment by the investigator

AE, adverse event; CI, confidence interval; MAE, medically attended adverse event; n, number of participants reporting the event at least once; N, number of participants with one or more vaccine dose; pIMD, potential immune-mediated disease; SAE, serious adverse event; TVC, total vaccinated cohort

pyrexia (each: n = 4; 2.6%; 95% CI 0.7, 6.5). The frequency of Grade 3 unsolicited AEs was low. Unsolicited AEs are summarized in **Table 2**.

The rate of MAEs up to Day 385 was 23.2% (n = 36; 95% CI 16.8, 30.7), which were most frequently pyrexia, upper respiratory tract infection, and cough, with each symptom reported at a rate of 2.6% (each n = 4; 95% CI 0.7, 6.5). There were 2 SAEs up to Day 385, which were scarlet fever and wound that were not considered by the investigator to be causally related to vaccination (each n = 1; 0.6%; 95% CI 0.2, 4.6). There were no pIMDs reported during Year 2.

Discussion

In this open-label, one-way, crossover safety extension phase, children who had received placebo in the randomized phase of the study (Year 1) were invited to receive a 2-dose primary series of $AS03_B$-H5N1 vaccine in Year 2. The rationale for the crossover phase was to ensure that, according to ethical practice, children in the placebo group in Year 1 had the opportunity to receive active vaccine. A further objective was to increase the safety data for $AS03_B$-H5N1 vaccine. Our results showed that the most frequent solicited AE (local and general) was injection site pain with mostly mild or moderate

intensity. Although the incidence of unsolicited AEs in Year 1 was consistent between the vaccine and placebo groups, the rate of unsolicited AEs in Year 2 was lower than that reported in vaccine recipients in Year 1.

Injection site pain was the most frequent solicited symptom during the 7-day postvaccination period reported across the development program for AS03-adjuvanted H5N1 vaccines in adults (Québec- and Dresden-manufactured vaccines) and in children (Dresden-manufactured vaccine) [12, 13]. In the previous open-label pediatric study of Dresden-manufactured H5N1 vaccine, 2 doses (1.9 μg HA) of AS03$_B$-H5N1 vaccine (n = 51) was associated with an overall rate of injection site pain of 60.8% in children aged 3–5 years and 86.3% in children aged 6–9 years [8]. Our study of Québec-manufactured AS03$_B$-H5N1 vaccine (1.9 μg HA) included children with a broader age range than that in the previous study and showed that the incidence of solicited injection site pain in vaccine recipients overall was 67.2% in Year 1 and 72.1% in Year 2 [14]. In both years, the incidence of Grade 3 pain was low (3.3% in Year 1 and 5.2% in Year 2), and the incidence of Grade 3 redness and swelling (>100 mm) was ≤0.5% in Year 1, with no reports in Year 2.

The profile of general solicited events overall showed that the vaccine was well tolerated by this pediatric population. Irritability or fussiness was reported in about one-third of younger children (aged <6 years) during the 7-day postvaccination period and was the most common solicited general event in this age group. A postvaccination temperature (≥38°C) was reported in 4 (5.1%) children, including reports of fever ≥39.0°C in 2 children who were aged <36 months. The most common solicited general AEs in older children (aged ≥6 years) were muscle aches, headache, and fatigue. These results are similar to those reported in the vaccine recipients group in Year 1 during the 7-day postvaccination period: irritability or fussiness was the most reported symptom in children aged <6 years with an incidence of 43.5%, and in children aged ≥6 years, muscle aches, headache, and fatigue were also included in the most commonly reported solicited general symptoms (incidence rates of these symptoms were 39.8%, 32.4%, and 28.8%, respectively, in Year 1) [14]. The AS03$_B$-H5N1 vaccine had a clinically acceptable safety profile up to 385 days post vaccination. Unsolicited AEs during the first 42 days of the safety follow-up and MAEs during the 385-day follow-up were most frequent symptoms associated with upper respiratory tract infection such as nasopharyngitis and cough, which are common conditions in children. During the 385-day follow-up, there were 2 SAEs (scarlet fever and wound), which were not considered to be vaccine related, and no pIMDs were reported.

These data increase the safety database for this vaccine from 607 to 762 children who received at least one dose of Québec-manufactured AS03$_B$-H5N1 (A/Indonesia) vaccine. Nevertheless, experience with this vaccine remains too limited to exclude uncommon AEs occurring at rates of <1 in 250.

In our study, the incidence of unsolicited AEs in children who received AS03$_B$-H5N1 vaccine was lower in Year 2 than in Year 1, including the rates of children with one or more AE at Day 42, which was 26.5% and 40.2% in Years 2 and 1, respectively [14]. However, the population samples are not directly comparable because of the differences in age and study environment, i.e. children in Year 2 were about a year older than those in Year 1, and the Year 2 crossover study included eligible children from Year 1 who opted to participate. Overall, the incidence of unsolicited AEs was consistent with that of the open-label pediatric study of Dresden-manufactured H5N1 (A/Vietnam) vaccine in children aged 3–9 years [11].

The main limitations of the Year 2 crossover phase were that it was an open-label phase and lacked a parallel control group. A further limitation was the potential for selection bias among families who accepted the invitation to receive the vaccine in Year 2. At the time of the study, human cases of avian-influenza infection were not widely reported and the threat of "bird flu" was not prominent in the media and in the public consciousness. As such, the perception of the likelihood of benefit from vaccination may not have outweighed the demands and discomfort of study participation. Despite this, participation in Year 2 was relatively high, suggesting that the experience in Year 1 was favorable and that the willingness to contribute to the understanding of influenza pandemic vaccines was good (of the 231 placebo recipients in Year 1, 155 [60%] enrolled in Year 2). Of note, the randomized-controlled part of this trial (Year 1) was the basis for the regulatory approval of the pediatric dose (1.9 μg HA with AS03$_B$) in the US and Canada for use according to official recommendations.

Conclusions

In summary, this open-label, one-way crossover extension phase (Year 2) included 155 children who were aged from 6 months to <18 years at study entry in the randomized blinded phase (Year 1). Eligible placebo recipients from Year 1 received a 2-dose primary series of AS03$_B$-H5N1 vaccine in Year 2. Safety in the crossover phase was acceptable and consistent with that observed in 607 vaccine recipients in the randomized, controlled, blinded study phase.

Author contributions. PI was the clinical development manager responsible for all aspects of the trial (study design, collection, analysis, and interpretation of results). PK and LF were principal investigators responsible for data collection and interpretation of results. MD was the statistician involved in the study design, assembly, analysis, and interpretation of

the results. BLI was mainly involved in the study design and interpretation of results. DWV was involved in all aspects of the trial (study design, collection, analysis, and interpretation of results). AS was involved in analysis of data and interpretation of results. All authors were involved in the writing and critical review of the manuscript, have approved the final manuscript, and take responsibility for the statements made in the article.

Acknowledgments. This work was supported by GlaxoSmithKline Biologicals SA and by the U.S. Department of Health and Human Services (HHS), Assistant Secretary of Preparedness and Response, and Biomedical Advanced Research and Development Authority (contract HHS O100200700029C). GlaxoSmithKline Biologicals SA was involved in all stages of study conduct, including analysis of the data, and paid the costs associated with the development and publication of this manuscript.

The authors are indebted to the study participants and their parents, as well as the clinicians and nurses at the study sites. The authors thank investigators Brandon Essink, Darrell Herrington, Ginette Girard, Robyn Hartvickson, William Douglas, and William Seger for their valuable contributions to this work. The authors also thank Stephanie Sharp (Veristat, on behalf of GSK) for writing the Year 2 study report, Janine Linden for integrating the clinical study report, Judy Napolitano and Amy Robey (SynteractHCR, on behalf of GSK) and Jennifer Gearhart (Hcr America, on behalf of GSK) for study coordination, Annick Moon (Moon Medical Communications Ltd, on behalf of GSK) for manuscript writing, Shirin Khalili and Julie Todoroff (XPE Pharma & Science, on behalf of GSK) for manuscript coordination, and the Independent Data Monitoring Committee for the study oversight.

Conflict of interest statement. PI, MD, DWV, and AS are employees of the GSK group of companies. BLI was an employee of the GSK group of companies during the study. PI, BLI, DWV, and AS own stock/stock options/restricted shares in the GSK group of companies. PK reports receiving a grant from the GSK group of companies to attend an academic meeting and training workshop outside the submitted work. LF reports receiving support for travel to meetings for this study or other purposes from the GSK group of companies.

References

[1] Trombetta C, Piccirella S, Perini D, Kistner O, Montomoli E. Emerging influenza strains in the last two decades: a threat of a new pandemic?. Vaccines. 2015; 3:172–85.

[2] World Health Organization. Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO. [online] 2016. [cited 2016 May 1]. Available from: *http://www.who.int/influenza/human_animal_interface/EN_GIP_20160404cumulativenumberH5N1cases.pdf?ua=1*

[3] Langley JM, Frenette L, Ferguson L, Riff D, Sheldon E, Risi G, et al. Safety and cross-reactive immunogenicity of candidate AS03-adjuvanted prepandemic H5N1 influenza vaccines: a randomized controlled phase 1/2 trial in adults. J Infect Dis. 2010; 201:1644–53.

[4] Langley JM, Risi G, Caldwell M, Gilderman L, Berwald B, Fogarty C, et al. Dose-sparing H5N1 A/Indonesia/05/2005 pre-pandemic influenza vaccine in adults and elderly adults: a phase III, placebo-controlled, randomized study. J Infect Dis. 2011; 203:1729–38.

[5] Leroux-Roels I, Bernhard R, Gérard P, Dramé M, Hanon E, Leroux-Roels G. Broad Clade 2 cross-reactive immunity induced by an adjuvanted clade 1 rH5N1 pandemic influenza vaccine. PLoS One. 2008; 3:e1665.

[6] Leroux-Roels I, Borkowski A, Vanwolleghem T, Dramé M, Clement F, Hons E, 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.

[7] Chu DW, Hwang SJ, Lim FS, Oh HM, Thongcharoen P, Yang PC, et al. Immunogenicity and tolerability of an $AS03_A$-adjuvanted prepandemic influenza vaccine: A phase III study in a large population of Asian adults. Vaccine. 2009; 27:7428–35.

[8] Gillard P, Chu DW, Hwang SJ, Yang PC, Thongcharoen P, Lim FS, et al. Long-term booster schedules with $AS03_A$-adjuvanted heterologous H5N1 vaccines induces rapid and broad immune responses in Asian adults. BMC Infect Dis. 2014; 14:142.

[9] Basta NE, Chao DL, Halloran ME, Matrajt L, Longini IM Jr. Strategies for pandemic and seasonal influenza vaccination of schoolchildren in the United States. Am J Epidemiol. 2009; 170:679–86.

[10] Jennings LC, Monto AS, Chan PK, Szucs TD, Nicholson KG. Stockpiling prepandemic influenza vaccines: a new cornerstone of pandemic preparedness plans. Lancet Infect Dis. 2008; 8:650–8.

[11] Díez-Domingo J, Baldó JM, Planelles-Catarino MV, Garcés-Sánchez M, Ubeda I, Jubert-Rosich A, et al. Phase II, randomized, open, controlled study of AS03-adjuvanted H5N1 pre-pandemic influenza vaccine in children aged 3 to 9 years: follow-up of safety and immunogenicity persistence at 24 months post-vaccination. Influenza Other Respir Viruses. 2015; 9:68–77.

[12] Díez-Domingo J, Garcés-Sánchez M, Baldó JM, Planelles MV, Ubeda I, JuBert A, et al. Immunogenicity and safety of H5N1 A/Vietnam/1194/2004 (Clade 1) AS03-adjuvanted prepandemic candidate influenza vaccines in children aged 3 to 9 years: a phase ii, randomized, open, controlled study. Pediatr Infect Dis J. 2010; 29:e35–46.

[13] Rümke HC, Bayas JM, de Juanes JR, Caso C, Richardus JH, Campins M, et al. Safety and reactogenicity profile of an adjuvanted H5N1 pandemic candidate vaccine in adults within a phase III safety trial. Vaccine. 2008; 26:2378–88.

[14] Kosalaraksa P, Jeanfreau R, Frenette L, Drame M, Madariaga M, Innis BL, et al. $AS03_B$-adjuvanted H5N1 influenza vaccine in children 6 months through 17 years of age: a phase 2/3 randomized, placebo-controlled, observer-blinded trial. J Infect Dis. 2015; 211:801–10.