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Short communication

Compatibility of AS03-adjuvanted H1N1pdm09 and seasonal trivalent influenza vaccines in adults: Results of a randomized, controlled trial☆

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ABSTRACT

When Canada chose a novel adjuvanted vaccine to combat the 2009 influenza pandemic, seasonal trivalent inactivated vaccine (TIV) was also available but compatibility of the two had not been assessed. To compare responses after concurrent or sequential administration of these vaccines, adults 20–59 years old were randomly assigned (1:1) to receive AS03-adjuvanted H1N1pdm09 vaccine (Arepanrix®, GSK, Quebec City, Quebec), with TIV (Vaxigrip®, Sanofi Pasteur, Toronto) given concurrently or 21 days later. Blood was obtained at baseline and 21 days after each vaccination to measure hemagglutination inhibition (HAI) titers. Adverse effects were assessed using symptom diaries and personal interviews. 282 participants completed the study (concurrent vaccines 145, sequential vaccines 137). HAI titers to H1N1pdm09 were ≥40 at baseline in 15–18% of participants and following vaccination in 91–92%. Initially seropositive subjects (titer ≥10) had lower H1N1pdm09 geometric mean HAI titers (GMT) after concurrent than separate vaccinations (320.0 vs 476.5, $p = 0.039$) but both exceeded GM responses of initially naïve participants, which were unaffected by concurrent TIV. Responses to TIV were not lower after concurrent than separate vaccination. Adverse event rates were not increased by concurrent vaccinations above those with H1N1pdm09 vaccine alone. This adjuvanted H1N1pdm09 vaccine was immunogenic and compatible with concurrently administered TIV.

1. Introduction

During the A/H1N1/2009 influenza pandemic [1], Canada used a novel, locally produced AS03-adjuvanted H1N1pdm09 vaccine (Arepanrix™, GSK Canada) [2]. This was manufactured equivalently to an AS03-adjuvanted H1N1pdm09 vaccine (Pandemrix™, GSK Belgium) [3,4] produced in Europe and widely used internationally. Studies of adults given either vaccine indicated that a single dose of 3.75 μg hemagglutinin was sufficiently immunogenic [2,4,5]. The H1N1pdm09 vaccines and trivalent inactivated seasonal influenza vaccines (TIV) were both available in late 2009 but had not been assessed for compatibility with concurrent administration. Our newly formed PHAC/CIHR Influenza Research Network [6,7] undertook an assessment of the compatibility of the two vaccines.

2. Methods (abbreviated)

The study methodology is fully described as Supplemental information (online). In brief, this multicenter, randomized, parallel-group trial compared immune responses and safety observations after concurrent or sequential administration of H1N1pdm09 and TIV vaccines. Participants were generally healthy adults 20–59 years of age, who provided informed consent at study entry. Ethics approval was granted by each participating institution. The ClinicalTrials.gov registration number was NCT01000584.

Participants were randomized centrally using a web-based method with stratification by age and sex to either concurrent

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H1N1pdm09 and TIV vaccinations in opposite arms or the pandemic vaccine alone, followed 21–28 days later by TIV. Vaccines were both egg-derived, formalin-inactivated, detergent-split preparations, with thimerosal preservative. Both were injected in the deltoid muscle in 0.5 mL doses. The pandemic vaccine was a monovalent A/California/7/2009 (H1N1v-like) product that was mixed just prior to use with ASO3® oil-in-water adjuvant (Arepanrix®, GSK, Quebec City, Quebec) delivering 3.75 μg hemagglutinin per dose. The TIV for 2009–2010 (Vaxigrip®, Sanofi Pasteur, Toronto, Ontario) contained 15 μg of each WHO-recommended strain per dose. Participants were asked to complete a daily symptom diary for a week after vaccination(s) and to note any health care utilization while enrolled. Observations were collected by interviews 7 and 21–28 days after each vaccination. Clotted blood samples were obtained at baseline and 21–28 days after vaccination(s). Sera were tested at a national reference laboratory for hemagglutination inhibiting (HAI) antibodies to each vaccine strain.

Serologic responses were assessed according to international (EMEA/CHMP) criteria [8,9] for adults <60 years of age. These include seroconversion rate >40%, seroprotection (titer ≥40) rate >70% and fold-increase in geometric mean titer (GMT) from baseline >2.5. Responses were assessed separately in subjects without and with baseline antibody (titer ≥10) to H1N1pdm09 virus (referred to as naïve and primed, respectively). Influences on responses were examined by multivariable analysis. The safety assessment [10] considered the daily and week-long cumulative rates of solicited local and general adverse events, rates of severe adverse events and rates of any vaccination-related health care utilization. Vaccines were considered compatible if concurrent administration did not significantly increase rates of adverse effects or decrease rates of immune responses, compared to separately administered vaccines. Intended enrollment was 150 subjects per group.

3. Results

Enrollment included 291 participants: 146 were randomly assigned concurrent and 144 sequential vaccinations, with 40–88 participants enrolled per center. The two study groups were well matched (Supplementary table). Protocol completion rates exceeded 95%, with >99% of intended vaccinations given and safety data obtained. Two blood samples had insufficient volume for testing (Supplementary figure). No safety observations or HAI results required exclusion, enabling analysis per protocol.

3.1. Sero-responses to H1N1pdm09 vaccine

As summarized in Table 1, seroprotection and seroconversion rates did not differ after separate or concurrent vaccination but those given TIV concurrently had lower post-vaccination GMT ($p = 0.053$) and fold-rise in GMT from baseline ($p = 0.003$). About one-third of subjects had detectable antibody (HAI titer ≥10) at baseline, more often in those 20–39 than 40–59 years old (42% vs 28%, respectively, $p = 0.01$). The proportion of primed subjects at baseline did not differ significantly with health status, prior TIV vaccination or sex (data not shown). Primed individuals boosted strongly after vaccination, with GMTs 3-fold greater than in naïve subjects (Table 1). Age influenced responses of naïve subjects, with titers ≥40 achieved by 137 of 138 (99.3%) 20–39 year olds and 124 of 147 (84.4%) 40–59 year olds ($p = 0.009$). In multivariable analyses age accounted for almost all of the variability in responses (data not shown). Giving TIV concurrently did not significantly reduce responses to pandemic vaccine in naïve subjects (Table 1) but primed subjects boosted less strongly, achieving one half the fold rise in GMT from baseline seen with concurrent vaccinations ($p = 0.002$).

Table 1
HAI antibody titers to adjuvanted H1N1pdm09 (H1N1) vaccine, measured before and 21–28 days after vaccination, in subjects given pandemic vaccine alone (H1N1 column) or with TIV (H1N1 + TIV column), distinguishing between those with (primed) and without (naïve) antibody to H1N1pdm09 prior to vaccination.

Parameter	H1N1 + TIV	H1N1 alone	*p* value
Baseline titer			
≥10[a]	53/146 (36.3%)	48/144 (33.3%)	0.623
≥40	27/146 (18.5%)	22/144 (15.3%)	0.532
GMT[c]	10.5 (8.7–12.8[b])	9.1 (7.7–10.7)	0.247
Post-vaccination titer ≥40			
All subjects	132/145 (91.0%) (85.2, 95.1[b])	129/140 (92.1%) (86.4, 96.0[b])	0.832
naïve subjects	79/92 (85.9%) (77.0, 92.3)	83/93 (89.2%) (81.1, 95.7)	0.512
Primed subjects	53/53 (100%) (93.3, 100)	46/47 (97.9%) (88.7, 99.9)	0.470
Post-vaccination GMT[c]			
All subjects	159.6 (132, 194[b])	212.7 (171, 265[b])	0.053
Naïve subjects	106.9 (84, 135)	141.5 (109, 183)	0.114
Primed subjects	320.0 (250, 410)	476.5 (355, 640)	0.039
GMT[c] fold rise from baseline			
All subjects	15.1 (12.3, 18.4[b])	23.4 (19.0, 28.7[b])	0.003
Naïve subjects	21.1 (16.7, 26.8)	27.5 (21.2, 35.6)	0.140
Primed subjects	8.4 (6.2, 11.4)	17.0 (12.1, 23.8)	0.002
Seroconversion rate[d]			
All subjects	133/145 (91.7%) (86.0, 95.7[b])	135/140 (96.4%) (91.9, 98.8[b])	0.132
Naïve subjects	88/92 (95.7%) (89.2, 98.8)	91/93 (97.8%) (92.4, 99.7)	0.444
Primed subjects	45/53 (84.9%) (72.4, 93.3)	44/47 (93.6%) (82.5, 98.7)	0.210

[a] Lower limit of detection.
[b] 95% confidence interval.
[c] GMT, geometric mean titer.
[d] Seroconversion defined as a ≥4-fold increase in titer or conversion from negative baseline to titer ≥40.

Table 2
HAI antibody titers to seasonal influenza vaccine strains in subjects given concurrent adjuvanted pandemic vaccine (H1N1 + TIV column) or delayed TIV alone, measured before and 21–28 days after TIV vaccination.

Parameter	H1N1 + TIV	Delayed TIV	*p* value
Baseline titer ≥40			
A/H3N2	35/146 (24.0%)	43/144 (29.9%)	0.290
H1N1/Brisbane	55/146 (37.7%)	43/144 (29.9%)	0.173
B/Brisbane	45/146 (30.8%)	33/144 (22.9%)	0.146
Post-vaccination:			
Titer ≥40 (seroprotection)			
A/H3N2	104/145 (71.7%) (63.7, 78.9[a])	96/137 (70.1%) (61.7, 77.6[a])	0.794
H1N1/Brisbane	117/145 (80.7%) (73.3, 86.8)	97/137 (70.8%) (62.4, 78.3)	0.070
B/Brisbane	107/145 (73.8%) (65.8, 80.7)	80/137 (58.4%) (49.7, 66.7)	0.008
Geometric mean titer (GMT)			
A/H3N2	57.9 (48.2, 69.6[a])	54.2 (44.8, 65.5[a])	0.618
H1N1/Brisbane	84.3 (68.7, 103.5)	54.3 (44.8, 65.8)	0.002
B/Brisbane	64.0 (51.9, 79.0)	44.5 (35.8, 55.3)	0.017
GMT fold rise from baseline			
A/H3N2	3.83 (3.1, 4.7[a])	3.32 (2.7, 4.1[a])	0.321
H1N1/Brisbane	4.32 (3.4, 5.5)	3.01 (2.5, 3.7)	0.021
B/Brisbane	3.6 (2.9, 4.4)	3.01 (2.5, 3.7)	0.210
Seroconversion[b]			
A/H3N2	57/145 (39.3%) (31.3, 47.8[a])	49/137 (35.8%) (27.8, 44.4[a])	0.623
H1N1/Brisbane	63/145 (43.4%) (35.2, 51.9)	47/137 (34.3%) (26.4, 42.9)	0.143
B/Brisbane	63/145 (43.4%) (35.2, 51.9)	44/137 (32.1%) (24.4, 40.6)	0.065

[a] 95% confidence interval.
[b] Seroconversion defined as a ≥4-fold rise in titer or conversion from a negative baseline to a titer ≥40.

3.2. Sero-responses to TIV strains

Responses to TIV components are summarized in Table 2. A minority of subjects had titers ≥40 to the vaccine strains at baseline. Responses after concurrent vaccination were not reduced by any measure compared with delayed vaccination. Unexpectedly, GMTs and seroprotection rates were higher after concurrent vaccination than after separate, delayed vaccination for H1N1/Brisbane and B strains.

3.3. Safety assessment following vaccinations

As Fig. 1A illustrates, injection site reactions were more common after H1N1pdm09 than TIV vaccine. Moderate/severe injection site pain followed 38–39% of H1N1pdm09 doses compared to 1–8% of TIV doses but 90% of H1N1pdm09 vaccinees were pain-free within 4 days (data not shown). Redness, swelling and armpit tenderness were more frequent after H1N1pdm09 than TIV vaccine.

No fevers followed the vaccinations. Concurrent vaccination did not significantly increase rates of general adverse events above those seen with H1N1pdm09 vaccine alone (Fig. 1B) but specific symptoms were about 3 times more frequent with pandemic than TIV vaccine. However, severe symptoms were infrequent during the week after H1N1pdm09 vaccine administration: tiredness 4%, myalgia 3%, malaise 5%, headache 2%, arthralgia 1%. Only 6% of subjects reported ongoing general symptoms 7 days after H1N1pdm09 vaccinations (data not shown). Four subjects reported respiratory illness, two in each group, but only one was influenza-like. Nine subjects reported other severe adverse events during the study, 4 of which were considered possibly, probably or very likely vaccine-related, including muscle spasms (1), asthma exacerbation (1), headache (1) and hallucination (1). Only two of these subjects sought medical attention. No serious neurological, auto-immune or other adverse events occurred.

4. Discussion

This study confirmed other reports [2,4,5,7,11] that a single injection of a dose-sparing formulation of ASO3-adjuvanted H1N1pdm09 vaccine was immunogenic in adults <60 years old. The EMEA/CHMP criteria [8,9] for evaluating influenza vaccines in this age group were exceeded by this pandemic vaccine. Subjects 20–39 years old had a 12% higher seroprotection rate than subjects 40–59 years old ($p = 0.009$) similar to the age effect reported by Roman et al. [5] for ASO3-adjuvanted H1N1pdm09 vaccine from Europe.

Our study is one of only a few [12–14] that assessed compatibility of concurrently administered pandemic and seasonal influenza vaccines in 2009. We found that giving ASO3-adjuvanted H1N1pdm09 vaccine and split TIV vaccine to naïve adults <60 years of age was associated with maintained immune responses to both. Subjects with pre-existing antibody to H1N1pdm09 boosted less well when TIV was given concurrently but all had titers ≥40 and the actual GMT after vaccination was still 3-fold higher than in naïve subjects. In other studies, concurrent administration of an MF59-adjuvanted H1N1pdm09 and subunit TIV vaccine [12] or alum-adjuvanted pandemic vaccine and a whole virion TIV [13] did not reduce immunogenicity of the H1N1pdm09 vaccine. An unadjuvanted, split H1N1pdm09 vaccine produced in China [14] given concurrently with TIV decreased by >50% the post-vaccination GMT for the pandemic strain but seroprotection and seroconversion rates were unaltered. These studies differed in methodology but suggest that concurrent TIV administration did not impair protection from the adjuvanted pandemic vaccines.

We did not observe any reduction of responses to TIV components as a result of co-administration with the pandemic vaccine. In fact, we saw greater GMT responses to the A/H1N1/Brisbane and the B/Brisbane strains with concurrent vaccinations. However, without a control group given TIV alone or prior to pandemic vaccine we cannot determine the validity of the observation. Enhancement of TIV responses by co-administration of adjuvanted H1N1pdm09 vaccine is not expected as ASO3 adjuvant reportedly exerts its

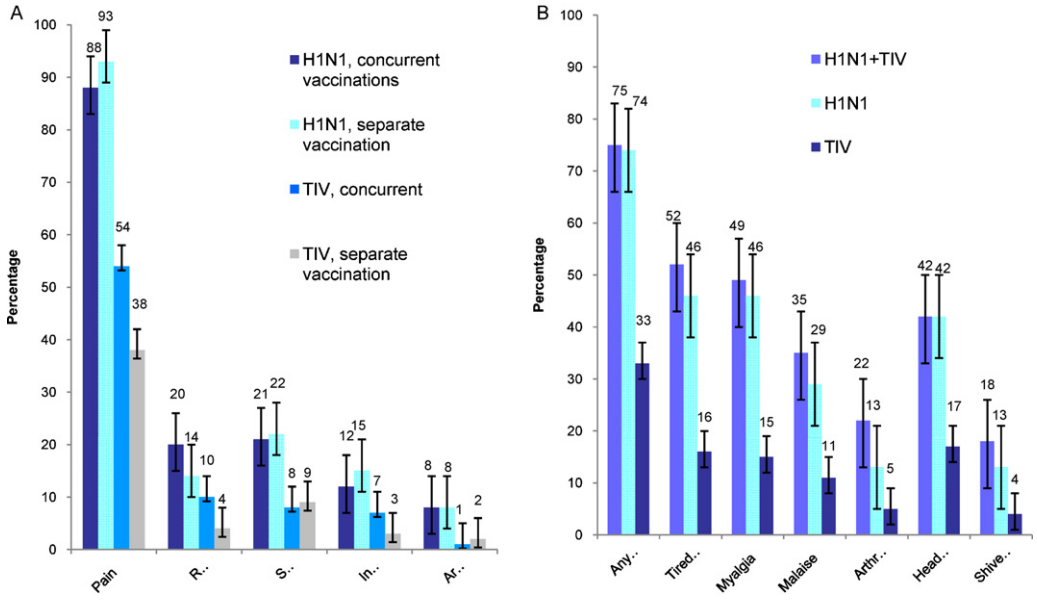

Fig. 1. Panel A shows rates of injection site reactions during the week after vaccination with pandemic vaccine (given alone [$n = 143$] or with concurrent TIV [$n = 146$]) and TIV (given alone [$n = 139$] or with concurrent pandemic vaccine). Observed rates (% affected) are given above the bars, along with 95% confidence intervals. Panel B shows rates of solicited general adverse events during the week after concurrent or separate vaccinations, formatted as above, with the same denominators.

effects only at the injection site and draining lymph nodes [3]. We could not identify similar observations in other reports but only one included comparison data for TIV responses when given alone [14].

The adjuvanted pandemic vaccine caused substantially more local and general symptoms than did TIV, consistent with other reports [2,4,5,11,15]. Concurrent administration of TIV and pandemic vaccines did not increase symptom rates above those seen with pandemic vaccine alone, in keeping with reports of other influenza vaccine combinations [12,13].

Limitations of this study included the infeasibility during a pandemic to include subjects given only TIV for comparison purposes. Lack of observer blinding and participant blinding with sequential vaccinations could have been sources of bias. More subjects (especially those 20–39 years old) had antibody to the pandemic virus at study entry than the ~20% anticipated and found in other studies [2], reducing the power of the study to detect small vaccine interactions. Seropositivity rates may have been influenced by occupational exposure as many participants were health care workers. The study was conducted during the second wave of the 2009 pandemic so intercurrent H1N1 infections might have added to post-immunization antibody levels. However, only one subject described having influenza-like illness while enrolled in the study. Participants had a high rate (~70%) of prior seasonal TIV vaccination so their responses may have been more resistant to interference by concurrent vaccination than in a general population. Serologic tests were performed at a government reference laboratory so results may not be directly comparable to tests performed by vaccine manufacturers. This is the likely explanation for the suboptimal response rates observed with the B/Brisbane strain in TIV, which met approval criteria in Europe and Canada.

In summary, this ASO3-adjuvanted H1N1pdm09 vaccine was immunogenic in a dose-sparing formulation. It was also moderately reactogenic, causing more local and systemic adverse effects than seen with TIV. The H1N1 and TIV vaccines studied were compatible when given concurrently, with no net increase in systemic adverse events or important reduction of the immune responses observed.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2012.05.029.

References

[1] Girard MP, Tam JS, Assossou OM, Kieny MP. The 2009 A (H1N1) influenza pandemic: a review. Vaccine 2010;28:4895–902.
[2] Ferguson M, Risi G, Davis M, Sheldon E, Baron M, Li P, et al. Safety and long-term immune response in adults after vaccination with an H1N1 2009 pandemic influenza vaccine with or without AS03 adjuvant. J Infect Dis 2012;205:733–44.
[3] Morel S, Didierlaurent A, Bourguinon P, Delhaye S, Baras B, Jacob V, et al. Adjuvant system ASO3 containing α-tocopherol modulates innate response and leads to improved adaptive immunity. Vaccine 2011;29:2461–73.
[4] Nicholson KG, Abrams KR, Batham S, Clark TW, Hoschler K, Lim WS, et al. Immunogenicity and safety of a two-dose schedule of whole-virion and $ASO3_A$-adjuvanted 2009 influenza A (H1N1) vaccines: a randomized, multicenter, age-stratified, head-to-head trial. Lancet Infect Dis 2011;11:91–101.

[5] Roman F, Vaman T, Gerlach B, Markendorf A, Gillard P, Devaster JM. Immunogenicity and safety in adults of one dose of influenza A H1N1v 2009 vaccine formulated with and without ASO3(A) adjuvant: a preliminary report of an observer-blind, randomized trial. Vaccine 2010;28:1740–5.
[6] Scheifele DW, Marty K, LaJeunesse C, Fan SY, Bjornson G, Langley JM, et al. Strategies for successful rapid trials of influenza vaccine. Clin Trials 2011;8:699–704.
[7] Rubinstein E, Predy G, Sauvé L, Hammond GW, Aoki F, Sikora C, et al. The responses of aboriginal Canadians to adjuvanted pandemic (H1N1) 2009 influenza vaccine. Can Med Assoc J 2011;183(13):E1033–7, http://dx.doi.org/10.1503/cmaj.110196.
[8] Wood JM, Newman RW, Pless K. The use of correlates of immunity in European Union licensing of influenza vaccines. Dev Biol 2003;115:9–16.
[9] European Agency for the Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products. Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context. Document EMEA/CHMP/VWP/263499/2006.
[10] European Medicine Agency. CHMP recommendations for the pharmacologic vigilance plan as part of the risk management plan to be submitted with the marketing authorization application for a pandemic influenza vaccine. Report No. EMEA/359381/2009 rev. EMA; 2009.
[11] Roman F, Vaman T, Kafeja F, Hanon E, Van Damme P. $ASO3_A$-adjuvanted influenza A (H1N1) vaccine for adults up to 85 years of age. Clin Infect Dis 2010;51:668–77.
[12] Gasparini R, Schioppa F, Lattanzi M, Barone M, Casula D, Pellegrini M, et al. Impact of prior or concomitant seasonal influenza vaccination on MF59-adjuvanted H1N1v vaccine (Focetria™) in adult and elderly subjects. Int J Clin Pract 2009, http://dx.doi.org/10.1111/j.1742-1241.2009.02309.x.
[13] Vajo Z, Tamas F, Sinka L, Jankovics I. Safety and immunogenicity of a 2009 pandemic influenza A H1N1 vaccine when administered alone or simultaneously with the seasonal influenza vaccine for the 2009–10 influenza season: a multicenter, randomized controlled trial. Lancet 2010;375:49–55.
[14] Wu J, Zhong X, Li CK, Zhou JF, Lu M, Huang KY, et al. Optimal vaccine strategies for 2009 pandemic H1N1 and seasonal influenza vaccines in humans. Vaccine 2011;29:1009–16.
[15] Mayet A, Ligier C, Gache K, Manet G, Nivoix P, Dia A, et al. Adverse events following pandemic influenza vaccine Pandemrix® reported in the French military forces—2009–2010. Vaccine 2011;29:2576–81.