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Efficacy of a trivalent influenza vaccine against seasonal strains and against 2009 pandemic H1N1: A randomized, placebo-controlled trial

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ABSTRACT

Background: Before pandemic H1N1 vaccines were available, the potential benefit of existing seasonal trivalent inactivated influenza vaccines (IIV3s) against influenza due to the 2009 pandemic H1N1 influenza strain was investigated, with conflicting results. This study assessed the efficacy of seasonal IIV3s against influenza due to 2008 and 2009 seasonal influenza strains and against the 2009 pandemic H1N1 strain.

Methods: This observer-blind, randomized, placebo-controlled study enrolled adults aged 18–64 years during 2008 and 2009 in Australia and New Zealand. Participants were randomized 2:1 to receive IIV3 or placebo. The primary objective was to demonstrate the efficacy of IIV3 against laboratory-confirmed influenza. Participants reporting an influenza-like illness during the period from 14 days after vaccination until 30 November of each study year were tested for influenza by real-time reverse transcription

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Seasonal influenza
Seasonal trivalent inactivated influenza vaccine

polymerase chain reaction.
Results: Over a study period of 2 years, 15,044 participants were enrolled (mean age ± standard deviation: 35.5 ± 14.7 years; 54.4% female). Vaccine efficacy of the 2008 and 2009 IIV3s against influenza due to any strain was 42% (95% confidence interval [CI]: 30%, 52%), whereas vaccine efficacy against influenza due to the vaccine-matched strains was 60% (95% CI: 44%, 72%). Vaccine efficacy of the 2009 IIV3 against influenza due to the 2009 pandemic H1N1 strain was 38% (95% CI: 19%, 53%). No vaccine-related deaths or serious adverse events were reported. Solicited local and systemic adverse events were more frequent in IIV3 recipients than placebo recipients (local: IIV3 74.6% vs placebo 20.4%, $p < 0.001$; systemic: IIV3 46.6% vs placebo 39.1%, $p < 0.001$).
Conclusions: The 2008 and 2009 IIV3s were efficacious against influenza due to seasonal influenza strains and the 2009 IIV3 demonstrated moderate efficacy against influenza due to the 2009 pandemic H1N1 strain.
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1. Introduction

Trivalent influenza vaccines (IIV3s) containing antigens of two influenza A strains (A/H1N1, A/H3N2) and one influenza B strain are effective in protecting against influenza [1,2]. As new influenza variants arise via frequent antigenic change, the influenza strains included in IIV3s frequently change between influenza seasons, based on recommendations by the World Health Organization (WHO) [3].

The 2009 H1N1 pandemic raised the question of whether existing seasonal IIV3s might provide protection against this novel influenza strain. Early analyses of stored sera from vaccine trials demonstrated limited antibody reactivity to this new virus; therefore, IIV3s were predicted to be of no benefit [4,5]. Over the course of the pandemic, numerous observational studies of IIV3 effectiveness were conducted and yielded conflicting results [6], suggesting seasonal vaccines to be protective [7–12], ineffective [13–17], or even detrimental [18] against influenza due to the pandemic H1N1 strain. A meta-analysis of 8 case-control studies with low risk of bias found that IIV3 s provided moderate cross-protection against laboratory-confirmed pandemic H1N1 influenza [19]. However, few randomized controlled trials have addressed this question.

The onset of the 2009 H1N1 pandemic in Australia and New Zealand coincided with the second year of a large, phase 4, randomized, placebo-controlled, efficacy study of a seasonal IIV3 (Fluvax®, CSL Limited, Parkville, Victoria, Australia). The aim of this study was to evaluate the clinical efficacy, safety, and tolerability of IIV3 in healthy adults during the 2008 and 2009 Southern Hemisphere influenza seasons. This timing afforded us the opportunity to evaluate the efficacy of the 2009 IIV3 in the prevention of laboratory-confirmed 2009 H1N1 influenza in a study cohort of 7500 adults. This report describes the efficacy of the 2008 and 2009 IIV3s against influenza due to seasonal influenza strains, as well as a post hoc analysis of the clinical efficacy of the 2009 IIV3 against the 2009 pandemic H1N1 strain.

2. Materials and methods

2.1. Study design

This phase 4, randomized, observer-blinded, placebo-controlled, efficacy study enrolled healthy adults aged 18 to less than 65 years over two consecutive influenza seasons (2008 and 2009) across 25 sites in Australia and New Zealand. The purpose of this study was to evaluate the clinical efficacy, safety, and tolerability of a IIV3 (Fluvax®, CSL Limited, Parkville, Victoria, Australia). All participants provided written informed consent under ethics approval from each participating institution and the study was conducted in accordance with the Declaration of Helsinki.

Healthy, non-pregnant adults were eligible for enrollment if they were 18 years to less than 65 years old at the time of vaccination. Main exclusion criteria were: allergy to any of the vaccine components; medically unstable clinical condition; planned or current pregnancy; lactation; history of Guillain-Barré Syndrome; confirmed or suspected immunosuppressive condition; current or recent immunosuppressive therapy; concurrent participation in a clinical trial or use of an investigational compound; or recommended for seasonal influenza vaccination according to guidelines in Australia [20] or New Zealand [21]. Participants enrolled in 2008 were ineligible to be enrolled in 2009.

2.2. Randomization and masking

Participants were randomized in a 2:1 ratio to receive a single injection of 0.5 mL IIV3 or placebo, administered intramuscularly into the deltoid muscle (23 gauge needle, 0.6 mm wide, 25 mm long). As there was a visual difference between IIV3 and placebo, study personnel who were involved in the preparation and administration of the study vaccine had no further involvement in the study conduct. Participants and investigational site staff involved in performing study assessments remained blinded to treatment allocation.

The randomization code was prepared by a statistician, employed by CSL Limited, with the use of SAS software (version 9.1.3; SAS Institute, Cary, NC, USA), using simple block randomization to maintain approximate allocation balance.

2.3. Vaccines and placebo

The two commercially available study vaccines fulfilled all of the applicable regulatory requirements and were composed of World Health Organization recommended strains for the Southern Hemisphere in 2008 and 2009, respectively (2008: A/Solomon Islands/3/2006 [H1N1], A/Brisbane/10/2007 [H3N2], B/Brisbane/3/2007; 2009: A/Brisbane/59/2007 [H1N1], A/Brisbane/10/2007 [H3N2], B/Florida/4/2006). Each vaccine contained 15 μg of each hemagglutinin antigen from the respective influenza strains per 0.5 mL dose. The thimerosal-free vaccine was prepared in the allantoic fluid of embryonated chicken eggs as previously described [22]. Placebo consisted of vaccine diluent and was composed of saline, dibasic sodium phosphate, and monobasic sodium phosphate. Batch numbers for the 2008 vaccine and placebo were 00749112A and FLUPLACEBO, respectively; batch numbers for the 2009 vaccine and placebo were 04749111A and IV313248B1, respectively.

2.4. Safety assessments

Solicited adverse events (AEs) and oral temperature were recorded in diary cards on the evening of vaccination and every evening for the next 4 days. Unsolicited AEs that occurred on the day of vaccination and for the 20 days after were recorded in diary cards. Information regarding the occurrence of serious adverse events (SAEs) was collected from the day of vaccination to 180 days after study vaccination. A data monitoring committee was established according to United States Food and Drug Administration guidelines [23].

2.5. Clinical and laboratory outcomes

Stimulated by weekly reminder contacts from investigators, participants reported signs and symptoms of an influenza-like illness (ILI) from day 14 after vaccination until 30 November of the respective study year, the time typically marking the end of influenza circulation in the Southern Hemisphere. An ILI was defined as at least one respiratory symptom (e.g., cough, sore throat, nasal congestion) and at least one systemic symptom (e.g., fever $\geqslant$37.8 °C [oral], feverishness, chills, body aches). This broad case definition was chosen to maximize the chance of detecting influenza infections. Participants who reported signs and symptoms of an ILI had nose and throat swab specimens collected within 72 h of symptom onset for laboratory confirmation of influenza infection. Laboratory-confirmed influenza was defined as a nose or throat specimen testing positive by viral culture and/or real-time reverse transcription polymerase chain reaction (rRT-PCR, Focus Diagnostics, Cypress, CA, USA). Laboratory-confirmed cases were typed to determine whether they matched the strains included in the vaccine. Except for those specimens identified to be 2009 H1N1 by rRT-PCR, influenza strain typing was determined by gene sequencing (for A subtypes H1N1 and H3N2) or pyrosequencing (for B strains) performed by the WHO Collaborating Centre (Melbourne, Australia) [24].

2.6. Statistical analysis

Vaccine efficacy was assessed for each influenza virus type and subtype only for laboratory-confirmed cases that occurred 14 or more days after vaccination and before 30 November of each trial year. Vaccine efficacy was defined as the relative reduction in influenza rate in the IIV3 group relative to the placebo group, i.e., vaccine efficacy = 1 − (IIV3 recipient infection rate/placebo recipient infection rate). The primary analysis tested whether vaccine efficacy versus placebo was significantly greater than or equal to 40%. The primary endpoint was achieved if the lower bound of the $(1-2\alpha)\times 100\%$ confidence interval (CI) for vaccine efficacy was 40% or higher.

The study was designed as a 2-year study with an interim analysis after the first season. A Pocock alpha-spending function was used to maintain an overall one-sided $\alpha = 0.025$ for the primary endpoint, whereby in the first season $\alpha = 0.01550$ and in the second season $\alpha = 0.01387$. Assuming an influenza attack rate of at least 3% and a vaccine efficacy of at least 70%, then a first season sample size of N = 7500 randomized participants in a 2:1 ratio to active vaccine and placebo (N = 5000 and 2500, respectively), with a 10% drop-out rate, yields at least 90% power for a one-sided test of vaccine efficacy being greater than 40% using $\alpha = 0.01550$ (PASS 2005, NCSS, LLC, Kaysville, UT, USA).

The primary analysis assessed vaccine efficacy against any influenza infection and infections caused by vaccine-matched strains. A post hoc analysis of efficacy against non-vaccine strains was also carried out to assess cross-protection. In addition, for the 2009 season, where most cases were of the pandemic H1N1 strain, vaccine efficacy was also analyzed by age strata (17–39 years, 40–54 years, and 55–65 years).

3. Results

3.1. Demographic and baseline clinical characteristics

The first year of the study was conducted between 25 February 2008 and 28 January 2009, and the second year between 9 March 2009 and 29 January 2010. A total of 15,479 individuals were assessed for eligibility, and 15,044 were randomly assigned to a study arm (7544 in 2008, 7500 in 2009, Fig. 1). The mean age of participants was 35.5 years and 9.6% reported having received a seasonal influenza vaccine during the 12 months before entering the study (Table 1). Approximately 90% of participants were White and approximately 55% were female. Most (63%) had never previously received an influenza vaccination, and most were non-smokers.

Protocol violations occurred in 41 (0.3%) participants and were distributed equally between study arms (IIV3 group: 28 [0.3%] participants; placebo group: 13 [0.3%] participants). Note that 2 participants aged 17 years and 2 participants aged 65 years were enrolled in the study and included in the evaluable population.

3.2. Concomitant medications

A total of 7194 (47.9%) participants were receiving concomitant medications at baseline. The most frequently recorded baseline medications were birth control medications (ethinylestradiol/levo norgestrel: 1122 [7.5%] participants; ethinylestradiol/cyproterone acetate; 419 [2.8%] participants) and salbutamol (375 [2.5%] participants), taken by similar proportions of participants in the IIV3 and placebo groups.

Influenza vaccines other than the study vaccine were received by 140 (0.9%) participants during on-study periods (IIV3 group: 108 [1.1%] participants; placebo group: 32 [0.6%] participants). Of these, 135 participants reported receiving the 2009 H1N1 pandemic influenza vaccine (Table 1). All 140 participants were excluded from the efficacy analysis before unblinding. An additional 40 participants who took other prohibited medications (e.g., immunosuppressive therapy) were excluded from the efficacy analysis before unblinding.

3.3. Vaccine efficacy

In the 2008 and 2009 influenza seasons combined, laboratory-confirmed influenza was identified in 222 of 9889 (2.2%) IIV3 recipients and 192 of 4960 (3.9%) placebo recipients (Table 2). The incidence of laboratory-confirmed influenza due to vaccine-matched strains was low during both study years (Table 2). Of the 179 participants with laboratory-confirmed influenza identified in the IIV3 and placebo groups in 2008, 107 (59.8%) were caused by influenza B strain; 64 of the 107 (59.8%) influenza B strains were antigenically dissimilar to the vaccine strains (Table 2). All influenza A strains identified in 2008 were antigenically similar to the vaccine strains. Of the 235 influenza infections identified in the IIV3 and placebo groups in 2009, 219 (93.2%) were caused by strains antigenically dissimilar to the vaccine strains. Of these 219 mismatched strains, 209 (95.4%) were characterized as 2009 H1N1 (Table 2).

Overall vaccine efficacy in the 2008 and 2009 influenza seasons combined was 42.0% (95% CI: 29.9%, 52.0%; $\alpha = 0.01387$ lower bound 28%; Table 2, Fig. 2). Vaccine efficacy against influenza strains contained in the vaccine, however, was higher at 60.1% (95% CI: 43.8%, 71.7%; $\alpha = 0.01387$ lower bound 41%; Table 2,

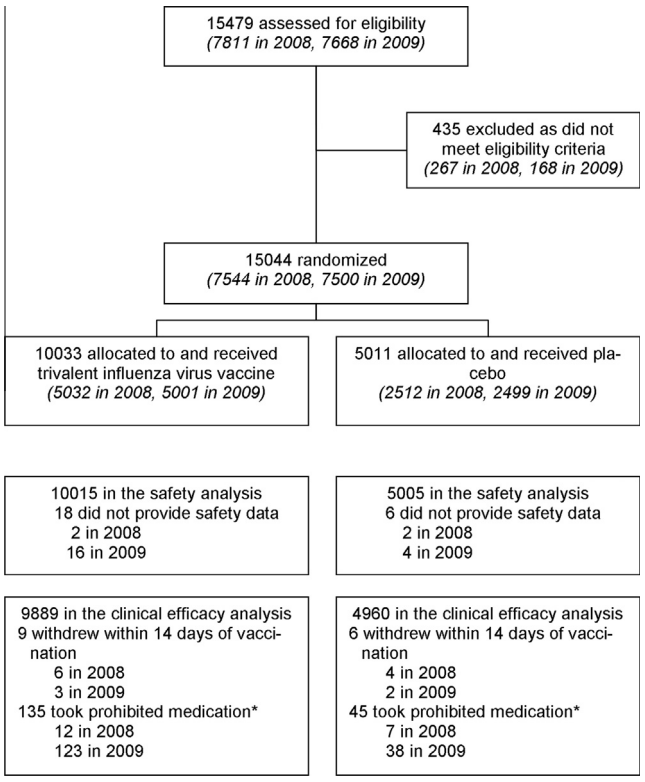

Fig. 1. Flow of study participants during the 2008 and 2009 Southern Hemisphere influenza seasons. *Prohibited medications were: any investigational compound; immunosuppressive or immunomodulating medications (with the exception of topical or inhaled corticosteroids); any vaccine; immunoglobulins or blood products.

Fig. 2). Post hoc analysis of vaccine efficacy against influenza strains not included in the vaccine yielded variable results. Vaccine efficacy against mismatched B strains (−9.7%; 95%CI: −85.8%, 35.2%) and against mismatched H3N2 (49.8%; 95% CI: −73.2%, 85.5%) was not statistically significant (Table 2, Fig. 2). By contrast, vaccine efficacy against the 2009 pandemic H1N1 strain was 38.3% (95% CI: 19.3%, 52.8%; Table 2, Fig. 2).

Post hoc analysis by age suggested that the efficacy of the 2009 IIV3 against the 2009 pandemic H1N1 strain was highest in older participants compared with younger participants. In participants 55–65 years of age, vaccine efficacy against the 2009 pandemic strain was 65.8% (95% CI: 4.6%, 87.7%), whereas in participants 17–39 years of age, vaccine efficacy was 38.1% (95% CI: 16.1%, 54.4%). Vaccine efficacy in participants 40–54 years of age was 21.6%; however, the CIs were wide and included 0 (95% CI: −56.3%, 60.7%). However, the differences in vaccine efficacy between age groups were not statistically significant for the 2009 pandemic H1N1 strain (logistic regression analysis, p = 0.416).

In contrast, post hoc analysis by age suggested similar vaccine efficacy against matched strains across 2008 and 2009 between age groups. In participants 55–65 years of age, vaccine efficacy against all matched strains was 68.4% (95% CI: 3.7%, 89.6%), whereas in participants 17–39 years of age, vaccine efficacy was 55.1% (95% CI: 30.3%, 71.1%). Vaccine efficacy in participants 40–54 years of age was 66.7% (95% CI: 37.2%, 82.3%). The differences in vaccine efficacy between age groups were not statistically significant for the matched strains (logistic regression analysis, p = 0.683).

3.4. Adverse events

No vaccine-related deaths or SAEs were reported. One or more solicited local AEs were reported by 74.6% of IIV3 recipients and by 20.4% of placebo recipients (p < 0.001; Fig. 2A). Pain and injection-site tenderness were the most frequently reported local AEs. Solicited systemic AEs were less common than local events, with one or more AEs reported by 46.6% of IIV3 recipients and 39.1% of placebo recipients (p < 0.001; Fig. 2B). Malaise, headache, and myalgia were the most frequently reported systemic AEs in both groups. The majority of solicited local and systemic AEs were of mild to moderate intensity and of limited duration (less than 3 days). The frequency of unsolicited AEs was similar between treatment groups (IIV3 group: 33.9%; placebo group: 35.1%).

4. Discussion

Despite being conducted during two influenza seasons with substantial mismatch between vaccine and circulating influenza strains (in 2008, influenza B was the predominant circulating type whereas in 2009, pandemic A(H1N1)pdm09 was predominant [25]), this large, randomized, placebo-controlled trial

Table 1
Demographic and baseline characteristics.

Characteristic	Placebo (N = 5011)	IIV3 (N = 10,033)	Total (N = 15,044)
Mean age, years (SD)	35.4 (14.7)	35.5 (14.7)	35.5 (14.7)
Sex, n (%)			
Female	2667 (53.2)	5523 (55.0)	8190 (54.4)
Ethnicity, n (%)			
Hispanic/Latino	75 (1.5)	155 (1.5)	230 (1.5)
Not Hispanic/Latino	4936 (98.5)	9878 (98.5)	14,814 (98.5)
Race, n (%)			
White	4526 (90.3)	9039 (90.1)	13,565 (90.2)
Nonwhite	485 (9.7)	994 (9.9)	1479 (9.8)
Smoking history[a], n (%)			
Current smoker	854 (17.0)	1671 (16.7)	2525 (16.8)
Past smoker	1139 (22.7)	2225 (22.2)	3364 (22.4)
Never smoked	2993 (59.7)	6093 (60.7)	9086 (60.4)
Prior year influenza vaccination, n (%)	467 (9.3)	976 (9.7)	1443 (9.6)
Have ever received an influenza vaccination, n (%)	1868 (37.3)	3769 (37.6)	5637 (37.5)
Pandemic H1N1 vaccination[b], n (%)	31 (0.6)	104 (1.0)	135 (0.9)

Abbreviations: SD = standard deviation; IIV3 = inactivated influenza vaccine, trivalent.
[a] Smoking history information was missing for 25 (0.5%) participants in the placebo group and 44 (0.4%) participants in the IIV3 group.
[b] 2009 season only.

Table 2
Laboratory-confirmed influenza cases, attack rates, and vaccine efficacy (overall, against vaccine-matched strains, and against non-vaccine strains).

Study year/influenza infections	Placebo		IIV3		Vaccine efficacy % (95% CI)
	Cases n	Attack rate %	Cases n	Attack rate %	
2008/2009 combined	n = 4960		n = 9889		
All	192	3.9	222	2.2	42.0% (29.9%, 52.0%)
Vaccine-matched	73	1.5	58	0.6	60.1% (43.8%, 71.7%)
2008	n = 2501		n = 5014		
All	82	3.3	97	1.9	41.0% (21.1%, 55.9%)
Vaccine-matched	62	2.5	53	1.1	57.4% (38.7%, 70.4%)
B	20	0.8	44	0.9	−9.7% (−85.8%, 35.2%)
2009	n = 2459		n = 4875		
All	110	4.5	125	2.6	42.7% (26.3%, 55.4%)
Vaccine-matched	11	0.5	5	0.1	77.1% (34.1%, 92.0%)
H3N2	5	0.2	5	0.1	49.8% (−73.2%, 85.5%)
H1N1[a] (pandemic)	94	3.8	115	2.4	38.3% (19.3%, 52.8%)

Abbreviations: CI = confidence interval; IIV3 = inactivated influenza vaccine trivalent.
[a] All H1N1 infections in 2009 were identified as pandemic H1N1.

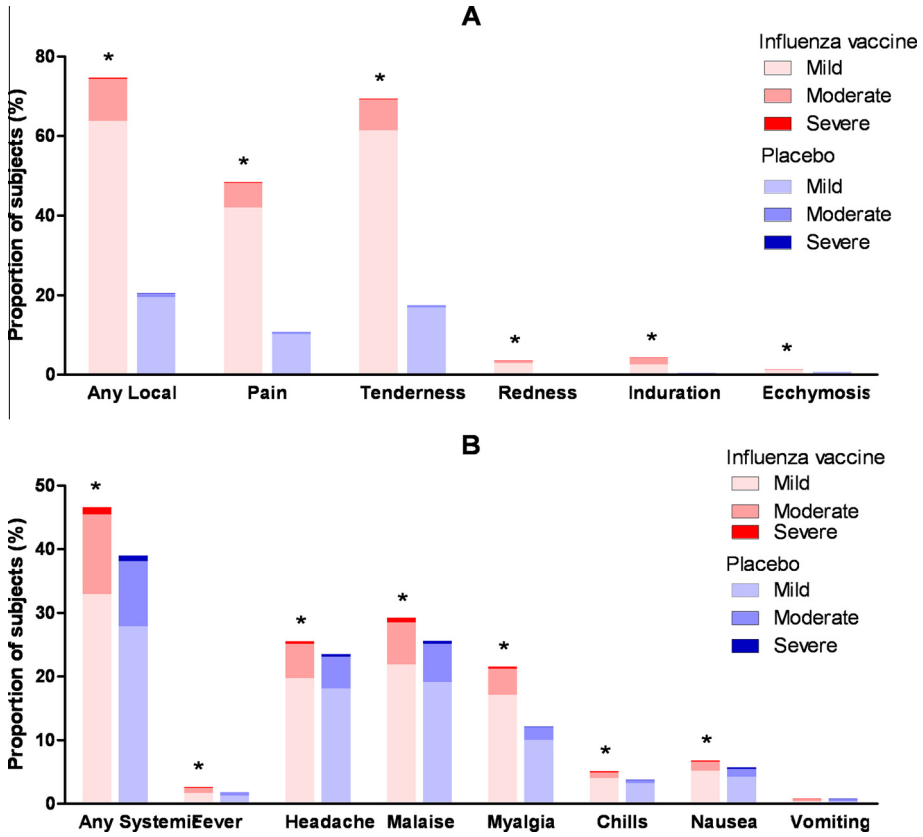

Fig. 2. Solicited adverse events within 5 days of vaccination. Panel A: Local adverse events; Panel B: Systemic adverse events; *p < 0.05 versus placebo.

demonstrated efficacy against influenza due to vaccine-matched influenza strains. Efficacy was also demonstrated for a seasonal influenza vaccine against influenza due to laboratory-confirmed 2009 H1N1 infection.

A possible explanation for the observed cross-protection of the 2009 IIV3 against the 2009 pandemic H1N1 strain is the stimulation of cross-reactive antibodies. Cross-reactive antibodies may be vaccine strain-specific or boosting of antibodies directed at earlier influenza strains to which the individual was exposed. We observed a boosting of cross-reactive antibodies in our clinical trials of monovalent 2009 H1N1 vaccine in adults and children in Australia [26,27], where individuals who had previously received 2009 IIV3 had higher pre-vaccination antibody titers to 2009 H1N1 than those who had not received the vaccine. The findings of the current study are supported by data from other studies of antibody cross-reactivity in individuals before and after receipt of IIV3 [28], although in those studies the effect was greater for those aged over 60 years [4,29]; the magnitude of efficacy was highest in those over 55 years in our study. This further suggests that protective efficacy may be a result of cross-protective immunity from multiple vaccinations or exposure to a related virus earlier in life, i.e., some degree of original antigenic sin. Induction of cross-reactive T cell responses to conserved viral epitopes may also be a factor underlying the cross-protection observed in this study [30].

This randomized controlled study demonstrated protection by seasonal IIV3 against laboratory-confirmed 2009 H1N1 influenza in adults. Two other randomized controlled studies that have investigated the efficacy of seasonal IIV3s against the 2009 pandemic H1N1 strain were conducted in children in Hong Kong [31,32]. The first small pilot study (N = 119) conducted during 2009 found no evidence of protection (or harm), but was not powered to investigate this outcome [30]. The second larger study (N = 796) conducted in 2009–2010 showed children who received IIV3 had a reduced risk of pandemic influenza A, with a vaccine efficacy estimate of 47% (95% CI, 15–67%) [32].

The 2008 and 2009 IIV3s were generally well tolerated, with no safety concerns identified. It should be noted that the subsequent 2010 IIV3 was associated with an unexpected increase in postmarketing reports of febrile seizure compared with previous seasonal IIV3 s, predominantly in children <5 years of age. This was likely due to the combination of the new influenza strains included in the 2010 IIV3 and the CSL standard method of manufacture. This method preserved strain-specific viral components of the new influenza strains, heightening immune activation of innate immune cells, which, in a small proportion of children <5 years of age, was associated with the occurrence of febrile seizures [33,34]. No patient in the current study reported febrile seizures during the study period.

The strengths of this study were the randomized, placebo-controlled design, relatively large size, and use of a clinical efficacy endpoint rather than a serological surrogate endpoint. As such, the study was less subject to the potential sources of bias and confounding associated with the previously reported observational studies. Nevertheless, this study is subject to certain limitations. There was no description of the clinical course of influenza infection among vaccinated and unvaccinated cases, so we cannot report the impact of vaccination on the course of illness or associated co-morbidity. Our study population was limited to healthy adults 17–65 years of age (mean, 35 years), so we cannot address the impact of seasonal IIV3 on preventing 2009 H1N1 in children, a group more immunologically naive to influenza. Most subjects were also female, non-smokers, influenza-vaccine naïve, white, and not Hispanic. In addition, our study did not measure serologic endpoints for influenza infection and, therefore, we can report efficacy only against symptomatic influenza infection.

The formulations for the 2009 Southern Hemisphere and 2009/10 Northern Hemisphere contained identical influenza A strains. As the monovalent H1N1 vaccine was not available during the first wave of the 2009 influenza pandemic, this study suggests that any use of seasonal vaccine in either the Southern or Northern Hemisphere may have had a positive impact on mitigating the peak incidence of pandemic H1N1 infections. Pre-pandemic mathematical modelling indicated that a vaccine, even one with low efficacy, used early in a pandemic could have meaningful benefit in reducing the amplitude of the pandemic wave [35].

5. Conclusions

The 2008 and 2009 seasonal IIV3s demonstrated clinical efficacy in healthy adults against influenza infection caused by the strains included in the vaccines. In addition, the 2009 seasonal IIV3 conferred significant clinical efficacy in healthy adults against laboratory-confirmed 2009 pandemic H1N1 infection.

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Role of the sponsor

The study sponsor was responsible for the final study protocol, oversaw the data management and analysis, and was involved in the interpretation of the data, the writing of the manuscript, and the decision to submit the manuscript for publication.

Role of contributors

PR, RB, LH, JK, TN, RLB, and GFH designed the study. IB was responsible for strain typing. PR, WPA, RB, SC, FDL, RE-P, LH, JK, HM, WJHM, JM, TN, WR, JR, and SS recruited subjects into the study. GFH was responsible for data analysis. All authors contributed to writing of the report. All authors saw and approved the final version of the report.

Conflict of interest

RLB, GFH, MHL, SR, and MEG are/were employees of CSL and hold shares. PR has received research funding and travel support for investigator meetings from CSL. IB has received grant funding from CSL under contract for influenza virus identification. RB has received funding from CSL, Roche, Sanofi Pasteur, GSK and Pfizer to conduct research or attend and present at scientific meetings. Any funding received is directed to a research account at The Children's Hospital at Westmead and is not personally accepted by RB. FDL has received support from Trialworks Clinical Research Services to attend investigator meetings. RE-P has received funding for clinical trial participation and trial-related travel from Auckland Clinical Studies and paid to his institution. LH has received research funding from CSL, Novartis, Sanofi-Aventis, Roche, and GSK, paid to his institution. JK has received funding from CSL for clinical trial recruitment and travel to investigator meetings. HM has received travel support from CSL and Novartis Vaccines to present independent scientific data and research grants paid to her institution from CSL, Novartis Vaccines, and Pfizer Vaccines. WJHM has received travel support for investigator meetings from CSL but no direct funds and holds shares in CSL. JM has received research funding and travel support for investigator meetings from CSL, has served as a consultant and speaker for Novartis, and as a consultant for the governments of Australia and Mongolia. All support has been paid directly to her institution. TN's institution (MCRI) has received research support from CSL, Sanofi Pasteur, Novartis, Pfizer, GSK, and Novavax, and TN has served on a data safety monitoring board for GSK (HPV vaccine, resigned in 2012) and GSK advisory boards (unpaid) for pertussis vaccine (2014 and 2016). SS has received funding for consultancy from CMAX Drug Studies Unit. All other authors: no conflicts.

The study centers were

Vaccine Trials Group, Princess Margaret Hospital; VIRTU staff of the Women's and Children's Hospital, Adelaide; VIRGo staff, University of Melbourne; National Centre for Immunisation Research & Surveillance of Vaccine Preventable Diseases, The Children's Hospital of Westmead; AUSTRIALS; CMAX; Trialworks Clinical Research Services; Cairns Base Hospital; Auckland Clinical Studies Limited; Southern Clinical Trials Limited; RMC Medical Research Limited; Emeritus Research; SEALS, Prince of Wales Hospital; Department of Clinical & Biomedical Science, Geelong Hospital; Clinical Trials Unit, the Australian National University

Hospital; Hobart Sexual Health Service; Gold Coast Hospital; Youth Health Centre, Christchurch; Lung Institute of Western Australia.

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