Influenza Vaccine Effectiveness and Uptake in Children at Risk of Severe Disease

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Background: Data demonstrating the effectiveness of inactivated trivalent influenza vaccine (TIV) for children at increased risk of severe disease are limited. Our objective was to determine the effectiveness of TIV in children with risk factors for severe disease and to compare vaccine uptake, parental attitudes and prescriber recommendations in children with and without risk factors for severe disease.

Methods: Children aged 6–59 months presenting for emergency care (2008 to 2014) with an influenza-like illness were eligible. Influenza polymerase chain reaction/culture was performed on nasopharyngeal samples. Vaccination status was confirmed via the national register and/or vaccine providers. The test-negative design was used to estimate vaccine effectiveness (VE). Risk factors, parental attitudes and prescriber recommendations were assessed by parental questionnaire.

Results: Two thousand seven hundred twenty-three children were recruited. Risk factors for severe disease included comorbid medical conditions (11.6%), preterm birth (13.0%) and indigeneity (5.0%). Influenza was identified in 546 (20.1%) participants. Overall VE (2008 and 2010 to 2014) was 70.0% (95% confidence interval: 47.7 to 82.9); VE for children with medical comorbidities, children born preterm and children <2 years were 82.5% (14.6 to 96.4), 79.2% (10.9 to 95.1) and 84.7% (49.6 to 95.3), respectively. After adverse events in 2010, the number of children fully vaccinated with TIV declined significantly. This included children with and without risk factors for severe disease. Attitudes were similar in parents of children with and without risk factors for severe disease.

Conclusions: VE for TIV in young children with and without risk factors for severe disease was ≥70%. Despite this, participation in the preschool influenza vaccination program remains low with parents and prescribers unconvinced of the benefits and safety of TIV.

Key Words: influenza, trivalent influenza vaccine, vaccine effectiveness, children

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Influenza viral infections remain a major contributor to the global burden of acute respiratory infection.[1] Young children, the elderly and others with underlying medical conditions are at greatest risk of hospitalization, morbidity and death.[2–4] Vaccination is the most effective method for preventing influenza virus infection and its complications and is therefore recommended for those at greatest risk.

The medical conditions that predispose to severe outcomes after influenza infection include underlying cardiac disease, chronic respiratory disorders, chronic neurological conditions, immunosuppressive conditions and medications, diabetes and pregnancy. In a recent systematic review of influenza-related complications in children presenting to primary and ambulatory care, Gill et al[5] identified neurological disorders, prematurity, sickle cell disease, immunosuppression, diabetes and age <2 years as the strongest risk factors for influenza-related hospital admission. Other authors have demonstrated that those with chronic lung disease, asthma, airways disease, cardiovascular disease, neuromuscular disease and immunocompromising conditions are at significant risk of complicated influenza infection.[6]

To date, the only vaccine against influenza available in the Southern Hemisphere has been an inactivated trivalent influenza vaccine (TIV). In Australia, vaccination is recommended for the elderly (≥65 years), pregnant women, indigenous Australians (≥15 years of age and from 2015 onward, indigenous children aged 6 months to 5 years) and persons ≥6 months with comorbid medical conditions predisposing to severe outcomes after influenza infection (hereafter referred to as medical comorbidities).[7] Although recommended for all Australian children 6 months to 5 years due to their increased risk of hospitalization, morbidity and mortality following influenza,[7] TIV is only funded nationally for young indigenous children.

In Western Australia, TIV is provided free of charge for all children aged 6–59 months under a state-funded immunization

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program. After introduction of the program in 2008, excellent uptake was initially achieved.[8] A high rate of febrile adverse events with one manufacturer's TIV in 2010 (bioCSL's Fluvax and Fluvax Junior, Parkville, Australia) resulted in temporary suspension of the national and WA pediatric influenza vaccine program.[9,10] The incidence of febrile convulsions with a bioCSL vaccine was 4.4 per 1000 doses [95% confidence interval (CI): 3.4 to 5.6]. More than half of the parents reported that their child sustained high fever after the receipt of a bioCSL product, >5 times that observed with alternative TIV products (odds ratio [OR]: 5.1; 95% CI: 2.9 to 9.2).[9,10] Subsequent to this, uptake in young children of alternative brands of influenza vaccine including Vaxigrip and Vaxigrip junior (Sanofi-Pasteur, Lyon, France), Influvac and Influvac Junior (Abbott, Weesp, The Netherlands), Fluarix (GlaxoSmithKline, Rixensart, Belgium) and Agrippal (Novartis, Sienna, Italy) has been low.[8]

The West Australian Influenza Vaccine Effectiveness (WAIVE) study commenced in 2008 to monitor the effectiveness of the state-based pediatric influenza vaccination program. This study has demonstrated the effectiveness of TIV in preschool children.[11] It also has demonstrated the significant impact of the 2010 adverse events on parent and prescriber attitudes toward influenza vaccination.[8] We undertook to extend the findings of the published vaccine effectiveness (VE) estimates and to determine the uptake and effectiveness of influenza vaccine in children with risk factors for severe disease, specifically children with medical comorbidities, children born preterm (<37 weeks of gestation), indigenous children and children <2 years of age. We also aimed to explore parental and prescriber attitudes toward vaccination of children with risk factors for severe disease.

MATERIALS AND METHODS

Children aged 6–59 months presenting with an influenza-like illness (ILI) to the Emergency Department of Princess Margaret Hospital during the influenza seasons of 2008 to 2014 inclusive were eligible for enrollment. ILI was defined by at least 1 acute respiratory symptom or sign plus either a documented fever ≥37.5°C or a history of fever in the past 96 hours. Children with known contraindication to influenza vaccine, immunodeficiency disorders, current or recent immunosuppressive treatment and administration of immunoglobulins in the past 3 months were excluded.

After written consent from parents or guardians, clinical data, parental attitudes and nasopharyngeal samples were collected. Bilateral mid-turbinate nasal swabs (Copan Diagnostics Inc, Murrieta, CA) placed into the viral transport medium or nasopharyngeal aspirates were collected on all enrolled children. Using previously published methods, nasopharyngeal samples were tested by polymerase chain reaction assay for respiratory viruses including influenza A, B and C.[12–14] Viral culture was performed using centrifuge-enhanced inoculation onto Madin-Darby canine kidney cells and diploid human lung fibroblasts and confirmed using immunofluorescent antibody detection with monoclonal antibodies directed at influenza A or B (Oxoid Microbiology; Thermo Fisher, Waltham, MA).

Medical comorbidities were defined as per the *Australian Immunisation Handbook* (10th edition) as the presence of an underlying condition increasing the risk of complications from influenza infection.[7] These included cardiac disease, chronic respiratory conditions, chronic neurological condition, diabetes, chronic renal failure, inherited metabolic diseases and obesity. Preterm birth was defined as birth <37 weeks of gestation.

Vaccination status was assessed during the parental interview and then confirmed by the Australian Childhood Immunisation Register (ACIR). If vaccination status could not be determined or discrepancies were noted, immunization providers were contacted. "Fully vaccinated" was defined as (1) 2 doses of TIV at least 21 days apart and at least 14 days before presentation or (2) 1 dose of TIV at least 14 days before presentation and 2 or more doses in a previous year.[7] "Partially vaccinated" was defined as the receipt of 1 dose of TIV at least 14 days before presentation without at least 2 doses in previous years. Children who had not received any vaccination in the year of presentation or were vaccinated <14 days before presentation were deemed unvaccinated.

Estimates of community vaccine uptake were calculated from influenza test-negative control subjects enrolled in the WAIVE study (2008 to 2014 inclusive). Fully vaccinated and partially vaccinated children were expressed as a proportion of the total influenza test-negative controls and 95% CIs calculated.

The effectiveness of influenza vaccine in children aged 6 months to 5 years was calculated in children presenting to the emergency department with ILI during influenza season in years 2008 and 2010 to 2014; children enrolled in 2009 were excluded from VE calculations given (1) the mismatch between pandemic A(H1N1)pdm09 and the 2009 southern hemisphere seasonal TIV and (2) the a priori focus on determining the effectiveness of TIV against seasonal influenza. Using the test-negative design,[15–17] children testing positive for influenza viruses (polymerase chain reaction and/or viral culture) were identified as cases. These were compared with enrolled children testing negative for influenza (ie, test-negative controls). VE was determined in the total population and separately in children with specific risk factors for severe diseases: those with medical comorbidities, indigenous children, children born preterm and children <2 years of age.

Parental attitudes toward influenza illness, influenza vaccination and immunization in general and parental-reported prescriber recommendations were assessed on all enrolled children. The questionnaire was administered to the parent or guardian when the child was recruited into the study. All questions could be answered as yes, no or unsure. To determine whether parental attitudes and prescriber recommendations varied according to the risk of complications after influenza infection, further analysis was undertaken: the attitudes of parents and recommendations of prescribers for children with and without medical comorbidities were compared as were the attitudes and recommendations of children born preterm and term, indigenous and nonindigenous children and children aged <2 years and ≥2 years.

Statistical analysis was performed using SPSS 20.0.0 (IBM Corp., New York, NY). Differences in categorical variables were tested by the χ^2 test or Fisher exact test. A P value (2-sided) of 0.05 was considered significant. With laboratory-confirmed influenza as the primary outcome and vaccine status as the primary exposure, ORs and 95% CIs were calculated using logistic regression models. Fully vaccinated children were compared with unvaccinated children. Season, month of disease onset, age, gender, indigenous status, prematurity and the presence of comorbidities (yes/no) were included as covariates. VE was calculated as 1 − OR.

Ethical approval for the study was obtained from the ethics committees of Princess Margaret Hospital for Children (1673/EP), the South Metropolitan Area Health Service and the Western Australian Aboriginal Health Information and Ethics Committee.

RESULTS

A total of 2851 children presenting to the emergency department with an ILI between 2008 and 2014 were recruited into the WAIVE study. One hundred twenty-eight children were excluded from the analysis leaving 2723 children available for analysis (consent was withdrawn in 38, 50 were older than 59 months, 30 had no respiratory sample collected and in 10 children, vaccination status could not be determined).

TABLE 1. Children Aged 6–59 mo Presenting With Influenza-like Illness During 2008 to 2014: Demographics and Risk Factors Divided by Influenza (TIV) Vaccination Status

	Unvaccinated (n = 2166)	Partially Vaccinated (n = 200)	Fully Vaccinated (n = 357)	Total (n = 2723)	Significance (*P*)
Age <2 years	1135 (52.8%)	102 (51.0%)	209 (58.5%)	1446 (53.4%)	0.103
Male gender	1173 (54.6%)	102 (51.0%)	188 (52.7%)	1463 (54.0%)	0.535
Indigenous	105 (5.0%)	13 (6.7%)	15 (4.2%)	133 (5.0%)	0.437
Preterm birth	272 (13.0%)	24 (12.2%)	48 (13.5%)	344 (13.0%)	0.910
Comorbidities	221 (10.8%)	24 (12.2%)	55 (15.8%)	300 (11.6%)	0.029
Asthma	166 (8.1%)	16 (8.2%)	32 (9.2%)	214 (8.3%)	
Other chronic respiratory disorder	23 (1.1%)	5 (2.6%)	8 (2.3%)	36 (1.4%)	
Congenital heart disease	22 (1.1%)	1 (0.5%)	2 (0.6%)	25 (1.0%)	
Chronic neurological condition	21 (1.0%)	2 (1.0%)	5 (1.4%)	28 (1.1%)	
Other significant comorbidity*	6 (0.3%)	2 (1.0%)	9 (2.5%)	17 (0.7%)	

Percentage represent the proportion of unvaccinated, partially and fully vaccinated children by demographic and risk factors.
*Including trisomy 21, chronic liver disease, chronic renal disease, inborn errors of metabolism and asplenia.

The median age of children enrolled was 1.9 years (interquartile range: 1.2–3.1 years) and 1463 of 2708 (54.0%) children were male (Table 1). Risk factors included indigeneity (5.0%), preterm birth (13.0%) and medical comorbidities (11.6%), including asthma (8.3%), other chronic respiratory disorders (1.4%), chronic neurological conditions (1.1%) and congenital heart disease (1.0%). No significant differences in demographics were identified when fully vaccinated, partially vaccinated and unvaccinated children were compared. Children with comorbidities were more likely to be fully vaccinated (55/300; 18.3%) compared with children without comorbidities (294/2282; 12.9%; $P < 0.03$).

Influenza was identified in 546 of 2723 (20.1%) of the recruited children and varied significantly between seasons [2008: 33/208 (15.7%); 2009: 75/389 (19.3%); 2010: 29/169 (17.2%); 2011: 59/494 (11.9%); 2012: 193/643 (30.0%); 2013: 54/386 (14.0%); 2014: 103/434 (23.7%); $P < 0.001$]. Influenza A/H1N1 was most frequently identified (218/2723: 8.0%) followed by influenza A/H3N2 (198/2723: 7.3%) and influenza B (130/2723: 4.8%).

To estimate vaccine uptake, influenza test-negative children were assessed. Vaccine uptake varied significantly between 2008 to 2009 and 2010 to 2014 with decreased uptake observed after 2010 (fully vaccinated: 2008 to 2009, 204/489, 41.7%; fully vaccinated: 2010 to 2014, 120/1688, 7.1%; $P < 0.001$; Fig. 1). In children with risk factors for severe influenza (children with medical comorbidities, children born preterm and indigenous children), a similar decrease in uptake was observed compared with those without risk factors (Fig. 1). Uptake has remained low since 2010: a nonsignificant trend toward increased uptake however was observed in those with comorbidities in 2014 (Fig. 2).

VE was calculated on those enrolled in the years 2008 and 2010 to 2014 (Table 2). Overall adjusted VE on all children was 70.0% (95% CI: 47.7 to 82.9). VE was demonstrated in the 2013 to 2014 cohort (VE: 87.5%; 95% CI: 45.8 to 97.1), confirming the results of previous analyses of data up to 2012.[11] Using the 2008 and 2010 to 2014 data, VE was demonstrated in children at increased risk of severe influenza infection. These included children with medical comorbidities (VE: 82.5%; 95% CI: 14.6 to 96.4). Significant VE was demonstrated in younger children (VE in children <2 years of age: 84.7%; 95% CI: 49.6 to 95.3). No influenza infections were observed in fully vaccinated preterm children. However, if fully and partially vaccinated children were compared with unvaccinated preterm children, adjusted VE was calculated to be 79.2% (95% CI: 10.9 to 95.1). Insufficient numbers of indigenous children were enrolled to demonstrate robust VE estimates.

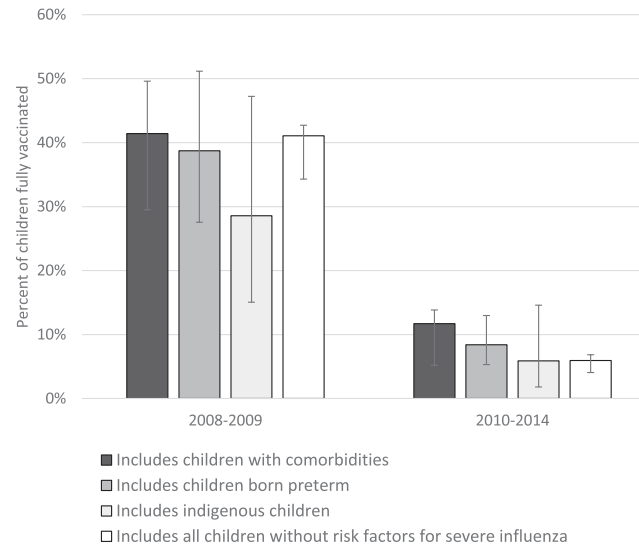

FIGURE 1. The proportion and 95% CI of children fully vaccinated with risk factors for severe influenza: 2008 to 2009 versus 2010 to 2014. Without risk factors for severe influenza (white bar) includes nonindigenous children and children born at term without comorbidities.

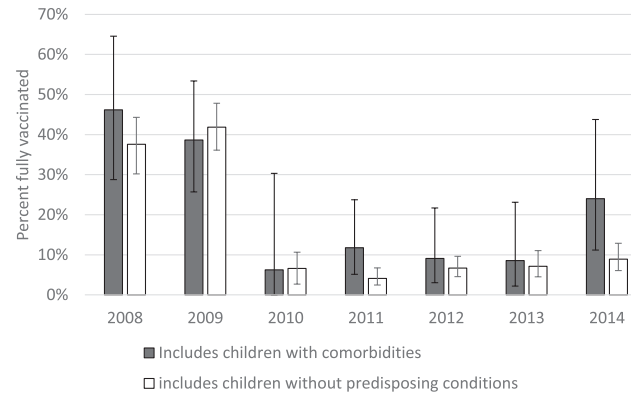

FIGURE 2. The proportion and 95% CI of children fully vaccinated with and without conditions predisposing to severe influenza: 2008 to 2009 versus 2010 to 2014.

TABLE 2. Unadjusted and Adjusted VE in Specific High-risk Conditions (Fully Vaccinated vs. Unvaccinated: 2008, 2010–2014 Only)

Risk Factor	Number of Cases and Controls				Unadjusted VE (95% CI)	Adjusted VE (95% CI)
	Fully Vaccinated Cases	Unvaccinated Cases	Fully Vaccinated Controls	Unvaccinated Controls		
All children	16	444	188	1557	70.2% (49.7 to 82.3)	70.0% (47.7 to 82.9)
Children with comorbidities	2	45	32	152	78.9% (8.5 to 95.1)	82.5% (14.6 to 96.4)
Preterm birth	0	52	23	200	100% (44.5 to 100)	79.2% (10.9 to 95.1)*
Indigenous children	1	29	5	62	57.2% (−282.8 to 95.2)	68.3% (−1150 to 99.2%)
Age <2 years	3	155	113	922	84.2% (49.7 to 95)	84.7% (49.6 to 95.3)

*If partially and fully vaccinated children included, adjusted VE estimate is 79.2% (95% CI: 10.9 to 95.1).

Parental attitudes of (1) children with and without medical comorbidities, (2) indigenous and nonindigenous children, (3) children born preterm and at term and (4) children aged <2 years and ≥2 years were compared. Few differences were noted when comparing response from parents of children with and without medical comorbidities. No significant differences were identified when comparing parental attitudes of children born preterm with those born at term, parental attitudes of indigenous and nonindigenous children and children aged <2 years and ≥2 years (data not shown).

Parents of children with medical comorbidities were similarly aware of the significance of influenza infection compared with the parents of children without comorbidities (Table 3): 94.3% of parents of children with and without comorbidities agreed with the statement "influenza can put young children in hospital." Parents of children with comorbidities also showed the same concern about vaccine safety as did parents of children without comorbidities: only 38.7% and 40.4% of parents, respectively, agreed with the statement "influenza vaccine is safe." Of note, parents of children with comorbidities less frequently agreed with the statements "I am worried about side effects of the influenza vaccine" and "It is better to have natural immunity against influenza" compared with parents without comorbidities. Parents of children with comorbidities were more likely to agree with the statement "My child has not been vaccinated because they have been unwell." A similar attitude toward vaccination in general was observed in both parental groups.

A small but significant change in parental attitudes was observed when parental attitudes toward influenza vaccine safety were assessed in 2014 (all parents) and compared with 2010 to 2013: in 2014, 46.2% of parents agreed and only 7.7% disagreed with the statement "influenza vaccine is safe" compared with 34.0% and 12.4%, respectively, in 2010 to 2013 ($P < 0.001$). Furthermore, a smaller proportion of parents (57.7%) agreed with the statement "I am worried about the side effects of the influenza vaccine" in 2014 compared with those in 2010 to 2013 (64.5%; $P = 0.03$), suggesting that attitudes are changing.

Parents of children with medical comorbidities were more likely to recall discussing influenza vaccination with their general practitioner compared with those without comorbidities (39.4% vs. 32.7%; $P < 0.02$). The proportion was significantly lower in both groups' post-adverse events in 2010. General practitioner recommendations appeared to vary significantly pre- and post-2010 adverse events. From parental questionnaires, general practitioners were equally likely to recommend vaccination in children with and without comorbidities in 2008 and 2009 (77.8% and 78.7%, respectively). After 2010, general practitioners were less likely to recommend vaccination to both those with and without comorbidities (59.7% and 51.2%, respectively), with a greater proportion recommending against (16.9% and 12.7%, respectively) or giving no recommendation (23.4% and 36.2%, respectively). The trend toward more frequent recommendation in those with medical comorbidities compared with those without after 2010 was not significant. Despite the encouraging trend observed in parental attitudes in 2014, the proportions of parental recalling their general practitioners recommending influenza vaccine in 2014 was unchanged.

DISCUSSION

Results of this study confirm and extend published studies evaluating the effectiveness of inactivated influenza vaccines in young children.[11,18–21] Using the test-negative design, we have previously demonstrated that adjusted VE against laboratory-confirmed influenza in children <5 years presenting to an emergency department (2008 and 2010 to 2012) was 64.7% (95% CI: 33.7 to 81.2).[11] Until now, too few children have been enrolled in this study to demonstrate the statistically significant VE estimates in those at greatest risk of severe influenza, including those with medical comorbidities, children born preterm and indigenous children. These data now demonstrate that VE in children with comorbidities, children born preterm and children <2 years of age is similar to total pooled estimates.

This study also enables us to describe vaccine uptake, parental attitudes and prescriber recommendations in those with and without risk factors for severe disease. Although vaccine uptake is higher in those with comorbidities, total vaccine uptake is still inadequate in all populations. Similar parental attitudes are observed in those with and without risk factors for severe disease: of note, parents of children with comorbidities appear to be less worried about side effects and less trusting on natural immunity to influenza. This study also further demonstrates the impact of adverse events observed in 2010 with bioCSL's Fluvax and Fluvax Junior on vaccine uptake and parental attitudes. Vaccine uptake was reduced in all populations, including those at greatest risk of severe influenza.

Our previous study using principal component analysis revealed that positive parental attitudes toward influenza vaccine safety and efficacy were the strongest predictor of vaccine uptake [adjusted OR: 3.38; 95% CI: 2.87 to 3.98].[8] It is anticipated that demonstrating the effectiveness and safety of TIV is central to restoring confidence in pediatric influenza vaccination for those with and without risk factors. The WAIVE study has demonstrated VE over a number of seasons. It remains essential to continue monitoring VE to confirm that vaccination is providing adequate protection and to further understand factors affecting VE.[18] Safety of non-bioCSL influenza vaccines has been demonstrated in children both in 2010 and in subsequent seasons,[9,10,22,23] with ongoing safety surveillance anticipated in future seasons. In a number of Australian states, robust centralized safety surveillance systems are in place, but a truly national system is yet to be developed. These programs are keys to restoring public confidence in pediatric influenza vaccination.

Vaccine uptake remains poor 4 years after the 2010 adverse events. The increased uptake in those with comorbidities in 2014

TABLE 3. Parental Attitudes Toward Influenza and Influenza Vaccine: Comparing Children With and Without Medical Comorbidities Predisposing to Severe Influenza

Parental Attitude	Medical Comorbidity	Parental Response			Significance (*P*)
		Agree (%)	Unsure (%)	Disagree (%)	
Attitudes toward influenza illness					
Influenza is a mild disease	Present	19.2	17.9	62.9	0.068
	Absent	25.1	15.0	59.9	
Influenza can put young children in hospital	Present	94.3	4.2	1.5	0.719
	Absent	94.3	4.7	1.0	
Influenza can kill young children	Present	80.8	15.8	3.4	0.353
	Absent	77.0	19.5	3.4	
Influenza is not easily caught from others	Present	6.5	6.9	86.5	0.678
	Absent	8.1	6.6	85.3	
Attitudes toward influenza vaccination					
Influenza vaccine is safe	Present	38.7	53.4	7.9	0.269
	Absent	40.4	49.1	10.5	
Influenza vaccine protects children against the influenza	Present	47.2	38.2	14.6	0.574
	Absent	46.4	40.9	12.7	
You can catch influenza from the vaccine	Present	25.2	36.1	38.7	0.847
	Absent	24.0	37.8	38.1	
I am worried about side effects of the influenza vaccine	Present	55.3	24.8	19.9	0.037
	Absent	59.4	18.3	22.3	
It is better to have natural immunityagainstinfluenza	Present	25.4	46.2	28.4	<0.001
	Absent	37.6	40.3	22.1	
Influenza vaccine will overload my child's immune system	Present	9.1	43.4	47.5	0.126
	Absent	6.3	48.6	45.1	
Attitudes toward access to influenza vaccine					
It is inconvenient to get an influenza vaccine	Present	18.0	13.2	68.8	0.328
	Absent	20.1	15.6	64.2	
Getting 2 needles in the first year is difficult to organize	Present	10.5	19.2	70.3	0.740
	Absent	11.9	17.9	70.1	
Vaccine being free is important	Present	72.8	12.8	14.3	0.132
	Absent	74.8	9.1	16.2	
I am too busy to get my child vaccinated against influenza	Present	7.9	4.9	87.2	0.323
	Absent	6.8	7.2	86.0	
My child has not been vaccinated because they have been unwell	Present	32.4	11.4	56.2	<0.001
	Absent	18.0	12.9	69.1	
Attitudes toward vaccination in general					
My child has had all their routine vaccines	Present	90.2	4.9	4.9	0.087
	Absent	92.8	2.5	4.6	
I do not believe that children should have any vaccinations	Present	2.7	8.1	89.2	0.297
	Absent	2.2	5.8	92.0	

is particularly encouraging and may demonstrate that public information campaigns undertaken since 2010 highlighting the risk of influenza, particularly to those with preexisting medical conditions, the safety of distributed brands and (from 2014 onward) the effectiveness of TIV, are having an impact. Previous research has demonstrated that discussion with a family doctor or general practitioner has a significant positive impact on vaccine uptake.[24–27] Of concern is that despite published efficacy and safety data, parents report that >40% of general practitioners continue to recommend against influenza vaccine or provide no specific advice. This is despite the existence of a funded state-based program for vaccinating young children with TIV and a recommendation by the Australian Technical Advisory Group on Immunisation, Australia's peak scientific advisory group on immunization.[7] Further research to confirm parents' observations and targeted education of health professionals is essential to ensure that families enquiring about influenza vaccine are provided with contemporary safety and effectiveness data. This is especially important in children with risk factors for severe influenza. Further research focusing on prescriber's attitudes is also essential to understand the factors influencing their recommendations.

There is consistent evidence from Australia and overseas that indigenous populations are at increased risk of hospitalization and morbidity from influenza.[28–30] In 2015, influenza vaccine will be provided free as a part of the national immunization program to indigenous children 6 months to <5 years extending the current recommendation for all indigenous Australians ≥15 years. Although point estimates are encouraging, to date, insufficient numbers of indigenous children have been recruited in studies to demonstrate VE in this group. Specific programs to evaluate VE in indigenous children should be undertaken to evaluate this extension to Australian national influenza vaccination program.

The strengths of this study include the number of children enrolled. This is the largest study evaluating southern hemisphere inactivated influenza vaccine in young children. The use of multiple methods to confirm immunization status and laboratory-confirmed medically attended influenza using highly sensitive and specific laboratory methods add further strength. The exclusion of

immunocompromised children has limited our ability to determine VE in all high-risk populations. The decreased vaccine uptake observed after the 2010 adverse events has constrained our ability to demonstrate VE: pooled analyses over many seasons have therefore been necessary to provide robust estimates. The lack of alternative vaccines in Australia such as live-attenuated has limited the generalizability of our findings to other countries. This is of particular importance, given both the increasing acceptance and the uptake of live-attenuated influenza vaccine in North America, its recommendation as a part of the childhood influenza vaccination program in the United Kingdom and recent concerns about VE of this product.[31,32] Determining prescriber recommendation by parental recall may have introduced potential biases.

CONCLUSIONS

Our findings extend influenza VE estimates in young children and further demonstrate effectiveness in a number of high-risk pediatric populations. Adverse events associated with the 2010 bioCSL's Fluvax and Fluvax Junior have impacted on uptake in all children including those at greatest risk of severe disease. Uptake remains poor. Despite demonstrated effectiveness and safety of alternative brands of inactivated influenza vaccines in young children, confidence and participation in the Western Australian preschool influenza vaccination programs remain low with many parents and prescribers remaining unconvinced of the safety and benefits of influenza vaccination in young children. Given the demonstrated effectiveness and safety of TIV, further research must now explore ways to improve uptake. Surveying prescribers' attitudes toward influenza vaccine in young children is required. Without improved uptake, significant, preventable, influenza morbidity and mortality will continue to be observed. Given the moderate VE demonstrated, access to alternate vaccines available in the Northern Hemisphere (eg, live-attenuated influenza vaccine) and increased research to develop more effective vaccines is also required.

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REFERENCES

1. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA*. 2004;292:1333–1340.
2. Fiore AE, Uyeki TM, Broder K, et al; Centers for Disease Control and Prevention (CDC). Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep*. 2010;59(RR-8):1–62.
3. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med*. 2000;342:232–239.
4. O'Brien MA, Uyeki TM, Shay DK, et al. Incidence of outpatient visits and hospitalizations related to influenza in infants and young children. *Pediatrics*. 2004;113(3 pt 1):585–593.
5. Gill PJ, Ashdown HF, Wang K, et al. Identification of children at risk of influenza-related complications in primary and ambulatory care: a systematic review and meta-analysis. *Lancet Respiratory Medicine.* 2014;3:139–149.
6. Mertz D, Kim TH, Johnstone J, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. *BMJ*. 2013;347:f5061.
7. Australian Technical Advisory Group on Immunisation. *Australian Immunisation Handbook*. 10th ed. Canberra: Department of Health, Australian Government, National Health and Medical Research Council; 2013.
8. Blyth CC, Richmond PC, Jacoby P, et al. The impact of pandemic A(H1N1)pdm09 influenza and vaccine-associated adverse events on parental attitudes and influenza vaccine uptake in young children. *Vaccine*. 2014;32:4075–4081.
9. Armstrong PK, Dowse GK, Effler PV, et al. Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine. *BMJ Open*. 2011;1:e000016.
10. Blyth CC, Currie AJ, Wiertsema SP, et al. Trivalent influenza vaccine and febrile adverse events in Australia, 2010: clinical features and potential mechanisms. *Vaccine*. 2011;29:5107–5113.
11. Blyth CC, Jacoby P, Effler PV, et al; WAIVE Study Team. Effectiveness of trivalent flu vaccine in healthy young children. *Pediatrics*. 2014;133: e1218–e1225.
12. Chidlow G, Harnett G, Williams S, et al. Duplex real-time reverse transcriptase PCR assays for rapid detection and identification of pandemic (H1N1) 2009 and seasonal influenza A/H1, A/H3, and B viruses. *J Clin Microbiol*. 2010;48:862–866.
13. Chidlow GR, Harnett GB, Shellam GR, et al. An economical tandem multiplex real-time PCR technique for the detection of a comprehensive range of respiratory pathogens. *Viruses*. 2009;1:42–56.
14. Hyypiä T, Auvinen P, Maaronen M. Polymerase chain reaction for human picornaviruses. *J Gen Virol*. 1989;70 (pt 12):3261–3268.
15. Foppa IM, Haber M, Ferdinands JM, et al. The case test-negative design for studies of the effectiveness of influenza vaccine. *Vaccine*. 2013;31:3104–3109.
16. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine*. 2013;31:2165–2168.
17. Orenstein EW, De Serres G, Haber MJ, et al. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. *Int J Epidemiol*. 2007;36:623–631.
18. Cowling BJ, Chan KH, Feng S, et al. The effectiveness of influenza vaccination in preventing hospitalizations in children in Hong Kong, 2009-2013. *Vaccine*. 2014;32:5278–5284.
19. Eisenberg KW, Szilagyi PG, Fairbrother G, et al; New Vaccine Surveillance Network. Vaccine effectiveness against laboratory-confirmed influenza in children 6 to 59 months of age during the 2003-2004 and 2004-2005 influenza seasons. *Pediatrics*. 2008;122:911–919.
20. Hoberman A, Greenberg DP, Paradise JL, et al. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial. *JAMA*. 2003;290:1608–1616.
21. Shuler CM, Iwamoto M, Bridges CB, et al. Vaccine effectiveness against medically attended, laboratory-confirmed influenza among children aged 6 to 59 months, 2003-2004. *Pediatrics*. 2007;119:e587–e595.
22. Blyth CC, Markus TY, Effler PV, et al. Ensuring safety of the 2011 trivalent influenza vaccine in young children. *Med J Aust*. 2011;195:52.
23. Wood NJ, Blyth CC, Willis GA, et al. The safety of seasonal influenza vaccines in Australian children in 2013. *Med J Aust*. 2014;201:596–600.

24. Daley MF, Crane LA, Chandramouli V, et al. Misperceptions about influenza vaccination among parents of healthy young children. *Clin Pediatr (Phila)*. 2007;46:408–417.
25. Grant VJ, Le Saux N, Plint AC, et al. Factors influencing childhood influenza immunization. *CMAJ*. 2003;168:39–41.
26. Nowalk MP, Lin CJ, Zimmerman RK, et al. Changes in parents' perceptions of infant influenza vaccination over two years. *J Natl Med Assoc*. 2007;99:636–641.
27. Nowalk MP, Zimmerman RK, Lin CJ, et al. Parental perspectives on influenza immunization of children aged 6 to 23 months. *Am J Prev Med*. 2005;29:210–214.
28. Flint SM, Davis JS, Su JY, et al. Disproportionate impact of pandemic (H1N1) 2009 influenza on Indigenous people in the Top End of Australia's Northern Territory. *Med J Aust*. 2010;192:617–622.
29. Harris PN, Dixit R, Francis F, et al. Pandemic influenza H1N1 2009 in north Queensland—risk factors for admission in a region with a large indigenous population. *Commun Dis Intell Q Rep*. 2010;34:102–109.
30. Trauer JM, Laurie KL, McDonnell J, et al. Differential effects of pandemic (H1N1) 2009 on remote and indigenous groups, Northern Territory, Australia, 2009. *Emerg Infect Dis*. 2011;17:1615–1623.
31. Grohskopf LA, Olsen SJ, Sokolow LZ, et al; Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2014-15 influenza season. *MMWR Morb Mortal Wkly Rep*. 2014;63:691–697.
32. Public Health England, Department of Health and NHS England. *Flu Plan: Winter 2015 to 2016*. London: GOV.UK; 2015. Available at: https://www.gov.uk/government/publications/flu-plan-2015-to-2016. Accessed July 10, 2015.