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ORIGINAL RESEARCH

Immunogenicity and clinical effectiveness of the trivalent inactivated influenza vaccine in immunocompromised children undergoing treatment for cancer

Rishi S. Kotecha[1,2,3], Ushma D. Wadia[4], Peter Jacoby[2], Anne L. Ryan[1], Christopher C. Blyth[2,3,4], Anthony D. Keil[5], Nicholas G. Gottardo[1,2,3], Catherine H. Cole[1,2,3], Ian G. Barr[6] & Peter C. Richmond[2,3,7]

[1]Department of Haematology and Oncology, Princess Margaret Hospital for Children, GPO Box D184, Perth, Western Australia 6840, Australia
[2]Telethon Kids Institute, University of Western Australia, PO Box 855, Perth, Western Australia 6872, Australia
[3]School of Paediatrics and Child Health, University of Western Australia, GPO Box D184, Perth, Western Australia 6840, Australia
[4]Department of Infectious Diseases, Princess Margaret Hospital for Children, GPO Box D184, Perth, Western Australia 6840, Australia
[5]Department of Microbiology, PathWest Laboratory Medicine WA, Princess Margaret Hospital for Children, GPO Box D184, Perth, Western Australia 6840, Australia
[6]WHO Collaborating Centre for Reference and Research on Influenza, VIDRL, Peter Doherty Institute for Infection and Immunity, 792 Elizabeth Street, Melbourne, Victoria 3000, Australia
[7]Department of Paediatrics, Princess Margaret Hospital for Children, GPO Box D184, Perth, Western Australia 6840, Australia

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Correspondence
Rishi S. Kotecha, Department of Haematology and Oncology, Princess Margaret Hospital for Children, GPO Box D184, Perth, Western Australia 6840, Australia.
Tel: +(618) 9340 8234; Fax: +(618) 9340 8384; E-mail: rishi.kotecha@health.wa.gov.au

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Abstract

Influenza is associated with significant morbidity and mortality in children receiving therapy for cancer, yet recommendation for, and uptake of the seasonal vaccine remains poor. One hundred children undergoing treatment for cancer were vaccinated with the trivalent inactivated influenza vaccine according to national guidelines in 2010 and 2011. Influenza-specific hemagglutinin inhibition antibody titers were performed on blood samples taken prior to each vaccination and 4 weeks following the final vaccination. A nasopharyngeal aspirate for influenza was performed on all children who developed an influenza-like illness. Following vaccination, seroprotection and seroconversion rates were 55 and 43% for H3N2, 61 and 43% for H1N1, and 41 and 33% for B strain, respectively. Overall, there was a significant geometric mean fold increase to H3N2 (GMFI 4.56, 95% CI 3.19–6.52, $P < 0.01$) and H1N1 (GMFI 4.44, 95% CI 3.19–6.19, $P < 0.01$) strains. Seroconversion was significantly more likely in children with solid compared with hematological malignancies and in children <10 years of age who received a two-dose schedule compared to one. Influenza infection occurred in 2% of the vaccinated study population, compared with 6.8% in unvaccinated controls, providing an adjusted estimated vaccine effectiveness of 72% (95% CI −26–94%). There were no serious adverse events and a low reactogenicity rate of 3%. The trivalent inactivated influenza vaccine is safe, immunogenic, provides clinical protection and should be administered annually to immunosuppressed children receiving treatment for cancer. All children <10 years of age should receive a two-dose schedule.

Introduction

The last 40 years have seen marked improvements in the treatment for childhood cancer, with a significant reduction in mortality in developed countries [1–4]. For a number of childhood malignancies, increased cure rates have been achieved by increasing the intensity and duration of chemotherapy. However, this leads to prolonged periods of immunosuppression and vulnerability to infectious and toxic complications. In particular, influenza infection remains a significant cause of morbidity, mortality, and health expenditure among children undergoing treatment and within 6 months following the completion of therapy for cancer [5–10].

Currently, annual vaccination with the inactivated influenza vaccine is recommended for all children undergoing treatment for cancer [11]. However, up to one-third of pediatric oncologists do not recommend yearly influenza vaccination [12, 13], with poor uptake (27–55%) identified in children with cancer [14–17]. The lack of knowledge regarding benefit of the influenza vaccine in this population has been identified as one of the reasons for poor compliance [14, 17]. The absence of literature correlating clinical outcome with immune response following influenza vaccination in children with cancer may reflect this lack of knowledge [18]. Given such findings, we undertook a prospective study to evaluate the immunogenicity and clinical effectiveness of the seasonal trivalent inactivated influenza vaccine in immunocompromised children receiving therapy for cancer, with the aim of providing evidence for annual influenza vaccination in this population and identifying risk factors that predict response.

Methods

Patient selection

Children between the ages of 6 months and 18 years who were receiving, or within 4 weeks from completion of immunosuppressive therapy for cancer were eligible. Recruitment was undertaken during the active influenza seasons of 2010 and 2011 (March–September) from the Department of Clinical Haematology and Oncology, Princess Margaret Hospital for Children (PMH) in Perth. PMH is the sole treatment center for all children with cancer in the state of Western Australia, which has a population of 2.6 million. Exclusion criteria included anaphylaxis to previous doses of any influenza vaccine, a history of egg anaphylaxis, receipt of intravenous immunoglobulin within the last 3 months, a neutrophil count of $\leq 0.5 \times 10^9$/L, a history of Guillain–Barré syndrome and children having undergone autologous stem cell rescue or allogeneic hematopoietic stem cell transplant. Informed consent was obtained from the parents of each child prior to recruitment.

Study design

Patients were vaccinated according to national Australian standards [19]. Children <10 years of age, receiving influenza vaccine for the first time, were given two doses of the trivalent inactivated influenza vaccine 1 month apart. Children <10 years of age who had previously received influenza vaccine and children who were ten or older, were given a single dose of the vaccine. A 0.25 mL dose was administered to children <3 years of age, whereas those three or older were given 0.5 mL. The strains included in the vaccine for the 2010 and 2011 seasons were A/Perth/16/2009 (H3N2), A/California/7/2009 (H1N1), and B/Brisbane/60/2008 (B). Children were observed for 20 min after each vaccination for immediate vaccine-related adverse events. Parents were given a daily diary for documentation of vaccine-related adverse events occurring in the 7 days following vaccination and this information was collected from the parents at each visit.

Blood was taken prior to each vaccination and 4 weeks following the final vaccination to assess influenza-specific immune responses. Following collection, blood samples were centrifuged and sera stored at −20°C. At the end of each season, the samples were sent to the World Health Organization (WHO) Collaborating Centre for Reference and Research on Influenza, Victorian Infectious Diseases Reference Laboratory (VIDRL) where influenza-specific hemagglutinin inhibition (HI) antibody titers were performed against each vaccine strain by standardized assay [20].

Susceptibility to a vaccine-like strain was defined as a prevaccination HI titer of <40. Seroprotection in an individual was defined as a postvaccination HI titer of ≥40. Seroconversion was defined as either a fourfold increase in HI antibody titer if the prevaccination titer was ≥10 or a rise in HI titer from <10 to ≥40 following vaccination [21]. The percentage (95% confidence interval [CI]) of patients who individually met these criteria for seroprotection and seroconversion to each strain of the vaccine was calculated.

Criteria as established by the Committee for Proprietary Medicinal Products (CPMP) [22], were used to determine whether the vaccine was considered to elicit an effective overall immunogenic response in our immunocompromised population. According to these criteria, the influenza vaccine is considered effective if it meets one of the following three criteria: seroprotection in >70% of patients; seroconversion in >40% of patients; or a geometric mean fold increase (GMFI) >2.5. These criteria were used to calculate one-sided *P* values in relation to the null hypotheses for overall seroprotection and seroconversion to each strain of the vaccine. GMFI was calculated for each strain as the geometric mean of the fold increase in antibody level after vaccination, with 95% CI and one-sided P values estimated using a log-normal approximation for the distribution of antibody levels pre and postvaccination and the CPMP defined threshold of GMFI >2.5.

Multivariate logistic regression models were used to assess the influence of clinically relevant variables to predict seroconversion to each strain and complete seroconversion to all three strains. The variables analyzed within the model were sex (male, female), age groups

as determined by the stratification according to the vaccination schedule (<3 years, 3–<10 years, 10–<18 years), tumor type (solid, hematological), treatment intensity in the 4 weeks preceding vaccination (low, high; classified according to anticipated extent and duration of immunosuppression (see Table S1) and lymphocyte count for age (normal range, less than lower limit of normal). Lower normal limits for absolute lymphocyte counts according to age were defined as 1.7×10^9/L for children <5 years of age, 1.1×10^9/L for 5–<10 years, and 1.0×10^9/L for ≥10 years [23]. The analyses were repeated on the subgroup of patients <10 years of age with the addition of vaccine doses received (one, two) as a variable in the model.

The standard procedure for all children with cancer in Western Australia who develop influenza-like illness, is to present for a clinical review and a nasopharyngeal aspirate is taken. Influenza-like illness is defined as an elevated temperature (≥37.5°C) or a clear history of fever (e.g., chills, rigors); the presence of at least one constitutional symptom from irritability, myalgia, headache, vomiting, diarrhea, or malaise; and the presence of at least one respiratory symptom from cough, sore throat, or rhinorrhea; with onset of symptoms occurring greater than 72 h after vaccine administration. The nasopharyngeal aspirates of all enrolled patients that were polymerase chain reaction positive for influenza were sent to the WHO Collaborating Centre for Reference and Research on Influenza, VIDRL, for culture and specific strain typing. Clinical effectiveness was assessed by comparing the proportion of laboratory confirmed influenza infection of vaccinated children on study with unvaccinated immunocompromised children receiving treatment for cancer who did not partake in the study at the time it was undertaken. Relative risk of infection comparing vaccinated and unvaccinated groups was estimated using log binomial regression, adjusting for age group and tumor type, with vaccine effectiveness calculated as 100 × (1 – relative risk). Clinical features of all children with cancer and laboratory proven influenza infection were documented and a qualitative assessment of clinical severity between vaccinated and unvaccinated patients was performed.

This study was approved by the Child and Adolescent Health Service Ethics Committee (Ethics Approval Number 1672/EP) with delegated authority from the PMH Institutional Review Board, within which the work was undertaken. It conforms to the provisions of the Declaration of Helsinki and the National Statement on Ethical Conduct in Human Research, Australian National Health and Medical Research Council. Statistical analyses were performed using SPSS Version 22.0: Armonk, NY, USA.

Results

There were 100 patients enrolled in the study, of which 80% were susceptible to H3N2, 67% to H1N1, and 88% to B strain prior to the first vaccination. Patient characteristics are listed in Table 1. Seroprotection was achieved in 55% for H3N2, 61% for H1N1, and 41% for B strain following vaccination. Seroconversion occurred in 43% for H3N2, 43% for H1N1, and 33% for B strain. A significant response to the H3N2 (GMFI 4.56, 95% CI 3.19–6.52, $P < 0.01$) and H1N1 (GMFI 4.44, 95% CI 3.19–6.19, $P < 0.01$) strains was observed using CPMP criteria. Table 2 shows the immunological response to each strain.

The multivariate analysis of predictive variables revealed that children with solid tumors were significantly more likely to seroresponse to each vaccine strain (H3N2: OR 7.39, 95% CI 2.42–22.53, $P < 0.01$; H1N1: OR 2.90, 95% CI 1.02–8.23, $P = 0.045$; B: OR 3.75, 95% CI 1.25–11.24, $P = 0.02$) and to undergo complete seroconversion to all three strains (OR 6.03, 95% CI 1.56–23.29, $P < 0.01$) compared to patients with hematological malignancies. Children with a lymphocyte count in the normal range for age were significantly more likely to seroresponse to B strain (OR 2.97, 95% CI 1.07–8.28, $P = 0.04$) than

Table 1. Patient demographics.

Characteristic	Number of patients (n = 100)
Sex	
Male	63
Female	37
Age	
6 months to <3 years	15
3 to <10 years	53
10 to <18 years	32
Cancer type	
Hematological	63
Pre-B acute lymphoblastic leukemia	39
T-cell acute lymphoblastic leukemia	8
Acute myeloid leukemia	6
Non-Hodgkin lymphoma	6
Hodgkin lymphoma	3
Langerhans cell histiocytosis	1
Solid	37
Central nervous system tumor	15
Wilms tumor	7
Ewing sarcoma	5
Rhabdomyosarcoma	4
Retinoblastoma	2
Germ cell tumor	2
Sex cord stromal tumor	1
Nasopharyngeal carcinoma	1
Dosing schedule	
One dose	67
Two doses	33

Table 2. Overall immunogenicity to trivalent inactivated influenza vaccine in immunocompromised children receiving treatment for cancer.

Vaccine strain	GMFI (95% CI)	*P* value	Seroprotection % (95% CI)	*P* value	Seroconversion % (95% CI)	*P* value
H3N2 (A)	4.56 (3.19–6.52)	<0.01	55 (45.2–64.8)	>0.99	43 (33.3–52.7)	0.27
H1N1 (A)	4.44 (3.19–6.19)	<0.01	61 (51.4–70.6)	0.98	43 (33.3–52.7)	0.27
B	3.07 (2.17–4.36)	0.12	41 (31.4–50.6)	>0.99	33 (23.8–42.2)	0.92

GMFI, geometric mean fold increase.

those with a low lymphocyte count at vaccination. Children who received low intensity therapy in the 4 weeks preceding vaccination were significantly more likely to seroerespond to the B (OR 3.16, 95% CI 1.09–9.18, $P = 0.03$) and H3N2 (OR 2.81, 95% CI 1.00–7.89, $P = 0.049$) strains compared with those who received high intensity therapy, with a trend for seroconversion demonstrated for H1N1 (OR 2.36, 95% CI 0.91–6.09, $P = 0.08$). Table 3 shows the multivariate analysis of factors predicting seroconversion. Multivariate analysis for the subgroup of patients <10 years of age revealed that vaccine naïve children who received two doses of the vaccine were significantly more likely to seroerespond to each strain (H3N2: OR 6.08, 95% CI 1.56–23.63, $P < 0.01$; H1N1: OR 6.03, 95% CI 1.74–20.90, $P < 0.01$; B: OR 14.72, 95% CI 2.80–77.36, $P < 0.01$), and to seroerespond to all three strains (OR 14.71, 95% CI 1.27–170.2, $P = 0.03$), than children who had been vaccinated in previous seasons and only received one dose of the vaccine.

The incidence of laboratory proven influenza infection in the vaccinated study population was 2% ($n = 2/100$), whereas in the unvaccinated control population there was an incidence of 6.8% ($n = 11/161$), giving an adjusted estimated vaccine effectiveness of 72% (95% CI −26– 94%). Of the children with laboratory proven influenza, there were 10 with acute lymphoblastic leukemia (ALL), including both vaccinated study patients, and individual patients with acute myeloid leukemia, Langerhans cell histiocytosis, and osteosarcoma. The two patients in the study had laboratory confirmed influenza B infection. Both patients failed to mount an immunological response to this strain with postvaccination HI titers <40. Unvaccinated children with influenza had an increased length of hospital admission (5.1 vs. 4 days, mean) and delay in the delivery of scheduled chemotherapy (4.5 vs. 0.5 days, mean) compared to vaccinated children with influenza. One unvaccinated control required supplemental oxygen for 3 days, however, there were no severe complications of influenza illness, such as admission to intensive care or death.

There were no vaccine-related serious adverse events. Reactogenicity, that was considered attributable to the vaccine, occurred in four children, who all developed fever within 24 h of receiving the vaccine, with no other cause identified. All four children required brief inpatient

Table 3. Multivariate analysis of factors predicting seroconversion to trivalent inactivated influenza vaccine in immunocompromised children receiving treatment for cancer.

	H3N2 (A)		H1N1 (A)		B	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sex						
Female	1		1		1	
Male	0.80 (0.29–2.19)	0.66	2.30 (0.83–6.37)	0.11	0.65 (0.24–1.78)	0.40
Age						
6 months to <3 years	1		1		1	
3 to <10 years	0.92 (0.19–4.42)	0.91	0.36 (0.07–1.73)	0.20	2.41 (0.50–11.59)	0.27
10 to <18 years	2.27 (0.45–11.48)	0.32	0.34 (0.07–1.70)	0.19	4.24 (0.87–20.69)	0.07
Tumor type						
Hematological	1		1		1	
Solid	7.39 (2.42–22.53)	<0.01	2.90 (1.02–8.23)	0.045	3.75 (1.25–11.24)	0.02
Treatment intensity						
High	1		1		1	
Low	2.81 (1.00–7.89)	0.049	2.36 (0.91–6.09)	0.08	3.16 (1.09–9.18)	0.03
Lymphocyte count						
Low	1		1		1	
Normal range	1.66 (0.59–4.66)	0.34	1.93 (0.72–5.16)	0.19	2.97 (1.07–8.28)	0.04

admissions for empiric antibiotic therapy until the fever subsided. The parent reported reactogenicity rate was 3% (n = 4/133 vaccinations).

Discussion

Influenza is a common respiratory pathogen associated with significant morbidity and mortality in children undergoing therapy for cancer [5–10], yet recommendation for and uptake of the seasonal influenza vaccine remains suboptimal [12–17]. Lack of knowledge regarding the benefit of the influenza vaccine in this population has been cited as a reason for poor uptake [14, 17]. Our study provides evidence that the trivalent inactivated influenza vaccine is safe, immunogenic and provides clinical protection for immunosuppressed children receiving treatment for cancer.

Our study confirms that immunocompromised children receiving treatment for cancer are able to mount a clinically significant immune response to the trivalent inactivated influenza vaccine. A wide range for seroprotection and seroconversion following administration of the trivalent influenza vaccine has been reported in this setting (summarized in Table 4) [24–35]. In our cohort, immunogenicity was toward the middle of these ranges: seroprotection H3N2 55% (range from published literature: 25–92%), H1N1 61% (5–96%), and B 41% (15–87%); seroconversion H3N2 43% (25–78%), H1N1 43% (16–84%), and B 33% (12–60%). Although this is reassuring, comparison between studies should be interpreted with caution due to the differences in methodology, season, and vaccine composition. In particular, different vaccination schedules, differing definitions of seroprotection and seroconversion, inclusion restricted to variables such as tumor type, and a broad range of methods to conduct statistical analyses have been used. The studies have been conducted over a large chronological time span, thus variations in susceptibility, differing circulating influenza strains, and vaccine composition need to be considered. Our study is only the second performed in the Southern Hemisphere using Southern Hemisphere influenza vaccine formulation, with the other study undertaken more than 30 years ago [35].

The CPMP have defined criteria to assess whether influenza vaccines are effective within a population. The vaccine can be considered immunologically effective in our cohort as it satisfied criteria for GMFI. Although the vaccine did not meet the numerical threshold for seroprotection and statistical significance was not achieved for seroconversion, this should be taken in the context of how the criteria have been defined and not interpreted as vaccine failure. Although the CPMP criteria have been used to assess influenza vaccines in children, they are more specific to adults. In addition, the CPMP criteria have not been defined according to an immunocompromised population. This highlights the need for revised definitions, which take into account age and immune competence, to determine whether influenza vaccines are effective within specific populations.

Our study is the first to identify that children with solid tumors mount a significantly higher immune response to each strain individually and all three strains collectively compared to those with hematological malignancies. A previous study identified superior seroconversion to the H1N1 strain in children with solid tumors compared to those with ALL [25], and the study reporting the highest seroprotection and seroconversion rates in children with cancer was undertaken in children with solid tumors [29] (Table 4). This difference can be explained by the direct adverse effect of hematological malignancies on the immune system, as well as therapy directed toward continuous myelosuppression for leukemia, whereas treatment for solid tumors is generally shorter and cyclical in nature. The influence of treatment on effector cells of the immune system has been examined previously, demonstrating prolonged suppression on the B-cell compartment in children receiving therapy for ALL compared with solid tumors [25].

Additional factors identified as predicting seroconversion from prior studies include higher white cell count, lymphocyte count, or IgG levels; increasing age; induction phase of therapy in ALL; and following completion of therapy (Table 4) [24, 25, 29–31, 34], which can all be considered correlates of underlying immune function. This is further emphasized by our results identifying a significantly superior seroconversion toward the B strain in children with a lymphocyte count in the normal range for age at vaccination and toward the B and H3N2 strains in children who received low compared with high intensity chemotherapy in the 4 weeks preceding vaccination. These correlates can be used as a guide to tailor the timing of vaccination on an individual basis, with optimal timing occurring prior to high intensity therapy, with normal lymphocyte counts and IgG levels in the patient. However, waiting for optimal conditions in an individual patient should not be at the expense of timely vaccination, given the risk of influenza to an unvaccinated immunocompromised child, the low chance of satisfying all predictive criteria at any one time in this population and that the vaccine remains safe and effective in children undergoing therapy for cancer despite immunosuppression.

Multivariate analysis of the subgroup of children <10 years of age has shown that vaccine naïve patients who received two doses of the vaccine were significantly more likely to seroconvert to each strain individually and all three strains collectively, than those vaccinated in

Table 4. Summary of the published literature assessing immunogenicity and variables predicting seroconversion to the trivalent inactivated influenza vaccine in immunocompromised children receiving treatment for cancer.

Study (Publication year)	No.	Cancer type	Hemisphere	Influenza season	Seroprotection (%)			Seroconversion (%)			Variables predicting superior seroconversion
					H3N2	H1N1	B	H3N2	H1N1	B	
Kotecha (Current study)	100	All types	Southern	2010–2011	55	61	41	43	43	33	Solid > Hematological tumors Children <10 years of age: 2 > 1 dose schedule B and H3N2: Low > High intensity therapy in 4 weeks prior to vaccination B: Lymphocyte count in normal range for age at vaccination
Ottoffy (2014) [24]	27	All types	Northern	2009–2011	78	48	15	37	22	22	Lymphocyte count >1.0 × 10^9/L at vaccination Normal IgG at vaccination
Kersun (2013) [25]	177	All types	Northern	2006–2010	_	_	_	_	_	_	H1N1: Solid tumors > ALL Induction phase of therapy in ALL Higher CD4 and CD8 influenza-specific T-cell responses in ALL B: Higher baseline B-cell count in ALL
Carr (2011) [26]	26	All types	Northern	2008–2009	92	73	31	46	27	12	No significant variables identified
Shahgholi (2010) [27]	32	ALL Maintenance	Northern	2007–2008	63	43	26	41	56	59	Not assessed
Reilly (2010) [28]	89	All types	Northern	2006–2008	_	_	_	34	22	35	Predictive variables assessed as part of Kersun et al. (2013) [25]
Bektas (2007) [29]	45	Solid[1]	Northern	2003–2004	98	96	87	78	84	60	B: Within 6 months from completion of therapy > On treatment
Matsuzaki (2005) [30]	44[2]	All types	Northern	2003-2004	25	42	29	25	38	33	H1N1 and H3N2: Completion of chemotherapy > On treatment H1N1 and B: IgG >690 mg/dL at vaccination B: White blood cell count >5 × 10^9/L at vaccination
Chisholm (2005) [31]	65	Solid[1]	Northern	2001-2003	77	60	48	33	52	51	H1N1: Lymphocyte count >1.0 × 10^9/L at vaccination
Porter (2004) [32]	20	ALL Maintenance	Northern	2001-2002	_	_	_	65	65	60	H1N1: 2 > 1 dose schedule
Hsieh (2002) [33]	25	ALL Maintenance	Northern	2000-2001	88	68	72	60	24	44	Not assessed
Chisholm (2001) [34]	42	ALL[3]	Northern	1995-1997	83	64	76	_	_	_	H1N1 and H3N2: Higher median age at vaccination
Feery (1979) [35][4]	19	ALL Maintenance	Southern	1978	58	5	21	42	16	_	Not assessed

[1]Includes lymphoma.

[2]Seroprotection and seroconversion given for up to 18 patients receiving chemotherapy; analysis of predictive variables undertaken on 44 patients of which 26 were up to 60 months following the completion of therapy.

[3]Includes one patient with acute myeloid leukemia and three with solid tumors.

[4]Results shown for patients who received trivalent inactivated influenza vaccine containing H1N1, H3N2, and B strains.

ALL, acute lymphoblastic leukemia.

previous seasons receiving one dose. This finding has previously been limited to seroconversion to the H1N1 strain in a small group of children with ALL [32]. Our findings provide conclusive evidence to recommend that all immunocompromised children <10 years of age undergoing therapy for cancer should receive two age-appropriate doses of the vaccine, regardless of prior vaccination history.

We have demonstrated that the trivalent inactivated influenza vaccine is clinically effective in immunocompromised children receiving treatment for cancer, with an adjusted estimated vaccine effectiveness of 72% (95% CI −26–94%). During the same influenza seasons, the estimated vaccine effectiveness in healthy children <5 years of age, recruited onto the Western Australian Influenza Vaccine Effectiveness study at PMH [36], was 60% (95% CI−70–91%); and for children <18 years of age presenting to general practitioners in Western Australia, as part of the Western Australian sentinel medical practice surveillance system for influenza [37], was 82% (95% CI 17–96%). The clinical effectiveness of the trivalent inactivated influenza vaccine in immunocompromised children receiving therapy for cancer was therefore comparable to geographically matched children during the same influenza seasons.

The average length of hospital admission and delay in the delivery of scheduled chemotherapy was noted to be greater in unvaccinated compared with vaccinated children with laboratory proven influenza infection. Although this study was not adequately powered for clinical features of influenza infection as an endpoint, these observations concur with outcomes of previous studies [6, 7, 38]. There were no serious adverse events and a parent reported reactogenicity rate of 3%, which is comparable to the low rates in the literature [24, 27, 29–31], further supporting the safety of the trivalent inactivated influenza vaccine in immunocompromised children receiving therapy for cancer.

There are several limitations upon which this study is based. Despite recruiting a large number of children in comparison to contemporary published studies, the statistical analyses were limited by patient number and may explain the lack of significance for some of the analyses. The relative rarity of childhood cancer and the low incidence of laboratory proven influenza contribute to this limitation. Future studies should focus on recruiting larger numbers of patients, which may be facilitated through the conduct of large collaborative multicenter trials. To provide additional strength to the data, future studies should also consider prospective comparison of immunogenicity and clinical effectiveness to healthy age-matched controls. It has been shown that children on maintenance therapy for ALL have an inferior but acceptable immune response when compared to healthy controls [27, 32], however, these findings have not been extended to other tumor types or other phases of ALL therapy. Finally, there is potential for variable exposure to influenza between the study and control population. This remains one of the generic limitations of testing clinical effectiveness in all influenza studies. It is also possible for test practices to vary between study and control populations, however, we do not expect this to influence the results of our study as children receiving therapy for cancer on our unit all routinely present for an assessment and nasopharyngeal aspirate if they develop influenza-like illness.

In conclusion, our data demonstrate that the trivalent inactivated influenza vaccine is safe, immunogenic, and provides clinical protection in immunosuppressed children receiving therapy for cancer. On the basis of these outcomes, we recommend administration of the inactivated influenza vaccination on an annual basis for children undergoing treatment for cancer. An age-appropriate two-dose schedule should be administered to all children <10 years of age, regardless of prior vaccination history. The optimal time for immunization is prior to high intensity therapy, with response more likely in individuals with normal lymphocyte counts and IgG levels. These clinical correlates are reflective of underlying immune function and can be used as a guide to tailor the timing of vaccination on an individual basis, although should not result in vaccination delays. Larger studies are required to further validate the variables predicting seroconversion and to determine the benefit of a two-dose schedule in all immunocompromised children receiving therapy for cancer regardless of age and prior vaccination history.

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Conflict of Interest

None declared.

References

1. Smith, M. A., S. F. Altekruse, P. C. Adamson, G. H. Reaman, and N. L. Seibel. 2014. Declining childhood and adolescent cancer mortality. Cancer 120:2497–2506.
2. Hunger, S. P., X. Lu, M. Devidas, B. M. Camitta, P. S. Gaynon, N. J. Winick, et al. 2012. Improved

survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J. Clin. Oncol. 30:1663–1669.
3. Youlden, D. R., P. D. Baade, P. C. Valery, L. J. Ward, A. C. Green, and J. F. Aitken. 2012. Childhood cancer mortality in Australia. Cancer Epidemiol. 36:476–480.
4. Bosetti, C., P. Bertuccio, L. Chatenoud, E. Negri, F. Levi, and C. La Vecchia. 2010. Childhood cancer mortality in Europe, 1970–2007. Eur. J. Cancer 46:384–394.
5. Cooksley, C. D., E. B. Avritscher, B. N. Bekele, K. V. Rolston, J. M. Geraci, and L. S. Elting. 2005. Epidemiology and outcomes of serious influenza-related infections in the cancer population. Cancer 104:618–628.
6. Feldman, S., R. G. Webster, and M. Sugg. 1977. Influenza in children and young adults with cancer: 20 cases. Cancer 39:350–353.
7. Tasian, S. K., J. R. Park, E. T. Martin, and J. A. Englund. 2008. Influenza-associated morbidity in children with cancer. Pediatr. Blood Cancer 50:983–987.
8. Kersun, L. S., S. E. Coffin, K. H. Leckerman, M. Ingram, and A. F. Reilly. 2010. Community acquired influenza requiring hospitalization: vaccine status is unrelated to morbidity in children with cancer. Pediatr. Blood Cancer 54:79–82.
9. Carr, S. B., E. E. Adderson, H. Hakim, X. Xiong, X. Yan, and M. Caniza. 2012. Clinical and demographic characteristics of seasonal influenza in pediatric patients with cancer. Pediatr. Infect. Dis. J. 31:e202–e207.
10. Esposito, S., V. Cecinati, B. Scicchitano, G. C. Delvecchio, N. Santoro, D. Amato, et al. 2010. Impact of influenza-like illness and effectiveness of influenza vaccination in oncohematological children who have completed cancer therapy. Vaccine 28:1558–1565.
11. Committee on Infectious Diseases. 2014. Recommendations for prevention and control of influenza in children, 2014–2015. Pediatrics 134:e1503–e1519.
12. Porter, C. C., K. A. Poehling, R. Hamilton, H. Frangoul, and W. O. Cooper. 2003. Influenza immunization practices among pediatric oncologists. J. Pediatr. Hematol. Oncol. 25:134–138.
13. Crawford, N. W., J. A. Heath, and J. P. Buttery. 2007. Immunisation practices of paediatric oncologists: an Australasian survey. J. Paediatr. Child Health 43:593–596.
14. Hale, K., and D. Isaacs. 2006. Survey of influenza immunisation uptake in 'high risk' children. J. Paediatr. Child Health 42:321.
15. Rees, H., M. Andrews, S. Broster, J. Nicholson, R. Skinner, and J. Chisholm; Supportive Care Group of the Children's Cancer Leukaemia Group. 2010. Influenza vaccination during cancer therapy. Arch. Dis. Child. 95:569–570.
16. Crawford, N. W., J. A. Heath, D. Ashley, P. Downie, and J. P. Buttery. 2010. Survivors of childhood cancer: an Australian audit of vaccination status after treatment. Pediatr. Blood Cancer 54:128–133.
17. Esposito, S., P. Marchisio, R. Droghetti, L. Lambertini, N. Faelli, S. Bosis, et al. 2006. Influenza vaccination coverage among children with high-risk medical conditions. Vaccine 24:5251–5255.
18. Goossen, G. M., L. C. Kremer, and M. D. van de Wetering. 2013. Influenza vaccination in children being treated with chemotherapy for cancer. Cochrane Database Syst. Rev. 8:CD006484.
19. Australian Technical Advisory Group on Immunisation. 2008. The Australian Immunisation Handbook, 9th ed. Australian Government Department of Health, Canberra.
20. WHO Global Influenza Surveillance Network. 2011. Manual for the laboratory diagnosis and virological surveillance of influenza. Available at http://whqlibdoc.who.int/publications/2011/9789241548090_eng.pdf?ua=1 (accessed 15 September 2015).
21. Fiore, A. E., C. B. Bridges, J. M. Katz, and N. J. Cox. 2013. Inactivated influenza vaccines. Pp. 257–293 *in* S. Plotkin, W. Orenstein and P. A. Offit, eds. Vaccines, 6th ed. Elsevier, Philadelphia, PA.
22. Committee for Proprietary Medicinal Products (CPMP). Note for guidance on harmonisation of requirements for influenza vaccines. CPMP/BWP/214/96. European Agency for the Evaluation of Medicinal Products (EMEA), March 1997.
23. Comans-Bitter, W. M., R. de Groot, R. van den Beemd, H. J. Neijens, W. C. Hop, K. Groeneveld, et al. 1997. Immunophenotyping of blood lymphocytes in childhood. Reference values for lymphocyte subpopulations. J. Pediatr. 130:388–393.
24. Ottoffy, G., P. Horvath, L. Muth, A. Solyom, M. Garami, G. Kovacs, et al. 2014. Immunogenicity of a 2009 pandemic influenza virus A H1N1 vaccine, administered simultaneously with the seasonal influenza vaccine, in children receiving chemotherapy. Pediatr. Blood Cancer 61:1013–1016.
25. Kersun, L. S., A. Reilly, S. E. Coffin, J. Boyer, E. T. Luning Prak, K. McDonald, et al. 2013. A prospective study of chemotherapy immunologic effects and predictors of humoral influenza vaccine responses in a pediatric oncology cohort. Influenza Other Respir. Viruses 7:1158–1167.
26. Carr, S., K. J. Allison, L. A. Van De Velde, K. Zhang, E. Y. English, A. Iverson, et al. 2011. Safety and immunogenicity of live attenuated and inactivated influenza vaccines in children with cancer. J. Infect. Dis. 204:1475–1482.

27. Shahgholi, E., M. A. Ehsani, P. Salamati, A. Maysamie, K. Sotoudeh, and T. Mokhtariazad. 2010. Immunogenicity of trivalent influenza vaccine in children with acute lymphoblastic leukemia during maintenance therapy. Pediatr. Blood Cancer 54:716–720.
28. Reilly, A., L. S. Kersun, K. McDonald, A. Weinberg, A. F. Jawad, and K. E. Sullivan. 2010. The efficacy of influenza vaccination in a pediatric oncology population. J. Pediatr. Hematol. Oncol. 32:e177–e181.
29. Bektas, O., C. Karadeniz, A. Oguz, S. Berberoglu, N. Yilmaz, and C. Citak. 2007. Assessment of the immune response to trivalent split influenza vaccine in children with solid tumors. Pediatr. Blood Cancer 49:914–917.
30. Matsuzaki, A., A. Suminoe, Y. Koga, N. Kinukawa, K. Kusuhara, and T. Hara. 2005. Immune response after influenza vaccination in children with cancer. Pediatr. Blood Cancer 45:831–837.
31. Chisholm, J., K. Howe, M. Taj, and M. Zambon. 2005. Influenza immunisation in children with solid tumours. Eur. J. Cancer 41:2280–2287.
32. Porter, C. C., K. M. Edwards, Y. Zhu, and H. Frangoul. 2004. Immune responses to influenza immunization in children receiving maintenance chemotherapy for acute lymphoblastic leukemia. Pediatr. Blood Cancer 42:36–40.
33. Hsieh, Y. C., M. Y. Lu, C. L. Kao, B. L. Chiang, D. T. Lin, K. S. Lin, et al. 2002. Response to influenza vaccine in children with leukemia undergoing chemotherapy. J. Formos. Med. Assoc. 101:700–704.
34. Chisholm, J. C., T. Devine, A. Charlett, C. R. Pinkerton, and M. Zambon. 2001. Response to influenza immunisation during treatment for cancer. Arch. Dis. Child. 84:496–500.
35. Feery, B. J., R. N. Matthews, M. G. Evered, and H. A. Gallichio. 1979. Antibody responses to influenza virus vaccine in patients with acute lymphocytic leukaemia. Aust. Paediatr. J. 15:177–180.
36. Blyth, C. C., P. Jacoby, P. V. Effler, H. Kelly, D. W. Smith, C. Robins, et al. 2014. Effectiveness of trivalent flu vaccine in healthy young children. Pediatrics 133:e1218–e1225.
37. Levy, A., S. G. Sullivan, S. S. Tempone, K. L. Wong, A. K. Regan, G. K. Dowse, et al. 2014. Influenza vaccine effectiveness estimates for Western Australia during a period of vaccine and virus strain stability, 2010 to 2012. Vaccine 32:6312–6318.
38. Kempe, A., C. B. Hall, N. E. MacDonald, H. R. Foye, K. A. Woodin, H. J. Cohen, et al. 1989. Influenza in children with cancer. J. Pediatr. 115:33–39.

Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1. Classification of treatment according to intensity.