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Vaccine 28 (2010) 1558–1565

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Impact of influenza-like illness and effectiveness of influenza vaccination in oncohematological children who have completed cancer therapy

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ARTICLE INFO

Article history:
Received 31 May 2009
Received in revised form
11 November 2009
Accepted 20 November 2009
Available online 8 December 2009

Keywords:
Influenza
Influenza vaccination
Oncohematology
Vaccines
Prevention

ABSTRACT

In order to evaluate the impact of influenza-like illness and the effectiveness of influenza vaccination in children with oncohematological disease who have completed cancer therapy, 182 children with a diagnosis of oncohematological disease were divided into two subgroups on the basis of the length of time off therapy (<6 months or 6–24 months) and randomised 1:1 to receive influenza vaccination or not. The controls were 91 otherwise healthy children unvaccinated against influenza. The results show that the clinical and socioeconomic impact of influenza-like illnesses and the effectiveness of influenza vaccination in oncohematological children who have completed cancer therapy are related to the length of the off therapy period, and seem to be significantly greater in those who have been off therapy for less than 6 months in comparison with healthy controls. This suggests that the administration of influenza vaccination should be strongly recommended only among oncohematological children who have been off therapy for less than 6 months.

1. Introduction

Although the use of influenza vaccine in healthy children is not universally recommended [1–3], all of the health authorities throughout the world agree that it should be recommended in subjects with underlying chronic severe disease [1–5]. These include children with cancer because they may experience longer lasting influenza and more frequent severe and fatal complications, and this can cause delays in administering chemotherapy [6–12]. Finally, children with cancer shed influenza viruses for a longer period of time than immunocompetent subjects, and therefore represent a possible infection reservoir for other children with similar diseases hospitalised in the same ward [9].

However, official guidelines do not indicate whether influenza should be prevented in the case of all neoplastic diseases, whether and how immunosuppressant therapy limits influenza vaccine administration, or whether vaccination should be recommended after the completion of cancer therapy. This information is important in order to verify whether children who have completed cancer therapy are really at higher risk of influenza complications and whether influenza vaccine administration is really needed to reduce this risk.

The main aim of this study was to evaluate the impact of influenza-like illness and the effectiveness of influenza vaccination in children with oncohematological disease who have completed cancer therapy.

2. Patients and methods

2.1. Study design

This prospective, randomised, single-blind study was carried out at the Oncohematological Pediatric Units of the Universities of Bari and Milano Bicocca (Italy) between 1 October 2006 and 30 April 2007.

The protocol was approved by the Institutional Review Board of both Universities, and the written informed consent of a parent or legal guardian was required; children aged more than 8 years were asked for their assent.

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doi:10.1016/j.vaccine.2009.11.055

The single-blind design was chosen because the preparation of a placebo containing all of the components of the formulation except the influenza antigens was technically impossible.

2.2. Study population and vaccine use

Fig. 1 shows the whole study population and how it has been divided into the different arms of the study.

Children aged more than 2 years who had not previously been vaccinated against influenza, who had completed cancer therapy for acute lymphoblastic leukemia (ALL), Hodgkin disease (HD) or non-Hodgkin's lymphoma (NHL) for less than 2 years, and who were regularly followed up at the two participating Oncohematologic Pediatric Units were considered eligible for the study. They were enrolled if written informed consent was provided by their parents or legal guardians after the nature of the study had been explained, if the children and their parents or legal guardians would be available throughout the duration of the trial, and if the parents or legal guardians could be reached by study staff for the post-vaccination contacts (telephone calls or clinic visits). The exclusion criteria were any serious chronic disease other than cancer (e.g. chronic pulmonary disease including asthma, signs of cardiac or renal failure, or severe malnutrition, progressive neurological disease); Down's syndrome or other known cytogenetic disorders; a known or suspected disease of the immune system or the administration of immunosuppressive therapy, including systemic corticosteroids (a prednisone-equivalent dose of 2 mg/kg/day) for more than 14 days; the administration of any blood product, including immunoglobulins, in the period from 6 months before vaccination to the conclusion of the study; the administration of a dose of any influenza vaccine (commercial or investigational) before enrolment; or a documented history of hypersensitivity to any component of the vaccine.

The following conditions were considered temporarily limiting, and the subjects could be enrolled once they had been resolved: a febrile illness (axillary temperature $\geq$37.5 °C or rectal temperature $\geq$38 °C) or other acute illness in the 36 h preceding vaccination; a respiratory illness in the subjects and/or household member in the 72 h preceding vaccination; wheezing in the 2 weeks before vaccination; the administration of a dose of any conventional or investigational influenza treatment (e.g. specific antivirals for the treatment of influenza) in the 2 weeks before enrolment; antibiotic treatment in the 72 h before vaccination.

The patients were divided into two groups on the basis of the length of time they had been off therapy (<6 months or 6–24 months), and then the subjects in each group were prospectively randomised 1:1 under blind conditions to receive an inactivated, trivalent, virosome-formulated subunit influenza vaccine (Inflexal V, Berna Biotech/Crucell, Switzerland) or not. The vaccine was administered intramuscularly in a single dose on day 1 in the case of children aged more than 9 years, or in two doses on days 1 and 31 in those aged less than 9 years. The randomised assignment was made by the study statistician (CP) for both centres, the vaccine was administered and adverse events (AEs) recorded by one investigator in each centre (GCD in Bari and MJ in Milano Bicocca), and the surveillance and treatment of influenza-like illnesses during the

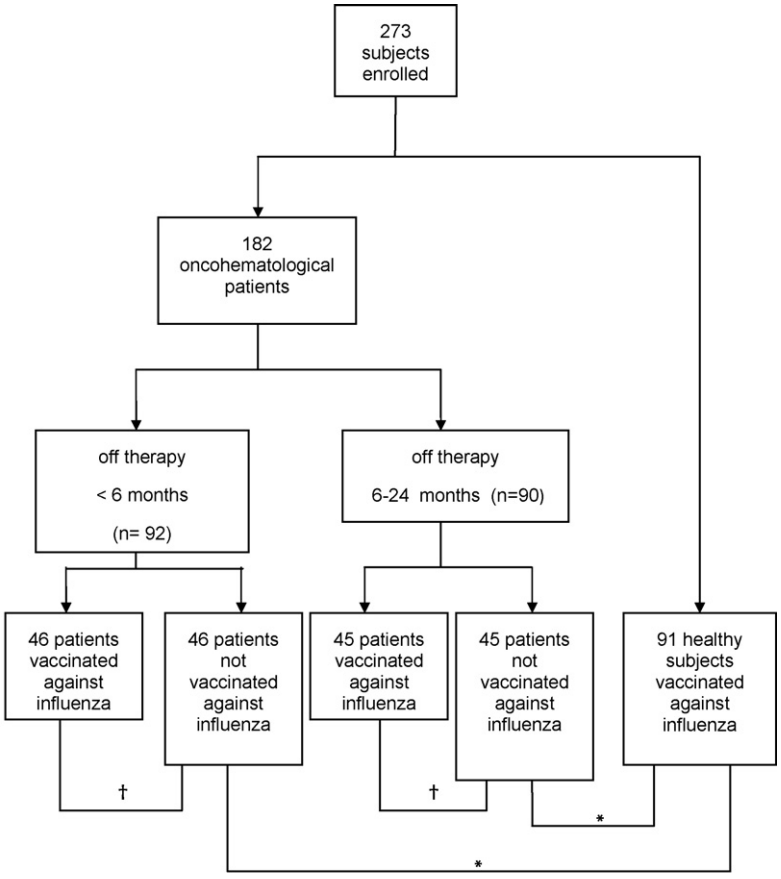

Fig. 1. Diagram showing the whole study population and how it has been divided into the different arms of the study.

influenza season was carried out by one investigator in each centre who was blinded to the study treatment assignment (VC in Bari and BS in Milano Bicocca). The children's parents and caregivers were asked to bring their child to the study centre in the case of any medical problems, and were told not to inform the examiner whether their child had received the vaccine or not.

All the children who received the vaccine were vaccinated before the onset of the influenza season, which was defined as the period including the dates of the first and last isolation of influenza virus as determined by the Italian national surveillance system. The surveillance was performed by means of a computerised network (http://www.influnet.it) that collected clinical reports from 500 sentinel physicians and integrated them with virological surveillance (by the Inter-university Research Centre on Influenza, Department of Health Sciences, University of Genoa, Italy) [13–15].

Immediately after randomisation, a further group of healthy subjects without any underlying chronic severe disease or disorder considered at risk of influenza-related complications but who were attending the outpatient clinics of the two Universities involved for minor surgery was enrolled. These children had not previously been vaccinated against influenza, and were matched by age and gender with the cancer patients who did not receive influenza vaccination. They were not vaccinated against influenza and their parents or legal guardians were asked to follow the same procedure for the surveillance and treatment of influenza-like illnesses as that designed for the cancer patients. The medical examinations during each episode of influenza-like illness were performed by two investigators blinded to their clinical history and influenza vaccination status (DA in Bari and SE in Milan). These healthy subjects represented the control group for the evaluation of the impact of influenza-like illness in children with oncohematologic disease who have completed cancer therapy. The healthy controls were not included in the evaluation of influenza vaccine effectiveness among oncohematological patients.

2.3. Procedures

Vaccination was administered only to oncohematologic children. Before vaccination, each subject's medical history was reviewed to ensure compliance with the inclusion and exclusion criteria. Upon enrolment, their demographic data and medical history (including current medications and previous vaccinations) were recorded, and they underwent a physical examination including rectal temperature. After the administration of the vaccine, each subject was observed for a minimum of 15 min. Emergency management supplies (AMBU bag, adrenalin and antihistamines) were available for the initial treatment of an allergic reaction if needed.

In order to be able to evaluate the occurrence of any AEs, the parents or legal guardians were given a digital thermometer and asked to keep a daily record on a diary card of the subject's rectal temperature and the occurrence of specific symptoms (including decreased activity, irritability, cough, sore throat, headache, muscle aches, chills, vomiting, a runny nose or nasal congestion, and sneezing) for 10 days after vaccination; the study personnel called each subject's home 1 and 10 days after vaccination to encourage compliance. The parents or legal guardians were also asked to record on the diary card any AEs or unscheduled physician visits during the study period, and the concomitant use of any prescription and non-prescription medication, and to contact the investigator immediately any significant illness or hospitalisation occurred.

The surveillance of influenza-related morbidity was performed in both oncohematologic children and healthy controls. During the surveillance of influenza-related morbidity, information regarding influenza-like illnesses and related morbidity among the study subjects and their household contacts was obtained by means of bi-weekly telephone interviews and monthly medical visits by the investigators blinded to the study treatment assignment using standardised questionnaires [16–19].

The definition of influenza-like illness used for the analysis included any upper or lower respiratory illness reported by the caregivers, and any respiratory illness associated with fever (axillary temperature $\geq$37.5 °C or rectal temperature $\geq$38 °C). The symptoms of a respiratory illness included at least one of the following: runny nose, nasal congestion, sore throat, cough, earache, wheezing and shortness of breath [17–19]. The respiratory symptoms had to last at least 3 days to be considered in the analysis, and only one new-onset illness could be included in any 2-week period. The upper respiratory tract infections (URTIs) included: (a) pharyngitis, defined as the presence of a sore throat and evidence of inflammation of the uvula and pharynx or tonsils with fever; (b) acute rhinosinusitis, defined as persistent rhinorrhea for more than 10 days and up to 3 weeks; and (c) croup, defined as inspiratory stridor, cough and hoarseness due to an obstruction in the laryngeal region [20]. The lower respiratory tract infections (LRTIs) included: (a) acute bronchitis, defined as cough and/or rhonchi in the chest radiographic absence of infiltrates beyond the perihilar area or consolidation or empyema; (b) wheezing, defined as cough and/or dyspnea with expiratory rales and/or wheezes unrelated to any known specific sensitisation; and (c) pneumonia, defined as fever, cough, tachypnea and decreased breath sounds or localised rales in the chest radiographic presence of infiltrates beyond the perihilar area or consolidation or empyema [20].

The parents or legal guardians were asked to answer a list of questions regarding the disease of their children (e.g. physician's final diagnosis, administered medication, hospitalisation, duration of signs/symptoms, medical visits, examinations, number of school days lost), and the involvement of other family members (e.g. influenza-like illness in household contacts, medication, hospitalisation, medical visits, number of working days lost by parents to care for their ill children and their own influenza-like illnesses, number of school days lost by the siblings because of their influenza-like illnesses). The caregivers could also freely contact an investigator on a 24-h basis in order to obtain an extra visit whenever the child developed symptoms of influenza-like illness.

2.4. Statistical analysis

The data regarding the oncohematological patients were compared between the subgroups (vaccinated *vs* unvaccinated, off therapy for <6 months *vs* off therapy for 6–24 months) and with those regarding the healthy children. The evaluation of the impact of influenza-like illness in children with oncohematologic disease who have completed cancer therapy was performed comparing oncohematological patients unvaccinated against influenza to unvaccinated healthy subjects. The evaluation of the effectiveness of influenza vaccination was performed comparing vaccinated oncohematological patients off therapy <6 months *vs* those off therapy for 6–24 months. All of the data were analysed using SAS for Windows version 12. The continuous variables are presented as mean values $\pm$ standard deviation (SD), and the categorical variables as numbers and percentages. A p value of <0.05 was considered significant for all statistical tests. Parametric data were analysed using analysis of variance (PROC GLM and LSD options) with terms for treatment; abnormally distributed or non-parametric data were analysed using the Kruskal–Wallis test. Categorical data were analysed using contingency tables and the chi-squared or Fisher's test. As previously described [16–19], to estimate the effectiveness vaccine in preventing influenza-related morbidity, a logistic model was fitted with the illness status of the child or household contact as the dependent variable,

and the vaccination status of the child as the predictor variable.

3. Results

A total of 182 children with a diagnosis of oncohematological disease were enrolled (ALL, 137; HD, 33; NHL, 12). Ninety-one (50.0%) received the influenza vaccine and 91 (50.0%) were not vaccinated. In each group, 46 children had been off therapy for less than 6 months and 45 for 6–24 months. The group of healthy unvaccinated children included 91 subjects.

Table 1 shows the demographic characteristics of the study population. There was no statistically significant difference between the vaccinated and unvaccinated oncohematological patients. However, full-time day-care or school attendance was significantly less frequent among the children who had been off therapy for less than 6 months than among those who had been off therapy for longer, and they also had a significantly higher number of respiratory infection, antibiotic courses and hospitalisations in the year before enrolment. The healthy children were comparable with those of the two cancer subgroups in terms of gender, mean age, mean number of household members, the frequency of exposure to passive smoking, and urban residence. However, their full-time day-care or school attendance, respiratory infections in the previous year, antibiotic courses, and hospitalisations were more similar to the cancer patients who had been off therapy for more than 6 months. Influenza vaccination among households was significantly more frequent among the oncohematological patients regardless of their own influenza vaccination status or length of time off therapy than among the healthy controls.

Table 2 summarises the impact of influenza-like illness on the oncohematological children not vaccinated against influenza. Those who had been off therapy for less than 6 months suffered from a statistically significant greater number of URTIs and LRTIs, infections other than influenza-like illness, hospitalisations, and days of fever, required antibiotics significantly more often, and lost more school days than those who had been off therapy for more than 6 months or the healthy children. On the contrary, the mean number of URTIs, LRTIs, infections other than influenza-like illness, and days of fever were similar in the unvaccinated oncohematological children who had been off therapy for more than six and in the healthy subjects during the study period. However, also these patients had a significantly higher mean number of hospitalisations, received a higher mean number of antibiotic courses, and lost a significantly greater number of school days than the healthy controls.

Table 3 shows that the household contacts of the unvaccinated cancer children who had been off therapy for less than 6 months had influenza-like illnesses, required medical visits, received antibiotic courses, and lost working days (parents) or school days (siblings) significantly more often than those of the unvaccinated cancer children who had been off therapy for longer or the healthy children. Except for the number of working days lost by mothers, the rates of all of the other variables were similar among the household contacts of the children with cancer who had been off therapy for more than 6 months and the healthy controls.

Table 4 shows that influenza vaccination was effective in reducing influenza-related morbidity among all of the vaccinated children, regardless of the time since their last cancer therapy. This table represented numbers observed in oncohematologic patients vaccinated against influenza off therapy for <6 months or off therapy for 6–24 months, and vaccine effectiveness was calculated comparing these numbers with those reported in Table 2 regarding oncohematological patients not vaccinated against influenza. One of the major benefits in both groups was the reduction in the number of hospitalisations, but the effectiveness of vaccination in decreasing the number of URTIs and LRTIs, days of fever, antibiotic courses, and lost school days was greater in the children who had been off therapy for less than 6 months.

Table 5 shows that influenza vaccination also reduced the clinical and socioeconomic costs of influenza-like illness in the households of the vaccinated oncohematological children, with better results once again being observed among the households of children who had been off therapy for less than 6 months in terms of the number of influenza-like illnesses, medical visits, hospitalisations, working days lost by parents, and school days lost by siblings. In this table, numbers represented what has been observed in households of oncohematological patients vaccinated against influenza off therapy for <6 months or off therapy for 6–24 months, and vaccine effectiveness was calculated comparing these numbers with those reported in Table 3 regarding households of oncohematological patients not vaccinated against influenza.

Table 6 shows the adverse events (AEs) observed in the influenza vaccinated children. The safety and tolerability of the vaccine was excellent after both doses (41 children received a second dose). Only a minority of children experienced AEs regardless of the time since the completion of cancer therapy or vaccine dose, and none of the AEs were serious; most of them were mild and did not require treatment. Fever was observed in only a few cases, with only two children who had been off therapy for less than 6 months (one after the first dose and one after the second), and one child who had been off therapy for more than 6 months (after the second dose) having a temperature of more than 39 °C.

4. Discussion

The results of this study show that the clinical and socioeconomic impact of influenza-like illness, and the effectiveness of influenza vaccination among children with ALL, HD or NHL who have completed cancer therapy, are related to the length of the off therapy period and seem to be significantly greater among those who have been off therapy for less than 6 months.

After an off therapy period of more than 6 months, the rates of clinical and socioeconomic problems caused by influenza-like illnesses do not seem to be significantly different from those observed in healthy subjects. The total number of infections diagnosed and the impact of the influenza-like illnesses of these children on their households were quite similar in the two groups, and the greater incidence of hospitalisation, the higher mean number of antibiotic courses, the higher number of lost school days, and the higher number of working days lost by mothers in this group of oncohematological children may have attributable to the greater attention paid by physicians and parents to all of the clinical problems of children affected by a severe disease. In this regard, it has been demonstrated that the parents of children with cancer show clinical or problem-indicative stress that can lead them to overestimate mild diseases [21].

The higher incidence of influenza-like illness in the children with ALL, HD or NHL who had been off cancer therapy for less than 6 months may have been attributable to the persistence of major cell immunodeficiency, which can outlast chemotherapy by months and enhance the risk of viral infections [22]. Chemotherapy for cancer is immunosuppressive, and B and T lymphocyte functions usually recover 6 months after its completion, although recovery and the normalisation of immunoglobulin levels may take up to 1 year [23–25]; furthermore, studies have shown that children vaccinated within a few months of completing cancer therapy show a lower (but in most cases equally protective) antibody response to a number of vaccines [26–35]. It is therefore not surprising that our children who had completed immunosuppressive therapy less than 6 months before the start of the study and who did not

Table 1
Demographic characteristics of the study population.

	Oncohematological patients vaccinated against influenza ($n = 91$)		Oncohematological patients not vaccinated against influenza ($n = 91$)		Healthy controls not vaccinated against influenza ($n = 91$)
	Off therapy <6 months ($n = 46$)	Off therapy 6–24 months ($n = 45$)	Off therapy <6 months ($n = 46$)	Off therapy 6–24 months ($n = 45$)	
Males, *n* (%)	27 (58.7)	25 (55.6)	28 (60.8)	24 (53.3)	54 (59.3)
Mean age ± SD (years)	9.7 ± 4.3	10.2 ± 3.7	10.1 ± 3.9	10.5 ± 3.5	9.7 ± 3.4
Type of cancer, *n* (%)					
ALL	34 (73.9)	33 (73.3)	36 (78.3)	34 (75.6)	n.a.
HD	8 (17.4)	9 (20.0)	7 (15.2)	9 (20.0)	n.a.
NHL	4 (8.7)	3 (6.7)	3 (6.5)	2 (4.4)	n.a.
Household contacts, mean number ± SD	3.31 ± 1.01	3.97 ± 0.76	4.01 ± 1.19	3.55 ± 0.69	3.80 ± 0.82
At least one household member vaccinated against influenza, *n* (%)	21 (45.7)[a]	24 (53.3)[b]	19 (41.3)[a]	20 (44.4)[a]	14 (15.4)
Exposure to passive smoking, *n* (%)	14 (30.4)	12 (26.7)	15 (32.6)	12 (26.7)	24 (26.3)
Urban residence, *n* (%)	44 (95.6)	42 (93.3)	43 (93.5)	43 (95.6)	90 (98.9)
Full-time day-care or school attendance, *n* (%)	9 (19.6)[b,d]	39 (86.7)	11 (23.9)[b,d]	40 (88.9)	88 (96.7)
Respiratory infections in the previous 12 months, mean *n* ± SD	3.55 ± 1.43[a,c]	1.88 ± 1.99[a]	3.90 ± 1.63[a,c]	1.73 ± 1.49[a]	1.03 ± 1.40
Antibiotic courses in the previous 12 months, mean *n* ± SD	3.69 ± 1.10[a,c]	1.61 ± 1.01[a]	3.99 ± 1.66[a,c]	1.82 ± 1.31[a]	0.63 ± 0.99
Hospitalisation in the previous 12 months, mean *n* ± SD	7 (15.2)[a,c]	0 (0.0)	6 (13.0)[a,c]	0 (0.0)	1 (1.1)

ALL, acute lymphoblastic leukemia; HD, Hodgkin disease; NHL, non-Hodgkin's lymphoma; n.a., not applicable; SD, standard deviation; [a] $p < 0.05$ and [b] $p < 0.0001$ *vs* healthy controls not vaccinated against influenza; [c] $p < 0.05$ and [d] $p < 0.0001$ *vs* oncohematological patients off therapy for 6–24 months.

Table 2
Impact of influenza-like illness in oncohematological children.

	Oncohematological patients not vaccinated against influenza ($n=91$)		Healthy controls not vaccinated against influenza ($n=91$)
	Off therapy <6 months ($n=46$)	Off therapy 6–24 months ($n=45$)	
N with at least one URTI (%)	42 (91.3)[a,c]	24 (53.3)	39 (42.9)
Mean *n* of URTIs ± SD	2.73 ± 1.49[a,c]	0.69 ± 0.73	0.47 ± 0.67
N with at least one LRTI (%)	15 (32.6)[b,d]	5 (11.1)	7 (7.7)
Mean *n* of LRTIs ± SD	0.67 ± 0.76[b,d]	0.17 ± 0.44	0.10 ± 0.33
N with at least one infection other than ILI (%)	24 (52.2)[b,d]	9 (20.0)	9 (9.9)
Mean *n* of infections other than ILIs ± SD	0.84 ± 0.96[b,d]	0.26 ± 0.88	0.15 ± 0.79
N with at least one hospitalisation (%)	36 (81.8)[a,c]	12 (26.7)[c]	1 (1.1)
Mean *n* of days with fever ± SD	4.74 ± 1.96[a,c]	1.66 ± 1.99	1.10 ± 1.99
Mean *n* of antibiotic courses ± SD	3.55 ± 2.55[a,c]	1.02 ± 0.93[d]	0.34 ± 0.76
Mean *n* of days lost from school ± SD	9.43 ± 3.69[a,c]	3.08 ± 2.01[d]	1.40 ± 1.33

URTI, upper respiratory tract infection; LRTI, lower respiratory tract infection; ILI, influenza-like illness; SD, standard deviation; [a] $p < 0.0001$ and [b] $p < 0.05$ *vs* oncohematological patients off therapy for 6–24 months; [c] $p < 0.0001$ and [d] $p < 0.05$ *vs* healthy controls.

receive influenza vaccination were affected by significantly more influenza-like illnesses than those who had been off therapy for more than 6 months.

The relative immunosuppression following the completion of cancer therapy may also explain the greater incidence of infections and their socioeconomic consequences among the households of the children who had been off therapy for less than 6 months, as previously published data indicate that the shedding of influenza viruses favouring the spread of infection is greater and lasts longer in immunocompromised children than in healthy subjects [36]. On the contrary, the medical and socioeconomic consequences of influenza-like illnesses in our children who had been off therapy for more than 6 months were similar to those observed in the healthy children. These findings suggest that children who have been off cancer therapy for less than 6 months should be considered at risk for influenza-related complications, but not those who have been off therapy for longer.

The different impact of influenza-like illnesses depending on the time since the completion of chemotherapy is further supported by our data regarding the effectiveness of influenza vaccination. Vaccine administration had a more substantial impact on the group of children who had been off therapy for less than 6 months and their household contacts which means that, despite the immunosuppression during the first months off therapy, it can still evoke a sufficient immune response to combat influenza viruses. This is in line with the finding of Matsuzaki et al. that influenza vaccination led to protective antibody titres against both influenza A and B viruses in most of their off therapy cases [32].

Our safety data show that the administration of virosomal adjuvanted influenza vaccine to oncohematologic children was very well tolerated regardless of the length of the off therapy period or vaccine dose, as the frequency of local and systemic reactions was similar to that reported in otherwise healthy children [3,19,37–39].

One limitation of this study is that it was not double-blind and placebo-controlled, but we believe that this was compensated by four factors: the two investigators responsible for the follow-up in the Oncohematologic Units, who are both experts in managing oncohematological children, were blinded to the treatment assignments; the follow-up in healthy children was performed by two different investigators blinded to the results in the oncohematological children; the families were instructed at study entry and reminded at each phone contact not to discuss group assignments

Table 3
Impact of influenza-like illness among households of oncohematological children.

	Households of oncohematological patients not vaccinated against influenza ($n=344$)		Households of healthy controls not vaccinated against influenza ($n=346$)
	Off therapy <6 months ($n=169$)	Off therapy 6–24 months ($n=175$)	
N with at least one ILI (%)	90 (53.3)[a,c]	63 (36.0)	116 (33.5)
Mean *n* of ILIs ± SD	0.82 ± 0.37[b,d]	0.40 ± 1.03	0.36 ± 1.16
N requiring medical visits (%)	82 (48.5)[a,c]	46 (26.3)	85 (24.6)
N requiring antibiotic courses (%)	69 (40.8)[a,c]	20 (11.4)	31 (8.9)
N requiring hospitalisations (%)	2 (1.2)	1 (0.6)	1 (0.3)
Mean *n* of working days lost by mother ± SD	14.47 ± 4.10[b,c]	7.02 ± 1.82[d]	4.36 ± 2.76
Mean *n* of working days lost by father ± SD	3.04 ± 1.16[b,d]	0.46 ± 0.69	0.36 ± 0.61
Mean *n* of school days lost by siblings ± SD	3.43 ± 0.98[b,d]	0.76 ± 0.91	0.58 ± 1.07

ILI, influenza-like illness; SD, standard deviation; [a] $p < 0.0001$ and [b] $p < 0.05$ *vs* oncohematological patients off therapy for 6–24 months; [c] $p < 0.0001$ and [d] $p < 0.05$ *vs* healthy controls.

Table 4
Effectiveness of influenza vaccination in oncohematological children.

	Oncohematological patients vaccinated against influenza ($n = 91$)			
	Off therapy <6 months ($n = 46$)	Effectiveness of vaccination (%)	Off therapy 6–24 months ($n = 45$)	Effectiveness of vaccination (%)
N with at least one URTI (%)	21 (45.7)	50.0[a]	18 (40.0)	25.0
Mean *n* of URTIs ± SD	0.52 ± 0.79	81.0[b]	0.46 ± 0.73	33.3
N with at least one LRTI (%)	5 (10.9)	66.6[b]	4 (8.9)	20.7
Mean *n* of LRTIs ± SD	0.15 ± 0.28	77.6[a]	0.08 ± 0.16	52.9
N with at least one infection other than ILI (%)	20 (43.4)	16.9	7 (15.5)	22.5
Mean *n* of infections other than ILI ± SD	0.67 ± 0.88	20.2	0.22 ± 0.64	16.0
N with at least one hospitalisation (%)	5 (10.9)	86.1	3 (6.7)	74.9
Mean *n* of days with fever ± SD	1.63 ± 1.91	65.6[b]	1.40 ± 1.63	15.7
Mean *n* of antibiotic courses ± SD	0.45 ± 1.01	87.3[b]	0.44 ± 0.96	56.9
Mean *n* of days lost from school ± SD	1.36 ± 1.90	85.6[b]	1.33 ± 1.49	56.8

URTI, upper respiratory tract infection; LRTI, lower respiratory tract infection; ILI, influenza-like illness; SD, standard deviation; [a] $p < 0.05$ and [b] $p < 0.0001$ *vs* oncohematological patients off therapy for 6–24 monts. Vaccine effectiveness = 1 minus attack rate (defined as the event rate divided by the total population) among vaccinated oncohematological children divided by the attack rate among unvaccinated oncohematological children [16]. This table represented numbers observed in oncohematologic patients vaccinated against influenza off therapy for <6 months or off therapy for 6–24 months, and vaccine effectiveness was calculated comparing these numbers with those reported in Table 2 regarding oncohematological patients not vaccinated against influenza.

Table 5
Effectiveness of influenza vaccination among households of oncohematological children.

	Households of oncohematological patients vaccinated against influenza ($n = 333$)			
	Off therapy <6 months ($n = 158$)	Effectiveness of vaccination (%)	Off therapy 6–24 months ($n = 175$)	Effectiveness of vaccination (%)
N with at least one ILI (%)	55 (34.8)	34.7	55 (31.4)	12.8
Mean *n* of ILIs ± SD	0.36 ± 1.22	56.1	0.34 ± 1.31	15.0
N requiring medical visits (%)	39 (24.7)	49.1	41 (23.4)	10.3
N requiring antibiotic courses (%)	18 (11.3)	27.7	15 (8.6)	24.6
N requiring hospitalisation (%)	1 (0.6)	52.7	1 (0.6)	0.0
Mean *n* of working days lost by mother ± SD	5.60 ± 2.10	61.3	5.00 ± 2.21	28.8
Mean *n* of working days lost by father ± SD	0.21 ± 0.77	93.1	0.22 ± 0.40	52.2
Mean *n* of school days lost by siblings ± SD	0.89 ± 1.10	74.1	0.60 ± 0.85	21.1

ILI, influenza-like illness; SD, standard deviation. Vaccine effectiveness = 1 minus attack rate (defined as the event rate divided by the total population) among vaccinated oncohematological children divided by the attack rate among unvaccinated oncohematological children [16]. In this table, numbers represented what has been observed in households of oncohematological patients vaccinated against influenza off therapy for <6 months or off therapy for 6–24 months, and vaccine effectiveness was calculated comparing these numbers with those reported in Table 3 regarding households of oncohematological patients not vaccinated against influenza.

with the investigators responsible for the children's follow-up; and all of the parents were contacted bi-weekly to inquire about their children's day-to-day status and reminded that they could freely contact an investigator at any time. Another limitation is the fact that no virological data are available because of the high cost of the virological assays and the absence of an adequate grant for influenza tests. However, the fact that no difference in the frequency of infections other than influenza-like illness was

Table 6
Occurrence of adverse events (AEs) in influenza vaccinated oncohematological children.

Adverse events	After 1st dose ($n = 91$)		After 2nd dose ($n = 41$)	
	Off therapy <6 months ($n = 46$)	Off therapy 6–24 months ($n = 45$)	Off therapy <6 months ($n = 21$)	Off therapy 6–24 months ($n = 20$)
Systemic events				
Fever ≥38 °C rectal	3 (6.5)	4 (8.9)	2 (9.5)	1 (5.0)
Irritability	4 (8.7)	5 (11.1)	2 (9.5)	2 (10.0)
Decreased appetite	3 (6.5)	3 (6.7)	1 (4.8)	1 (5.0)
Rhinitis	2 (4.3)	2 (4.4)	1 (4.8)	1 (5.0)
Cough	3 (6.5)	4 (8.9)	2 (9.5)	2 (10.0)
Vomiting	1 (2.2)	1 (2.2)	1 (4.8)	0 (0.0)
Local events				
Redness	2 (4.3)	1 (2.2)	1 (4.8)	1 (5.0)
Swelling/in duration	1 (2.2)	2 (4.4)	0 (0.0)	0 (0.0)
Total with at least one AE	9 (19.6)	10 (22.2)	5 (19.0)	4 (20.0)

Percentages in parentheses. No other AEs were reported.

observed in the vaccinated and unvaccinated children regardless of the length of the off therapy period supports the benefits of vaccination on influenza-like illnesses. Furthermore, given the high mean age of our study population, other respiratory viruses (e.g. respiratory syncytial virus, human metapneumovirus, and human coronaviruses) play a minor role in causing influenza-like illnesses in comparison with influenza viruses, especially if strict enrolment criteria are used as in our study. Despite these limitations, our study represents a major contribution to our knowledge of the role of influenza and the benefits of influenza vaccination in oncohematological patients and may allow the better evaluation of the real risk of influenza-related complications in such subjects. On the other hand, a recently published Cochrane review focused on influenza vaccination in children being treated with chemotherapy for their cancer highlighted the need for getting more knowledge on the efficacy and effectiveness of influenza vaccination in oncohematologic children [40].

In conclusion, the findings of this study suggest that the administration of influenza vaccine should be strongly recommended only for those oncohematological children who have recently completed cancer therapy. The patients who have been off therapy for more than 6 months can be considered in the same way as healthy children.

Acknowledgements

This study was supported by a grant from the Italian Ministry of Universities, Project No. 2005068289_001.

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