

# Influenza vaccination in children being treated with chemotherapy for cancer (Review)

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[Intervention Review]

# Influenza vaccination in children being treated with chemotherapy for cancer

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## ABSTRACT

### Background

Influenza infection is a potential cause of severe morbidity in children with cancer, therefore vaccination against influenza is recommended. However, there are conflicting data concerning the immune response to influenza vaccination in children with cancer and the value of vaccination remains unclear.

### Objectives

1. To assess the efficacy of influenza vaccination in stimulating immunological response in children with cancer during chemotherapy, compared to control groups.
2. To assess the efficacy of influenza vaccination in preventing confirmed influenza and influenza-like illness and/or stimulating immunological response in children with cancer treated with chemotherapy, compared to placebo, no intervention or different dosage schedules.
3. To determine the adverse effects associated with influenza vaccination in children with cancer.

### Search strategy

We searched CENTRAL, MEDLINE (1966 to 2007) and EMBASE (1980 to 2007) up to February 2007. We also searched reference lists of relevant articles and conference proceedings of ICAAC, IDSA, MASCC and SIOP.

### Selection criteria

We considered randomised controlled trials (RCTs) and controlled clinical trials (CCTs) in which the serologic response to influenza vaccination of children with cancer was compared to other control groups. We also considered RCTs and CCTs comparing the effects of influenza vaccination on clinical response and/or immunological response in children with cancer, with placebo, no intervention or different dosage schedules.

### Data collection and analysis

Two independent authors assessed the methodological quality of included studies and extracted data.

## Main results

We included 1 RCT and 8 CCTs (total number of participants=708). None of the included studies reported on clinical outcome. All included studies reported on influenza immunity and adverse reactions to vaccination. In five studies, immune responses to influenza vaccine were compared in 272 children on chemotherapy with 166 children not on chemotherapy. In three studies, responses to influenza vaccine were assessed in 204 children on chemotherapy compared with responses in 112 healthy children. The measures used to assess immune responses were: a four-fold rise in antibody titre after vaccination, development of haemagglutination inhibition (HI) titre > 32, and pre- and post-vaccination geometric mean titres (GMT). Immune responses in children receiving chemotherapy were consistently weaker (four-fold rise of 25% to 52%) than in those children who had completed chemotherapy (50% to 86%) and in healthy children (71% to 89%). Concerning adverse effects, 359 paediatric oncology patients received influenza vaccine and the side effects described were mild local reactions and low grade fever. No life-threatening or persistent adverse effects were reported.

## Authors' conclusions

Paediatric oncology patients receiving chemotherapy are able to generate an immune response to the influenza vaccine, but it remains unclear whether this immune response protects them from influenza infection or its complications. We are awaiting results from well-designed RCTs addressing the clinical benefit of influenza vaccination in these patients.

## PLAIN LANGUAGE SUMMARY

### Influenza vaccination in children being treated with chemotherapy for cancer

Children with cancer are prone to developing infections. One of the viral infections is influenza (flu). This can run an innocent course in these children but some can develop severe complications. This review therefore focused on the efficacy of influenza vaccination in children with cancer. We identified no studies which assessed the clinical efficacy of influenza vaccination, however we identified nine studies which assessed immune response after vaccination in children with cancer. It was shown that these children, receiving chemotherapy, mount poorer immune responses than healthy children, but that the vaccine can be safely administered. Based on this review it is not possible to recommend or discourage influenza vaccination in children with cancer being treated with chemotherapy. There should be a future trial addressing the clinical benefits of influenza vaccination in children with cancer being treated with chemotherapy.

## BACKGROUND

Recent advances in the diagnosis and treatment of opportunistic viral infections have led to the discovery that common community-acquired respiratory viruses are major pathogens associated with significant morbidity and mortality in immunocompromised or chronically ill patient populations (Hicks 2003). In oncology patients, the main risk factor associated with viral infection is disruption of the cellular immune response. The duration and severity of chemotherapy induced neutropenia are of lesser importance (Sandherr 2006). It has been shown that in 30% to 60% of immunocompromised patients with a diagnosis of idiopathic pneumonia (clinical or radiological findings in accordance with pneumonia), it is caused by viruses among which influenza is a major contributor (Hicks 2003).

Influenza virus infection occurs in yearly epidemics. An influenza epidemic may last five to six weeks and can be associated with attack rates as high as 20% in the general population, and possibly higher in the immunocompromised population. In patients

who are hospitalised (mainly elderly and immunocompromised patients) nosocomial transmission rates reach 55% to 83% (Dykewicz 2001; Raad 1997). Paediatric oncology patients are highly susceptible to influenza infection (Chisholm 2001), have an increased rate of influenza infection compared to healthy controls and may have prolonged influenza infections compared to healthy controls (Feldman 1977; Kempe 1989). Although the illness usually runs a mild course in children with cancer, it may result in hospitalisation, interruption of chemotherapy and the administration of antibiotics. Severe and fatal complications have also been reported in paediatric oncology patients with influenza infection, involving mainly secondary infections and haemophagocytic syndromes (Feldman 1977; Kempe 1989; Potter 1991).

The mainstay of influenza prophylaxis in the general population is vaccination. It is safe and immunogenic and shows 70% to 90% efficacy in preventing influenza when a good antigenic match exists between the vaccine and the epidemic virus (Hicks 2003). Ac-

According to the Advisory Committee on Immunization Practices (ACIP) 2006 guidelines (CID 2007) used in the USA, vaccination with the inactivated influenza vaccine is recommended for the following groups who are at increased risk of complications from influenza: 1) persons aged > 65 years; 2) residents of nursing homes; 3) adults and children with chronic pulmonary or cardiovascular disorders; 4) adults and children who have required medical follow up or hospitalisation during the preceding year because of chronic metabolic diseases, renal dysfunction, haemoglobinopathies or immunosuppression; 5) children between six months and 18 years of age who are receiving long-term aspirin therapy; 6) women who will be pregnant during the influenza season; 7) children aged six to 23 months; 8) adults and children who have any condition that can compromise respiratory function or the handling of respiratory secretions and increase the risk for aspiration (Smith 2006).

With the inactivated vaccine, there is no risk of introducing active infection and the vaccine is regarded as safe in immunocompromised individuals, even in paediatric oncology patients. Defects involving both cell-mediated and humoral immunity are frequent accompaniments of malignancies and chemotherapy induces myelosuppression, so that suboptimal responses to vaccination might be expected in patients with malignant disease. Immunological responses are generally lower than expected in healthy persons and may depend on the timing of vaccination relative to chemotherapy. However, in paediatric oncology patients there is a paucity of data, and the patient groups are heterogeneous with regard to underlying malignancy, chemotherapeutic regimens, and the type, dose, timing and route of administration of influenza vaccines. Antibody levels considered protective in healthy individuals may not prevent clinical infection in those with malignant disease (Ring 2002). To gain insight into the efficacy of influenza vaccination in paediatric oncology patients who are treated with chemotherapy, we systematically reviewed all data; not only clinical consequences (including adverse effects) but also immunological responses.

## OBJECTIVES

1. To assess the efficacy of influenza vaccination in stimulating immunological response in children with cancer during chemotherapy, compared to other control groups.
2. To assess the efficacy of influenza vaccination in preventing confirmed influenza and influenza-like illness and/or stimulating immunological response, compared to placebo, no intervention or different dosage schedules in children with cancer being treated with chemotherapy.
3. To determine the adverse effects associated with influenza vaccines in children with cancer treated with

chemotherapy, compared to other control groups.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We considered randomised controlled trials (RCTs) and controlled clinical trials (CCTs) in which the serologic response to influenza vaccination of children with cancer was compared to other control groups. We also considered RCTs and CCTs of influenza vaccination looking at preventing influenza and/or influenza-like illness and/or stimulating immunological response in children with cancer being treated with chemotherapy, compared to placebo, no intervention or different dosage schedules.

#### Types of participants

Children with cancer (one to 18 years) who are being treated with chemotherapy or who have been off chemotherapy for less than one month.

#### Types of interventions

Vaccination with any influenza vaccine, in any dose, preparation or time schedule.

#### Types of outcome measures

1. Laboratory confirmed influenza infection.
  - i) Influenza-like illness (as defined by the authors; most often non-specific respiratory illness characterised by fever, fatigue and cough).
  - ii) Pneumonia (radiographically documented, clinically diagnosed) or any secondary infection.
  - iii) Hospitalisation.
  - iv) Days in intensive care unit (ICU).
  - v) Delay in chemotherapy.
  - vi) Mortality.
2. Influenza immunity (difference in pre- and post-influenza vaccination haemagglutinin inhibition antibody titre).
3. Adverse reactions related to influenza vaccination (such as arm soreness, fever, myalgia, fatigue, malaise or headache).

### Search methods for identification of studies

We searched the following electronic databases to identify reports: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, issue 1), MEDLINE/Pubmed (1966 to February 2007) and EMBASE/Ovid (1980 to February 2007). We used the subject headings and text words shown in Appendix 1.

We located information on trials not registered in MEDLINE, EMBASE or CENTRAL, either published or unpublished, by searching the reference lists of relevant articles and review articles. We also scanned, electronically if available and otherwise by handsearching, the five latest issues (2001 to 2006) of the conference proceedings of the International Society for Paediatric Oncology (SIOP), the Multinational Association of Supportive Care in Cancer (MASCC), the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA). We also contacted researchers involved in this area. No language restriction was imposed.

## Data collection and analysis

### Selection of studies

Two authors (GG and MvdW) independently identified studies meeting the eligibility criteria. We based decisions on which trials to include on the methods section of the trial. We resolved discrepancies by discussion. If this was unsuccessful, there was to be arbitration by a third party. We clearly stated reasons for exclusion of any study considered for review.

### Data extraction and management

The two authors independently performed data extraction using standardised forms. We extracted data on the characteristics of participants (age, sex, tumour type, received anti-cancer treatment), interventions (description of vaccine, dose, timing and route of delivery of vaccine), outcome measures (immunological response to vaccination, laboratory confirmed influenza, influenza-like illness, pneumonia or any secondary infection, cases of influenza admitted to hospital, days in ICU, delay to chemotherapy, mortality, adverse events related to influenza vaccine), length of follow up and study design. In cases of disagreement, we re-examined and discussed the abstracts and articles until consensus was achieved. When data were missing, we made an attempt to contact the authors for additional information. We obtained extra information on one study (Chisholm 2005). This information contained: 1) the protective response rate, seroresponse rate and geometric mean titre (GMT) for each of the three viral strains four to six weeks after final vaccination in children on chemotherapy and 2) the protective response rate, seroresponse rate and GMT for each of the three viral strains four to six weeks after final vaccination in children off chemotherapy. We entered the data into RevMan 5 software (RevMan 2008).

### Assessment of risk of bias in included studies

The two authors independently assessed trial quality. We assessed the methodological quality of the RCTs according to the guidelines of the Cochrane Childhood Cancer Group (see Table 1). We used the Newcastle-Ottawa Scale (NOS 2007) for quality assessment of CCTs (see Table 2). We contacted authors for additional information where necessary. Disagreements were resolved by discussion between the authors.

**Table 1. Cochrane Childhood Cancer Group guidelines on quality assessment of randomised controlled trials**

Assessment of methodological quality of randomised controlled trials
<p><b>Selection bias</b></p> <p>Allocation concealment:</p> <p>A. Adequate: use of randomisation method that did not allow investigator and participant to know or influence the allocation of treatment before eligible participants entered the study.</p> <p>B. Unclear: randomisation stated but no information on method used is available.</p> <p>C. Inadequate: use of alternate medical record numbers or unsealed envelopes as randomisation method, and/or there is information in the study indicating that investigators or participants could have influenced the allocation of treatment.</p> <p><b>Performance bias</b></p> <p>Blinding of care providers: Yes/No/Unclear</p> <p>Blinding of participants: Yes/No/Unclear</p> <p>Care providers and patients are considered not blinded if the intervention group can be identified in &gt; 20% of participants because of side effects of treatment.</p>

**Table 1. Cochrane Childhood Cancer Group guidelines on quality assessment of randomised controlled trials** (Continued)

<p><b>Detection bias</b> Blinding of outcome assessors: Yes/No/Unclear</p> <p><b>Attrition bias</b> Intention-to-treat analysis: A. Yes: all participants are analysed in the treatment group to which they were allocated, regardless of whether or not they received the allocated intervention. B. No: some participants (&lt; 5%, 5% to 10%, 10% to 20%, &gt; 20%) are not analysed in the treatment group to which they were randomised because they did not receive the study intervention, they withdrew from the study, or because of protocol violation. C. Unclear: inability to determine if patients were analysed according to the intention-to-treat principle after contact with the authors.</p> <p><b>Completeness of follow up</b> Percentage of participants excluded or lost to follow up for the different treatment groups for the primary and secondary outcomes (&lt; 5%, 5% to 10%, 10% to 20%, &gt; 20%).</p>
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**Table 2. Newcastle - Ottawa quality assessment scale**

<p><b>Scale</b></p> <p><b>Cohort studies</b></p> <p>Note: A study can be awarded a maximum of 1 star for each numbered item within the Selection and Outcome categories. A maximum of 2 stars can be given for Comparability. A total of 9 stars can be awarded.</p> <p><i>Selection</i></p> <ol style="list-style-type: none"> <li>1. Representativeness of the exposed cohort (1 star*)             <ol style="list-style-type: none"> <li>a) Truly representative of the exposed cohort</li> <li>b) Somewhat representative of the exposed cohort</li> <li>c) Selected group of users e.g. nurses, volunteers</li> <li>d) No description of the derivation of the cohort</li> </ol> </li> <li>2. Selection of the non exposed cohort (1 star*)             <ol style="list-style-type: none"> <li>a) Drawn from the same community as the exposed cohort</li> <li>b) Drawn from a different source</li> <li>c) No description of the derivation of the non exposed cohort</li> </ol> </li> <li>3. Ascertainment of exposure (1 star*)             <ol style="list-style-type: none"> <li>a) Secure record</li> <li>b) Structured interview</li> <li>c) Written self-report</li> <li>d) No description</li> </ol> </li> <li>4. Demonstration that outcome of interest was not present at start of study (1 star*)</li> </ol>
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**Table 2. Newcastle - Ottawa quality assessment scale** (Continued)

a) Yes
b) No
<i>Comparability</i>
1. Comparability of cohorts on the basis of the design or analysis (max 2 stars**)
a) Study controls for age
b) Study controls for time on chemotherapy
<i>Outcome: (1 star*)</i>
1: Assessment of outcome
a) Independent blind assessment
b) Record linkage
c) Self-report
d) No description
2. Was follow up long enough for outcomes to occur (1 star*)
(1) Yes
(2) No
3. Adequacy of follow up of cohorts (1 star*)
a) Complete follow up - all subjects accounted for
b) Subjects lost to follow up unlikely to introduce bias - small number lost > 80% follow up
c) Follow-up rate < 80% and no description of those lost
d) No statement

### Data synthesis

We analysed the data according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Handbook). We analysed non-randomised trials separately and described the study results separately in the Results section. The results are presented as described by the authors. Some of them used an intention-to-treat analysis; others did not. Pooling of data was not possible because different study groups and different vaccines were described in the included studies.

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

The searches of CENTRAL, MEDLINE and EMBASE identified 3172 titles of reports of potentially relevant studies, which were screened for retrieval. We excluded 3136 reports by screening of titles and abstracts. We then retrieved 36 reports for detailed assessment; a further 28 were then excluded. After searching the conference proceedings and reference lists of the relevant studies and reviews, we identified nine additional reports for detailed assessment. None of these were included. A complete list with reasons for exclusion is presented in the table of 'Characteristics of excluded studies' (n = 36). One of the excluded studies is also mentioned as an ongoing study. Thus, we included eight studies (total number of participants of 708) in this systematic review.

## RESULTS

### Description of studies

### Included studies

Characteristics of the eight included studies are presented in the table 'Characteristics of included studies'. One of the studies comprised both a RCT (Hsieh 2002a) and a CCT (Hsieh 2002b). The remaining seven studies were all CCTs, thus one RCT and eight CCTs were included. None of the included studies compared influenza vaccine to placebo and no clinical outcomes of influenza infection were assessed. In five of these studies (Chisholm 2005; Gross 1978; Lange 1979; Matsuzaki 2005; Steinherz 1980), responses to different strains of influenza vaccine, in a total of 272 children with cancer receiving chemotherapy, were compared to those of 166 children with cancer not receiving chemotherapy during the last four weeks prior to vaccination. In three studies (Lange 1979; Porter 2004; Steinherz 1980), responses to different strains of influenza vaccine in a total of 204 children with cancer receiving chemotherapy were compared to those in 112 healthy children. In one study, responses to different strains of influenza vaccine in 25 children receiving maintenance chemotherapy for acute lymphoblastic leukaemia (ALL) were compared to those in 30 children with asthma in remission (Hsieh 2002b). Furthermore, two vaccination protocols were compared in a total of 25 children with ALL on maintenance chemotherapy (Hsieh 2002a). In one study (Chisholm 2001) serology of 42 immunised paediatric oncology patients was compared to that of 42 non-immunised paediatric oncology patients.

### Risk of bias in included studies

Data on quality assessment of the eight included CCTs are shown in additional Table 3. The CCTs were of almost equal quality scoring. Each scored between seven and nine stars, where the maximum possible was nine.

**Table 3. Quality of included CCTs**

	Selection	Comparability	Outcome	Total
Chisholm 2001	4 stars (classified A)	1 star	2 stars (poor follow up) classified as B	7 stars
Chisholm 2005	4 stars (classified A)	1 star	2 stars (poor follow up) classified as B	7 stars
Gross 1978	4 stars (classified A)	2 stars	3 stars	9 stars
Hsieh 2002a	4 stars (classified A)	2 stars	3 stars	9 stars
Lange 1979	4 stars (classified A)	2 stars	2 stars (poor follow up) classified as B	8 stars

**Table 3. Quality of included CCTs** (Continued)

Matsuzaki 2005	4 stars (classified A)	2 stars	3 stars	9 stars
Porter 2004	4 stars (classified A)	2 stars	2 stars (poor follow up) classified as B	8 stars
Steinherz 1980	4 stars (classified A)	1 star	2 stars (poor follow up) classified as B	7 stars

Five of the included studies did not have a complete follow up (Chisholm 2001; Chisholm 2005; Lange 1979; Porter 2004; Steinherz 1980). In two of these studies (Chisholm 2005; Porter 2004), the number of subjects lost to follow up was small and unlikely to introduce bias. In the remaining studies a large percentage of subjects was lost to follow up; respectively 36% of non-immunised patients in Chisholm 2001, 29% of patients receiving chemotherapy in Lange 1979 and 52% of patients receiving chemotherapy in Steinherz 1980. These three studies are susceptible to attrition bias as loss to follow up is greater than 20%. Reasons for loss to follow up were stated in Chisholm 2001 and Steinherz 1980. In Lange 1979 reasons for loss to follow up were not stated. However, the high percentage of loss to follow up is at 12 months after first vaccination, while outcomes relevant to this review are assessed one month after last vaccination. Loss to follow up one month after the last vaccination was less than 20%.

Ages of children in the different groups (i.e. children receiving chemotherapy, children not receiving chemotherapy and healthy children) were comparable, except in three studies (Chisholm 2001; Chisholm 2005; Steinherz 1980). In two of these (Chisholm 2001; Chisholm 2005) the mean age or range of age of the children is not stated. In the other study (Steinherz 1980), children on chemotherapy were about three years younger than those off chemotherapy. Age is a possible confounder for immune response.

In the one included RCT (Hsieh 2002a) (Table 4), the method of randomisation was not stated, allocation concealment and blinding of care providers was unclear, and there was no blinding of participants. This makes the trial susceptible to bias.

**Table 4. Quality of RCT**

Scored items	Hsieh 2002
Randomisation performed	Yes, method not stated
Allocation concealment	Unclear

**Table 4. Quality of RCT** (Continued)

Blinding of care providers	Unclear
Blinding of participants	No
Blinding of outcome assessors	Yes
Intention-to-treat analysis	Yes
Completeness of follow up	None lost to follow up

Attempts to gain additional information from the authors concerning methodological quality were partly successful. We obtained additional data on one study (Chisholm 2005).

### Effects of interventions

Because pooling was not possible, we present only descriptive results.

#### Outcomes

##### 1. Laboratory confirmed influenza infection within the epidemic period

This was not reported as an outcome measure in any of the included studies. In one study (Matsuzaki 2005), it is mentioned in the results section that none of the patients who received two doses of influenza vaccine were diagnosed as having influenza during the following influenza season. However, it is not stated what methods were used to determine influenza infection.

##### 2. Influenza-like illness, pneumonia, hospitalisation, days in ICU, delay in chemotherapy and mortality

These were not reported as outcome measures in any of the included studies.

##### 3. Influenza immunity (difference in pre- and post-influenza vaccination haemagglutinin inhibition (HI) antibody titre)

Various measures to assess immune response after vaccination were used. Five studies (Chisholm 2005; Hsieh 2002a, Matsuzaki 2005; Porter 2004; Steinherz 1980) assessed a four-fold rise in antibody titre after vaccination. Six studies defined development of haemagglutination inhibition (HI) antibody titre of > 32 (Chisholm 2005; Steinherz 1980) or > 40 (Chisholm 2001; Gross 1978; Hsieh 2002b; Matsuzaki 2005) after vaccination as protective. In six studies (Chisholm 2001; Chisholm 2005; Gross 1978; Hsieh 2002b; Lange 1979; Porter 2004), pre- and post-vaccination geometric mean titres (GMTs) were provided. These results have been summarised in the following comparisons.

##### 4. Adverse effects

See below.

#### Comparisons related to objective 1: the efficacy of influenza vaccination in children with cancer during chemotherapy compared to other control groups

##### Comparison 01: influenza immunity in vaccinated children on chemotherapy compared to vaccinated children off chemotherapy

Five studies (Chisholm 2005; Gross 1978; Lange 1979; Matsuzaki 2005; Steinherz 1980) reported on this comparison. Results on protective HI titre, four-fold rise in antibody titre, and pre- and post-vaccination GMT are presented in Analysis 1.1 to Analysis 1.3. Immune responses to influenza vaccine in children receiving chemotherapy were weaker than those in children who completed chemotherapy in four studies (Gross 1978; Lange 1979; Matsuzaki 2005; Steinherz 1980). As is demonstrated in Analysis 1.1, this is not true for all the tested influenza strains. Within two studies (Matsuzaki 2005; Steinherz 1980), one influenza strain showed comparable results in children on chemotherapy compared to children off chemotherapy. In one study, comparable immune responses were found for all three influenza strains, after obtaining extra information from the author (Chisholm 2005).

##### Comparison 02: influenza immunity in vaccinated children on chemotherapy compared to vaccinated healthy children

Three studies (Lange 1979; Porter 2004; Steinherz 1980) reported on this comparison. Results on four-fold rise in antibody titre and pre- and post-vaccination GMT are presented in Analysis 2.1 and Analysis 2.2. Immune responses in children receiving chemotherapy were weaker than those in healthy children. After vaccination, 38% to 65% of children on chemotherapy had a four-fold rise in antibody titre compared to 71% to 89% of healthy children, but no significance was reached except for one influenza strain in the Porter study in which children on chemotherapy had a significantly weaker immune response to influenza vaccination than healthy children (Porter 2004). Healthy children showed signifi-

cantly higher GMTs after vaccination than those on chemotherapy [Porter 2004](#). This was not found in the study of Lange et al ([Lange 1979](#)).

### **Comparison 03: influenza immunity in vaccinated children with acute lymphoblastic leukaemia (ALL) on chemotherapy compared to vaccinated children with asthma**

One study ([Hsieh 2002b](#)) reported on this comparison. Results on seroconversion, seroprotection and pre-and post-vaccination GMT are presented in Analysis 3.1 to Analysis 3.3. Immune responses in children receiving chemotherapy were weaker than those in children with asthma. After vaccination, 24% to 60% of children with ALL developed a four-fold rise in antibody titre compared to 63% to 77% of children with asthma, and 57% to 85% compared to 73% to 90% developed protective HI-titres. After vaccination, children with asthma showed higher GMTs than those with ALL. It is noteworthy that a higher percentage of children with ALL developed protective antibody titres against the A/Pan/2007/99 viral strain; 85% compared to 73% of children with asthma, therefore no difference was found between the two groups using this strain concerning their immune response.

### **Comparisons related to objective 2: the efficacy of influenza vaccination compared to placebo, no intervention or different dosage schedules in children with cancer treated with chemotherapy**

#### **Comparison 04: influenza immunity in vaccinated compared to non-vaccinated paediatric oncology patients**

One study ([Chisholm 2001](#)) reported on this comparison. Results on seroprotection and pre- and post-vaccination GMT in the immunised group are presented in Analysis 4.1 and Analysis 4.2. After vaccination, there was a significant rise in GMT and 48% to 70% of immunised children developed protective HI-titres after vaccination. A comparison with the non-immunised group cannot be made, as information on GMT and achieving protective titres in this group is missing.

#### **Comparison 05: influenza immunity in two vaccination schedules in children with ALL on maintenance chemotherapy**

One study ([Hsieh 2002a](#)) reported on this comparison (Analysis 5.1; Analysis 5.2). Two vaccination protocols were compared in children with ALL on maintenance chemotherapy. One group received the first dose of vaccine on the same day as their scheduled reinduction chemotherapy and the second dose four weeks later. The other group received the first dose of vaccine without chemotherapy and the second dose on the same day as their reinduction chemotherapy. Comparable rates in four-fold antibody rise and achieving protective antibody titres were found in both vaccination protocols and no significant difference was found.

### **Adverse reactions related to influenza vaccination (such as arm soreness, fever, myalgias, fatigue, malaise, headache)**

In the included studies, a total of 359 paediatric oncology patients being treated with chemotherapy received influenza vaccine. In all of the included studies a statement was made concerning adverse effects after vaccination. Six studies ([Chisholm 2005](#); [Gross 1978](#); [Hsieh 2002a](#); [Hsieh 2002b](#); [Lange 1979](#); [Porter 2004](#); [Steinherz 1980](#)) described the procedure that was used for assessment of adverse effects. Assessment of outcome in these studies was mostly performed by parents.

There were no reports of life-threatening or persistent adverse effects. The studies reported "occasional" mild local reactions and low-grade fever ([Lange 1979](#); [Steinherz 1980](#)). The number and severity of adverse reactions after vaccination in the children on chemotherapy and the healthy controls did not differ significantly ([Porter 2004](#)). In one study, patients on chemotherapy were less likely to experience adverse reactions than patients off chemotherapy ([Gross 1978](#)). Patients on chemotherapy had a higher incidence of malaise and poor appetite than those with asthma after vaccination ([Hsieh 2002b](#)). Patients with asthma were more likely to report local pain and had more episodes of fever in the days following vaccination. One study reported upper respiratory tract symptoms and fever after vaccination in a paediatric oncology patient, requiring oral antibiotics ([Chisholm 2005](#)).

## **DISCUSSION**

This is the first systematic review on the effectiveness of influenza vaccination in children being treated for cancer. We have identified a total of eight controlled clinical trials (CCTs) and one randomised controlled trial (RCT) that were extracted from eight studies fulfilling our inclusion criteria. Unfortunately, there is no study available which compares influenza vaccine to placebo in children being treated for cancer. Furthermore, none of the included studies have reported on clinical outcome measures, such as confirmed influenza during the influenza season, hospitalisation, delay in chemotherapy and mortality. All included studies reported on the outcome measures of influenza immunity and adverse reactions to vaccination.

The included studies demonstrated that paediatric oncology patients receiving chemotherapy were able to generate an immune response to influenza vaccine. However, they had weaker immune responses compared to healthy children, children with asthma or compared to paediatric oncology patients who had completed chemotherapy more than one month prior to vaccination. Immune responses of the latter were comparable to those of healthy children. The differences in immune response between the above mentioned groups were seen irrespective of the method used to assess the immune response (i.e. four-fold rise in antibody titre,

seroprotection or pre- and post-vaccination GMT) and irrespective of the type of malignancy. The difference in response between these groups is most likely explained by immunosuppression, as much from chemotherapeutic agents as from the malignancy as such. Only one study found comparable immune responses in patients with solid tumours on chemotherapy compared to patients off chemotherapy (Chisholm 2005). The difference might be that solid tumours and not haematological malignancies were studied, and that the control group was very small compared to the experimental group.

In reports of influenza vaccination in paediatric oncology patients it is often stated that there are conflicting data concerning the immune response to influenza vaccination, as some studies reveal a sufficient immune response while others fail to do so (Gross 1978; Hsieh 2002a; Lange 1979; Matsuzaki 2005; Porter 2004). This can be explained by a difference in patient population in these studies. A more sufficient immune response is generally found in studies in which the majority of children had completed chemotherapy more than one month ago. As the objective of this review was to evaluate response in children receiving chemotherapy, the aforementioned studies were excluded.

Influenza vaccine was safely administered to paediatric oncology patients in the included studies. Since adverse effect outcomes were mostly assessed by parents, the studies were susceptible to detection bias. There were no reports of life-threatening or persistent adverse reactions in any of the included studies. However, it should be noted that children can develop fever in response to vaccination and in such a case administration of antibiotics may be required in children with cancer. Patients on chemotherapy had a higher incidence of malaise and poor appetite after vaccination than those with asthma (Hsieh 2002b). However, patients receiving chemotherapy are known to experience these symptoms frequently as a consequence of their treatment (Collins 2000).

The immune response generated by influenza vaccination in children with cancer may reduce the risk of influenza infection in these children. However, as previously mentioned, none of the studies included in this review reported on clinical outcome measures. It is not known whether the antibody titres achieved after vaccination are effective in protecting these children from influenza infection and its complications during the following influenza season or in decreasing the severity of such infection. Therefore, the question of whether influenza vaccination is clinically beneficial for paediatric oncology patients receiving chemotherapy remains unanswered.

## Limitations

The included studies used different immunisation schedules (according to guidelines from Japan, UK and USA), routes of administration (subcutaneous and intramuscular) and dosages. The

results of the studies using different vaccinations were comparable. However, this could not be verified by statistical analysis, as no meta-analysis could be carried out due to a lack of included RCTs. The children in the different studies were all less than 18 years of age. Ages of children in the different groups (i.e. children receiving chemotherapy, children not receiving chemotherapy and healthy children) were comparable, except in three studies (Chisholm 2001; Chisholm 2005; Steinherz 1980). In two of these (Chisholm 2001; Chisholm 2005) the mean age or range of age of the children is not stated. In the other study (Steinherz 1980) children on chemotherapy were about three years younger than those off chemotherapy. Age is a possible confounder for immune response. The included studies had relatively small sample sizes. The results described are all based on separate small studies. Larger trials are needed to verify the results of these studies.

## AUTHORS' CONCLUSIONS

### Implications for practice

In national guidelines it is recommended to vaccinate children being treated for cancer against influenza. Clinical evidence from randomised controlled studies to support this recommendation is lacking. It has been shown in the trials included in this review that these patients are able to generate immune response to influenza vaccine, but it remains unclear whether this immune response protects them from influenza infection or its complications. Influenza vaccination appears to be safe in these children. Clinicians must consider the benefits and risks of influenza vaccination in children with cancer, while awaiting results from randomised controlled trials addressing the clinical benefit of influenza vaccination in these patients.

### Implications for research

To evaluate clinical outcome a well-designed prospective, multi-centre, randomised controlled trial of influenza vaccination in children being treated for cancer is necessary. This trial should have a minimal risk of bias and should carefully define and measure clinically relevant outcomes including laboratory confirmed influenza infection, pneumonia, hospitalisation and mortality. It should be realised that there are many practical difficulties in conducting such a trial. Many patients would have to be included, as the incidence of influenza is fairly low, particularly in non-epidemic years. The effectiveness of the vaccine is best determined in epidemic years in which a good match between the vaccine and circulating strains exists. However, the degree of matching is not known until the influenza season starts and by this time the trial should already have begun. Also, a diagnosis of laboratory confirmed influenza may be difficult to retrieve, as paediatric oncology patients may receive supportive care in centres other than their primary oncol-

ogy centre. Only when such a trial has been conducted can evidence based judgements on the value of influenza vaccine in these children be made. We welcome suggestions on all aspects of such a multi-centre trial, as well as potential participating centres.

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## REFERENCES

### References to studies included in this review

#### Chisholm 2001 *{published data only}*

Chisholm JC, Devine T, Charlett A, Pinkerton CR, Zoambon M. Response to influenza immunisation during treatment for cancer. *Archives of Disease in Childhood* 2001;**84**(6):496–500.

#### Chisholm 2005 *{published data only}*

Chisholm J, Howe K, Taj M, Zambon M. Influenza immunization in children with solid tumours. *European Journal of Cancer* 2005;**41**(15):2280–7.

#### Gross 1978 *{published data only}*

Gross PA, Lee H, Wolff JA, Hall CB, Minnefore AB, Lazicki ME. Influenza immunization in immunosuppressed children. *Journal of Pediatrics* 1978;**92**(1):30–5.

#### Hsieh 2002a *{published data only}*

Hsieh Y, Lu MY, Kao CL, Chiang BL, Lin DT, Lin KS, et al. Response to influenza vaccine in children with leukemia undergoing chemotherapy [RCT]. *Journal of the Formosan Medical Association* 2002; **101**(10):700–4.

#### Hsieh 2002b *{published data only}*

Hsieh Y, Lu MY, Kao CL, Chiang BL, Lin DT, Lin KS, et al. Response to influenza vaccine in children with leukemia undergoing chemotherapy [CCT]. *Journal of the Formosan Medical Association* 2002; **101**(10):700–4.

#### Lange 1979 *{published data only}*

Lange B, Shapiro SA, Waldman MT, Proctor E, Arbeter A. Antibody responses to influenza immunization of children with acute lymphoblastic leukemia. *Journal of Infectious Diseases* 1979;**140**(3):402–6.

#### Matsuzaki 2005 *{published data only}*

Matsuzaki A, Suminoe A, Koga Y, Kinukawa N, Kusuhara K, Hara T. Immune response after influenza vaccination in children with cancer. *Pediatric Blood & Cancer* 2005;**45**(6):831–7.

#### Porter 2004 *{published data only}*

Porter CC, Edwards KM, Zhu Y, Frangoul H. Immune responses to influenza immunization in children receiving maintenance chemotherapy for acute lymphoblastic leukemia. *Pediatric Blood & Cancer* 2004;**42**(1):36–40.

#### Steinherz 1980 *{published data only}*

Steinherz PG, Brown AE, Gross PA, Braun D, Ghavimi F, Wollner N, et al. Influenza immunization of children with neoplastic diseases. *Cancer* 1980;**45**(4):750–6.

### References to studies excluded from this review

#### Adell 2002 *{published data only}*

Adell C, Bayas JM, Vilella A, Perales M, Vidal J, Bertran MJ, et al. Post-transplantation vaccination of bone-marrow transplant recipients [Vacunación de pacientes receptores de trasplante de progenitores hemotopoyéticos]. *Medicina Clínica* 2002;**119**(11):405–9.

#### Ahmed 1996 *{published data only}*

Ahmed AH, Nicholson KG. The efficacy of influenza vaccine. *Reviews in Medical Microbiology* 1996;**7**(1):23–30.

#### Allison 1977 *{published data only}*

Allison JE, Glezen WP, Taber LH, Paredes A, Webster RG. Reactogenicity and immunogenicity of bivalent influenza A and monovalent influenza B virus vaccines in high-risk children. *Journal of Infectious Diseases* 1977;**136** Suppl:S672–6.

#### Arola 1995 *{published data only}*

Arola M, Ruuskanen O, Ziegler T, Salmi TT. Respiratory virus infections during anticancer treatment in children. *Pediatric Infectious Disease Journal* 1995;**14**(8):690–4.

#### Barnes 2001 *{published data only}*

Barnes R, Stallard N. Severe infections after bone marrow transplantation. *Current Opinion in Critical Care* 2001;**7**(5):362–6.

- Borella 1971** *{published data only}*  
Borella L, Webster RG. The immunosuppressive effects of long-term combination chemotherapy in children with acute leukemia in remission. *Cancer Research* 1971;**31**(4):420–6.
- Brown 1982** *{published data only}*  
Brown AE, Steinherz PG, Miller DR, Armstrong D, Kellick G, Gross PA, et al. Immunization against influenza in children with cancer: results of a three-dose trial. *Journal of Infectious Diseases* 1982;**145**(1):126.
- Brown 1983** *{published data only}*  
Brown AE. Influenza and pneumococcal immunization of patients with neoplastic diseases. *Schweizerische Medizinische Wochenschrift Supplementum* 1983;**14**:30–4.
- Brunell 1977** *{published data only}*  
Brunell PA. Immunologic response of immunosuppressed children to influenza vaccine. *Morbidity and Mortality Weekly Report* 1977;**26**:54.
- Brydak 1997** *{published data only}*  
Brydak LB, Rokicka-Milewska R, Jackowska T, Rudnicka H, Regnery H, Cox N. Kinetics of humoral response in children with acute lymphoblastic leukemia immunized with influenza vaccine in 1993 in Poland. *Leukemia and Lymphoma* 1997;**26**(1-2):163–9.
- Brydak 1998** *{published data only}*  
Brydak LB, Rokicka-Milewska R, Machala M, Jackowska T, Sikorska-Fic B. Immunogenicity of subunit trivalent influenza vaccine in children with acute lymphoblastic leukemia. *Pediatric Infectious Disease Journal* 1998;**17**(2):125–9.
- Engelhard 1993** *{published data only}*  
Engelhard D, Nagler A, Hardan I, Morag A, Aker M, Baciu H, et al. Antibody response to a two-dose regimen of influenza vaccine in allogeneic T cell-depleted and autologous BMT recipients. *Bone Marrow Transplantation* 1993;**11**(1):1–5.
- Feery 1979** *{published data only}*  
Feery BJ, Matthews RN, Evered MG, Gallichio HA. Antibody responses to influenza virus vaccine in patients with acute lymphocytic leukaemia. *Australian Paediatric Journal* 1979;**15**(3):177–80.
- Ganz 1978** *{published data only}*  
Ganz PA, Shanley JD, Cherry JD. Responses of patients with neoplastic diseases to influenza virus vaccine. *Cancer* 1978;**42**(5):2244–7.
- Gribabis 1994** *{published data only}*  
Gribabis DA, Panayiotidis P, Boussiotis VA, Hannoun C, Pangalis GA. Influenza virus vaccine in B-cell chronic lymphocytic leukaemia patients. *Acta Haematologica* 1994;**91**(3):115–8.
- Gross 1985** *{published data only}*  
Gross PA, Gould AL, Brown AE. Effect of chemotherapy on the immune response to influenza virus vaccine: review of published studies. *Review of Infectious Diseases* 1985;**7**(5):613–8.
- Hayden 2000** *{published data only}*  
Hayden FG. Advances in the prophylaxis and treatment of influenza illness. *American Journal of Managed Care* 2000;**6**(5 Suppl):S247–54.
- Hicks 2003** *{published data only}*  
Hicks KL, Chemaly RF, Kontoyiannis DP. Common respiratory viruses in patients with cancer: more than just “common colds”. *Cancer* 2003;**97**(10):2576–87.
- Jackowska 1996** *{published data only}*  
Jackowska T, Brydak L, Rokicka-Milewska R, Lukowska K, Gosk B, Rudnicka H, et al. Vaccination against influenza in children with acute lymphoblastic leukaemia [Szczepienia przeciw grypie dzieci chorych na ostrą białaczkę limfoblastyczną]. *Pediatrics Polska* 1996;**71**(4):302–6.
- Kandel 2005** *{published data only}*  
Kandel R, Hartshorn KL. Novel strategies for prevention and treatment of influenza. *Expert Opinion on Therapeutic Targets* 2005;**9**(1):1–22.
- Kempe 1989** *{published data only}*  
Kempe A, Hall CB, MacDonald NE, Foye HR, Woodin KA, Cohen HJ, et al. Influenza in children with cancer. *Journal of Pediatrics* 1989;**115**(1):33–9.
- Louie 2006** *{published data only}*  
Louie JK, Schechter R, Honarmand S, Guevara HF, Schoemaker TR, Madrigal NY, et al. Severe pediatric influenza in California, 2003–2005: implications for immunization recommendations. *Pediatrics* 2006;**117**(4):e610–8.
- Mayr 1974** *{published data only}*  
Mayr AC, Nagel GA, Dick HJ, Pavlicek LP. Proceedings: influenza vaccination in patients with cancer? [Grippeschutzimpfung bei Tumorpacienten?]. *Helvetica Medica Acta* 1974;**37**(5-6):395.
- McIntosh 2003** *{published data only}*  
McIntosh ED, Paradiso PR. Recent progress in the development of vaccines for infants and children. *Vaccine* 2003;**21**(7-8):601–4.
- Modlin 1977** *{published data only}*  
Modlin JF, Smith DH, Harding L. Clinical trials of bivalent A/New Jersey/76-A/Victoria/75 influenza vaccines in high-risk children. *Journal of Infectious Diseases* 1977;**136** Suppl:S626–31.
- Morris 1990** *{published data only}*  
Morris DJ. Virus infections in children with cancer. *Reviews in Medical Microbiology* 1990;**1**(1):49–57.
- Pauksen 2000** *{published data only}*  
Pauksen K, Linde A, Hammarström V, Sjölin J, Carneskog J, Jonsson G, et al. Granulocyte-macrophage colony-stimulating factor as immunomodulating factor together with influenza vaccination in stem cell transplant patients. *Clinical Infectious Diseases: an official publication of the Infectious Diseases Society of America* 2000;**30**(2):342–8.
- Ridgway 1993** *{published data only}*  
Ridgway D, Wolff LJ. Active immunisation of children with leukemia and other malignancies. *Leukemia and Lymphoma* 1993;**9**(3):177–92.
- Schafer 1979** *{published data only}*  
Schafer AI, Churchill WH, Ames P, Weinstein L. The influence of chemotherapy on response of patients with hematologic malignancies to influenza vaccine. *Cancer* 1979;**43**(1):25–30.
- Smithson 1978** *{published data only}*  
Smithson WA, Siem RA, Ritts RE, Gilchrist GS, Burgert EO, Ilstrup DM, et al. Response to influenza virus vaccine in children receiving

chemotherapy for malignancy. *Journal of Pediatrics* 1978;**93**(4):632–4.

**Somani 1995** {published data only}

Somani J, Larson RA. Reimmunization after allogeneic bone marrow transplantation. *American Journal of Medicine* 1995;**98**(4):389–98.

**Stiver 1978** {published data only}

Stiver HG, Weinerman BH. Impaired serum antibody response to inactivated influenza A and B vaccine in cancer patients. *Canadian Medical Association Journal* 1978;**119**(7):733–8.

**Sumaya 1977** {published data only}

Sumaya CV, Williams TE, Brunell PA. Bivalent influenza vaccine in children with cancer. *Journal of Infectious Diseases* 1977;**136** Suppl: S656–60.

**Sumaya 1982** {published data only}

Sumaya CV, Williams TE. Persistence of antibody after the administration of influenza vaccine to children with cancer. *Pediatrics* 1982;**69**(2):226–9.

**Uchaikin 1999** {published data only}

Uchaikin VE, Skachkova LO, Shamsheva OV, Smirnov AV, Polesko IV, Lezhneva LN, et al. The vaccination of children with severe somatic pathology [Vaktsinatsiia detei s tiazhelei somaticheskoi patologiei]. [*Zhurnal Mikrobiologii, Epidemiologii, i Immunobiologii* 1999;**4**:30–4.

**Yamada 1982** {published data only}

Yamada A, Yamawaki H, Tsuda N, Baba K, Yabuuchi H, Maeda A, et al. Trial of split-product trivalent influenza vaccine in high risk children. *Biken Journal* 1982;**25**(2):89–95.

## References to ongoing studies

**Karadeniz 2005** {published data only}

Karadeniz C, Karadeniz C, Bektas O, Oguz A, Berberoglu S, Yy'maz N, et al. PG1.015 Responses of children with solid tumours to influenza virus vaccine. In: 37th Annual Conference of the International Society of Paediatric Oncology, SIOP 2005, Vancouver, Canada, 21–24 September 2005. Abstracts. *Pediatric Blood & Cancer* 2005;**45**(4):503.

## Additional references

**CID 2007**

CID. American Academy of Pediatrics: prevention of influenza: recommendations for influenza immunization of children, 2006–2007. *Pediatrics* 2007;**119**:846–51.

**Cochrane Handbook**

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.5 [updated May 2005]. *The Cochrane Library*, Issue 3. Chichester, UK: John Wiley & Sons, Ltd, 2005.

**Collins 2000**

Collins J, Byrnes M, Dunkel I, Lapin J, Nadel T, Thaler H, et al. The measurement of symptoms in children with cancer. *Journal of Pain and Symptom Management* 2000;**19**(5):323–77.

**Dykewicz 2001**

Dykewicz CA. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients: focus on community respiratory virus infections. *Biology of Blood and Marrow Transplantation* 2001;**7** Suppl:19S–22S.

**Feldman 1977**

Feldman S, Webster RG, Sugg M. Influenza in children and young adults with cancer. *Cancer* 1977;**39**:350–3.

**NOS 2007**

Wells G, Shea B, O'Connell D, Peterson J, et al. Newcastle Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.htm](http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm) 2007.

**Potter 1991**

Potter MN, Foot ABM, Oakhill A. Influenza A and the virus associated haemophagocytic syndrome: cluster of three cases in children with acute leukaemia. *Journal of Clinical Pathology* 1991;**44**:297–9.

**Raad 1997**

Raad I, Abbas J, Whimbey E. Infection control of nosocomial respiratory viral disease in the immunocompromised host. *American Journal of Medicine* 1997;**102**:48–52.

**RevMan 2008**

The Nordic Cochrane Centre. The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration, 2008.

**Ring 2002**

Ring A, Gavin M, Steer C, Harper P. Influenza vaccination and chemotherapy: a shot in the dark?. *Supportive Care in Cancer* 2002;**10**: 462–5.

**Sandherr 2006**

Sandherr M, Einsele H, Hebart H, Kahl C, Kern W, Kiehl M, et al. Antiviral prophylaxis in patients with haematological malignancies and solid tumours: Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Oncology (DGHO). *Annals of Oncology* 2006;**17**(7):1051–9.

**Smith 2006**

Smith NM, Bresee JS, Shay DK, Uyeki TM, Cox NJ, Strikas RA, Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP). Prevention and control of influenza: recommendations of the Advisory Committee in Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report* 2006;**55**:1–41.

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Chisholm 2001

Methods	Single-centre CCT conducted in the United Kingdom during the 1995-1996 and 1996-1997 influenza seasons Serology of non-immunised paediatric oncology patients is compared to that of immunised paediatric oncology patients
Participants	42 immunised and 42 non-immunised children with various malignancies. Most children were on chemotherapy, but patients who had completed chemotherapy within the past 6 months were also included. Children < 6 months of age were excluded, otherwise age not specified.
Interventions	Trivalent inactivated (split virion; Aventis Pasteur MSD) influenza vaccine subcutaneously, which contained the following strains in 1995: A/Taiwan/1/86, A/Johannesburg/34/94, B/Beijing/184/93. In 1996 A/Wahun/359/95 replaced the H3N2 component Subjects received 2 doses of 0.5 ml for children > 4 years and 0.25 ml for children =< 4 years at 4-week intervals
Outcomes	(1) Development of protective HI titre ( $\geq 40$ ) post-vaccination (2) Pre- and post-vaccination GMT (3) Adverse reactions, although it is not specified how this outcome was measured (1) and (3) only for immunised group
Notes	(1) No follow-up serum was taken from 15/42 (36%) non-immunised children (2) Children who had completed chemotherapy within the last 6 months were also immunised, contrary to the inclusion criteria for this review. However, in subgroup analysis the difference in post-vaccination titre of those on chemotherapy compared to those off chemotherapy was not significant.

#### *Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

#### Chisholm 2005

Methods	Single-centre CCT conducted in the United Kingdom during the 2001-2002 and 2002-2003 influenza seasons
Participants	59 children with various non-leukaemic malignancies who were receiving chemotherapy and 10 children with various non-leukaemic malignancies who had been off chemotherapy for 4 weeks to 6 months. Age between 6 months and 16 years.

**Chisholm 2005** (Continued)

Interventions	Trivalent inactivated split virion (Aventis Pasteur MSD) subcutaneously, with the following strains in 2001-2002: A/New Cal/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Sichuan/379/99. In 2002-2003 B/Hong Kong/331/01 replaced B/Sichuan/379/99. Age-dependent schedule: < 4 years: 2 doses of 0.25 ml 3 to 4 weeks apart. 4 to 12 years: 2 doses of 0.5 ml 3 to 4 weeks apart. > 13 years: 1 dose of 0.5 ml. Previously immunised children: 1 dose 0.25 ml (< 4 years) or 0.5 ml (> 4 years).
Outcomes	(1) Seroconversion (defined as 4-fold rise in antibody titre) after vaccination (2) Development of protective HI titre ( $\geq 32$ ) post-vaccination (3) Pre- and post-vaccination GMT (4) Adverse reactions
Notes	Results of children off chemotherapy only stated as “no impact” in subgroup analysis, no separate results were presented. Authors were contacted for additional information on the results of children off chemotherapy and these results were obtained.

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

**Gross 1978**

Methods	Multi-centre CCT conducted in New York, USA Response to influenza vaccine in children with cancer who were receiving chemotherapy was compared to that of children with cancer off chemotherapy
Participants	68 children with various malignancies who were receiving chemotherapy and 74 children with various malignancies who had been off chemotherapy for at least the last 1 month. Mean age 10 years (range 3 to 18 years).
Interventions	Various influenza vaccines were used: (1) split-product vaccine (Parke-Davis) containing 400 CCA units of A/NJ/8/76 and 400 CCA of A/Vic/3/75 per dose, (2) whole virus vaccine (Merrell-National vaccine) containing 100 CCA units of A/NJ/8/76 and 100 CCA units of A/Vic/3/75, (3) whole virus vaccine (Merck Sharp & Dohme vaccine) containing 50 CCA units of A/NJ/8/76 and 50 CCA units of A/Vic/3/75. Subjects received 2 injections, with a 1-month interval between doses. 3 to 5-year olds received half the amount given to older children.
Outcomes	(1) Pre- and post-vaccination GMT (2) Development of protective HI titre ( $\geq 40$ ) post-vaccination (3) Adverse reactions
Notes	

Gross 1978 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

**Hsieh 2002a**

Methods	A) RCT conducted in Taiwan during the 2000-2001 influenza season Children with ALL were randomly assigned to 1 of 2 vaccination protocols	
Participants	25 children with ALL on maintenance chemotherapy. Mean age 7.3 years.	
Interventions	Trivalent inactivated split virus (Vaxigrip) influenza vaccine A/Panama/2007/99 (H3N2), A/New Caledonis/20/99 (H1N1), B/Yamanashi/166/98. Subjects received 2 0.5 ml doses containing 15 µg hemagglutinin, 4 weeks apart. Of the children with ALL, n = 14 received dose 1 of vaccine and reinduction chemotherapy on the same day; 4 weeks later dose 2. N = 11 received dose 1 alone, 4 weeks later dose 2 + reinduction chemotherapy on the same day.	
Outcomes	(1) GMT pre- and post-vaccination (2) Development of protective HI titre ( $\geq 40$ ) post-vaccination (3) 4-fold rise in antibody titre after vaccination (4) Adverse reactions	
Notes	Additional information on randomisation methods was requested and not obtained	

*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Hsieh 2002b**

Methods	B) CCT conducted in Taiwan during the 2000-2001 influenza season Response to influenza vaccine in children with ALL is compared to that of children with asthma	
Participants	30 children with asthma in remission (no inhaled steroids within 2 weeks or oral steroids within 1 month prior to influenza vaccination), mean age 6.5 years, compared to 25 children with ALL on maintenance chemotherapy, mean age 7.3 years	

**Hsieh 2002b** (Continued)

Interventions	Trivalent inactivated split virus (Vaxigrip) influenza vaccine A/Panama/2007/99 (H3N2), A/New Caledonis/20/99 (H1N1), B/Yamanashi/166/98. Subjects received 2 0.5 ml doses containing 15 µg hemagglutinin, 4 weeks apart.	
Outcomes	(1) GMT pre- and post-vaccination (2) Development of protective HI titre ( $\geq 40$ ) post-vaccination (3) 4-fold rise in antibody titre after vaccination (4) Adverse reactions	
Notes	Dosage: > 8 years received 1 dose, and children younger than 8 received 2 doses of vaccine	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	D - Not used

**Lange 1979**

Methods	CCT conducted in the USA Responses to influenza vaccine of children with ALL on maintenance chemotherapy were compared to those of healthy siblings and children with ALL off chemotherapy	
Participants	22 children with ALL in first remission on maintenance chemotherapy (mean age 9.8 years, range 5 to 15). Controls were 22 age-matched siblings (age 10.8 years range 2 to 18) and 16 similarly matched children with ALL, who were no longer receiving chemotherapy for 4 to 30 months (mean age 10.9 years, range 7 to 16).	
Interventions	Bivalent split-product influenza vaccine containing the following strains: A/Vic/75, A/NJ/76. Subjects received 2 doses of 0.5 ml 4 weeks apart, each dose containing 200 CCA of A/Vic/75 and A/NJ/76.	
Outcomes	(1) Pre- and post-vaccination GMT (2) Adverse reactions	
Notes	There is a discrepancy in the number of sibling controls: 50 sibling controls were included according to the abstract and table 1, while 22 sibling controls are mentioned in the article under Materials and Methods	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	D - Not used

**Matsuzaki 2005**

Methods	CCT conducted in Japan during the 2003-2004 influenza season Response to influenza vaccine in children with cancer who are receiving chemotherapy is compared to that of children with cancer off chemotherapy
Participants	44 children with various types of malignancies, of which 18 were on chemotherapy and 26 had finished chemotherapy for 1 to 60 months. Age 1 to 18 years.
Interventions	Trivalent inactivated split (KAKETSUKEN) influenza vaccine subcutaneously, containing 30 µg HA per ml of each of the following strains: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99, B/Shangdong/7/97. Patients received 2 doses, 2 to 4 weeks apart at doses of 0.2 ml for children aged 1 to < 6 years, 0.3 ml for 6 to < 13 years and 0.5 ml at least 13 or more years, according to recommendations in Japan.
Outcomes	(1) Seroconversion (defined as 4-fold rise in antibody titre) after 2 vaccinations (2) Achieving protective antibody titre (HI antibody titre $\geq$ 40) after 2 vaccinations (3) Adverse effects
Notes	No numbers concerning adverse effects stated

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

**Porter 2004**

Methods	Single-centre CCT conducted in Nashville, USA, during the 2001-2002 influenza season Responses of children with ALL to influenza vaccine were compared to those of healthy children
Participants	20 children with ALL in first remission receiving maintenance chemotherapy, who had completed their last delayed intensification at least 4 weeks earlier. Mean age 7.7 years. 49 healthy children (14 healthy siblings and 35 additional healthy children in the community) were enrolled as controls, mean age 9.2 years.
Interventions	Trivalent inactivated (Fluzone) influenza vaccine, containing the following strains: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Victoria/504/2000. According to ACIP guidelines, children aged 9 years or more and those previously immunised with influenza vaccine received 1 dose (0.5 ml), children aged < 9 years and previously unimmunised children received 2 doses (each 0.5 ml), 1 month apart.
Outcomes	(1) Pre- and post-vaccination GMT (2) Seroconversion (defined as 4-fold rise in antibody titre) after the last vaccination (3) Adverse reactions after vaccination

**Porter 2004** (Continued)

Notes	Data of 3/49 healthy children were not included, since they did not provide post-vaccination serology In this study it was not stated what HI titre was considered protective, nor what percentage of subjects reached a protective HI titre	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	D - Not used

**Steinherz 1980**

Methods	Single-centre CCT conducted in New York, USA during the 1976-1977 influenza season Responses to influenza vaccine of children with cancer who are receiving chemotherapy were compared to those of healthy siblings and children with cancer off chemotherapy	
Participants	160 children, of whom 147 children had various types of malignancies, (median age 11.6 years) and 13 siblings served as normal controls (median age 8.6 years). Of the 147 children with cancer, 106 were on chemotherapy and 41 had been off chemotherapy for at least 30 or more days.	
Interventions	Bivalent split-product influenza A vaccine intramuscularly, containing the following strains: A/New Jersey/8/76 (Hsw1N1), A/Victoria/3/75 (H3N2). 2 doses of 0.5 ml containing 200 CCA units each were administered 4 weeks apart.	
Outcomes	(1) Significant antibody response (defined as 4-fold rise in HI titre) four to six weeks after 2 immunisations (2) Achieving protective HI antibody titre (defined as $\geq 32$ ) four to six weeks after 2 immunisations (3) Adverse reactions after vaccination	
Notes	The National Influenza Immunization Program ended in December 1976. By that time only 50/106 patients on chemotherapy and 21/41 patients off chemotherapy had received both immunisations. The age and sex distributions remained similar to that of the original group of 160 participants. Age and sex distributions of the healthy sibling controls are not mentioned.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	D - Not used

Please note that the last column (allocation concealment) is not applicable to most of the included studies, as they were not RCTs.

ALL = acute lymphoblastic leukaemia

CCT = controlled clinical trial

GMT = geometric mean titre

HI = haemagglutination inhibition

RCT = randomised controlled trial

### Characteristics of excluded studies *[ordered by study ID]*

Adell 2002	(1) Patient population consisted mainly of adults (2) No outcomes relevant to this review assessed (3) Patients who did not receive chemotherapy in the month prior to vaccination were included in the chemotherapy group
Ahmed 1996	Review on efficacy of influenza vaccine
Allison 1977	Details concerning chemotherapy not adequately specified therefore not clear if patients who received vaccine were on chemotherapy, or had received chemotherapy during the past month before vaccinating, therefore not clear how treatment group was defined
Arola 1995	No vaccines administered
Barnes 2001	Review on infections after bone marrow transplantation
Borella 1971	Not clear how outcome of influenza-like illness was assessed; not specified by whom symptoms of influenza-like illness were scored and how many symptoms were necessary for diagnosis of influenza-like illness, therefore many viral illnesses were included. Impossible to specify the treatment and control group.
Brown 1982	(1) Presented as summary, insufficient information provided on characteristics of patients and controls (2) Control group data are obtained from another trial
Brown 1983	Review on influenza and pneumococcal vaccination in cancer patients
Brunell 1977	(1) Insufficient information provided on methodology, characteristics of patients and controls (2) Results are not presented
Brydak 1997	42/49 patients had already finished chemotherapy (6 months to 3 years)
Brydak 1998	Only 2 subjects were receiving chemotherapy at time of study
Engelhard 1993	(1) Lack of a control group (2) Patients did not receive chemo- or radiotherapy in the month prior to vaccination (3) Adults included in study population, results of children not presented separately
Feery 1979	Control group data are obtained from another trial
Ganz 1978	Adult study population
Gribabis 1994	Adult study population
Gross 1985	Review of influenza vaccine in cancer patients on chemotherapy

(Continued)

Hayden 2000	Review on treatment and prophylaxis of influenza
Hicks 2003	Review on various viral infections in cancer patients
Jackowska 1996	Same patient population as <a href="#">Brydak 1997</a>
Kandel 2005	Review on prevention and treatment of influenza
Kempe 1989	Subjects were not vaccinated
Louie 2006	Only 3 children with leukaemia/blood dyscrasia in study population; not stated whether they were vaccinated
Mayr 1974	Adult study population
McIntosh 2003	Review on vaccines for children
Modlin 1977	Children with malignancies were not included in the study
Morris 1990	Review on viral infections in children with cancer
Pauksen 2000	Adult study population
Ridgway 1993	Review on 8 vaccines (including influenza vaccine) in children with cancer
Schafer 1979	(1) Adult study population (2) Not clear whether patients received chemotherapy in the month prior to vaccination
Smithson 1978	Control group data are obtained from another trial
Somani 1995	Review on re-immunisation with various vaccines following bone marrow transplantation
Stiver 1978	Adult study population
Sumaya 1977	Control group data are obtained from other trials
Sumaya 1982	Lack of a control group
Uchaikin 1999	Patients did not receive chemotherapy in the month prior to vaccination
Yamada 1982	6/8 patients had already finished chemotherapy

## Characteristics of ongoing studies *[ordered by study ID]*

### Karadeniz 2005

Trial name or title	Responses of children with solid tumours to influenza virus vaccine
Methods	-
Participants	45 children with solid tumours
Interventions	Vaccination with trivalent influenza vaccine A/Moscow/10/99, A/new Caledonia/20/99, B Hongkong/22/2001
Outcomes	Antibody titre
Starting date	2003
Contact information	Not mentioned
Notes	Abstract from SIOP XXXVII annual conference (page 503 abstract PG 1.015)

## DATA AND ANALYSES

### Comparison 1. Influenza immunity in vaccinated children on chemotherapy compared to vaccinated children off chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients achieving protective titre post-vaccination (> 32 or 40) after last immunisation			Other data	No numeric data
2 Number of patients with four-fold rise in antibody titre after last immunisation			Other data	No numeric data
3 Geometric mean titre (GMTs) pre- and post-vaccination			Other data	No numeric data

### Comparison 2. Influenza immunity in vaccinated children on chemotherapy compared to vaccinated healthy children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients with four-fold rise in antibody titre after last immunisation			Other data	No numeric data
2 Geometric mean titre (GMTs) pre- and post-vaccination			Other data	No numeric data

### Comparison 3. Influenza immunity in vaccinated children with ALL on chemotherapy compared to vaccinated children with asthma

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients with four-fold rise in antibody titre 4 weeks after the last immunisation			Other data	No numeric data
2 Number of patients achieving protective titre post-vaccination (> 40) after last immunisation			Other data	No numeric data

3 Geometric mean titre (GMTs) pre- and post-vaccination	Other data	No numeric data
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#### Comparison 4. Influenza immunity in vaccinated compared to non-vaccinated paediatric oncology patients

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients achieving protective titre post-vaccination (> 40) after last immunisation			Other data	No numeric data
2 Geometric mean titre (GMTs) pre- and post-vaccination			Other data	No numeric data

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#### Comparison 5. Influenza immunity in two vaccination schedules in children with ALL on maintenance chemotherapy

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients with four-fold rise in antibody titre 4 weeks after last immunisation			Other data	No numeric data
2 Number of patients achieving protective titre post-vaccination (> 40) after immunisation			Other data	No numeric data

## HISTORY

Protocol first published: Issue 2, 2011

Review first published: Issue 2, 2009

16 December 2008	Amended	Converted to new review format
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## **CONTRIBUTIONS OF AUTHORS**

GM Goossen: reference search, article retrieval, assessment of studies inclusion/exclusion, data extraction analysis and manuscript preparation.

L Kremer: search strategy, methodology and manuscript preparation.

MD van de Wetering: article retrieval, assessment of studies for inclusion and exclusion, data extraction, data analysis and reviewing of manuscript.

## **DECLARATIONS OF INTEREST**

None.

## **SOURCES OF SUPPORT**

### **Internal sources**

- No sources of support supplied

### **External sources**

- Stichting Kinderen Kankervrij (KiKa), Netherlands.

## **DIFFERENCES BETWEEN PROTOCOL AND REVIEW**

Objective 1 (To assess the efficacy of influenza vaccination in stimulating immunological response in children with cancer during chemotherapy, compared to other control groups) was not reported in the protocol.