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

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966 to 2012) and EMBASE (1980 to 2012) up to August 2012. We also searched reference lists of relevant articles and conference proceedings of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the Infectious Diseases Society of America (IDSA), the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Paediatric Oncology (SIOP).

Selection criteria

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

Data collection and analysis

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

Main results

We included 1 RCT and 9 CCTs (total number of participants = 770). None of the included studies reported clinical outcomes. 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 receiving chemotherapy and 166 children not receiving chemotherapy. In four studies, responses to influenza vaccine were assessed in 236 children receiving chemotherapy compared with responses in 142 healthy children. Measures used to assess immune responses included a four-fold rise in antibody titre after vaccination, development of a haemagglutination inhibition (HI) titre > 32 and pre- and post-vaccination geometric mean titres (GMTs). Immune responses in children receiving chemotherapy were consistently weaker (four-fold rise of 38% to 65%) than those in children who had completed chemotherapy (50% to 86%) and in healthy children (53% to 89%). In terms of adverse effects, 391 paediatric oncology patients received influenza vaccine, and the adverse effects described included 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 infection. 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 that assessed the clinical efficacy of influenza vaccination; however, we identified one additional controlled clinical trial in our update, which brings the total to nine studies that assessed immune responses after vaccination in children with cancer. It was shown that children receiving chemotherapy mount poorer immune responses than healthy children, but that the vaccine can be safely administered. On the basis of this updated review, it is not possible to recommend or discourage influenza vaccination in children with cancer who are treated with chemotherapy. A future trial should address the clinical benefits of influenza vaccination in children with cancer who are treated with chemotherapy.

BACKGROUND

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), the condition 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 with healthy controls and may have prolonged influenza infections compared with 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 administration of antibiotics. Severe and fatal complications involving mainly secondary infections and haemophagocytic syndromes have been reported in paediatric oncology patients with influenza infection (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). According to the 2010 guidelines of the Advisory Committee on Immunization Practices (ACIP) (Fiore 2010) 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) all children aged 6 months to 5 years (59 months); (2) all persons aged > 50 years; (3) adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurological, hematological, or metabolic disorders (including diabetes mellitus); (4) persons who have immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus (HIV)); (5) women who are or will be pregnant during the influenza season; (6) children and adolescents (aged 6 months to 18 years) who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye syndrome after influenza virus infection; (7) residents of nursing homes and other long-term-care facilities; (8) American Indians/Alaskan Natives; (9) persons who are morbidly obese (body mass index (BMI) > 40); (10) health care professionals (HCPs); (11) household contacts and caregivers of children aged < 5 years and adults aged > 50 years, with particular emphasis on vaccinating contacts of children aged < 6 months; and (12) household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza (Fiore 2010).

The inactivated vaccine involves no risk of introducing active infection, and it is regarded as safe in immunocompromised individuals, even in paediatric oncology patients. Defects involving both cell-mediated and humoral immunity frequently accompany malignancies, and chemotherapy induces myelosuppression, so that suboptimal responses to vaccination might be expected in patients with malignant disease. Immunological responses are generally less than expected in healthy persons and may depend on the timing of vaccination relative to chemotherapy. However, a paucity of data is available for paediatric oncology patients, 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). This is an update of the first systematic review (Goossen 2009) undertaken to evaluate the state of evidence on the efficacy of influenza vaccination in paediatric oncology patients 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 an immunological response in children with cancer during chemotherapy, compared with control groups.
2. To assess the efficacy of influenza vaccination in preventing confirmed influenza and influenza-like illness and/or in stimulating immunological response in children with cancer treated with chemotherapy, compared with placebo, no intervention or different dosage schedules .
3. To identify the adverse effects associated with influenza vaccines in children with cancer treated with chemotherapy, compared with 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 serological response to influenza vaccination of children with cancer was compared with that of control groups. We also considered RCTs and CCTs that compared the effects of influenza vaccination on influenza and/or influenza-like illness and/or stimulated immunological response in children with cancer being treated with chemotherapy, compared with placebo, no intervention or different dosage schedules.

Types of participants

Children with cancer (1 to 18 years of age) 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

- Laboratory-confirmed influenza infection.

- Influenza-like illness (as defined by the authors; most often non-specific respiratory illness characterised by fever, fatigue and cough) with or without one of the following complications:
  - Pneumonia (radiographically documented, clinically diagnosed) or any secondary infection.
  - Hospitalisation.
  - Days in intensive care unit (ICU).
  - Delay in chemotherapy.
  - Mortality.
- Influenza immunity (difference in pre- and post-influenza vaccination haemagglutinin inhibition antibody titre).
- 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, for the original review; and *The Cochrane Library* 2012, issue 8, for the update), MEDLINE/PubMed (from 1966 to February 2007 for the original review; and to August 2012 for the update) and EMBASE/Ovid (1980 to February 2007 for the original review; and to August 2012 for the update). We used the subject headings and text words shown in Appendix 1, Appendix 2 and Appendix 3.

We located information on trials not registered in CENTRAL, MEDLINE or EMBASE, published or unpublished, by searching the reference lists of relevant articles and review articles. We scanned, electronically if available and otherwise by handsearching, the ten latest issues (2001 to 2006 for the original review; and 2007 to 2011 for the update) of the conference proceedings of the International Society of 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 clinical area, and we applied no language restrictions in our search.

Data collection and analysis

Selection of studies

Two review authors (GMG and MDvdW) independently identified studies that met the eligibility criteria. The Methods section of the trial served as the basis for our decisions on which trials to include in this systematic review update. We resolved discrepancies by discussion. If this approach was unsuccessful, arbitration by a third party was obtained. We clearly stated reasons for exclusion of any study considered in this review process.

Data extraction and management

The two review authors (GMG and MDvdW) independently performed data extraction using standardised forms. We extracted data on the characteristics of participants (age, sex, tumour type and anti-cancer treatment received), interventions (description of vaccine, dose and 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 and adverse events related to influenza vaccine), length of follow-up and study design. In cases of disagreement, we reexamined and discussed the abstracts and articles until consensus was achieved. When data were missing, we made an attempt to contact the study authors for additional information. We obtained extra information on one study (Chisholm 2005), including (1) the protective response rate, the seroresponse rate and the 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, the seroresponse rate and the 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 review authors independently assessed trial quality. We assessed the methodological quality of the RCTs in accordance with the guidelines recommended by the Cochrane Childhood Cancer Group at the time of the original version of the review (see Table 1). We used the Newcastle-Ottawa Scale (NOS 2007) for quality assessment of CCTs (see Table 2) and contacted study authors for additional information where necessary. Disagreements were resolved by discussion between the review authors.

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 investigators 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.

RESULTS

Description of studies

After performing searches of the electronic databases the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE/PubMed and EMBASE/Ovid (in February 2007), we identified 3172 titles of reports of potentially relevant studies, which we screened for retrieval. We excluded 3136 reports by screening 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 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 (Bektas 2007) was mentioned as an ongoing study in the original review (Karadeniz 2005). Thus, we included eight studies (total number of participants of 708) from the original systematic review.

Running searches for the update in CENTRAL, MEDLINE/PubMed and EMBASE/Ovid (in August 2012) yielded a total of 598 new references. After screening titles, abstracts or both, we excluded 595 references that clearly did not meet all inclusion criteria for this review. We retrieved three reports for detailed assessment, of which two were excluded (Esposito 2009; Reilly 2010; see the 'Characteristics of excluded studies' table for the exact reason).

Upon scanning the reference lists of relevant studies and reviews as well as conference proceedings, we did not identify any eligible studies. We identified no eligible ongoing studies by scanning the ongoing trials databases.

In the update of August 2012, one study was included (total number of participants in this study was 62). In total (original review and update), nine studies were included in this current update with a total number of participants of 770.

Included studies

Characteristics of the nine included studies are presented in the table 'Characteristics of included studies'. One of the studies comprised both an RCT (Hsieh 2002a) and a CCT (Hsieh 2002b). All of the remaining eight studies were CCTs; thus one RCT and nine CCTs were included. None of the included studies compared influenza vaccine with 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 with those of 166 children with cancer not receiving chemotherapy during the four weeks before vaccination. In four studies (Lange 1979; Porter 2004; Shahgholi 2010; Steinherz 1980), responses to different strains of influenza vaccine in a total of 236 children with cancer receiving chemotherapy were compared with those in 142 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 with 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 participants was compared with that of 42 non-immunised paediatric oncology participants.

Risk of bias in included studies

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

Six of the included studies did not have a complete follow-up (Chisholm 2001; Chisholm 2005; Lange 1979; Porter 2004; Shahgholi 2010; Steinherz 1980). In two of these studies (Chisholm 2005; Porter 2004), the number of participants lost to follow-up was small and was unlikely to introduce bias. In one study (Shahgholi 2010), data on adverse reactions were available for only 56% of participants. No loss to follow-up was reported for other outcomes. In the remaining studies, a large percentage of participants was lost to follow-up, respectively, 36% of non-immunised participants in Chisholm 2001, 29% of participants receiving chemotherapy in Lange 1979 and 52% of participants receiving chemotherapy in Steinherz 1980. These three studies are susceptible to attrition bias because 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 noted at 12 months after the first vaccination, althoughoutcomes relevant to this review are assessed one month after the 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 receiving 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 no blinding of participants was performed. This makes the trial susceptible to bias.

Attempts to gain additional information from the study authors regarding methodological quality met with some success. We obtained additional data from the author of one study (Chisholm 2005).

Effects of interventions

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

Outcomes

- **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 participants 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 identify influenza infection.

- **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.

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

Various measures were used to assess immune response after vaccination. Five studies (Chisholm 2005; Hsieh 2002a; Matsuzaki 2005; Porter 2004; Steinherz 1980) assessed a four-fold rise in antibody titre after vaccination. Seven studies defined as protective the development of haemagglutination inhibition (HI) antibody titre of > 32 (Chisholm 2005; Steinherz 1980) or > 40 (Chisholm 2001; Gross 1978; Hsieh 2002b; Matsuzaki 2005; Shahgholi 2010) after vaccination. In seven studies (Chisholm 2001; Chisholm 2005; Gross 1978; Hsieh 2002b; Lange 1979; Porter 2004; Shahgholi 2010), pre- and post-vaccination GMTs were provided. These results have been summarised in the following comparisons.

- **Adverse effects**

See later.

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

Comparison 01: influenza immunity in vaccinated children receiving chemotherapy compared with 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 GMTs 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 tested influenza strains. Within two studies (Matsuzaki 2005; Steinherz 1980), one influenza strain showed comparable results in children receiving chemotherapy compared with children off chemotherapy. In another study, comparable immune responses were found for all three influenza strains, after extra information was obtained from the author (Chisholm 2005).

Comparison 02: influenza immunity in vaccinated children receiving chemotherapy compared with vaccinated healthy children

Four studies (Lange 1979; Porter 2004; Shahgholi 2010; Steinherz 1980) reported on this comparison. Results on four-fold rise in antibody titre and pre-and post-vaccination GMTs 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 receiving chemotherapy had a four-fold rise in antibody titre compared with 53% to 89% of healthy children, but no significance was reached except in three influenza strains. One influenza strain was included in the Porter study and two in the Shahgholi study, in which children receiving chemotherapy had a significantly weaker immune response to influenza vaccination when compared with healthy children (Porter 2004; Shahgholi 2010). Healthy children showed significantly higher GMTs after vaccination than were noted in those receiving chemotherapy for all three strains in the Porter study (Porter 2004) and for one strain in the Shahgholi study (Shahgholi 2010). This finding was not reported in the study of Lange et al (Lange 1979).

Comparison 03: influenza immunity in vaccinated children with acute lymphoblastic leukaemia (ALL) receiving chemotherapy compared with 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 with 63% to 77% of children with asthma, and 57% to 85% compared with 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 with 73% of children with asthma; therefore no difference in immune response was noted between the two groups using this strain.

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

Comparison 04: influenza immunity in vaccinated compared with non-vaccinated paediatric oncology participants

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, a significant rise in GMT was reported, and 48% to 70% of immunised children developed protective HI titres after vaccination. A comparison with the non-immunised group cannot be made because information on GMTs and achieving protective titres in this group is missing.

Comparison 05: influenza immunity in two vaccination schedules in children with ALL receiving 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 receiving maintenance chemotherapy. One group received the first dose of vaccine on the same day as the 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 the 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 reported.

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

In the included studies, a total of 391 paediatric oncology participants who were being treated with chemotherapy received influenza vaccine. In all of the included studies, a statement was made concerning adverse effects after vaccination. Eight studies (Chisholm 2005; Gross 1978; Hsieh 2002a; Hsieh 2002b; Lange 1979; Porter 2004; Shahgholi 2010; Steinherz 1980) described the procedure that was used for assessment of adverse effects. Assessment of outcomes in these studies was performed most often by parents.

No reports described life-threatening or persistent adverse effects. The studies reported "occasional" mild local reactions and low-grade fever (Lange 1979; Steinherz 1980; Shahgholi 2010 (last study not complete data for adverse events)). The number and severity of adverse reactions after vaccination in the children receiving chemotherapy and in the healthy controls did not differ significantly (Porter 2004; Shahgholi 2010 (last study not complete data for adverse events)). In one study, participants receiving chemotherapy were less likely to experience adverse reactions than participants off chemotherapy (Gross 1978). Participants receiving chemotherapy had a higher incidence of malaise and poor appetite than did those with asthma after vaccination (Hsieh 2002b). Participants with asthma were more likely to report local pain and had more episodes of fever in the days after vaccination. One study reported upper respiratory tract symptoms and fever after vaccination in a paediatric oncology participant, requiring oral antibiotics (Chisholm 2005).

DISCUSSION

This is an update of the first systematic review on the effectiveness of influenza vaccination in children being treated for cancer. We have identified a total of nine CCTs and one RCT that were extracted from nine studies fulfilling our inclusion criteria. Unfortunately, no available study compares influenza vaccine with 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 participants receiving chemotherapy were able to generate an immune response to influenza vaccine. However, they had weaker immune responses compared with healthy children, children with asthma or paediatric oncology participants who had completed chemotherapy more than one month before vaccination. Immune responses of the latter were comparable with those of healthy children. The differences in immune response between these groups were noted, 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 participants with solid tumours receiving chemotherapy compared with participants off chemotherapy (Chisholm 2005). The differences might be that solid tumours, not haematological malignancies, were studied, and that the control group was very small compared with the experimental group.

In reports of influenza vaccination in paediatric oncology participants, it is often stated that data are conflicting regarding the immune response to influenza vaccination, as some studies reveal a sufficient immune response but others fail to do so (Gross 1978; Hsieh 2002a; Lange 1979; Matsuzaki 2005; Porter 2004). This can be explained by a difference in participant populations in these studies. A more sufficient immune response is generally found in studies in which most of the children had completed chemotherapy longer than one month ago. Because 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 participants in the included studies. Adverse effect outcomes were most often assessed by parents; therefore the studies were susceptible to detection bias. No reports described 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. Participants receiving chemotherapy had a higher incidence of malaise and poor appetite after vaccination than did 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 has been 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 because of the lack of included RCTs.

All children in the different studies were younger 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 the range of age of the children is not stated. In the other study (Steinherz 1980), children receiving 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 that children who are being treated for cancer should be vaccinated 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 an 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 many practical difficulties are involved in conducting such a trial. Many participants 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 during 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 achieve as paediatric oncology patients may receive supportive care in centres other than their primary oncology 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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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 participants is compared with that of immunised paediatric oncology participants
Participants	42 immunised and 42 non-immunised children with various malignancies. Most children were receiving chemotherapy, but participants who had completed chemotherapy within the past 6 months were also included. Children < 6 months of age were excluded; otherwise age was 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 two 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 (≥ 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 with those off chemotherapy was not significant

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
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: two doses of 0.25 ml 3 to 4 weeks apart. 4 to 12 years: two doses of 0.5 ml 3 to 4 weeks apart. > 13 years: one dose of 0.5 ml. Previously immunised children: one dose 0.25 ml (< 4 years) or 0.5 ml (> 4 years)

Chisholm 2005 *(Continued)*

Outcomes	(1) Seroconversion (defined as four-fold rise in antibody titre) after vaccination (2) Development of protective HI titre (≥ 32) post-vaccination (3) Pre- and post-vaccination GMT (4) Adverse reactions
Notes	Results of children off chemotherapy stated only 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

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 with 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 two 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 (≥ 40) post-vaccination (3) Adverse reactions
Notes	

Hsieh 2002a

Methods	RCT conducted in Taiwan during the 2000-2001 influenza season Children with ALL were randomly assigned to one of two vaccination protocols
Participants	25 children with ALL receiving 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. Participants received two 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, they received dose 2. N = 11 received dose 1 alone, 4 weeks later, they received dose 2 + reinduction chemotherapy on the same day
Outcomes	(1) GMT pre- and post-vaccination (2) Development of protective HI titre (≥ 40) post-vaccination (3) Four-fold rise in antibody titre after vaccination (4) Adverse reactions

Hsieh 2002a *(Continued)*

Notes	Additional information on randomisation methods was requested and not obtained

Hsieh 2002b

Methods	CCT conducted in Taiwan during the 2000-2001 influenza season Response to influenza vaccine in children with ALL is compared with that of children with asthma
Participants	30 children with asthma in remission (no inhaled steroids within 2 weeks or oral steroids within 1 month before influenza vaccination), mean age 6.5 years, compared with 25 children with ALL receiving 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. Participants received two 0.5 ml doses containing 15 µg hemagglutinin, 4 weeks apart
Outcomes	(1) GMT pre- and post-vaccination (2) Development of protective HI titre (≥ 40) post-vaccination (3) Four-fold rise in antibody titre after vaccination (4) Adverse reactions
Notes	Dosage: > 8 years received 1 dose, and children younger than 8 received two doses of vaccine

Lange 1979

Methods	CCT conducted in the USA Responses to influenza vaccine of children with ALL on maintenance chemotherapy were compared with 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 (mean 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. Participants received two doses of 0.5 ml 4 weeks apart, with each dose containing 200 CCA of A/Vic/75 and A/NJ/76
Outcomes	(1) Pre- and post-vaccination GMT (2) Adverse reactions
Notes	A discrepancy in the number of sibling controls was noted: 50 sibling controls were included according to the abstract and table 1, but 22 sibling controls are mentioned in the article under Materials and Methods

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 with that of children with cancer off chemotherapy

Matsuzaki 2005 *(Continued)*

Participants	44 children with various types of malignancies, of whom 18 were receiving 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. Participants received two doses, 2 to 4 weeks apart at doses of 0.2 ml for children aged 1 to < 6 years, 0.3 ml for those aged 6 to < 13 years and 0.5 ml for those 13 years of age or older, according to recommendations in Japan
Outcomes	(1) Seroconversion (defined as four-fold rise in antibody titre) after two vaccinations (2) Achieving protective antibody titre (HI antibody titre ≥ 40) after two vaccinations (3) Adverse effects
Notes	No numbers pertaining to adverse effects stated

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 with 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 9 years of age or older and those previously immunised with influenza vaccine received one dose (0.5 ml), and children aged < 9 years and previously non-immunised children received two doses (each 0.5 ml), 1 month apart
Outcomes	(1) Pre- and post-vaccination GMT (2) Seroconversion (defined as four-fold rise in antibody titre) after the last vaccination (3) Adverse reactions after vaccination
Notes	Data on 3/49 healthy children were not included because they did not provide post-vaccination serology In this study it was not stated what HI titre was considered protective, nor what percentage of participants reached a protective HI titre

Shahgholi 2010

Methods	Single-centre controlled clinical trial conducted in Iran during the 2007-2008 influenza season. Responses of children with ALL on maintenance therapy to influenza vaccine were compared with those of healthy siblings
Participants	32 children aged 1 to 18 years with ALL in first remission on maintenance chemotherapy. Controls were 30 healthy siblings, similar in age and gender distribution Previously vaccinated children were excluded from the study
Interventions	Trivalent inactivated influenza vaccine (Influvac), containing the following strains: A/Solomon Islands 3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/2004. Participants received two doses of

Shahgholi 2010 *(Continued)*

	0.25 ml 3 to 4 weeks apart for children < 36 months of age, two doses of 0.5 ml for children 36 months to 13 years and one dose of 0.5 ml for children aged > 13 years
Outcomes	(1) Development of protective HI titre (> 40) post-vaccination; this is considered seroconversion (defined as four-fold rise in antibody titre) after vaccination (3) Pre- and post-vaccination GMT (4) Adverse reactions
Notes	Data on adverse reactions were available for 35 of 62 participants (56%)

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 with 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 receiving chemotherapy and 41 had been off chemotherapy for 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). Two doses of 0.5 ml, each containing 200 CCA units, were administered 4 weeks apart
Outcomes	(1) Significant antibody response (defined as four-fold rise in HI titre) four to six weeks after two immunisations (2) Achieving protective HI antibody titre (defined as ≥ 32) 4 to 6 weeks after two immunisations (3) Adverse reactions after vaccination
Notes	The National Influenza Immunization Program ended in December 1976. By that time, only 50/106 participants receiving chemotherapy and 21/41 participants off chemotherapy had received both immunisations. The age and sex distributions remained similar to those of the original group of 160 participants. Age and sex distributions of the healthy sibling controls are not mentioned

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]*

Study	Reason for exclusion
Adell 2002	(1) Participant population consisted mainly of adults (2) No outcomes relevant to this review were assessed (3) Participants who did not receive chemotherapy in the month before vaccination were included in the chemotherapy group
Ahmed 1996	Review on efficacy of influenza vaccine

Study	Reason for exclusion
Allison 1977	Details pertaining to chemotherapy were not adequately specified; therefore, not clear whether participants who received vaccine were receiving chemotherapy or had received chemotherapy during the month before vaccination. Not clear how treatment group was defined
Arola 1995	No vaccines administered
Barnes 2001	Review on infections after bone marrow transplantation
Bektas 2007	Lack of a control group
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 groups
Brown 1982	(1) Presented as summary; insufficient information provided on characteristics of participants and controls (2) Control group data were 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 participants and controls (2) Results are not presented
Brydak 1997	42/49 participants had already finished chemotherapy treatment (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) Participants did not receive chemotherapy or radiotherapy in the month before vaccination (3) Adults included in study population, results of children not presented separately
Esposito 2009	Commentary on influenza vaccination in children with cancer receiving chemotherapy
Feery 1979	Control group data were obtained from another trial
Ganz 1978	Adult study population
Gribabis 1994	Adult study population
Gross 1985	Review of influenza vaccine in cancer patients receiving chemotherapy
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 in Brydak 1997
Kandel 2005	Review on prevention and treatment of influenza
Kempe 1989	Participants 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

Study	Reason for exclusion
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
Reilly 2010	Lack of a control group
Ridgway 1993	Review on eight vaccines (including influenza vaccine) in children with cancer
Schafer 1979	(1) Adult study population (2) Not clear whether participants received chemotherapy in the month before vaccination
Smithson 1978	Control group data were obtained from another trial
Somani 1995	Review on re-immunisation with various vaccines after bone marrow transplantation
Stiver 1978	Adult study population
Sumaya 1977	Control group data were obtained from other trials
Sumaya 1982	Lack of a control group
Uchaikin 1999	Participants did not receive chemotherapy in the month before vaccination
Yamada 1982	6/8 participants had already finished chemotherapy

DATA AND ANALYSES

Comparison 1. Influenza immunity in vaccinated children receiving chemotherapy compared with vaccinated children not receiving chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants achieving protective titre post-vaccination (> 32 or 40) after last immunisation			Other data	No numeric data
2 Number of participants 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

Analysis 1.1. Comparison 1 Influenza immunity in vaccinated children receiving chemotherapy compared with vaccinated children not receiving chemotherapy, Outcome 1 Number of participants achieving protective titre post-vaccination (> 32 or 40) after last immunisation.

		Number of participants achieving protective titre post-vaccination (> 32 or 40) after last immunisation				
Study	Influenza strain	On chemotherapy n%	On chemotherapy Total N	Off chemotherapy n%	Off chemotherapy Total N	P-value
Chisholm 2005	A/NC/20/99	16 (42%)	38	3 (43%)	7	1.00
Chisholm 2005	A/PAN/2007/99	12 (50%)	24	2 (40%)	5	0.70
Chisholm 2005	B/Sichuan 379 99	26 (49%)	53	3 (33%)	9	0.48
Gross 1978	A/NJ/76	20 (29%)	68	63 (85%)	74	< 0.001
Gross 1978	A/Vic/75	33 (49%)	68	65 (88%)	74	< 0.01
Gross 1978						
Matsuzaki 2005	A/NC/20/99	5 (42%)	12	18 (90%)	20	0.006
Matsuzaki 2005	A/PAN/2007/99	2 (25%)	8	10 (83%)	12	0.019
Matsuzaki 2005	B/Sha/7/97	5 (29%)	17	11 (44%)	25	0.518
Steinherz 1980	A/NJ/76	13 (26%)	50	12 (57%)	21	< 0.05
Steinherz 1980	A/Vic/75	31 (61%)	50	16 (75%)	21	0.380
Steinherz 1980						

Analysis 1.2. Comparison 1 Influenza immunity in vaccinated children receiving chemotherapy compared with vaccinated children not receiving chemotherapy, Outcome 2 Number of participants with four-fold rise in antibody titre after last immunisation.

		Number of participants with four-fold rise in antibody titre after last immunisation				
Study	Influenza strain	On chemotherapy n%	On chemotherapy Total N	Off chemotherapy n%	Off chemotherapy Total N	P-value
Chisholm 2005	A/NC/20/99	30 (53%)	56	4 (44%)	9	0.13
Chisholm 2005	A/PAN/2007/99	19 (34%)	56	3 (33%')	9	0.85
Chisholm 2005	B/Sichuan 379 99	28 (50%)	56	5 (55%)	9	0.86
Matsuzaki 2005	A/NC/20/99	6 (38%)	16	20 (83%)	24	0.004
Matsuzaki 2005	A/PAN/2007/99	4 (25%)	16	12 (50%)	24	0.105
Matsuzaki 2005	B/Shan/7/97	6 (33%)	18	14 (54%)	26	0.227
Steinherz 1980	A/NJ/76	19 (38%)	50	16 (76%)	21	< 0.01
Steinherz 1980	A/Vic/75	26 (52%)	50	18 (86%)	21	< 0.05
Steinherz 1980						

Analysis 1.3. Comparison 1 Influenza immunity in vaccinated children receiving chemotherapy compared with vaccinated children not receiving chemotherapy, Outcome 3 Geometric mean titre (GMTs) pre- and post-vaccination.

		Geometric mean titre (GMTs) pre- and post-vaccination				
Study	Influenza strain	On chemotherapy GMT pre-vaccination	On chemotherapy GMT post-vaccination	Off chemotherapy GMT pre-vaccination	Off chemotherapy GMT post-vaccination	P-value
Chisholm 2005	A/NC/20/99	< 8-16	290	< 8-16	284	1.00
Chisholm 2005	A/PAN/2007/99	< 8-16	87.2	< 8-16	148	0.30
Chisholm 2005	B/Sichuan 379 99	<8	65.3	<8	72	0.84
Gross 1978	A/NJ/76	0	14	5	84*	< 0.001
Gross 1978	A/Vic/75	11	23	17	133*	< 0.01
Gross 1978						
Lange 1979	A/NJ/76	< 8	37.74 ± 1.28	< 8	176.88 ±1.14	< 0.01
Lange 1979	A/Vic/75	10.62 ± 1.14	61.92 ±1.26	12.88 ± 1.15	203,19 ±1.26	< 0.01
Lange 1979						

Comparison 2. Influenza immunity in vaccinated children receiving chemotherapy compared with vaccinated healthy children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants 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

Analysis 2.1. Comparison 2 Influenza immunity in vaccinated children receiving chemotherapy compared with vaccinated healthy children, Outcome 1 Number of participants with four-fold rise in antibody titre after last immunisation.

		Number of participants with four-fold rise in antibody titre after last immunisation				
Study	Influenza strain	On chemotherapy n%	On chemotherapy Total N	Healthy n%	Healthy Total N	P-value
Porter 2004	A/NC/20/99	13 (65%)	20	41 (89%)	46	P = 0.034
Porter 2004	A/PAN/2007/99	13 (65%)	20	36 (78%)	46	P = 0.258
Porter 2004	B/Vic/504/2000	12 (60%)	20	35 (76%)	46	P = 0.185
Shahgholi 2010	A/SI 3/2006	18 (56,2%)	32	24 (80%)	30	P = 0.04
Shahgholi 2010	A/Wis/67/2005	13 (40,6%)	32	16 (53,3%)	30	P = 0.31
Shahgholi 2010	B/Mal/2506/2004	19 (59,4%)	32	25 (83,3%)	30	P = 0.038
Steinherz 1980	A/NJ/76	19 (38%)	50	5 (71%)	7	P = 0.204
Steinherz 1980	A/Vic/75	26 (52%)	50	6 (86%)	7	P = 0.202
Steinherz 1980						

Analysis 2.2. Comparison 2 Influenza immunity in vaccinated children receiving chemotherapy compared with vaccinated healthy children, Outcome 2 Geometric mean titre (GMTs) pre- and post-vaccination.

		Geometric mean titre (GMTs) pre- and post-vaccination				
Study	Influenza strain	On chemotherapy GMT pre-vaccination	On chemotherapy GMT post-vaccination	Healthy GMT pre-vaccination	Healthy GMT post-vaccination	P-value
Lange 1979	A/NJ/76	<8 ± 0.00	37.74 ± 1.28	<8 ± 0.00	52.39 ± 1.13	0.53
Lange 1979	A/Vic/75	10.62 ± 1.14	61.92 ±1.26	12.51 ±1.12	70.34 ± 1.12	0.80
Lange 1979						
Porter 2004	A/NC/20/99	6.50	53.82	15.06	367.03	< 0.001
Porter 2004	A/Pan/2007/99	29.86	152.22	72.20	577.59	< 0.03
Porter 2004	B/Vic/504/2000	8.57	39.4	13.15	165.37	< 0.003
Shahgholi 2010	A/SI 3/2006	32,5	52,87	31,5	76,38	0,13
Shahgholi 2010	A/Wis/67/2005	54	81,87	54	145,41	0.04
Shahgholi 2010	B/Mal/2506/2004	12,8	25,41	17	38.07	0.10

Comparison 3. Influenza immunity in vaccinated children with ALL receiving chemotherapy compared with vaccinated children with asthma

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with four-fold rise in antibody titre 4 weeks after the last immunisation			Other data	No numeric data
2 Number of participants 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

Analysis 3.1. Comparison 3 Influenza immunity in vaccinated children with ALL receiving chemotherapy compared with vaccinated children with asthma, Outcome 1 Number of participants with four-fold rise in antibody titre 4 weeks after the last immunisation.

Number of participants with four-fold rise in antibody titre 4 weeks after the last immunisation

Study	Influenza strain	ALL on chemotherapy n%	ALL on chemotherapy Total N	Asthma n%	Asthma Total N	P-value
Hsieh 2002a	A/NC/20/99	6 (24%)	25	23 (77%)	30	P < 0.0001
Hsieh 2002a	A/Pan/2007/99	15 (60%)	25	19 (63%)	30	P = 0.980 NS
Hsieh 2002a	B/Yam/166/98	11 (44%)	25	20 (67%)	30	P = 0.157

Analysis 3.2. Comparison 3 Influenza immunity in vaccinated children with ALL receiving chemotherapy compared with vaccinated children with asthma, Outcome 2 Number of participants achieving protective titre post-vaccination (> 40) after last immunisation.

Number of participants achieving protective titre post-vaccination (> 40) after last immunisation

Study	Influenza strain	ALL on chemotherapy n%	ALL group Total N	Asthma %n	Asthma Total N	P-value
Hsieh 2002a	A/NC/20/99	6 (60%)	10	9 (90%)	10	P = 0.302
Hsieh 2002a	A/PAN/2007/99	11 (85%)	13	8 (73%)	11	P = 0.834
Hsieh 2002a	B/Yam/166/98	8 (57%)	14	10 (83%)	12	P = 0.309

Analysis 3.3. Comparison 3 Influenza immunity in vaccinated children with ALL receiving chemotherapy compared with vaccinated children with asthma, Outcome 3 Geometric mean titre (GMTs) pre- and post-vaccination.

Geometric mean titre (GMTs) pre- and post-vaccination

Study	Influenza strain	ALL GMT pre-vaccination	ALL GMT post-vaccination	Asthma GMT pre-vaccination	Asthma GMT post-vaccination	P-value
Hsieh 2002a	A/NC/20/99	39.8	50.1	50.1	631	P < 0.001
Hsieh 2002a	A/Pan/2007/99	31.6	125.9	50.1	158.5	P = 0.34
Hsieh 2002a	B/Yam/166/98	25.1	79.4	39.8	199.5	P = 0.105

Comparison 4. Influenza immunity in vaccinated compared with non-vaccinated paediatric oncology participants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants 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

Analysis 4.1. Comparison 4 Influenza immunity in vaccinated compared with non-vaccinated paediatric oncology participants, Outcome 1 Number of participants achieving protective titre post-vaccination (> 40) after last immunisation.

Number of participants achieving protective titre post-vaccination (> 40) after last immunisation

Study	Influenza strain	Vaccinated n%	Vaccinated Total N	Non-vaccinated n%
Chisholm 2001	H1N1	14 (48%)	29	Not available
Chisholm 2001	H3N2	16 (70%)	23	Not available
Chisholm 2001	B	18 (64%)	28	Not available
Chisholm 2001				

Analysis 4.2. Comparison 4 Influenza immunity in vaccinated compared with non-vaccinated paediatric oncology participants, Outcome 2 Geometric mean titre (GMTs) pre- and post-vaccination.

Geometric mean titre (GMTs) pre- and post-vaccination

Study	Influenza strain	GMT pre vacc	GMT post vacc	P-value
Chisholm 2001	H1N1	12.6 (95%CI 8.6-19.2)	60.4 (95% CI 32.4-112.8)	< 0.0001
Chisholm 2001	H3N2	23.2 (95% CI 8.6-16.7)	124.9 (95% CI 72-216.0)	<0.0001
Chisholm 2001	B	12 (95% CI 8.6-16.7)	48.0 (95% CI 30-76.7)	<0.0001

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

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

Analysis 5.1. Comparison 5 Influenza immunity in two vaccination schedules in children with ALL receiving maintenance chemotherapy, Outcome 1 Number of participants with four-fold rise in antibody titre 4 weeks after last immunisation.

Number of participants with four-fold rise in antibody titre 4 weeks after last immunisation										
Study	**Influenza strain**	**Group 1. First dose n%**	**Total N of partic-ipants**	**Group 1. Sec dose n%**	**Total N of partic-ipants**	**Group 2. First dose n%**	**Total N of partic-ipants**	**Group 2. Sec dose n%**	**Total N of partic-ipants**	**P-value**
Hsieh 2002a	A/NC/20/99	6 (42.9%)	14	6 (42.9%)	14	5 (45,5%	11	5 (45.5%)	11	0.84 = NS comparing Group 1 Se-cond dose to Group 2 Second dose
Hsieh 2002a	A/ Pan/2007/99	4 (28.6%)	14	5 (35.7%)	14	0 (0%)	11	1 (9.1%)	11	0.12 = NS comparing Group 1 Se-cond dose to Group 2 Second dose
Hsieh 2002a	B/ Yam/166/98	7 (50%)	14	8 (57.1%)	14	8 (72.7%)	11	7 (63.6%)	11	0.84 = NS comparing Group 1 Se-cond dose to Group 2 Second dose

Analysis 5.2. Comparison 5 Influenza immunity in two vaccination schedules in children with ALL receiving maintenance chemotherapy, Outcome 2 Number of participants achieving protective titre post-vaccination (> 40) after immunisation.

Number of participants achieving protective titre post-vaccination (> 40) after immunisation										
Study	**Influenza strain**	**Group 1. First dose n%**	**Total N**	**Group 1. Sec dose n%**	**Total N**	**Group 2. First dose n%**	**Total N**	**Group 2. Sec dose n%**	**Total N**	**P-value**
Hsieh 2002a	A/NC/20/99	5 (55.6%)	9	5 (55.6%)	9	3 (60%)	5	3 (60%)	5	0.79= NS compar-ing Group 1 second dose to Group 2 second dose
Hsieh 2002a	A/ Pan/2007/99	2 (28.6%)	7	5 (71.4%)	7	0 (0%)	3	1 (33.3%)	3	0.35 = NS compar-ing Group 1 second dose to Group 2 second dose
Hsieh 2002a	B/ Yam/166/98	6 (85.7%)	7	6 (85.7%)	7	5 (83.3%)	6	5 (83.3%)	6	0.73 = NS compar-ing Group 1 second dose to Group 2 second dose

ADDITIONAL TABLES

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

Assessment of methodological quality of randomised controlled trials
Selection bias Allocation concealment: 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 B. Unclear: randomisation stated but no information on method used is available C. Inadequate: use of alternate medical record numbers or unsealed envelopes as randomisation method, and/or information in the study indicates that investigators or participants could have influenced the allocation of treatment
Performance bias Blinding of care providers: yes/no/unclear Blinding of participants: yes/no/unclear Care providers and participants are considered not blinded if the intervention group can be identified in > 20% of participants because of side effects of treatment
Detection bias Blinding of outcome assessors: yes/no/unclear
Attrition bias Intention-to-treat analysis: A. Yes: all participants analysed in the treatment group to which they were allocated, regardless of whether or not they received the allocated intervention B. No: some participants (< 5%, 5% to 10%, 10% to 20%, > 20%) not analysed in the treatment group to which they were randomly assigned because they did not receive the study intervention or they withdrew from the study, or because of a protocol violation C. Unclear: inability to determine whether participants were analysed according to the intention-to-treat principle after contact with the authors
Completeness of follow-up Percentage of participants excluded or lost to follow-up for the different treatment groups for primary and secondary outcomes (< 5%, 5% to 10%, 10% to 20%, > 20%)

Table 2. Newcastle-Ottawa quality assessment scale

Scale
Cohort studies 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. *Selection* 1. Representativeness of the exposed cohort (1 star*) a) Truly representative of the exposed cohort b) Somewhat representative of the exposed cohort c) Selected group of users, e.g. nurses, volunteers d) No description of the derivation of the cohort 2. Selection of the non-exposed cohort (1 star*) a) Drawn from the same community as the exposed cohort b) Drawn from a different source c) No description of the derivation of the non-exposed cohort 3. Ascertainment of exposure (1 star*) a) Secure record b) Structured interview c) Written self-report d) No description

Table 2. Newcastle-Ottawa quality assessment scale *(Continued)*

4. Demonstration that outcome of interest was not present at start of study (1 star*)
a) Yes
b) No

Comparability
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

Outcome (1 star*)
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 participants accounted for
b) Participants 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

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
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
Shahgholi 2010	4 stars (classified A)	2 stars	2 stars (poor follow-up of adverse events classified as B)	8 stars
Steinherz 1980	4 stars (classified A)	1 star	2 stars (poor follow-up) classified as B	7 stars

Table 4. Quality of RCT

Scored items	Hsieh 2002

Table 4. Quality of RCT *(Continued)*

Randomisation performed	Yes, method not stated
Allocation concealment	Unclear
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

APPENDICES

Appendix 1. Search strategy for Cochrane Central Register of Controlled Trials (CENTRAL)

1. For **Children,** the following text words were used:

infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy

2. For **Childhood cancer,** the following text words were used:

leukemia OR leukemi* OR leukaemi* OR ALL OR AML OR lymphoma OR lymphom* OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR primitive neuroectodermal tumors OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR immune tolerance OR immunosuppression OR immunosuppressions OR immunosuppres* OR immunocompromised host OR immunocompromised hosts OR immunocompromised patient OR immunocompromised patients OR immunocompromis* OR immunosuppres* OR immunosuppressed host OR immunosuppressed hosts OR neoplasm OR neoplasms OR neoplas* OR carcinoma OR carcinomas OR carcinom* OR malignancy OR malignan* OR tumour OR tumours OR tumor OR tumors OR tumor* OR tumour* OR cancer OR cancer* OR oncology OR oncolo* OR metastases OR metastasis OR metastatic OR metasta* OR pediatric oncology OR paediatric oncology OR hematologic neoplasms OR hematologic malignancy OR hematolog* OR hematooncolo* OR hemato oncolo* OR hemato-oncolo*

3. For **Influenza vaccines,** the following text words were used:

influenza OR influenzas OR human influenza OR human influenzas OR grippe OR human flu OR orthomyxoviridae OR influenza viruses OR influenza virus OR influenzavirus A OR influenza A virus OR influenza A viruses OR influenza viruses type A OR orthomyxovirus type A OR influenzavirus B OR influenza B virus OR influenza B viruses OR influenza viruses type B OR orthomyxoviruses type B OR influenza virus C OR influenza viruses type C OR orthomyxoviruses type C OR influenza C virus OR influenza C viruses OR influenz* OR orthomyxovirid* OR influenza virus* OR orthomyxovirus* OR myxovirus* OR influenzavirus* OR influenza vaccines OR influenza vaccine OR influenza vaccin* OR flu OR FluMist OR CAIV-T vaccine OR MedImmune Vaccines Brand of Trivalent Live Attenuated Influenza Vaccine OR Trivalent Live Attenuated Influenza Vaccine OR LAIV vaccine OR fluzone OR fluarix OR fluinsure OR fluviral OR invivac OR cold-adapted influenza virus vaccine OR DNA vaccine OR influvac OR influject OR flubiok OR flumist OR fluvirin OR vaxigrip OR imomax gripe OR istivac OR mutagrip OR flushield OR fluogen

Final search 1 AND 2 AND 3

[*=zero or many characters]

The search of the original version of the review was performed in All Text. For the update (August 2012), the search was performed in Title, Abstract or Keywords.

Appendix 2. Search strategy for PubMed

1. For **Children,** the following MeSH headings and text words were used:

infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools, nursery OR infant, newborn

2. For **Childhood cancer,** the following MeSH headings and text words were used:

neoplasm OR neoplasms OR neoplas* OR carcinoma OR carcinomas OR carcinom* OR malignancy OR malignan* OR tumour OR tumours OR tumor OR tumors OR tumor* OR tumour* OR cancer OR cancer* OR oncology OR oncolo* OR metastases OR metastasis OR metastatic OR metasta* OR pediatric oncology OR paediatric oncology OR hematologic neoplasms OR hematologic malignancy OR hematolog* OR hematooncolo* OR hemato oncolo* OR hemato-oncolo* OR immune tolerance OR tolerance, immune OR immunosuppression OR immunosuppressions OR immunosuppres* OR immunocompromised host OR immunocompromised hosts OR host, immunocompromised OR hosts, immunocompromised OR immunocompromised patient OR immunocompromised patients OR patient, immunocompromised OR patients, immunocompromised OR immunocompromis* OR immunosuppres* OR immunosuppressed host OR immunosuppressed hosts OR host, immunosuppressed OR hosts, immunosuppressed OR leukemia OR leukemi* OR leukaemi* OR ALL OR AML OR lymphoma OR lymphom* OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*

3. For **Influenza vaccines,** the following MeSH headings and text words were used:

FluMist OR CAIV-T vaccine OR MedImmune Vaccines Brand of Trivalent Live Attenuated Influenza Vaccine OR Trivalent Live Attenuated Influenza Vaccine OR LAIV vaccine OR vaccine, LAIV OR fluzone OR fluarix OR fluinsure OR fluviral OR invivac OR cold-adapted influenza virus vaccine OR DNA vaccine OR influvac OR influject OR flubiok OR flumist OR fluvirin OR vaxigrip OR imomax gripe OR istivac OR mutagrip OR flushield OR fluogen OR influenza, human OR influenzas, human OR influenza OR influenzas OR human influenza OR human influenzas OR grippe OR human flu OR flu, human OR orthomyxoviridae OR influenza viruses OR influenza virus OR influenzavirus A OR influenza A virus OR influenza A viruses OR influenza viruses type A OR orthomyxovirus type A OR influenzavirus B OR influenza B virus OR influenza B viruses OR influenza viruses type B OR orthomyxoviruses type B OR influenza virus C OR influenza viruses type C OR orthomyxoviruses type C OR influenza C virus OR influenza C viruses OR virus, influenza C OR viruses, influenza C OR influenz* OR orthomyxovirid* OR influenza virus* OR orthomyxovirus* OR myxovirus* OR influenzavirus* OR influenza vaccines OR vaccines, influenza OR vaccine, influenza OR influenza vaccine OR influenza vaccin*

4. For identifying **RCTs and CCTs** in the original version of the review, we used the highly sensitive search strategy as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Handbook).

For the update (August 2012), the most recent Cochrane Highly Sensitive Search strategy was used (Higgins 2008):

((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) AND (humans[mh])

Final search 1 AND 2 AND 3 AND 4

[*=zero or many characters; RCT = randomized controlled trial; CCT = controlled clinical trial]

Appendix 3. Search strategy for Embase (OVID)

1. For **Children,** the following Emtree terms and text words were used:

1. infant/ or infancy/ or newborn/ or baby/ or child/ or preschool child/ or school child/
2. adolescent/ or juvenile/ or boy/ or girl/ or puberty/ or prepuberty/ or pediatrics/
3. primary school/ or high school/ or kindergarten/ or nursery school/ or school/
4. or/1-3
5. (infant$ or (newborn$ or new born$) or (baby or baby$ or babies) or neonate$).mp.
6. (child$ or (school child$ or schoolchild$) or (school age$ or schoolage$) or (pre school$ or preschool$)).mp.

7. (kid or kids or toddler$ or adoles$ or teen$ or boy$ or girl$).mp.
8. (minors$ or (under ag$ or underage$) or juvenil$ or youth$).mp.
9. (puber$ or pubescen$ or prepubescen$ or prepubert$).mp.
10. (pediatric$ or paediatric$ or peadiatric$).mp.
11. (school or schools or (high school$ or highschool$) or primary school$ or nursery school$ or elementary school or secondary school $ or kindergar$).mp.
12. or/5-11
13. 4 or 12

2. For **Childhood cancer,** the following Emtree terms and text words were used:

1. (leukemia or leukemi$ or leukaemi$).mp.
2. (lymphoma or lymphom$ or hodgkin$ or T-cell or B-cell or non-hodgkin).mp.
3. (sarcoma or sarcom$ or Ewing$ or osteosarcoma or osteosarcom$ or wilms tumor or wilms$).mp.
4. (nephroblastom$ or neuroblastoma or neuroblastom$ or rhabdomyosarcoma or rhabdomyosarcom$ or teratoma or teratom$ or hepatoma or hepatom$ or hepatoblastoma or hepatoblastom$).mp.
5. (PNET or medulloblastoma or medulloblastom$ or PNET$ or neuroectodermal tumors or retinoblastoma or retinoblastom$ or meningioma or meningiom$ or glioma or gliom$).mp.
6. (neoplasm or neoplasms or neoplas$ or carcinoma or carcinomas or carcinom$ or malignancy or malignan$ or tumour or tumours or tumor or tumors or tumor$ or tumour$ or cancer or cancer$ or oncology or oncolo$ or metastases or metastasis or metastatic or metasta $ or pediatric oncology or paediatric oncology or hematologic neoplasms or hematologic malignancy or hematolog$ or hematooncolo$ or hemato oncolo$ or hemato-oncolo$).mp.
7. CANCER/ or ONCOLOGY/ or Neoplasm/ or CARCINOMA/ or LEUKEMIA/ or LYMPHOMA/ or TUMOR/ or METASTASIS/ or HEMATOLOGIC MALIGNANCY/ or CHILDHOOD CANCER/ or SARCOMA/ or EWING SARCOMA/ or OSTEOSARCOMA/ or NEPHROBLASTOMA/ or NEUROBLASTOMA/ or RHABDOMYOSARCOMA/ or TERATOMA/ or HEPATOBLASTOMA/ or MEDULLOBLASTOMA/ or NEUROECTODERM TUMOR/ or RETINOBLASTOMA/ or MENINGEOMA/ or GLIOMA/
8. (immune tolerance or immunosuppression or immunosuppressions or immunosuppres$ or immunocompromised host or immunocompromised hosts).mp.
9. (immunocompromised patient or immunocompromised patients or immunocompromis$ or immunosuppres$ or immunosuppressed host or immunosuppressed hosts).mp. or IMMUNOLOGICAL TOLERANCE/
10. or/1-10

3. For**Influenza vaccines,** the following Emtree terms and text words were used:

1. INFLUENZA/ or influenza.mp. or influenzas.mp. or human influenza.mp. or human influenzas.mp. or grippe.mp. or human flu.mp. or orthomyxoviridae.mp. or influenza viruses.mp. or influenza virus.mp. or influenzavirus A.mp. or influenza A virus.mp. or influenza A viruses.mp. or influenza viruses type A.mp. or orthomyxovirus type A.mp. or influenzavirus B.mp. or influenza B virus.mp. or influenza B viruses.mp. or influenza viruses type B.mp. or orthomyxoviruses type B.mp. or influenza virus C.mp. or influenza viruses type C.mp. or orthomyxoviruses type C.mp. or influenza C virus.mp. or influenza C viruses.mp. or influenz$.mp. or orthomyxovirid$.mp. or influenza virus $.mp. or orthomyxovirus$.mp. or myxovirus$.mp. or influenzavirus$.mp. or influenza vaccines.mp. or influenza vaccine.mp. or influenza vaccin$.mp.
2. INFLUENZA VIRUS A/ or INFLUENZA VIRUS/ or INFLUENZA VIRUS C/ or INFLUENZA VIRUS B/ or INFLUENZA A/ or flu.mp. or (flue or influenza infection or influenza syndrome or human influenza virus or influenza virus type a).mp. or orthomyxovirus.mp. or influenzae.mp. or Influenza Vaccine/
3. (FluMist or CAIV-T vaccine or MedImmune Vaccines Brand of Trivalent Live Attenuated Influenza Vaccine or Trivalent Live Attenuated Influenza Vaccine or LAIV vaccine or fluzone or fluarix or fluinsure or fluviral or invivac or cold-adapted influenza virus vaccine or DNA vaccine or influvac or influject or flubiok or flumist or fluvirin or vaxigrip or imomax gripe or istivac or mutagrip or flushield or fluogen or Admune or Agrippal or Anti Grippe Vaccine or Anti Influenza Vaccine or Antiinfluenza Vaccine or Begrivac or Begrivac S or B Type Influenza Vaccine).mp.
4. (Fluax or Flugen or Flugene or Flu Immune or Flu Imune or Flushield or Flustat or Flu-Vac or Flu Vaccine or Fluviron or Grippovac or Influenza a Vaccine or Influenza A2 Vaccine or Influenza a Virus Vaccine or Influenza B Vaccine or Influenza Virus A2-Taiwan Vaccine or Influenza Virus A2 Vaccine or Influenza Virus B Vaccine or Influenza Virus Vaccine or Influject or Influsplit or Inviron-Ol or Invivac or Iradogen or Live Influenza Vaccine or Mfv Ject or Munevan or Mutagrip or Nivgrip or Polyvalent Influenza Vaccine or Polyvalent Influenza Vaccine 1967 or Previgrip or Skf 106160 or 'Trivalent').mp.
5. or/1-4

4. For **RCTs and CCTs,** the following Emtree terms and text words were used for the original version of the review:

1. Clinical Trial/
2. Controlled Study/
3. Randomized Controlled Trial/
4. Double Blind Procedure/
5. Single Blind Procedure/

6. Comparative Study/
7. RANDOMIZATION/
8. Prospective Study/
9. PLACEBO/
10. Phase 2 Clinical Trial/
11. phase 3 clinical study.mp.
12. phase 4 clinical study.mp.
13. Phase 3 Clinical Trial/
14. Phase 4 Clinical Trial/
15. or/1-14
16. allocat$.mp.
17. blind$.mp.
18. control$.mp.
19. placebo$.mp.
20. prospectiv$.mp.
21. random$.mp.
22. ((singl$ or doubl$ or trebl$ or tripl$) and (blind$ or mask$)).mp.
23. (versus or vs).mp.
24. (randomized controlled trial$ or randomised controlled trial$).mp.
25. controlled clinical trial$.mp.
26. clinical trial$.mp.
27. or/16-26
28. Human/
29. Nonhuman/
30. ANIMAL/
31. Animal Experiment/
32. or/29-31
33. 32 not 28
34. (15 or 27) not 33

For the update (August 2012), the following Emtree terms and text words were used:

1. Randomized Controlled Trial/
2. Controlled Clinical Trial/
3. randomized.ti,ab.
4. placebo.ti,ab.
5. randomly.ti,ab.
6. trial.ti,ab.
7. groups.ti,ab.
8. drug therapy.sh.
9. or/1-8
10. Human/
11. 9 and 10

Final search 1 AND 2 AND 3 AND 4

[mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; sh = subject heading; ti,ab = title or abstract; / = Emtree term; $= zero to many characters; RCT = randomized controlled trial; CCT = controlled clinical trial]

WHAT'S NEW

Date	Event	Description
16 April 2019	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 2011

Review first published: Issue 2, 2009

Date	Event	Description
4 January 2013	New search has been performed	The search for eligible studies was updated to August 2012.
4 January 2013	New citation required but conclusions have not changed	The search for eligible studies was updated to August 2012. One CCT added to the update looked at responses of children with ALL receiving maintenance therapy of influenza vaccine compared with responses of healthy siblings. Conclusions of this updated review have not changed.

CONTRIBUTIONS OF AUTHORS

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

LCM Kremer: search strategy, methodology and manuscript preparation.

MD van de Wetering: article retrieval, assessment of studies for inclusion and exclusion, data extraction and analysis and review 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 an immunological response in children with cancer during chemotherapy, compared with control groups) was not reported in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [therapeutic use]; Controlled Clinical Trials as Topic; Influenza Vaccines [adverse effects] [immunology] [*therapeutic use]; Influenza, Human [immunology] [*prevention & control]; Neoplasms [*drug therapy] [immunology]; Vaccination [*adverse effects]

MeSH check words

Child; Humans