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Author(s)	Cheuk, DK; Chiang, AK; Lee, TL; Chan, GC; Ha, SY
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Vaccines for prophylaxis of viral infections in patients with hematological malignancies (Review)

Cheuk DKL, Chiang AKS, Lee TL, Chan GCF, Ha SY

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[Intervention Review]

Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Daniel KL Cheuk[1], Alan KS Chiang[1], Tsz Leung Lee[1], Godfrey CF Chan[1], Shau Yin Ha[1]

[1]Department of Pediatrics and Adolescent Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China

Contact address: Daniel KL Cheuk, Department of Pediatrics and Adolescent Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong SAR, China. cheukkld@hkucc.hku.hk.

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ABSTRACT

Background

Viral infections cause significant morbidity and mortality in patients with hematological malignancies. It remains uncertain whether viral vaccinations in these patients are supported by good evidence.

Objectives

We aimed to determine the effectiveness and safety of viral vaccines in patients with hematological malignancies.

Search methods

We searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL (June 2010), reference lists of relevant papers, abstracts from scientific meetings and contacted vaccine manufacturers.

Selection criteria

Randomized controlled trials (RCTs) evaluating viral vaccines in patients with hematological malignancies were included.

Data collection and analysis

Relative risk (RR) was used for binary data and mean difference (MD) for continuous data. Primary outcome was incidence of infection. Secondary outcomes were mortality, incidence of complications and severe viral infection, hospitalization, immune response and adverse effects. Fixed-effect model was used in meta-analyses.

Main results

Eight RCTs were included, with 305 patients in the intervention groups and 288 in the control groups. They evaluated heat-inactivated varicella zoster virus (VZV) vaccine (two trials), influenza vaccines (five trials) and inactivated poliovirus vaccine (IPV) (one trial). Seven trials had high and one trial had moderate risk of bias.

VZV vaccine might reduce herpes zoster compared to no vaccine (RR 0.54, 95% CI 0.3 to 1.0, P=0.05), but not statistically significant. Vaccination also demonstrated efficacy in immune response but frequently caused local adverse effects. One trial reported severity score of zoster, which favored vaccination (MD 2.6, 95% CI 0.94 to 4.26, P=0.002).

Two RCTs compared inactivated influenza vaccine with no vaccine and reported lower risk of lower respiratory infections (RR 0.39, 95% CI 0.19 to 0.78, P=0.008) and hospitalization (RR 0.17, 95% CI 0.09 to 0.31, P<0.00001) in vaccine recipients. However, vaccine recipients more frequently experienced irritability and local adverse effects. There was no significant difference in seroconversion between one and two doses of influenza vaccine (one trial), or between recombinant and standard influenza vaccine (one trial), or influenza vaccine given with or without re-induction chemotherapy (one trial).

The IPV trial comparing vaccination starting at 6 versus 18 months after stem cell transplant (SCT) found no significant difference in seroconversion.

Authors' conclusions

Inactivated VZV vaccine might reduce zoster severity in adult SCT recipients. Inactivated influenza vaccine might reduce respiratory infections and hospitalization in adults with multiple myeloma or children with leukemia or lymphoma. However, the quality of evidence is low. Local adverse effects occur frequently. Further high-quality RCTs are needed.

PLAIN LANGUAGE SUMMARY

Varicella and influenza vaccines may reduce morbidity in patients with blood cancers

Viral infections cause significant disease and even death in patients with blood cancers. In the current systematic review of randomized controlled trials (RCTs) we aimed to evaluate the efficacy and safety of viral vaccines in these patients. The pre-defined primary outcome was incidence of the infection concerned. Secondary outcomes were mortality due to the viral infection, all-cause mortality, incidence of complications, incidence of severe viral infection, hospitalization rate, in vitro immune response and frequency of adverse effects. Eight RCTs were included. They evaluated heat-inactivated varicella zoster virus (VZV) vaccine (two trials), influenza vaccines (five trials) and inactivated poliovirus vaccine (one trial). There were no RCTs on other viral vaccines (hepatitis A, hepatitis B, measles, mumps, rubella). Only the two trials on VZV vaccine reported our pre-defined primary outcome. All trials reported some of the pre-defined secondary outcomes. We found that inactivated VZV vaccine might reduce the severity of herpes zoster when given before and after stem cell transplant in adults with lymphoma or leukemia. Inactivated influenza vaccine might reduce upper and lower respiratory infections and hospitalization in adults with multiple myeloma who are undergoing chemotherapy, or children with leukemia or lymphoma within two years post-chemotherapy. However, the quality of evidence is not high. Local adverse effects occur frequently with the vaccines, although serious adverse effects appear uncommon. Further high-quality RCTs are needed to clarify the benefits and optimal regimens of viral vaccines for patients with blood cancers.

BACKGROUND

Description of the condition

Viral infections are important causes of morbidity or even mortality in patients with hematological malignancies who are immunocompromised. In addition, viral infections may delay chemotherapy and necessitate hospitalization and antibiotic administration (Feldman 1977; Elting 1995; Yousuf 1997).

Description of the intervention

Some viral infections can be prevented by vaccinations, such as influenza, varicella and herpes zoster. However, the practice of viral vaccination in patients with hematological malignancies is highly variable among different treatment centres. It is generally held that patients with hematological malignancies have altered immune function, either as a result of the underlying hematological malignancy or treatment with chemotherapy; and vaccination in these patients might be ineffective. In addition, there is often a concern that vaccination in patients with hematological malignancies might be associated with more adverse effects (Henning 1997; Irish 1998; Booth 2000), especially in the case of live-attenuated vaccines.

American and British guidelines recommend annual vaccination against influenza for adults and children who are immunosuppressed because of disease or treatment (DOH 1996; ACIP 2005). However, there is no clear-cut recommendation as to whether and

when patients with hematological malignancies should receive influenza vaccination. A recent study indicated that one-third of pediatric oncologists and hematologists did not routinely recommend yearly influenza vaccination for children with cancer (Porter 2003).

As modern influenza vaccines contain hemagglutinin and neuraminidase surface antigens obtained from chemically inactivated influenza virus strains, there is no risk of introducing active infection in immunocompromised individuals. Many studies have documented seroconversion in patients with hematological malignancies on chemotherapy (Feery 1977; Ortbals 1977; Sumaya 1977; Ganz 1978; Smithson 1978; Hodges 1979; Lange 1979; Shildt 1979; Sumaya 1982; Engelhard 1993; Lo 1993; Gribabis 1994; Jackowska 1996; Brydak 1997; Brydak 1998; Brydak 1999; Robertson 2000; Chisholm 2001; Hsieh 2002; Nordoy 2002; Rapezzi 2003; Porter 2004; Brydak 2006) but other studies did not reveal sufficient immune response in patients with cancer (Borella 1971; Allison 1977; Gross 1978; Stiver 1978; Schafer 1979; Steinherz 1980; Brown 1982; Robertson 2000; van der Velden 2001; Matsuzaki 2005; Mazza 2005). Although the rate of seroconversion is generally lower than in healthy adult volunteers, the use of multiple doses of influenza vaccine may increase the antibody response (Feery 1977; Gribabis 1994). Influenza vaccination is generally safe, with only mild adverse effects, as found in patients with chronic lymphocytic leukemia or multiple myeloma (Gribabis 1994; Rapezzi 2003).

Many case series have documented seroconversion in large proportions of leukemic patients who received live-attenuated varicella vaccine (Hattori 1976; Nakagawa 1978; Brunell 1982; Brunell 1984; Gershon 1984; Kamiya 1984; Konno 1984; Oka 1984; Austgulen 1985; Gershon 1985; Haas 1985; Heller 1985; Slordahl 1985; Gershon 1989; Arbeter 1990; Gershon 1990; Bancillon 1991; Yeung 1992; Ecevit 1996; LaRussa 1996; Lou 1996; Navajas 1999; Leung 2004) mostly after chemotherapy or during maintenance chemotherapy. Protective efficacy may last for at least a few years (Torigoe 1981; Oka 1984; Gershon 1989). In addition, leukemic patients who receive the live-attenuated varicella vaccine might have lower incidence of zoster than patients who have natural varicella infections (Hardy 1991; LaRussa 1996; Navajas 1999). Inactivated varicella vaccines might also reduce the risk of zoster in recipients of an hematopoietic stem cell transplant (Hata 2002). Adverse effects of varicella vaccine are usually mild but varicella or herpes zoster caused by the vaccine virus strain can occur (Ninane 1985; Christensen 1999).

Measles, mumps, rubella and oral poliomyelitis vaccines are live-attenuated vaccines given routinely in early childhood in many countries. However, loss of antibodies has been demonstrated in patients with hematological malignancies (Bosu 1975; Feldman 1998; Nilsson 2000; Nilsson 2002; Reinhardt 2003; Zignol 2004). Re-vaccination has been an important consideration in this group of patients but the safety and efficacy of re-vaccination in these patients are not entirely certain (Mitus 1962; Stiehm 1966; Torigoe 1981; Nilsson 2002; Reinhardt 2003). These vaccines are considered to be contraindicated in patients receiving chemotherapy because of risks of infection with the vaccine strains. Nevertheless, a study found that when measles vaccine was given three to six months after chemotherapy in leukemic patients, the patients might still develop protective antibodies though the seropositivity rate was lower than in healthy controls (Ercan 2005).

A study demonstrated that 85% of leukemic patients who received hepatitis B vaccine after chemotherapy developed protective antibodies (Fioredda 2005); and one-third of the leukemic children undergoing maintenance chemotherapy responded to the vaccine (Yetgin 2001). However, during intensive chemotherapy the serological response was reported to be very low (Moryl 2004); passive immunization in the aggressive phase followed by active immunization after cessation of intense chemotherapy might increase the rates of protective antibody levels (Somjee 2002).

Why it is important to do this review

Although available viral vaccines are shown to be effective in healthy children for prevention of the respective viral infections, it is uncertain whether existing evidence is rigorous enough to show that the vaccines are also effective and safe in patients with hematological malignancies. These patients are immunocompromised as a result of their diseases or the treatments. Therefore we examined the efficacy and safety of viral vaccines in patients with hematological malignancies in a systematic review of randomized controlled trials.

OBJECTIVES

The objectives of this systematic review were to determine the effectiveness and safety of viral vaccines in patients with hematological malignancies:

1. whether viral vaccines are effective in preventing viral infections in patients with hematological malignancies;

2. whether viral vaccines are effective in preventing complications or mortality associated with viral infections, or reduction in severity of the viral infections, in patients with hematological malignancies;

3. whether a particular type of vaccine or dosing schedule is more effective than others in patients with hematological malignancies;

4. whether viral vaccines administered to patients with hematological malignancies are associated with adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) were included in the review.

Types of participants

Patients of all ages with hematological malignancies, including acute and chronic leukemias, lymphomas (Hodgkin's and non-Hodgkin's) and myelomas, were included.

Types of interventions

Trials evaluating all forms of viral vaccines, including influenza, varicella, hepatitis A, hepatitis B, measles, mumps, rubella, and poliomyelitis, were included in the review. The control interventions could be placebo vaccine, no vaccine or an alternative form of vaccine; or alternative dosing regimens or schedules.

Types of outcome measures

Primary outcomes

Incidence of the viral infection concerned

Secondary outcomes

- Mortality due to the viral infection
- All-cause mortality
- Incidence of complications due to the viral infection
- Incidence of severe viral infection
- Rate of hospitalization due to the viral infection
- In vitro immune response to the vaccine (titre of protective antibodies, T-cell proliferation)
- Frequency of systemic and local adverse effects

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* June 2010), MEDLINE (1966 to Dec 2009), EMBASE (1980 to Dec 2009) and CINAHL (1982 to Dec 2009).

The search strategies for the different electronic databases (using a combination of controlled vocabulary and text word terms) are provided in the appendices (Appendix 1, Appendix 2, Appendix 3, Appendix 4).

The reference lists of all relevant papers were searched for further studies. Other internet sources were also explored:

- NHS National Research Register (www.update-software.com/national);
- NIH Clinical Trials Database (www.clinicaltrials.gov);
- Meta-register of Clinical Trials (www.controlled-trials.com);
- Digital Dissertations website (www.lib.umi.com/dissertations);
- Vaccine Adverse Event Reporting System website (www.vaers.org).

Searching other resources

We also handsearched abstracts from the meetings of the American Society of Hematology (ASH), American Society for Clinical Oncology (ASCO), European Haematology Association (EHA) and European Society for Medical Oncology (ESMO) (1993 to 2009).

Articles published only in abstract form would also be included if authors could be contacted to provide essential details for appraisal and analysis. The process of searching many different sources might bring to light direct or indirect references to unpublished studies. We would seek to obtain copies of such unpublished material. In addition, we contacted colleagues and experts in the field to ascertain any unpublished or ongoing studies. Vaccine manufacturers listed at the World Health Organization (WHO) website were also contacted.

There was no language restriction in the search and inclusion of studies. However, multiple publications reporting the same group of patients or subsets of the group would be excluded.

Data collection and analysis

Selection of studies

Two authors (first and second authors) independently reviewed titles and abstracts of references retrieved from the searches and selected all potentially relevant studies. Copies of these articles were obtained and reviewed independently by the same authors against our pre-defined inclusion criteria. Authors were not blinded to the names of the trial authors, institutions or journal of publication. All disagreements about selection of studies were resolved by consensus.

Data extraction and management

Two authors (first and second authors) independently extracted data from included trials. All disagreements were resolved by consensus. The following data were extracted, when available.

1. Study methods
    i) Design (e.g. randomized or non-randomized)
    ii) Randomization method (including list generation)
    iii) Method of allocation concealment
    iv) Blinding method
    v) Stratification factors
2. Participants
    i) Inclusion and exclusion criteria
    ii) Number (total, per group)
    iii) Age and gender distribution
    iv) Underlying hematological malignancies
    v) Treatments for the underlying hematological malignancies (chemotherapy, autologous stem cell transplant, allogeneic stem cell transplant)
    vi) Phase of treatments (e.g., before chemotherapy, during intensive chemotherapy, during maintenance chemotherapy, post-therapy)
    vii) Previous vaccine history
    viii) Baseline antibody levels
3. Intervention and control
    i) Type of vaccine
    ii) Type of control
    iii) Details of vaccine administration including dosage and schedules
    iv) Details of co-interventions
4. Follow-up data
    i) Duration of follow up
    ii) Loss to follow up
5. Outcome data as described above
6. Analysis data
    i) Methods of analysis (intention-to-treat or per protocol analysis)
    ii) Comparability of groups at baseline (yes or no)
    iii) Statistical techniques

The data were entered into Review Manager (RevMan) by one author and then checked by the other authors. Since adverse events are rarely adequately dealt with by controlled clinical trials, because the numbers are small and follow up too short, adverse events would be discussed by taking into account the non-trial literature.

Assessment of risk of bias in included studies

Two authors (first and second authors) independently assessed the quality of each eligible trial. All disagreements were resolved by consensus.

The following items were included to assess the methodological quality of RCTs.

(1) Selection bias, allocation concealment

A. Yes: use of randomization method that did not allow investigator and participant to know or influence the allocation of treatment before eligible participants entered the study.

B. Unclear: randomization stated but no information on method used was available.

C. No: use of alternate medical record numbers or unsealed envelopes as randomization method, or there was information in the study indicating that investigators or participants could have influenced the allocation of treatment.

(2) Performance bias

Blinding of care providers: Yes, No, Unclear.

Blinding of participants: Yes, No, Unclear.

Care providers and patients were considered not blinded if the intervention group could be identified in > 20% of participants because of the side effects of treatment.

(3) Detection bias

Blinding of outcome assessors: Yes, No, Unclear.

(4) Attrition bias, intention-to-treat analysis

A. Yes: all participants were analysed in the treatment group to which they were allocated, regardless of whether of not they received the allocated intervention.

B. No: some participants were not analysed in the treatment group to which they were randomized because they did not receive study intervention 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.

We summarized the quality of a trial into one of three categories.

A. Low risk of bias: all the validity criteria met.

B. Moderate risk of bias: one or more validity criteria partly met but none not met.

C. High risk of bias: one or more criteria not met.

Measures of treatment effect

Relative risk (RR) estimations with 95% confidence intervals (CI) were used for binary outcomes. Weighted mean difference (WMD) estimations with 95% CI were used for continuous outcomes. All analyses included all participants in the treatment groups to which they were allocated (intention-to-treat analysis).

Dealing with missing data

The authors of included studies were contacted to supply missing data. Missing data and drop-outs or attrition were assessed for each included study and the extent to which the results and conclusions of the review could be altered by the missing data were assessed and discussed. If less than 70% of patients allocated to the treatments were reported on at the end of the trial, for a particular outcome, those data were considered to be prone to bias.

Assessment of heterogeneity

Clinical heterogeneity were assessed by comparing the distribution of important participant factors between trials (age, underlying hematological malignancy, phase of treatment), and trial

factors (randomization concealment, blinding of outcome assessment, losses to follow up, vaccine regimens). Statistical heterogeneity was assessed by examining the I^2 statistic (Deeks 2009), a quantity which approximately describes the proportion of variation in point estimates that is due to heterogeneity rather than sampling error. We followed the guide on interpretation of the I^2 statistic as suggested by the Cochrane Handbook:

- 0% to 40%, might not be important;
- 30% to 60%, may represent moderate heterogeneity;
- 50% to 90%, may represent substantial heterogeneity;
- 75% to 100%, considerable heterogeneity.

In addition, a Chi^2 test of homogeneity was employed to determine the strength of evidence that heterogeneity was genuine. If significant heterogeneity ($P < 0.1$) was present, trials would be investigated for possible explanations. Sensitivity analyses excluding outlying results would be performed.

Assessment of reporting biases

Funnel plots (estimated differences in treatment effects against their standard errors) would be drawn if sufficient studies (more than 10) were found. Asymmetry could be due to publication bias but could also be due to a relationship between trial size and effect size. In the event that a relationship was found, clinical diversity of the studies would be examined (Sterne 2009).

Data synthesis

Where the interventions were the same, or similar enough, we would synthesized results in a meta-analysis if there was no important clinical heterogeneity. Meta-analyses would be performed using a fixed-effect model (for example the generic inverse variance method for survival data outcomes and the Mantel-Haenszel method for dichotomous data outcomes).

Subgroup analysis and investigation of heterogeneity

If data permitted, we would conduct subgroup analyses for:

1. different age groups (younger than 12 years, 12 to 18 years, older than 18 years);
2. different types of underlying hematological malignancies (acute leukemia, chronic leukemia, lymphoma, etc);
3. different phases of therapy (before chemotherapy, during intensive chemotherapy, during maintenance chemotherapy, post-therapy);
4. whether patients had or had not received hematopoietic stem cell transplant;
5. whether previous similar vaccines have been given (yes, no).

Sensitivity analysis

Sensitivity analyses would be conducted to assess the impact of study quality. These would include:

1. all studies;
2. only those studies with adequate allocation concealment.

Sensitivity analyses would also be conducted to assess the impact of heterogeneity, by excluding those studies with outlying results.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of ongoing studies.

Results of the search

The search of CENTRAL (*The Cochrane Library*), MEDLINE, EMBASE and CINAHL yielded 194, 125, 326 and 4 results respectively. The search of other sources yielded one additional study. There were a total of 565 articles for screening after duplicates were removed; 557 studies were excluded based on information in the title or abstract. Full texts of the remaining eight studies were further assessed for eligibility and were included (Table 1). There was one additional RCT that had just completed recruitment and analysis results are pending (NCT01016548). This was therefore excluded from further analyses in the current review.

Included studies

Altogether, eight RCTs met the inclusion criteria (Musto 1997; Parkkali 1997; Redman 1997; Hata 2002; Hsieh 2002; Ljungman 2005; Safdar 2006; Esposito 2010). Details of the included studies are given in the 'Characteristics of included studies' table and are summarized below.

The eight trials included a total of 593 people with hematological malignancies, with 305 in the intervention groups and 288 in the control groups. Two of the trials evaluated the efficacy of heat-inactivated varicella zoster virus (VZV) vaccines (Redman 1997; Hata 2002). Five trials evaluated influenza vaccines (Musto 1997; Hsieh 2002; Ljungman 2005; Safdar 2006; Esposito 2010). In one of these trials, the patients were randomized to three different intervention groups (with nine, six and six participants) of three different doses of the recombinant vaccine and one control group (with six participants) of the standard vaccine. One trial evaluated inactivated poliovirus (IPV) vaccine (Parkkali 1997). There were no randomized controlled trials on other viral vaccines in patients with hematological malignancies.

Trials on heat-inactivated varicella zoster vaccine

Both of the VZV vaccine trials compared inactivated VZV vaccine with conventional care alone or placebo (Redman 1997; Hata 2002). The first trial included patients who had lymphoma and were scheduled for autologous stem cell transplantation (Hata 2002) while the second trial included patients with leukemia or lymphoma who were to receive autologous or allogeneic stem cell transplantation (Redman 1997). In the first trial, the patients in the intervention group received four doses of VZV vaccine, with the first dose given within the 30 days before stem cell transplantation (SCT), and subsequent doses given at 30, 60, and 90 days after SCT (Hata 2002). Patients in the control group received conventional care without VZV vaccine.

The second trial actually included two protocols in two different study periods (Redman 1997). In the first study protocol in 1993, the patients in the intervention group received a single dose of VZV vaccine at one month post-SCT. In the second study protocol in 1994 to 1995, the patients in the intervention group were given three doses of VZV vaccine at one, two and three months post-SCT.

The first trial (Hata 2002) included patients 18 to 60 years old while the second trial (Redman 1997) included patients aged 18 to 49 years. The first trial recruited 119 patients, with 59 randomly allocated to the intervention group and 60 allocated to the control group (Hata 2002). The baseline characteristics of patients in both groups were not entirely comparable because there were more patients with Hodgkin's disease in the control group and more post-first remission non-Hodgkin lymphoma patients in the intervention group. In the second trial, 28 patients were recruited to the first protocol, with 14 allocated to the intervention group and 14 to the control group (Redman 1997). The second protocol included 47 participants, with 24 in the intervention group and 23 in the control group. The baseline characteristics of the patients in the two groups were not entirely comparable because there were more patients with chronic myeloid leukemia in the control group in the second protocol.

All included patients in both trials had to be seropositive for VZV before SCT but there was no history of zoster or exposure to VZV within one month after SCT. In both trials, the baseline VZV titre of the participants were between 1:256 and 1:16384 and did not differ between the intervention and control groups. Both trials reported outcomes of incidence of herpes zoster, mortality due to varicella or herpes zoster, all-cause mortality, frequency of patients with a 4-fold rise in antibody titres and in vitro mean lymphocyte stimulation index. Both trials also evaluated cytokine production but the results were presented in different ways. The first trial evaluated the percentage of CD4+ T-cells that produced TNF-alpha or Interferon-gamma (Hata 2002) while the second trial reported the concentrations of interferon-gamma and interleukin-10 (Redman 1997). The zoster severity score was reported in the second trial (Redman 1997) but there was no data on complications and hospitalization due to zoster infection in either trial. Frequencies of systemic and local adverse effects were reported in both trials.

Trials on influenza vaccines

Two of the influenza vaccine trials compared the standard trivalent inactivated influenza vaccine with no vaccine (Musto 1997; Esposito 2010). One trial compared the standard split virus trivalent inactivated influenza vaccine with three different doses of a recombinant baculovirus-expressed trivalent influenza vaccine (Safdar 2006). Another trial compared two doses of trivalent inactivated influenza vaccine with a single dose (Ljungman 2005). The remaining trial compared two different schedules involving two doses of trivalent inactivated influenza vaccine (Hsieh 2002). The trial by Esposito only included children who had acute lymphoblastic leukemia or lymphoma (Esposito 2010). The trial by Musto only included adults who had multiple myeloma (Musto 1997). The trial by Safdar only included adult patients with non-Hodgkin's lymphoma (Safdar 2006). The trial by Ljungman included patients with leukemia, lymphoma, multiple myeloma or Waldenstrom's macroglobulinemia (Ljungman 2005). The trial by Hsieh only included children with acute lymphoblastic leukemia (Hsieh 2002). Patients in these trials had received chemotherapy with or without antibody therapy (rituximab, alemtuzumab or bortezomib).

The trial by Esposito randomly allocated 182 patients to receive one to two doses (depending on age) of influenza vaccine or no vaccine after stratifying into two groups according to the length of time after completion of chemotherapy (< 6 months or 6 to 24 months) (Esposito 2010). The trial by Musto randomly allocated 50 patients who were undergoing conventional chemotherapy in November 1995 to either receive or not receive influenza vaccine (Musto 1997). The trial by Safdar randomly allocated 27 patients to three intervention groups of recombination vaccine at different doses (15 μg hemagglutinin protein/0.5 ml, 45 μg/0.5 ml and 135 μg/0.5 ml) and one control group of standard vaccine at 15 μg hemagglutinin protein/0.5 ml (Safdar 2006). The timing of vaccination in relation to diagnosis and completion of chemotherapy was variable but was at least three months after chemotherapy. The trial by Ljungman randomly allocated 70 patients to a 2-dose regime given four weeks apart or a 1-dose regime (Ljungman 2005). Again the timing of vaccination in relation to diagnosis and completion of chemotherapy was variable but was during or within six months of completion of chemotherapy. The trial by Hsieh randomly allocated 25 patients to two different schedules of two doses of vaccine (Hsieh 2002). In protocol one (intervention group), the first dose of vaccine was given with re-induction chemotherapy and a second dose was given four weeks later. In protocol two (control group), the first dose of vaccine was given four weeks before re-induction chemotherapy and a second dose was given with re-induction chemotherapy four weeks later.

Previous vaccination history of the participants and baseline an-

tibody levels were not mentioned in any of the five trials. The baseline characteristics of the participants were not presented in three trials (Musto 1997; Hsieh 2002; Safdar 2006). In one of the remaining trials, the baseline characteristics of the participants in the intervention and the control groups were not entirely comparable because patients in the control group had a higher median age (Ljungman 2005). The trials by Esposito and Musto both reported the frequency of upper respiratory infections (Musto 1997; Esposito 2010). The trial by Esposito also reported the frequency of lower respiratory tract infections, at least one infection other than influenza-like illness, at least one hospitalization, the number of upper and lower respiratory tract infections, the number of days with fever, the number of antibiotic courses and the number of days lost from school (Esposito 2010). The trial by Musto also reported the frequency of upper respiratory illnesses, pneumonia, mortality and hospitalization due to pneumonia, the duration of febrile respiratory episodes and the number of non-programmed visits to hospital (Musto 1997). Three trials evaluated the frequency of patients with a 4-fold rise in antibody titres four weeks after vaccination (Hsieh 2002; Ljungman 2005; Safdar 2006). The trial by Ljungman also reported the frequency of patients with protective antibodies (titre > 40) (Ljungman 2005) while the trial by Hsieh reported the frequency of patients with seroconversion (increase in titre from below 40 to no less than 40) (Hsieh 2002). Frequency of adverse effects were mentioned in four trials (Musto 1997; Hsieh 2002; Safdar 2006; Esposito 2010), but in three trials these frequencies were not separately reported for the intervention and the control groups (Musto 1997; Hsieh 2002; Safdar 2006). There were no data on incidence of or mortality from influenza infection, all-cause mortality, or complications and hospitalization due to influenza infection in any of the trials.

Trial on inactivated poliovirus vaccine (IPV)

There was only one included RCT on IPV vaccine (Parkkali 1997). The trial compared two different dosing schedules of IPV vaccine for patients, aged above 16 years, with hematological malignancies and who had received matched sibling SCT. The authors aimed to test whether earlier IPV vaccination after SCT induced similar immunological responses compared to delayed vaccination post-SCT. Patients in the intervention group in this trial received IPV vaccine subcutaneously at 6, 8 and 14 months after SCT while the control group received the vaccine at 18, 20 and 26 months post-SCT. Forty-five participants were randomized, with 23 allocated to the early vaccination arm and 22 to the late vaccination arm. There were no differences in the gender ratio or median age between the two groups. However, there were more patients with chronic myeloid leukemia in the late vaccination group and more patients with chronic graft-versus-host disease in the early vaccination group. The vaccination history of the participants was not reported. The geometric mean titres of the participants before vaccination ranged from 180 to 1029 for the three poliovirus serotypes and were significantly higher in the early vaccination group compared to the late vaccination group. Outcomes reported were geometric mean antibody titre and the frequency of patients with a 4-fold rise in protective antibodies.

Risk of bias in included studies

Seven of the eight included trials had high risk of bias (Musto 1997; Parkkali 1997; Redman 1997; Hata 2002; Hsieh 2002; Ljungman 2005; Esposito 2010) and one trial had moderate risk of bias (Safdar 2006) by our pre-defined criteria.

Allocation

None of the trials reported on randomization sequence generation or allocation concealment and hence whether the trials were at risk of selection bias is unclear.

Blinding

Four trials blinded the treating physicians (Redman 1997; Hata 2002; Safdar 2006; Esposito 2010) but only one trial blinded the patients as well (Safdar 2006). Blinding of outcome assessors was unknown in five trials (Parkkali 1997; Redman 1997; Hata 2002; Safdar 2006; Esposito 2010) and not used in the remaining three trials (Musto 1997; Hsieh 2002; Ljungman 2005).

Incomplete outcome data

The trial by Hata (Hata 2002) reported nine drop-outs (15.3%) in the intervention group, including two patients who withdrew at 30 days for unexplained reasons. For the other seven patients, the reasons for drop-out were probably unrelated to vaccination (six did not undergo transplantation after randomization and one withdrew because of disease progression). There were altogether 16 patients in the intervention group (27.1%) who did not complete the intended four doses of vaccine. There were two patient withdrawals (3.3%) in the control group, both because of no transplantation after randomization. For individual outcomes, the amount of missing data was variable and up to 67.8% for two outcomes (the proportion of CD4+ T-cells that produced TNF-alpha and the proportion of CD4+ T-cells that produced interferon-gamma). In the trial by Redman (Redman 1997), there was no drop-out reported but missing data occurred in up to 73.9% in the intervention and the control groups in one of the outcomes (post-stimulation interleukin-10 concentrations at 12 months). In the trial by Hsieh (Hsieh 2002), no drop-out was reported but missing data occurred in up to 72.7% in the control group in two of the outcomes (seroconversion in influenza A/H1 antibody after one and two doses of vaccine). In the trials by Musto (Musto 1997) and Ljungman (Ljungman 2005), no drop-out was reported but reported data were insufficient to assess the amount of missing data.

In the trial by Esposito (Esposito 2010) and Safdar (Safdar 2006), no drop-out was reported and data on outcomes were complete. In the trial by Parkkali (Parkkali 1997), nine drop-outs (34.6%) occurred in the treatment group, including two who died before vaccination, one who had not received the vaccine and six losses to follow up for unknown reasons. There were 12 drop-outs (41.4%) in the control group, including six who died before vaccination, one who relapsed and was not vaccinated, and five losses to follow up with unknown reasons. Missing data occurred in up to 31.8% in the control group for several outcomes (4-fold rise of antibody titres to poliovirus types 1, 2 and 3; and geometric mean titre of poliovirus antibody to poliovirus types 1, 2 and 3).

Other potential sources of bias

None of the included trials mentioned the use of intention-to-treat analysis. In addition, the intervention and the control groups were not entirely comparable at baseline in four trials (Parkkali 1997; Redman 1997; Hata 2002; Ljungman 2005). In three trials, the comparability of the two groups at baseline was doubtful because of inadequate information (Musto 1997; Hsieh 2002; Safdar 2006).

Effects of interventions

There were only trials for evaluation of varicella zoster vaccine, influenza vaccine and poliomyelitis virus vaccine. There were no included trials evaluating vaccines for hepatitis A, hepatitis B, measles, mumps or rubella.

Trials on varicella zoster vaccine (VZV)

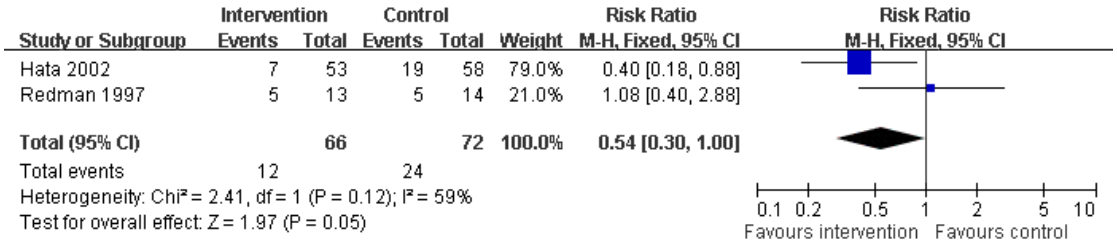
VZV vaccine versus no vaccine

Primary outcome

Incidence of herpes zoster

VZV vaccine seemed to be associated with a reduced risk of herpes zoster (RR 0.54, 95% CI 0.30 to 1.00, P = 0.05) when the results of the two included trials (Redman 1997; Hata 2002) were combined, but this was not statistically significant (Analysis 1.1; Figure 1). There appeared to be heterogeneity between the two included trials, with one trial showing a dramatic difference in the incidence of herpes zoster between the intervention and the control groups (Hata 2002) and the other trial showing a remarkably similar incidence in the two groups (Redman 1997). This might be explained by the marked differences between the participants (different age groups, underlying diseases, types of transplants received), which is more heterogeneous in the trial showing the negative result (Redman 1997). There were also differences between the trials with respect to co-interventions, acyclovir not routinely given in one trial (Hata 2002) but given during a herpes simplex virus (HSV) outbreak in another trial (Redman 1997), and the schedules of the vaccines given, which may influence the efficacy of the vaccines.

Figure 1. Forest plot of comparison: 1 VZV vaccine vs. no vaccine, outcome: 1.1 Incidence of herpes zoster.



Secondary outcomes

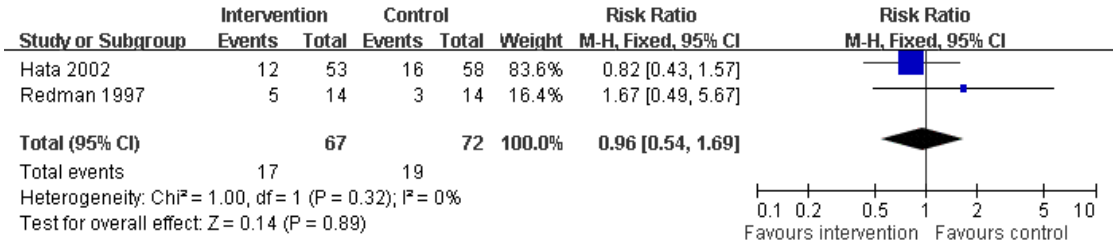
Mortality due to infection

There was no reported mortality due to varicella or herpes zoster in any of the treatment groups in the two included trials (Redman 1997; Hata 2002) (Analysis 1.2).

All-cause mortality

There was no significant differences in all-cause mortality between the intervention and the control groups (Analysis 1.3; Figure 2) when the results of the two included trials were combined (Redman 1997; Hata 2002).

Figure 2. Forest plot of comparison: 1 VZV vaccine vs. no vaccine, outcome: 1.3 All cause mortality.

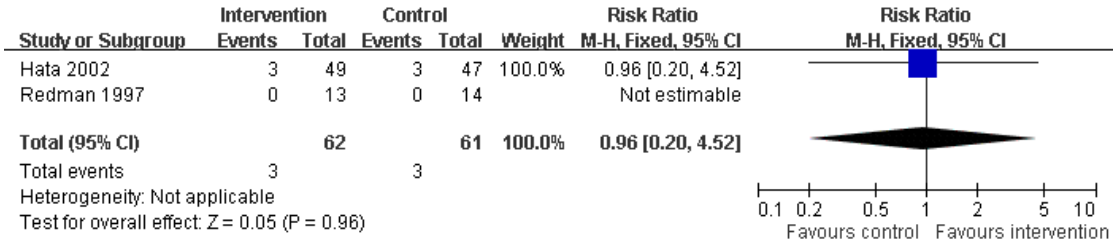


In vitro immune response

Four-fold rise in VZV antibody titre

There was no significant difference between the intervention and the control groups in the frequency of participants who had at least a 4-fold rise in VZV antibody titre when the results of the two trials were combined (Redman 1997; Hata 2002) (Analysis 1.4; Figure 3).

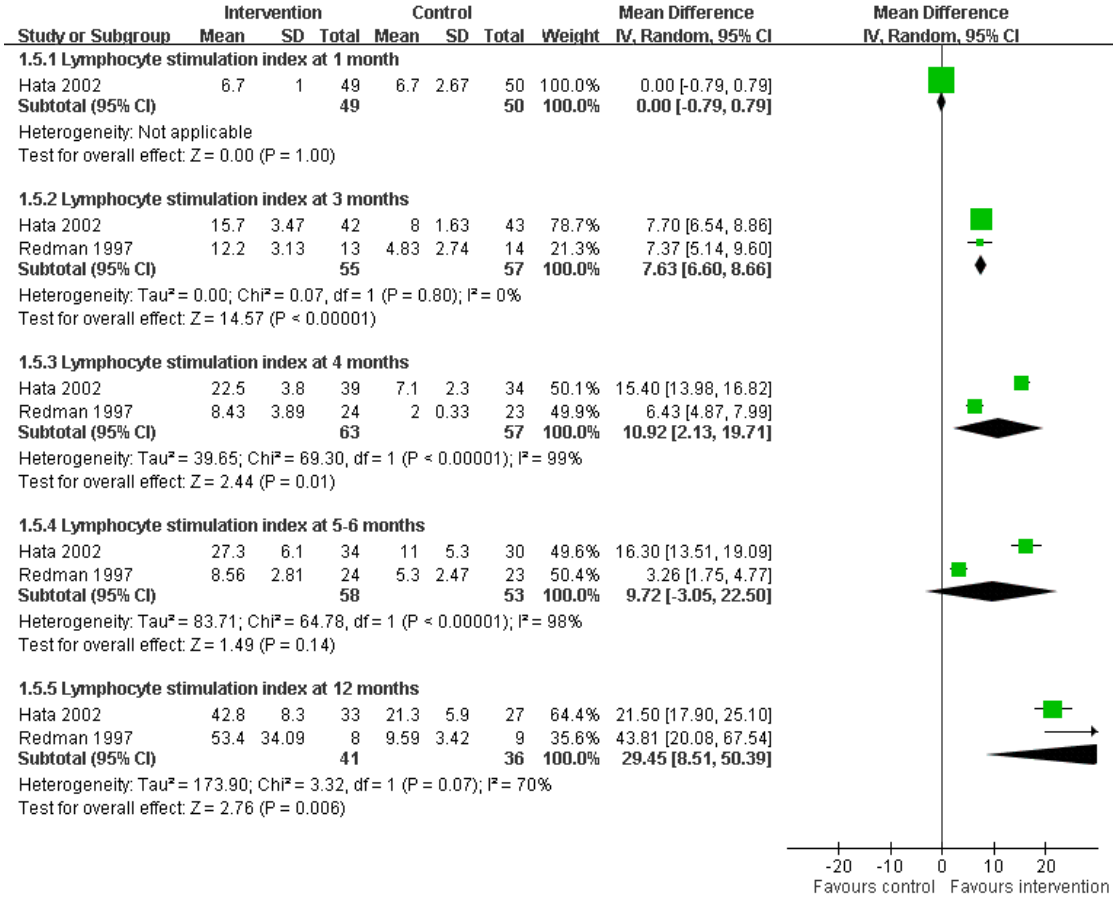
Figure 3. Forest plot of comparison: 1 VZV vaccine vs. no vaccine, outcome: 1.4 4-fold rise in VZV antibody titre.



Lymphocyte stimulation index

When results of the two trials were combined (Redman 1997; Hata 2002), the lymphocyte stimulation indices were significantly higher in the intervention group compared to the control group when measured at three months (MD 7.63, 95% CI 6.60 to 8.66, P < 0.00001), four months (MD 10.92, 95% CI 2.13 to 19.71, P = 0.01) or 12 months (MD 29.45, 95% CI 8.51 to 50.39, P = 0.006) but not at one month or five to six months after the vaccination (Analysis 1.5; Figure 4).

Figure 4. Forest plot of comparison: 1 VZV vaccine vs. no vaccine, outcome: 1.5 Lymphocyte stimulation index.



Percentages of CD4+ T-cells producing TNF-alpha or interferon-gamma

One trial (Hata 2002) reported these outcomes and showed higher percentages of CD4+ T-cells producing TNF-alpha (MD 31.00, 95% CI 24.75 to 37.25, P < 0.00001) (Analysis 1.6) or interferon-gamma (MD 22.00, 95% CI 16.57 to 27.43, P < 0.00001) in the intervention group compared to the control group (Analysis 1.7).

Post-stimulation interferon-gamma or interleukin-10 concentrations

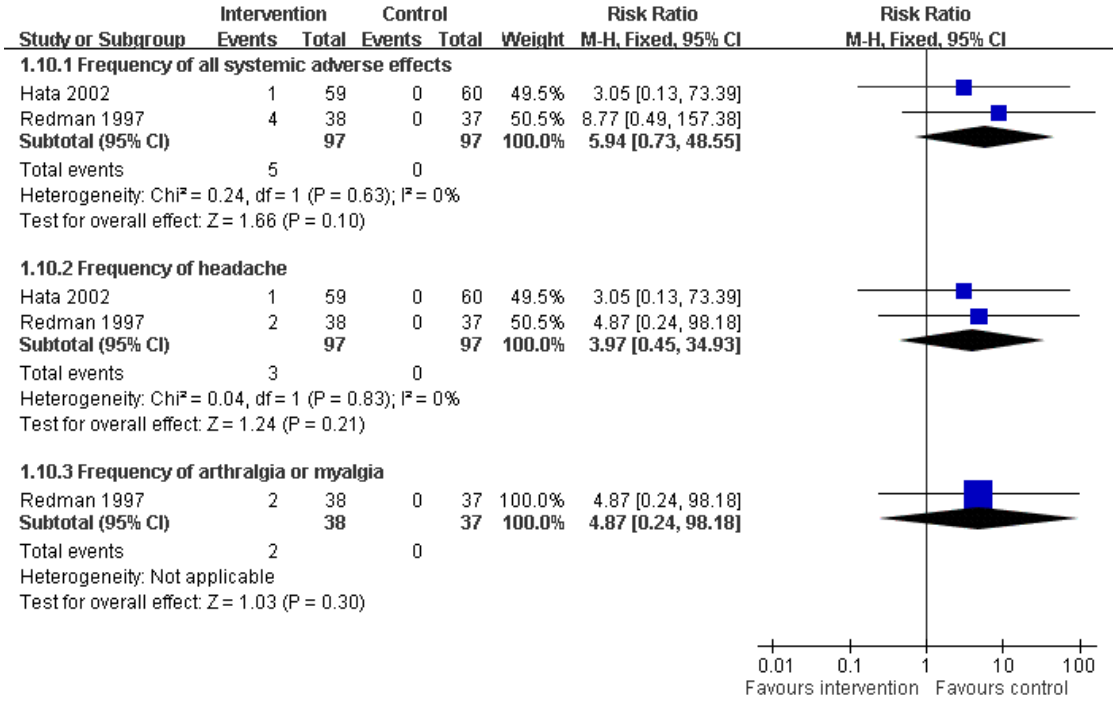
One trial (Redman 1997) evaluated these cytokine levels and found that the post-stimulation interferon-gamma concentration in the intervention group was significantly higher at one month (MD 8.00, 95% CI 2.39 to 13.61, P = 0.005) and four months (MD 74.00, 95% CI 22.75 to 125.25, P = 0.005), but significantly lower at two months (MD -107.00, 95% CI -206.58 to -7.42, P = 0.04) and not significantly different from the control group at three months, five months and 12 months (Analysis 1.8). The post-stimulation interleukin-10 concentration in the intervention group was significantly lower at one month (MD -33.00, 95% CI -56.78 to -9.22, P = 0.007) and four months (MD -56.00, 95% CI -97.22 to -14.78, P = 0.008) but not at two months, three months, five months and 12 months (Analysis 1.9).

Frequency of adverse effects

Frequency of systemic adverse effects

When the results of the two trials were combined (Redman 1997; Hata 2002) there seemed to be more systemic adverse effects in the intervention group, which did not reach statistical significance (RR 5.94, 95% CI 0.73 to 48.55, P = 0.1) (Analysis 1.10; Figure 5).

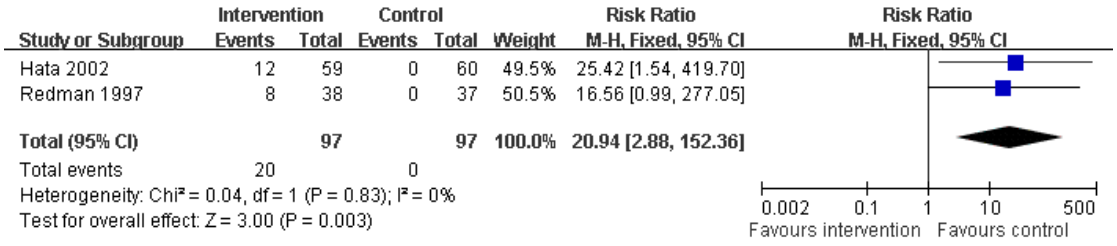
Figure 5. Forest plot of comparison: 1 VZV vaccine vs. no vaccine, outcome: 1.10 Frequency of systemic adverse effects.



Frequency of local adverse effects

After combining the results of the two trials (Redman 1997; Hata 2002), significantly more patients in the intervention group experienced local adverse effects at the injection site (RR 20.94, 95% CI 2.88 to 152.36, P = 0.003) (Analysis 1.11; Figure 6).

Figure 6. Forest plot of comparison: 1 VZV vaccine vs. no vaccine, outcome: 1.11 Frequency of local adverse effects.



There were no data on other pre-defined secondary outcomes (incidence of complications or severe infections or rate of hospitalization).

Additional outcomes

Severity score of herpes zoster

One trial (Redman 1997) reported a significantly higher herpes zoster severity score in patients who developed herpes zoster in the control group compared to the intervention group. The mean difference in the score was 2.6 points out of a maximum of 20 points (MD 2.60, 95% CI 0.94 to 4.26, P = 0.002) (Analysis 1.12). The other included trial just commented that the severity of the herpes zoster did not differ between the intervention and control groups and actual data were not available (Hata 2002).

Trials on influenza vaccines

Influenza vaccine versus no vaccine

Primary outcome

Incidence of influenza

There was no data on this pre-defined primary outcome from the included trials (Musto 1997; Esposito 2010).

Secondary outcomes

Mortality due to infection (pneumonia)

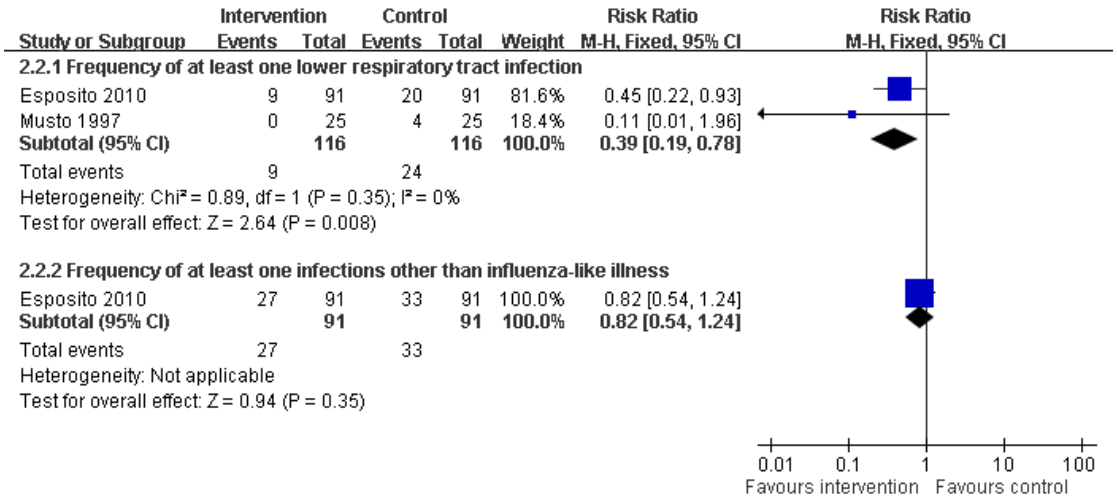
The mortality due to pneumonia was reported in one included trial (Musto 1997), which was not significantly different between the intervention and control groups (Analysis 2.1).

Incidence of complications

Frequency of at least one lower respiratory infection

When the results of the two included trials were combined (Musto 1997; Esposito 2010), the risk of at least one lower respiratory infection was significantly lower in the intervention group (RR 0.39, 95% CI 0.19 to 0.78, P = 0.008) (Analysis 2.2; Figure 7).

Figure 7. Forest plot of comparison: 2 Influenza vaccine vs. no vaccine, outcome: 2.2 Incidence of complications.



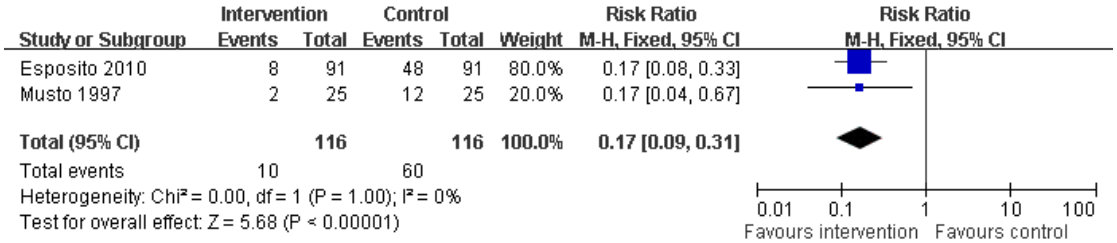
Frequency of at least one infection other than influenza-like illness

One trial (Esposito 2010) reported the number of patients with at least one infection other than influenza-like illness and found no significant difference between the intervention and control groups (Analysis 2.2).

Rate of hospitalization

When the results of the two included trials (Musto 1997; Esposito 2010) were combined, the hospitalization rate was significantly lower in the intervention group (RR 0.17, 95% CI 0.09 to 0.31, P < 0.00001) (Analysis 2.3; Figure 8). One included trial (Musto 1997) also reported that the number of non-programmed visits to hospital was significantly lower in the intervention group compared to the control group (0.5 versus 2.3, P < 0.001). However, the results could not be tabulated or verified.

Figure 8. Forest plot of comparison: 2 Influenza vaccine vs. no vaccine, outcome: 2.3 Rate of hospitalization.

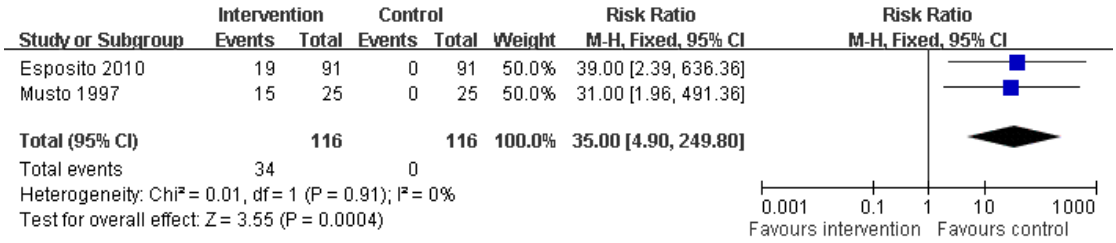


Frequency of adverse effects

Frequency of at least one adverse effects

When the results of the two included trials were combined (Musto 1997; Esposito 2010), the frequency of at least one adverse effects was significantly higher in the intervention group (RR 35, 95% CI 4.9 to 249.8, P = 0.0004) (Analysis 2.4; Figure 9).

Figure 9. Forest plot of comparison: 2 Influenza vaccine vs. no vaccine, outcome: 2.4 Frequency of at least one adverse effects.



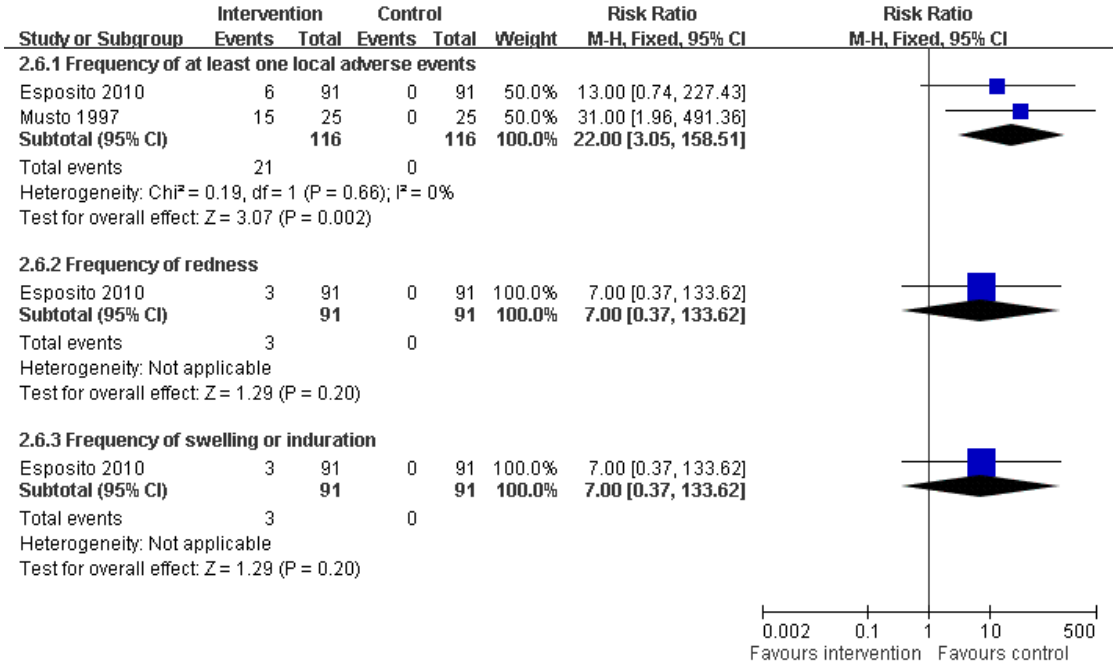
Frequency of systemic adverse effects

One of the included trials (Esposito 2010) reported the frequencies of different systemic adverse effects and showed a significantly higher frequency of irritability in the intervention group (RR 19, 95% CI 1.12 to 321.07, P = 0.04) (Analysis 2.5). The frequency of other systemic adverse effects, including fever, decreased appetite, rhinitis, cough and vomiting, were not significantly different between the intervention and control groups (Analysis 2.5).

Frequency of local adverse effects

When the results of the two included trials were combined (Musto 1997; Esposito 2010), the frequency of at least one local adverse effect was significantly higher in the intervention group (RR 22, 95% CI 3.05 to 158.51, P = 0.002) (Analysis 2.6; Figure 10). One trial (Esposito 2010) reported the frequency of different local adverse effects (redness, swelling or induration), which were not significantly different between the intervention and control groups (Analysis 2.6).

Figure 10. Forest plot of comparison: 2 Influenza vaccine vs. no vaccine, outcome: 2.6 Frequency of local adverse effects.



There were no data on other pre-defined secondary outcomes (all-cause mortality, incidence of severe infections or in vitro immune response).

Additional outcomes

Frequency of at least one upper respiratory infections

When the results of the two included trials were combined (Musto 1997; Esposito 2010), participants in the intervention group had a significantly lower risk of experiencing at least one upper respiratory infection (RR 0.56, 95% CI 0.44 to 0.72, P < 0.00001) (Analysis 2.7).

Number of upper respiratory tract infections

One included trial (Esposito 2010) reported that the intervention group had significantly fewer upper respiratory tract infections (MD -1.23, 95% CI -1.52 to -0.94, P < 0.00001) (Analysis 2.8).

Number of lower respiratory tract infections

One included trial (Esposito 2010) reported that the intervention group had significantly fewer lower respiratory tract infections (MD -0.3, 95% CI -0.44 to -0.16, P < 0.00001) (Analysis 2.9).

Number of infections other than influenza-like illness

One included trial (Esposito 2010) reported the outcome of number of infections other than influenza-like illness, which was not significantly different between the intervention and control groups (Analysis 2.10).

Number of days with fever

One included trial (Esposito 2010) reported that the intervention group had significantly fewer days with fever (MD -1.7, 95% CI -2.25 to -1.15, P < 0.00001) (Analysis 2.11).

Number of antibiotics courses

One included trial (Esposito 2010) reported that the intervention group received significantly fewer antibiotics courses (MD -1.85, 95% CI -2.3 to -1.4, P < 0.00001) (Analysis 2.12).

Number of days lost from school

One included trial (Esposito 2010) reported that the intervention group had significantly lower number of days lost from school (MD -4.94, 95% CI -5.65 to -4.23, P < 0.00001) (Analysis 2.13).

Duration of febrile respiratory episodes

One included trial (Musto 1997) reported that the mean duration of febrile respiratory episodes was significantly lower in the intervention group compared to the control group (5 days versus 12 days, P < 0.001). However, since no standard deviation, CI or actual P value was provided the results could not be tabulated or verified.

Influenza vaccine, two doses versus single dose

Primary outcome

Incidence of influenza

There were no data on this pre-defined primary outcome from the included trial (Ljungman 2005).

Secondary outcomes

In vitro immune response

Four-fold rise in antibody titre

In the trial comparing two doses to one dose of influenza vaccine (Ljungman 2005), there was no significant difference between the two groups in the proportion of patients who attained a 4-fold rise in antibody titres to any of the three components (A/H3, A/H1, B) of the vaccine (Analysis 3.1).

Antibody titre above 1:40

Consistent with the above results, there was no significant difference between the intervention and the control groups in the proportion of patients who attained antibody titres above 1:40 to any of the three components (A/H3, A/H1, B) of the vaccine (Analysis 3.2).

There were no data on other pre-defined secondary outcomes (mortality due to infection, all-cause mortality, incidence of complications or severe infections, rate of hospitalization or frequency of adverse effects).

Recombinant influenza vaccine versus standard influenza vaccine

Primary outcome

Incidence of influenza

There were no data on this pre-defined primary outcome from the included trial (Safdar 2006).

Secondary outcomes

In vitro immune response

Four-fold rise in antibody titre

In the trial comparing recombinant influenza vaccine to standard inactivated influenza vaccine (Safdar 2006), when the dose of 15 μg recombinant vaccine was compared to control vaccine, there was no significant difference between the two groups in the proportion of patients who attained 4-fold rise in antibody titres to any of the three components (A/H3, A/H1, B) of the vaccine, whether this was measured by hemoagglutination inhibition (Analysis 4.1), neutralizing antibody (Analysis 4.2) or both results combined (Analysis 4.3).

When the dose of 45 μg recombinant vaccine was compared to control vaccine, there was generally no significant difference between the intervention and the control groups in the proportion of patients who attained a 4-fold rise in antibody titres to any of the three components (A/H3, A/H1, B) of the vaccine, whether this was measured by hemoagglutination inhibition (Analysis 5.1), neutralizing antibody (Analysis 5.2) or both results combined (Analysis 5.3). The only exception was that there was a marginally significantly higher frequency of patients in the intervention group who attained a 4-fold rise in neutralizing antibody titre to the A/H3 component (RR 4.33, 95% CI 1.03 to 18.17, P = 0.04) (Analysis 5.2).

When the dose of 135 μg recombinant vaccine was compared to control vaccine, there was no significant difference between the intervention and the control groups in the proportion of patients who attained a 4-fold rise in antibody titres to any of the three components (A/H3, A/H1, B) of the vaccine, whether this was measured by hemoagglutination inhibition (Analysis 6.1), neutralizing antibody (Analysis 6.2) or both results combined (Analysis 6.3).

There were no data on other pre-defined secondary outcomes (mortality due to infection, all-cause mortality, incidence of complications or severe infections, rate of hospitalization or frequency of adverse effects).

Comparison of different influenza vaccine schedules: first dose versus second dose given with re-induction

Primary outcome

Incidence of influenza

There were no data on this pre-defined primary outcome from the included trial (Hsieh 2002).

Secondary outcomes

In vitro immune response

Four-fold rise in antibody titre

In the trial comparing different influenza schedules of two doses (Hsieh 2002), there was no significant difference between the two groups in the proportion of patients who attained a 4-fold rise in antibody titres to any of the three components (A/H3, A/H1, B) of the vaccine after the first dose (Analysis 7.1) or the second dose (Analysis 7.2).

Seroconversion

Consistent with the above results, there was also no significant difference between the two groups in the proportion of patients who achieved seroconversion (increase of antibody titre from below 40 to no less than 40) to any of the three components (A/H3, A/H1, B) of the vaccine after the first dose (Analysis 7.3) or the second dose (Analysis 7.4).

There were no data on other pre-defined secondary outcomes (mortality due to infection, all-cause mortality, incidence of complications or severe infections, rate of hospitalization or frequency of adverse effects).

Trial on inactivated poliovirus vaccine

Early schedule versus late schedule

Primary outcome

Incidence of poliomyelitis

There were no data on this pre-defined primary outcome from the included trial (Parkkali 1997).

Secondary outcomes

In vitro immune response

Four-fold rise in antibody titre

In the trial comparing early (starting six months after stem cell transplant) and late (starting 18 months after stem cell transplant) schedules of inactivated poliovirus vaccine in three doses (Parkkali 1997), there was generally no significant difference between the two groups in the proportion of patients who attained a 4-fold rise in antibody titres to any of the three poliovirus serotypes after the first dose (Analysis 8.1), the second dose (Analysis 8.2) or the third dose of the vaccine (Analysis 8.3). The only exception was that there were significantly fewer patients in the early schedule group who attained a 4-fold rise in antibody titre to polio type 2 (RR 0.34, 95% CI 0.15 to 0.8, P = 0.01) and type 3 (RR 0.57, 95% CI 0.34 to 0.96, P = 0.03) after the first dose (Analysis 8.1).

Geometric mean titre of protective antibody

The authors reported the geometric mean titres of protective antibody to poliovirus types 1, 2 and 3 before and after each dose of vaccination. There was no significant difference between the two groups in any of these antibody titres. Since no standard deviation, CI or actual P value for these geometric means were provided, the results could not be tabulated or verified.

There were no data on other pre-defined secondary outcomes (mortality due to infection, all-cause mortality, incidence of complications or severe infections, rate of hospitalization or frequency of adverse effects).

Assessment of reporting biases

Since there were at most only two trials reporting on the same comparisons, funnel plots were not constructed.

Subgroup analysis and investigation of heterogeneity

Since no individual or stratified data on pre-defined subgroups were available, subgroup analysis was not performed. Since there were at most only two trials reporting on the same comparisons, formal investigation of heterogeneity was impossible.

Sensitivity analyses

Sensitivity analyses were not performed to assess the impact of including studies of different quality since there were only two trials at most for all comparisons. Similarly, sensitivity analyses were not performed to assess the impact of heterogeneity.

DISCUSSION

Summary of main results

In the current review on the use of viral vaccines for patients with hematological malignancies, evidence from randomized controlled trials is limited and available for only three viral diseases, namely varicella zoster virus (VZV), influenza virus and poliovirus. There are no included trials evaluating vaccines for hepatitis A, hepatitis B, measles, mumps or rubella. Only the two trials on VZV vaccine reported our pre-defined primary outcome (Redman 1997; Hata 2002). All trials reported some of the pre-defined secondary outcomes. Two trials on VZV vaccine (Redman 1997; Hata 2002) and one trial on influenza vaccine (Esposito 2010) also reported some additional outcomes not pre-defined in the current review.

There are only two small RCTs evaluating heat-inactivated VZV vaccine compared to no vaccine for patients with leukemia or lymphoma (Redman 1997; Hata 2002). The combined results of the two trials suggest that VZV vaccine might be effective in preventing herpes zoster or reducing the severity of herpes zoster. However, the immunogenicity of the vaccine in these patients is inconclusive. The VZV vaccine is associated with significantly more local adverse effects. Systemic adverse effects such as headache, arthralgia and myalgia also appear to be more common in vaccine recipients, although this was not statistically significant.

Although there are five RCTs evaluating influenza vaccines for patients with hematological malignancies, the objectives of the trials and the target patient populations are very heterogeneous. The results from two RCTs (Musto 1997; Esposito 2010) could be combined. These two trials compared influenza vaccine with no vaccine in entirely different patient groups, one in adults with multiple myeloma undergoing chemotherapy and the other in children who had finished chemotherapy treatment for leukemia or lymphoma. The pooled results suggest that inactivated influenza vaccine might be effective in preventing upper and lower respiratory infections and reducing hospitalization. One trial (Esposito 2010) also suggested that the vaccine may reduce the number of days with fever, the number of antibiotics courses and the number of days lost from school. However, it is uncertain whether the reported respiratory illnesses and hospitalizations were related to influenza or not; and there is no conclusive evidence that influenza vaccine reduces influenza-related mortality in patients with hematological malignancies. The trial comparing two doses with one dose of the influenza vaccine in patients with various hematological malignancies within six months of completion of chemotherapy shows no significant differences in antibody response (Ljungman 2005). The antibody response after different doses of recombinant influenza vaccine was similar to the standard trivalent inactivated influenza vaccine in non-Hodgkin's lymphoma patients who had finished chemotherapy for at least three months (Safdar 2006). The antibody response was also similar whether or not influenza vaccine was given with re-induction chemotherapy in children with acute lymphoblastic leukemia (Hsieh 2002). Systemic and local adverse effects are not uncommon in influenza vaccine recipients, although it is uncertain from the trial reports whether the frequency of adverse effects is different in different types of vaccines or different vaccination schedules.

For inactivated poliovirus vaccine in adult stem cell transplant recipients, the antibody response was generally not significantly different whether the 3-dose vaccination series was started at six months or 18 months post-transplant, although the frequency of patients achieving 4-fold rise in antibody titre tended to be lower with the early schedule (Parkkali 1997). There was no information on adverse effects in the included trial.

The patient population and clinical setting in the included trials were highly variable and therefore a generalizable conclusion is difficult to make. In adults who have received hematopoietic stem cell transplantation for leukemia or lymphoma, VZV vaccination might be effective in preventing herpes zoster (Redman 1997; Hata 2002). Immunogenicity of inactivated poliovirus vaccine is variable and there was no significant difference whether it was given early or late post-SCT (Parkkali 1997). In adults with hematological malignancies undergoing or in the period shortly after chemotherapy, influenza vaccine might reduce upper respiratory infections and hospitalizations (Musto 1997). However, there was no sigificant difference between one and two doses (Ljungman 2005), or between recombinant and standard vaccine (Safdar 2006). In children with acute lymphoblastic leukemia or lymphoma, influenza vaccine given within two years of completon of chemotherapy might reduce upper and lower respiratory infections (Esposito 2010). There was no significant difference whether influenza vaccine was given with re-induction or not during maintenance chemotherapy (Hsieh 2002).

Overall completeness and applicability of evidence

High level evidence on the efficacy and safety of viral vaccines in patients with hematological malignancies is scarce, incomplete and limited to varicella zoster, influenza and poliomyelitis viruses only. There are no included trials evaluating vaccines for hepatitis A, hepatitis B, measles, mumps or rubella. Only the two trials on VZV vaccine reported our pre-defined primary outcome (Redman 1997; Hata 2002). All trials reported some of the pre-defined secondary outcomes. Two trials on VZV vaccine (Redman 1997; Hata 2002) and one trial on influenza vaccine (Esposito 2010) also reported some additional outcomes not pre-defined in the current review. As the type of underlying malignancies and treatments are restricted in many of these trials, the results of these trials cannot be generalized to all patients with hematological malignancies.

VZV vaccine, when given before and after stem cell transplant in adults with lymphoma or leukemia, might be efficacious in reducing the incidence and severity of herpes zoster, which parallels development of certain cell-mediated immunity (Hata 2002;

Redman 1997). Whether VZV vaccine has similar efficacy in patients with other hematological malignancies or patients treated with chemotherapy is uncertain.

Influenza vaccine might be effective in reducing the incidence of upper and lower respiratory infections and hospitalization in adults with multiple myeloma undergoing chemotherapy (Musto 1997) or children with leukemia and lymphoma who finished chemotherapy in the preceding two years (Esposito 2010). However, it was uncertain what proportions of these infections or hospitalizations were caused by influenza. There appears to be no significant difference between one and two doses (Ljungman 2005), recombinant or standard inactivated vaccines (in adults with non-Hodgkin's lymphoma) (Safdar 2006) or scheduling the dose with or without re-induction chemotherapy (in children with acute lymphoblastic leukemia) (Hsieh 2002). However, these negative results might be attributable to inadequate statistical power since only small samples have been studied. In addition, the results cannot be generalized to patients with malignancy types different from patients recruited in these trials.

The only RCT on inactivated poliovirus vaccine compared different starting times of the vaccination series after stem cell transplantation, which demonstrates variable seroresponse to the vaccine that does not differ significantly whether the vaccination was started at six or 18 months post-transplant (Parkkali 1997). Again the sample size was limited and the conclusion may be falsely negative. The results are not applicable to patients other than transplant recipients.

Adverse effects to these viral vaccines are not uncommon, especially local adverse effects, which occur in up to 60% of patients who have received influenza vaccine (Musto 1997). However, no serious adverse effects are reported in the included RCTs. Since the number of patients recruited in each of these RCTs was small, rare serious adverse events might not have been detected.

Quality of the evidence

Most of the RCTs included in the current review are considered to have a high risk of bias and hence the quality of the evidence is low. Most of the trials also focused on laboratory outcomes of immunological response to vaccines instead of clinically relevant outcomes in terms of morbidity or mortality prevented. As a result, whether the surrogate outcomes translate into relevant clinical benefits remains uncertain. All included RCTs recruited only small numbers of patients and only one trial (Hata 2002) pre-calculated the sample size; they therefore lack statistical power in detecting differences between the intervention groups and are susceptible to false negative conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

VZV vaccine might be efficacious in reducing the incidence and severity of herpes zoster when given before and after stem cell transplant in adults with lymphoma or leukemia. Influenza vaccine might be effective in reducing the incidence of upper and lower respiratory infections and hospitalization due to pneumonia in adults with multiple myeloma undergoing chemotherapy and children with leukemia and lymphoma who finished chemotherapy in the preceding two years. However, the quality of evidence supporting these findings is low. Adverse effects to these viral vaccines, both systemic and local, occur frequently although serious adverse effects appear uncommon and most adverse effects are tolerable. There is no RCT supporting the use of other viral vaccines in patients with hematological malignancies. Clinicians who wish to administer viral vaccines to these patients should balance the potential benefits against the potential risks and discuss them with patients adequately so that they can make individual informed choices.

Implications for research

The existing evidence on the efficacy and safety of viral vaccines for patients with hematological malignancies is inadequate, incomplete and of low quality. Further randomized controlled trials are needed to evaluate more of the available viral vaccines. These trials should encompass patients of different age groups and a variety of hematological malignancies treated with different modalities (chemotherapy, immunotherapy, targeted therapy, autologous or allogeneic stem cell transplant), although individual trials might be restricted to specific patient population to enhance homogeneity among trial participants. Ideally, the trials should compare active vaccines against placebo to determine the clinical efficacy of the particular vaccine in these patient groups. Trials comparing different forms of vaccines in different doses, dosing schedules and timings are also invaluable to inform clinicians on the optimal use of available vaccines. The outcomes employed should be patient-oriented and important, such as all-cause mortality, disease specific mortality, incidence of severe complications and hospitalizations, and incidence of the specific infection and severity scores, in addition to the usual immunological laboratory parameters. The sample size should be pre-calculated to ensure adequate statistical power to detect important differences in the primary outcome. The conduct of the trials should adhere to the current standards, of which important components include concealed randomization sequence generation; adequate blinding of participants, healthcare teams, outcome reporters and analysts; intention-to-treat analyses; and adequate reports of all outcomes and drop-outs. Cost-effectiveness analyses are also needed before appropriate recommendation can be made on the use of viral vaccines in patients with hematological malignancies.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[author-defined order]*

Hata 2002

Methods	Design: RCT Randomization method: Block randomization Stratification factor: None Setting of recruitment: Hospital
Participants	Inclusion criteria: 18 to 60 years old who were seropositive for varicella-zoster virus and who had lymphoma and were scheduled for autologous hematopoietic cell transplantation within the upcoming 30 days. Eligibility criteria included lack of a response, at least once, to standard treatment for Hodgkin's disease or non-Hodgkin's lymphoma or a high risk of early recurrence. Exclusion criteria: history of zoster within 12 months before the transplantation, exposure to varicella-zoster virus within 4 weeks, administration of another vaccine within 4 months, or neomycin sensitivity. Number of subjects (intervention : comparison): 59 : 60 Number of males (intervention : comparison): 37 : 37 Age in years (intervention : comparison): (mean) 44 : 44 Underlying hematological malignancies: Hodgkin's disease or non-Hodgkin's lymphoma Treatments for the underlying hematological malignancies: autologous stem cell transplant Phase of treatments: Before SCT and after SCT Previous vaccine history: Not reported Baseline antibody levels: 1:256 to 1:16,384 (not differ between 2 groups)
Interventions	Intervention (type of vaccines): inactivated VZV vaccine Comparison (type of control): no vaccine Details of treatment regimes in intervention group: 0.5 ml dose by subcutaneous injection into the upper arm. A dose was given to patients in the vaccine group within 30 days before hematopoietic-cell transplantation, regardless of the apheresis schedule, and then again 30, 60, and 90 days after transplantation. Details of treatment regimens in comparison group: no vaccine, conventional care Details of co-interventions: 29 patients in the vaccine group and 28 in the control group received intravenous or oral acyclovir for oral lesions, mucositis, or genital herpes during the first 120 days after transplantation; the dose of intravenous acyclovir ranged from 375 to 600 mg every eight hours, and that of oral acyclovir ranged from 200 to 800 mg five times a day. The average duration of treatment with intravenous or oral acyclovir was 10.8 days among the vaccinated patients and 9.8 days among those who were not vaccinated; one patient in each group was treated for more than 21 days. Duration of FU: 12 months
Outcomes	Incidence of the viral infection Mortality due to the viral infection All-cause mortality Frequency of 4-fold rise of protective antibodies Cellular immune response (mean stimulation Index at 90 days, 120 days, 6 months, 12

	months) Proportion of CD4 T-cells that produced TNFα at 6 months Proportion of interferon-positive CD4 T-cells at 6 months Frequency of systemic adverse effects Frequency of local adverse effects
Notes	Risk of bias: high

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not reported.
Blinding? All outcomes	No	Blinding of treating physicians but not patients. Blinding of outcome assessors unknown
Incomplete outcome data addressed? All outcomes	No	There were 9 drop-outs (15.3%) in the treatment group, including 2 patients who withdrew at 30 days for unexplained reasons, 6 who did not undergo transplantation after randomization and 1 who withdrew because of disease progression. Sixteen patients in the treatment group (27.1%) did not complete the intended 4 doses of vaccine. There were 2 patient withdrawals (3.3%) in the control group, both because of no transplantation after randomization. For individual outcomes, the amount of missing data was variable, and up to 67.8% for two outcomes (the proportion of CD4+ T-cells that produced TNF-alpha and the proportion of CD4+ T-cells that produce interferon-gamma)
Free of other bias?	No	The treatment groups were not comparable at baseline because there were more patients with Hodgkin's disease in the control group, and more post-first remission NHL patients in the intervention group
Intention-to-treat analysis?	Unclear	Not reported.

Redman 1997

Methods	Design: RCT Randomization method: Stratified block randomization Stratification factor: graft type (autologous versus allogeneic) Setting of recruitment: Stanford University Medical Center
Participants	Inclusion criteria: 18 to 49 years old scheduled to undergo SCT at Stanford University Medical Center, and who had leukemia or lymphoma. Serological evidence of VZV before transplantation, no history of herpes zoster, no exposure to VZV or other immunization during the 1st month after SCT. Exclusion criteria: None Number of subjects (intervention : comparison): 1st protocol 14 : 14; 2nd protocol 24 : 23 Number of males (intervention : comparison): 1st protocol 9 : 11; 2nd protocol 13 : 11 Age in years (intervention : comparison): (mean) 1st protocol 38 : 38; 2nd protocol 34 : 39 Underlying hematological malignancies: leukemia or lymphoma Treatments for the underlying hematological malignancies: autologous or allogeneic stem cell transplant Phase of treatments: 1-3 months after SCT Previous vaccine history: Not reported Baseline antibody levels: 1:256 to 1:16384 (no difference between 2 groups)
Interventions	Intervention (type of vaccines): inactivated VZV vaccine Comparison (type of control): no vaccine Details of treatment regimes in intervention group: 1st protocol in 1993: single dose (0.5ml sc) at 1month post-SCT; 2nd protocol in 1994-1995: 3 doses sc at 1, 2, 3 months post-SCT Details of treatment regimens in comparison group: no vaccine, conventional care Details of co-interventions: acyclovir given to all patients during HSV outbreaks. IV ganciclovir and IVIG given to all allogeneic SCT recipients for 3 months after SCT and all patients with CMV disease. Duration of FU: 12 months
Outcomes	Incidence of the viral infection Mortality due to the viral infection All-cause mortality Mean severity score Frequency of 4-fold rise of protective antibodies Cellular immune response (mean stimulation Index at 3 months, 4 months, 5 months, 12 months) Frequency of systemic adverse effects Frequency of local adverse effects
Notes	Risk of bias: high

Risk of bias

Item	**Authors' judgement**	**Description**

Redman 1997 (*Continued*)

Allocation concealment?	Unclear	Not reported.
Blinding? All outcomes	No	Blinding of treating physicians but not patients. Blinding of outcome assessors unknown
Incomplete outcome data addressed? All outcomes	No	There was no drop-out reported but missing data occurred in up to 73.9% in the treatment and the control groups respectively in one of the outcomes (post-stimulation interleukin 10 concentrations at 12 months)
Free of other bias?	No	The treatment groups were not comparable at baseline because in protocol 2, there were more CML patients in the control group
Intention-to-treat analysis?	Unclear	Not reported.

Esposito 2010

Methods	Design: RCT Randomization method: not reported Stratification factor: Length of time after completion of chemotherapy (<6 months versus 6-24 months) Setting of recruitment:Pediatric Units of The Universities of Bari and Milano Bicocca, Italy
Participants	Inclusion criteria: Children >2 years who had not previously been vaccinated against influenza, who had completed cancer therapy for acute lymphoblastic leukemia, Hodgkin disease or non-Hodgkin lymphoma for <2 years, and who were regularly followed up at the two participating Oncohematologic Pediatric Units were included. Exclusion criteria: Any serious chronic disease other than cancer (e.g., chronic pulmonary disease including asthma, signs of cardiac or renal failure, or severe malnutrition, progressive neurological disease), Down syndrome or other known cytogenetic disorders, a known or suspected disease of the immune system or the administration of immunosuppressive therapy, including systemic corticosteroids (a prednisone-equivalent dose of 2mg/kg/day) for more than 14 days, the administration of any blood product, including immunoglobulins, in the period from 6 months before vaccination to the conclusion of the study, the administration of a dose of influenza vaccine (commercial or investigational) before enrolment, or a documented history of hypersensitivity to any component of the vaccine. Number of subjects (intervention : comparison): 91 : 91 Number of males: 52 : 52 Age in years: off therapy <6 months: mean 9.7 (SD 4.3) : mean 10.1 (SD 3.9); off therapy 6-24 months: mean 10.2 (SD 3.7) : mean 10.5 (SD 3.5) Underlying hematological malignancies: acute lymphoblastic leukemia, Hodgkin disease or non-Hodgkin lymphoma

Esposito 2010 (*Continued*)

	Treatments for the underlying hematological malignancies: chemotherapy Phase of treatments: within 2 years after completion of chemotherapy Previous vaccine history: no previous influenza vaccine Baseline antibody levels: not reported
Interventions	Intervention (type of vaccines): inactivated trivalent virosome-formulated subunit influenza vaccine Comparison (type of control): no vaccine Details of treatment regimes in intervention group:1 dose im for children >9 years, 2 doses im 30 days apart for children <9 years Details of treatment regimens in comparison group: no vaccine Details of co-interventions: not reported Duration of FU: 1 influenza season
Outcomes	Frequency of at least one upper respiratory tract infection Frequency of at least one lower respiratory tract infection Frequency of at least one infection other than influenza-like illness Frequency of at least one hospitalization Number of upper respiratory tract infections Number of lower respiratory tract infections Number of infections other than influenza-like illness Number of days with fever Number of antibiotics courses Number of days lost from school Frequency of systemic adverse effects Frequency of local adverse effects
Notes	Risk of bias: high Other outcomes reported included measures on effectiveness of influenza vaccination among households of the participants. These were not included in the current review

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not reported.
Blinding? All outcomes	No	Blinding of treating physicians but not patients. Blinding of outcome assessors unknown
Incomplete outcome data addressed? All outcomes	Yes	Outcomes of all participants were reported.
Free of other bias?	Unclear	The groups are comparable at baseline with respect to measured characteristics. However, baseline influenza immunity is unknown for the participants

Esposito 2010 (*Continued*)

Intention-to-treat analysis?	Unclear	Not reported.

Musto 1997

Methods	Design: RCT Randomization method: not reported Stratification factor: None Setting of recruitment: IRCCS Casa Sollievo Della Sofferenza Hospital, S. Giovanni Rotaondo, Italy
Participants	Inclusion criteria: Patients with multiple myeloma and undergoing conventional chemotherapy Exclusion criteria: None Number of subjects (intervention : comparison): 25 : 25 Number of males: not reported Age in years: not reported Underlying hematological malignancies: multiple myeloma Treatments for the underlying hematological malignancies: chemotherapy Phase of treatments: during chemotherapy Previous vaccine history: not reported Baseline antibody levels: not reported
Interventions	Intervention (type of vaccines): trivalent subvirion influenza vaccine 1 dose Comparison (type of control): no vaccine Details of treatment regimes in intervention group: 1 dose of vaccine sc Details of treatment regimens in comparison group: no vaccine Details of co-interventions: not reported Duration of FU: 4 months
Outcomes	Frequency of at least one upper respiratory illnesses Duration of febrile respiratory episodes Frequency of hospitalizations related to respiratory illnesses Mortality due to pneumonia Frequency of pneumonia Number of non-programmed visits to hospital Frequency of local adverse effects
Notes	Risk of bias: high

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not reported.
Blinding? All outcomes	No	No blinding of treating physicians, patients or outcome assessors

Musto 1997 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	No drop-out was reported but reported data were insufficient to assess for amount of missing data
Free of other bias?	Unclear	The treatment groups were commented to be comparable at baseline but data were not provided. "There were no relevant differences between the two groups with respect to treatments and routine clinical or laboratory parameters."
Intention-to-treat analysis?	Unclear	Not reported.

Ljungman 2005

Methods	Design: RCT Randomization method: not reported Stratification factor: None Setting of recruitment: Haematology Centre, Karolinska University Hospital, Stockholm
Participants	Inclusion criteria: Patients having ongoing or recently discontinued chemotherapy (within the last 6 months) for lymphoma, myelodysplastic syndrome (MDS), acute leukemia, multiple myeloma or myeloproliferative disorders. Exclusion criteria: None Number of subjects (intervention : comparison): 2 doses (34) : 1 dose (36) Number of males (intervention : comparison): not reported Age in years (intervention : comparison): (median) 2 dose (59.1) : 1 dose (68.8) Underlying hematological malignancies: lymphoma, leukemia, multiple myeloma or Waldenstrom's macroglobulinemia Treatments for the underlying hematological malignancies: chemotherapy, rituximab, alemtuzumab Phase of treatments: during or within 6 months of chemotherapy Previous vaccine history: not reported Baseline antibody levels: not reported
Interventions	Intervention (type of vaccines): trivalent inactivated influenza vaccine 2 doses Comparison (type of control): trivalent inactivated influenza vaccine 1 dose Details of treatment regimes in intervention group: 2 doses of vaccine sc 4 weeks apart Details of treatment regimens in comparison group: 1 dose of vaccine sc Details of co-interventions: minimum of 1 week between vaccination and the next scheduled chemotherapy course Duration of FU: 4 weeks
Outcomes	Frequency of 4-fold rise of protective antibodies
Notes	Risk of bias: high

Ljungman 2005 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not reported.
Blinding? All outcomes	No	No blinding of treating physicians, patients or outcome assessors
Incomplete outcome data addressed? All outcomes	Unclear	No drop-out was reported but reported data were insufficient to assess for amount of missing data
Free of other bias?	No	The treatment groups were not comparable at baseline because patients in the single dose group were significantly older
Intention-to-treat analysis?	Unclear	Not reported.

Safdar 2006

Methods	Design: RCT Randomization method: not reported Stratification factor: None Setting of recruitment: adult lymphoma clinic at M.D. Anderson Cancer Center (MDACC)
Participants	Inclusion criteria: Patients with biopsy-proven NHL who had not received chemotherapy in the 3 months before enrolment. Exclusion criteria: allergic to influenza vaccine or egg products or had undergone splenectomy. Individuals who had received rituximab and parenteral immunoglobulin within the 6-month period before enrolment were also excluded. Patients who had received systemic corticosteroids, other investigational vaccine, or anti-neoplastic medications in the 4 weeks before enrolment were excluded. Number of subjects (comparison : comparison): Standard vaccine (SV) : recombinant vaccine (RV) 15μg : RV 45μg : RV 135μg = 6 : 9 : 6 : 6 Number of males (intervention : comparison): 15 overall Age in years (intervention : comparison): (mean): 55 years overall Underlying hematological malignancies: NHL Treatments for the underlying hematological malignancies: chemotherapy+/- rituximab or bortezomib; no anti-neoplastic therapy in 2 patients Phase of treatments: at least 3 months after chemotherapy Previous vaccine history: not reported Baseline antibody levels: not reported
Interventions	Intervention (type of vaccines): Recombinant vaccines: the recombinant HA protein vaccine consisted of HA expressed in insect (SF9) cells by recombinant baculovirus. The HA genes of the 3 influenza viruses contained in the vaccine (A/Panama/2007/99

Safdar 2006 (*Continued*)

	H3N2, A/New Caledonia/20/99 H1N1, and B/Hong Kong/330/2001) were independently cloned into the plasmid baculovirus expression vector pPSC12. The vector contained the AcNPV baculovirus polyhedron promoter, the baculovirus 61K signal peptide, and flanking baculovirus DNA derived from the EcoRII fragment of AcNPV. After confirmation of the correct sequences, the DNA sequences were inserted into AcNPV by homologous recombination. Recombinant virus containing the respective HA genes were then used to express the HAs in the high-yield SF9-derived insect cell line. The vaccine was supplied at a final concentration of either 15 ug, 45 ug, or 135 ug of each HA per 0.5-mL dose (45-ug, 135-ug, or 405-ug total doses of rHAO). Comparison (type of control): standard vaccine: split-virus TIV from a single lot containing 15 ug/0.5mL each of the HA of influenza A/Panama/2007/99(H3N2), A/New Caledonia/20/99(H1N1), and B/Hong Kong/330/2001 (Sanofi Pasteur). Details of treatment regimes in intervention group: 1 dose Details of treatment regimens in comparison group: 1 dose Details of co-interventions: not reported Duration of FU: 4 weeks for antibody response, 6 months for safety
Outcomes	Frequency of 4-fold rise of protective antibodies Frequency of systemic adverse effects Frequency of local adverse effects
Notes	Risk of bias: moderate

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not reported.
Blinding? All outcomes	Yes	Blinding of treating physicians and patients. Blinding of outcome assessors unknown
Incomplete outcome data addressed? All outcomes	Yes	No drop-out was reported and data on outcomes were complete.
Free of other bias?	Unclear	Comparability of the treatment groups at baseline was uncertain because baseline data (age, gender, type of lymphoma and treatments) of different groups were not presented
Intention-to-treat analysis?	Unclear	Not reported.

Hsieh 2002

Methods	Design: RCT Randomization method: not reported Stratification factor: None Setting of recruitment: Far Eastern Memorial Hospital, Taipei
Participants	Inclusion criteria: Children with acute lymphoblastic leukemia in the maintenance stage who received 6-mercaptopurine daily, methotrexate weekly, and reinduction with vincristine and prednisolone every 2 months Exclusion criteria: None Number of subjects (intervention : comparison): 14 : 11 Number of males: total 14 Age in years: mean 7.3 years Underlying hematological malignancies: acute lymphoblastic leukemia Treatments for the underlying hematological malignancies: chemotherapy Phase of treatments: during maintenance stage Previous vaccine history: not reported Baseline antibody levels: not reported
Interventions	Intervention (protocol 1): inactivated influenza vaccine (Vaxigrip) first dose given at the time of reinduction chemotherapy and second dose 4 weeks later Comparison (protocol 2): inactivated influenza vaccine (Vaxigrip) first dose given 4 weeks before reinduction chemotherapy and second dose at the time of reinduction chemotherapy Details of treatment regimes in intervention group: 2 doses of 0.5ml Vaxigrip inactivated influenza vaccine sc 4 weeks apart Details of treatment regimens in comparison group: 2 doses of 0.5ml Vaxigrip inactivated influenza vaccine sc 4 weeks apart Details of co-interventions: 6-mercaptopurine daily, methotrexate weekly, reinduction chemotherapy with vincristine and prednisolone every 2 months Duration of FU: 4 weeks
Outcomes	Frequency of 4-fold rise of protective antibodies Frequency of seroconversion (increase of antibody titre from below 40 to no less than 40) Frequency of systemic adverse effects Frequency of local adverse effects
Notes	The study includes 2 more non-randomized control groups of children with asthma and healthy children. These control groups were excluded because they were not randomly assigned to one of the 2 protocols Risk of bias: high

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not reported.

Hsieh 2002 (*Continued*)

Blinding? All outcomes	No	No blinding of treating physicians, patients or outcome assessors
Incomplete outcome data addressed? All outcomes	No	No drop-out was reported but missing data occurred in up to 72.7% in the control group in two of the outcomes (seroconversion in influenza A/H1 antibody after 1 and 2 doses of vaccine)
Free of other bias?	Unclear	Comparability of the treatment groups at baseline was uncertain because baseline characteristics of the two groups were not mentioned separately
Intention-to-treat analysis?	Unclear	Not reported.

Parkkali 1997

Methods	Design: RCT Randomization method: not reported Stratification factor: None Setting of recruitment: Helsinki University Central Hospital
Participants	Inclusion criteria: adults (age >16 years) who had received a bone marrow transplant from a sibling donor between January 1985 and November 1989 Exclusion criteria: not reported Number of subjects (intervention : comparison): 23 : 22 Number of males (intervention : comparison): 12 : 12 Age in years (intervention : comparison): (median): 31 : 30 (range 16-48 : 18-49) Underlying hematological malignancies: AML, ALL, CML, multiple myeloma, Burkitt's lymphoma, lymphoblastic lymphoma, severe aplastic anemia Treatments for the underlying hematological malignancies: allogeneic matched sibling stem cell transplant Phase of treatments: 6-18 months post-transplant Previous vaccine history: not reported Baseline antibody levels: geometric mean titre (GMT) overall: PV1 (707), PV2 (1029), PV3 (180)
Interventions	Intervention (type of vaccines): Inactivated trivalent poliovirus vaccine (Polio Novum, RIVM, Bilthoven, The Netherlands) at 6, 8 and 14 months after BMT Comparison (type of control): Inactivated trivalent poliovirus vaccine (Polio Novum, RIVM, Bilthoven, The Netherlands) at 18, 20 and 26 months after BMT Details of treatment regimes in intervention group: 3 doses sc at 6, 8 and 14 months after BMT Details of treatment regimens in comparison group: 3 doses sc at 18, 20 and 26 months after BMT Details of co-interventions: Three doses of tetanus toxoid vaccine (manufactured by National Public Health Institute, Helsinki, Finland) were given with the same sched-

Parkkali 1997 (*Continued*)

	ule as the polio vaccine. At the time of the first dose of polio vaccine the patients received Haemophilus influenzae type b polysaccharide-diphtheria toxoid conjugate vaccine (ProHIBIT; Connaught Laboratories, Swiftwater, PA, USA). At the time of the second dose of polio vaccine the recipients were immunized with pneumococcal polysaccharide vaccine. (Pneumovax; Merck, Sharp and Dohme, West Point, PA, USA), and with meningococcal polysaccharide vaccine (Mencevax ACW135Y; Smith Kline RIT, Rixensart, Belgium). Duration of FU: 22 months
Outcomes	Frequency of 4-fold rise of antibody after each dose Geometric mean titre of protective antibody after each dose
Notes	Risk of bias: high

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not reported.
Blinding? All outcomes	No	No blinding of treating physicians or patients. Blinding of outcome assessors unknown
Incomplete outcome data addressed? All outcomes	Unclear	There were 9 drop-outs (34.6%) in the treatment group, including 2 who died before vaccinations, 1 who had not received the vaccine and 6 losses to follow-up with unknown reasons. There were 12 drop-outs (41.4%) in the control group, including 6 who died before vaccination, 1 who relapsed and not vaccinated, and 5 loss to follow-up with unknown reasons. Missing data occurred up to 31.8% in the control group in several outcomes (4-fold rise of antibody titres to poliovirus type 1, 2 and 3, and geometric mean titre of poliovirus antibody to poliovirus type 1, 2 and 3)
Free of other bias?	No	The treatment groups were not comparable at baseline because there were more CML patients in late schedule group and there were more patients with chronic GVHD in early schedule group
Intention-to-treat analysis?	Unclear	Not reported.

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

NCT01016548

Trial name or title	Evaluation of Influenza H1N1 Vaccine in Adults With Lymphoid Malignancies on Chemotherapy
Methods	Open label randomized controlled trial
Participants	Patients ages 20-65 years with lymphoproliferative disorder undergoing active chemotherapy or immunotherapy at enrollment or completed within the last 3 months, or autologous or allogeneic stem cell transplant recipient within the past 12 months
Interventions	AS03-adjuvanted H1N1 pandemic influenza vaccine 2 doses versus 1 dose
Outcomes	Primary outcome: seroconversion rates on day 21 and 42. Secondary outcome: adverse events to vaccination on day 7, 21, and 28
Starting date	November 2009
Contact information	Location: Princess Margaret Hospital, Toronto, Ontario, Canada. Principal investigator: John Kuruvilla
Notes	Completed study, pending analysis results.

DATA AND ANALYSES

Comparison 1. Varicella zoster vaccine (VZV) vaccine versus no vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of herpes zoster	2	138	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.30, 1.00]
2 Mortality due to infection	2	194	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 All cause mortality	2	139	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.54, 1.69]
4 4-fold rise in VZV antibody titre	2	123	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.20, 4.52]
5 Lymphocyte stimulation index	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Lymphocyte stimulation index at 1 month	1	99	Mean Difference (IV, Random, 95% CI)	Not estimable
5.2 Lymphocyte stimulation index at 3 months	2	112	Mean Difference (IV, Random, 95% CI)	7.63 [6.60, 8.66]
5.3 Lymphocyte stimulation index at 4 months	2	120	Mean Difference (IV, Random, 95% CI)	10.92 [2.13, 19.71]
5.4 Lymphocyte stimulation index at 5-6 months	2	111	Mean Difference (IV, Random, 95% CI)	9.72 [-3.05, 22.50]
5.5 Lymphocyte stimulation index at 12 months	2	77	Mean Difference (IV, Random, 95% CI)	29.45 [8.51, 50.39]
6 Percentage of CD4+ T cells producing TNF-alpha	1	38	Mean Difference (IV, Fixed, 95% CI)	31.0 [24.75, 37.25]
7 Percentage of CD4+ T cells producing interferon-gamma	1	38	Mean Difference (IV, Fixed, 95% CI)	22.0 [16.57, 27.43]
8 Post-stimulation interferon-gamma concentration	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Post-stimulation interferon-gamma concentration at 1 month	1	29	Mean Difference (IV, Fixed, 95% CI)	8.0 [2.39, 13.61]
8.2 Post-stimulation interferon-gamma concentration at 2 months	1	20	Mean Difference (IV, Fixed, 95% CI)	-107.00 [-206.58, -7.42]
8.3 Post-stimulation interferon-gamma concentration at 3 months	1	20	Mean Difference (IV, Fixed, 95% CI)	8.0 [-56.07, 72.07]
8.4 Post-stimulation interferon-gamma concentration at 4 months	1	23	Mean Difference (IV, Fixed, 95% CI)	74.0 [22.75, 125.25]
8.5 Post-stimulation interferon-gamma concentration at 5 months	1	18	Mean Difference (IV, Fixed, 95% CI)	-110.0 [-220.39, 0.39]
8.6 Post-stimulation interferon-gamma concentration at 12 months	1	13	Mean Difference (IV, Fixed, 95% CI)	-148.0 [-305.09, 9.09]
9 Post-stimulation interleukin-10 concentration	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

9.1 Post-stimulation interleukin-10 concentration at 1 month	1	29	Mean Difference (IV, Fixed, 95% CI)	-33.0 [-56.78, -9.22]
9.2 Post-stimulation interleukin-10 concentration at 2 months	1	20	Mean Difference (IV, Fixed, 95% CI)	-39.0 [-78.31, 0.31]
9.3 Post-stimulation interleukin-10 concentration at 3 months	1	20	Mean Difference (IV, Fixed, 95% CI)	-39.0 [-84.26, 6.26]
9.4 Post-stimulation interleukin-10 concentration at 4 months	1	23	Mean Difference (IV, Fixed, 95% CI)	-54.00 [-97.22, -14.78]
9.5 Post-stimulation interleukin-10 concentration at 5 months	1	18	Mean Difference (IV, Fixed, 95% CI)	-26.0 [-85.74, 33.74]
9.6 Post-stimulation interleukin-10 concentration at 12 months	1	13	Mean Difference (IV, Fixed, 95% CI)	-53.0 [-128.70, 22.70]
10 Frequency of systemic adverse effects	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Frequency of all systemic adverse effects	2	194	Risk Ratio (M-H, Fixed, 95% CI)	5.94 [0.73, 48.55]
10.2 Frequency of headache	2	194	Risk Ratio (M-H, Fixed, 95% CI)	3.97 [0.45, 34.93]
10.3 Frequency of arthralgia or myalgia	1	75	Risk Ratio (M-H, Fixed, 95% CI)	4.87 [0.24, 98.18]
11 Frequency of local adverse effects	2	194	Risk Ratio (M-H, Fixed, 95% CI)	20.94 [2.88, 152.36]
12 Severity score of herpes zoster	1	10	Mean Difference (IV, Random, 95% CI)	2.60 [0.94, 4.26]

Comparison 2. Influenza vaccine versus no vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality due to infection (pneumonia)	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 3.97]
2 Incidence of complications	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Frequency of at least one lower respiratory tract infection	2	232	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.19, 0.78]
2.2 Frequency of at least one infections other than influenza-like illness	1	182	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.54, 1.24]
3 Rate of hospitalization	2	232	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.09, 0.31]
4 Frequency of at least one adverse effects	2	232	Risk Ratio (M-H, Fixed, 95% CI)	35.0 [4.90, 249.80]
5 Frequency of systemic adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Frequency of fever	1	182	Risk Ratio (M-H, Fixed, 95% CI)	15.0 [0.87, 258.82]
5.2 Frequency of irritability	1	182	Risk Ratio (M-H, Fixed, 95% CI)	19.0 [1.12, 321.67]

5.3 Frequency of decreased appetite	1	182	Risk Ratio (M-H, Fixed, 95% CI)	13.0 [0.74, 227.43]
5.4 Frequency of rhinitis	1	182	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.49, 164.78]
5.5 Frequency of cough	1	182	Risk Ratio (M-H, Fixed, 95% CI)	15.0 [0.87, 258.82]
5.6 Frequency of vomiting	1	182	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.24, 102.72]
6 Frequency of local adverse effects	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Frequency of at least one local adverse events	2	232	Risk Ratio (M-H, Fixed, 95% CI)	22.0 [3.05, 158.51]
6.2 Frequency of redness	1	182	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.37, 133.62]
6.3 Frequency of swelling or induration	1	182	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.37, 133.62]
7 Frequency of at least one upper respiratory infections	2	232	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.44, 0.72]
8 Number of upper respiratory tract infections	1	182	Mean Difference (IV, Fixed, 95% CI)	-1.23 [-1.52, -0.94]
9 Number of lower respiratory tract infections	1	182	Mean Difference (IV, Fixed, 95% CI)	-0.3 [-0.44, -0.16]
10 Number of infections other than influenza-like illness	1	182	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.35, 0.15]
11 Number of days with fever	1	182	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-2.25, -1.15]
12 Number of antibiotics courses	1	182	Mean Difference (IV, Fixed, 95% CI)	-1.85 [-2.30, -1.40]
13 Number of days lost from school	1	182	Mean Difference (IV, Fixed, 95% CI)	-4.94 [-5.65, -4.23]

Comparison 3. Influenza vaccine, two doses versus single dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 4-fold rise in influenza antibody titre	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 4-fold rise in influenza A/H3 antibody titre	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [0.71, 5.12]
1.2 4-fold rise in influenza A/H1 antibody titre	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.31, 2.05]
1.3 4-fold rise in influenza B antibody titre	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.52, 2.73]
2 Antibody titre above 1:40	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Antibody titre above 1:40 for influenza A/H3	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.38, 2.28]
2.2 Antibody titre above 1:40 for influenza A/H1	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.48, 2.35]
2.3 Antibody titre above 1:40 for influenza B	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.30, 2.63]

Comparison 4. Recombinant influenza vaccine 15 ug versus standard influenza vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 4-fold rise in influenza hemoagglutination inhibiting antibody titre	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 4-fold rise in influenza A/H3 antibody titre	1	15	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.23, 4.31]
1.2 4-fold rise in influenza A/H1 antibody titre	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 4.93]
1.3 4-fold rise in influenza B antibody titre	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.91]
2 4-fold rise in influenza neutralizing antibody titre	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 4-fold rise in influenza A/H3 antibody titre	1	15	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [0.39, 18.42]
2.2 4-fold rise in influenza A/H1 antibody titre	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.91]
2.3 4-fold rise in influenza B antibody titre	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.91]
3 4-fold rise in influenza antibody titre (either hemoagglutination inhibiting or neutralizing)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 4-fold rise in influenza A/H3 antibody titre	1	15	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.35, 5.13]
3.2 4-fold rise in influenza A/H1 antibody titre	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.91]
3.3 4-fold rise in influenza B antibody titre	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.91]

Comparison 5. Recombinant influenza vaccine 45 ug versus standard influenza vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 4-fold rise in influenza hemoagglutination inhibiting antibody titre	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 4-fold rise in influenza A/H3 antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.06, 4.15]
1.2 4-fold rise in influenza A/H1 antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.08, 12.56]
1.3 4-fold rise in influenza B antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 3.46]
2 4-fold rise in influenza neutralizing antibody titre	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

2.1 4-fold rise in influenza A/H3 antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [1.03, 18.17]
2.2 4-fold rise in influenza A/H1 antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.38, 6.00]
2.3 4-fold rise in influenza B antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 3.46]
3 4-fold rise in influenza antibody titre (either hemoagglutination inhibiting or neutralizing)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 4-fold rise in influenza A/H3 antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.38, 6.00]
3.2 4-fold rise in influenza A/H1 antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.38, 6.00]
3.3 4-fold rise in influenza B antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 3.46]

Comparison 6. Recombinant influenza vaccine 135 ug versus standard influenza vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 4-fold rise in influenza hemoagglutination inhibiting antibody titre	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 4-fold rise in influenza A/H3 antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.38, 6.00]
1.2 4-fold rise in influenza A/H1 antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.08, 12.56]
1.3 4-fold rise in influenza B antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.20, 4.95]
2 4-fold rise in influenza neutralizing antibody titre	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 4-fold rise in influenza A/H3 antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.42, 21.30]
2.2 4-fold rise in influenza A/H1 antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.20, 4.95]
2.3 4-fold rise in influenza B antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.20, 4.95]
3 4-fold rise in influenza antibody titre (either hemoagglutination inhibiting or neutralizing)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 4-fold rise in influenza A/H3 antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.38, 6.00]
3.2 4-fold rise in influenza A/H1 antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.20, 4.95]
3.3 4-fold rise in influenza B antibody titre	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.20, 4.95]

Comparison 7. Comparison of different influenza vaccine schedules: first dose versus second dose given with re-induction

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 4-fold rise in influenza antibody titre after first vaccine dose	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 4-fold rise in influenza A/H3 antibody titre	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.36, 1.30]
1.2 4-fold rise in influenza A/H1 antibody titre	1	25	Risk Ratio (M-H, Fixed, 95% CI)	7.20 [0.43, 120.96]
1.3 4-fold rise in influenza B antibody titre	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.39, 2.29]
2 4-fold rise in influenza antibody titre after second vaccine dose	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 4-fold rise in influenza A/H3 antibody titre	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.48, 1.70]
2.2 4-fold rise in influenza A/H1 antibody titre	1	25	Risk Ratio (M-H, Fixed, 95% CI)	3.93 [0.53, 28.93]
2.3 4-fold rise in influenza B antibody titre	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.39, 2.29]
3 Seroconversion after first vaccine dose (increase of antibody titre from <40 to >=40)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Seroconversion in influenza A/H3 antibody	1	13	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.64, 1.64]
3.2 Seroconversion in influenza A/H1 antibody	1	10	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.15, 40.67]
3.3 Seroconversion in influenza B antibody	1	14	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.37, 2.33]
4 Seroconversion after second vaccine dose (increase of antibody titre from <40 to >=40)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Seroconversion in influenza A/H3 antibody	1	13	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.64, 1.64]
4.2 Seroconversion in influenza A/H1 antibody	1	10	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.40, 11.35]
4.3 Seroconversion in influenza B antibody	1	14	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.37, 2.33]

Comparison 8. Inactivated poliovirus vaccine early schedule versus late schedule

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 4-fold rise in poliovirus antibody titre after first vaccine dose	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 4-fold rise in poliovirus type 1 antibody titre	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.20, 1.01]
1.2 4-fold rise in poliovirus type 2 antibody titre	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.15, 0.80]
1.3 4-fold rise in poliovirus type 3 antibody titre	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.34, 0.96]
2 4-fold rise in poliovirus antibody titre after second vaccine dose	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 4-fold rise in poliovirus type 1 antibody titre	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.34, 1.05]
2.2 4-fold rise in poliovirus type 2 antibody titre	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.34, 1.05]
2.3 4-fold rise in poliovirus type 3 antibody titre	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.48, 1.01]
3 4-fold rise in poliovirus antibody titre after third vaccine dose	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 4-fold rise in poliovirus type 1 antibody titre	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.45, 1.13]
3.2 4-fold rise in poliovirus type 2 antibody titre	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.41, 1.16]
3.3 4-fold rise in poliovirus type 3 antibody titre	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.61, 1.09]

Analysis 1.1. Comparison 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine, Outcome 1 Incidence of herpes zoster.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine

Outcome: 1 Incidence of herpes zoster

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hata 2002	7/53	19/58		79.0 %	0.40 [0.18, 0.88]
Redman 1997	5/13	5/14		21.0 %	1.08 [0.40, 2.88]
Total (95% CI)	**66**	**72**		**100.0 %**	**0.54 [0.30, 1.00]**
Total events: 12 (Intervention), 24 (Control)					
Heterogeneity: Chi^2 = 2.41, df = 1 (P = 0.12); I^2 =59%					
Test for overall effect: Z = 1.97 (P = 0.049)					

Analysis 1.2. Comparison 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine, Outcome 2 Mortality due to infection.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine

Outcome: 2 Mortality due to infection

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Hata 2002	0/59	0/60		0.0 [0.0, 0.0]
Redman 1997	0/38	0/37		0.0 [0.0, 0.0]
Total (95% CI)	**97**	**97**		**0.0 [0.0, 0.0]**

Total events: 0 (Intervention), 0 (Control)

Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%

Test for overall effect: Z = 0.0 (P < 0.00001)

Analysis 1.3. Comparison 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine, Outcome 3 All cause mortality.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine

Outcome: 3 All cause mortality

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hata 2002	12/53	16/58		83.6 %	0.82 [0.43, 1.57]
Redman 1997	5/14	3/14		16.4 %	1.67 [0.49, 5.67]
Total (95% CI)	**67**	**72**		**100.0 %**	**0.96 [0.54, 1.69]**

Total events: 17 (Intervention), 19 (Control)

Heterogeneity: Chi^2 = 1.00, df = 1 (P = 0.32); I^2 =0%

Test for overall effect: Z = 0.14 (P = 0.89)

Analysis 1.4. Comparison 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine, Outcome 4 4-fold rise in VZV antibody titre.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine

Outcome: 4 4-fold rise in VZV antibody titre

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Hata 2002	3/49	3/47		0.96 [0.20, 4.52]
Redman 1997	0/13	0/14		0.0 [0.0, 0.0]
Total (95% CI)	**62**	**61**		**0.96 [0.20, 4.52]**

Total events: 3 (Intervention), 3 (Control)

Heterogeneity: $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

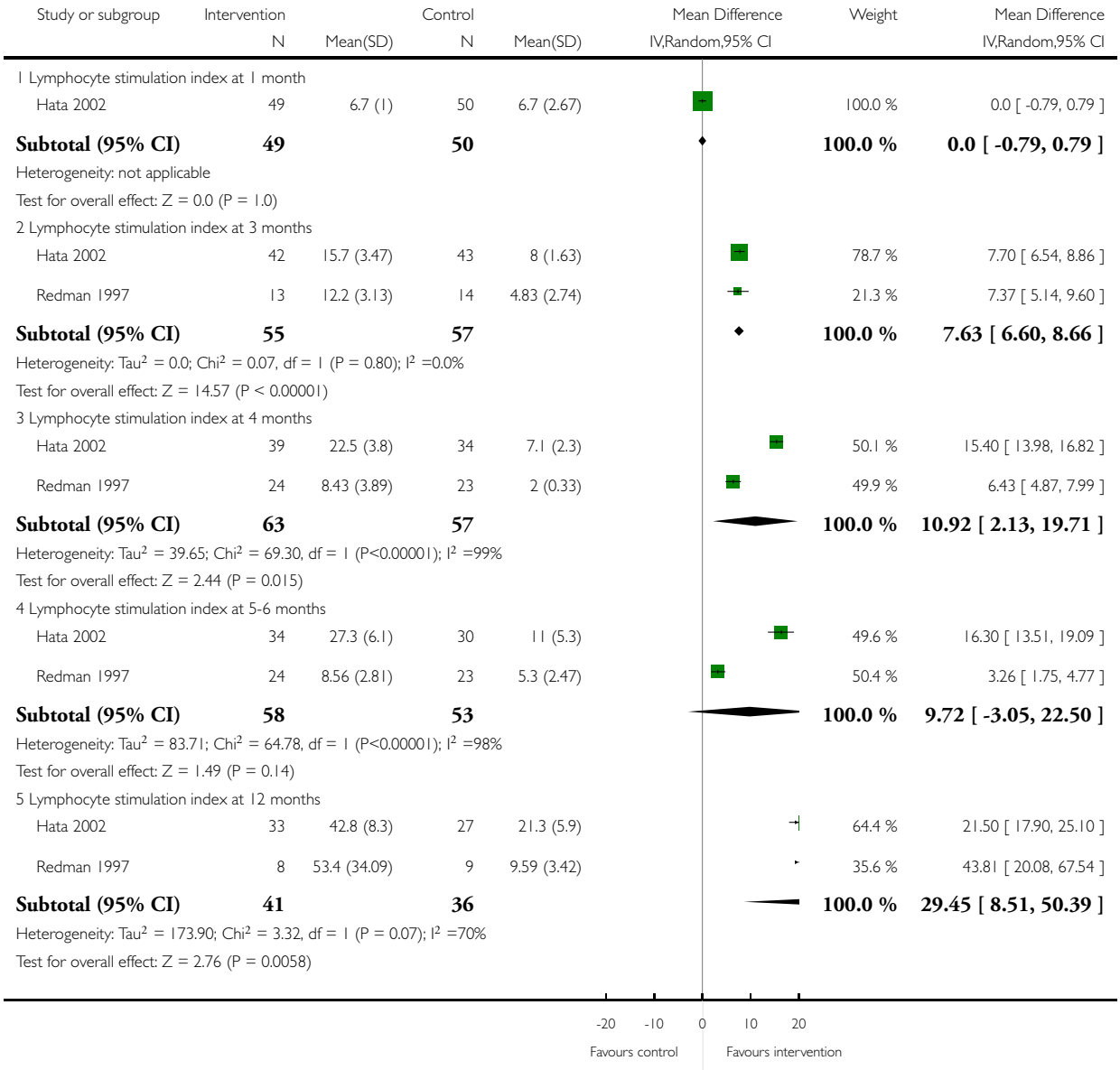
Test for overall effect: Z = 0.05 (P = 0.96)

Analysis 1.5. Comparison 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine, Outcome 5 Lymphocyte stimulation index.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine

Outcome: 5 Lymphocyte stimulation index



Analysis 1.6. Comparison 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine, Outcome 6 Percentage of CD4+ T cells producing TNF-alpha.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine

Outcome: 6 Percentage of CD4+ T cells producing TNF-alpha

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Hata 2002	19	50 (12)	19	19 (7)		100.0 %	31.00 [24.75, 37.25]
Total (95% CI)	**19**		**19**			**100.0 %**	**31.00 [24.75, 37.25]**

Heterogeneity: not applicable

Test for overall effect: Z = 9.73 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine, Outcome 7 Percentage of CD4+ T cells producing interferon-gamma.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine

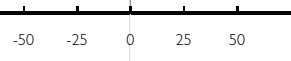
Outcome: 7 Percentage of CD4+ T cells producing interferon-gamma

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Hata 2002	19	33 (11)	19	11 (5)		100.0 %	22.00 [16.57, 27.43]
Total (95% CI)	**19**		**19**			**100.0 %**	**22.00 [16.57, 27.43]**

Heterogeneity: not applicable

Test for overall effect: Z = 7.94 (P < 0.00001)

Test for subgroup differences: Not applicable

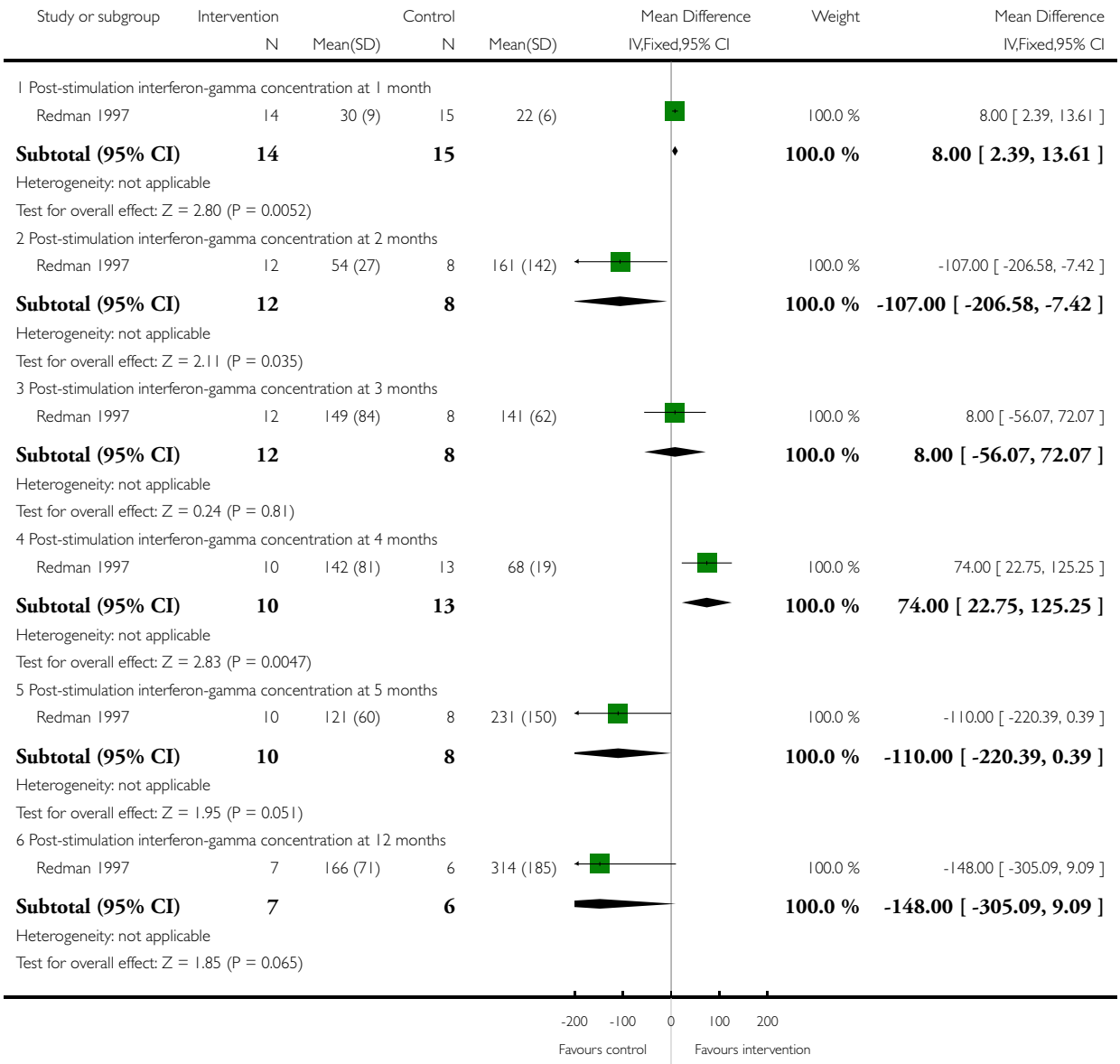


Analysis 1.8. Comparison 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine, Outcome 8 Post-stimulation interferon-gamma concentration.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine

Outcome: 8 Post-stimulation interferon-gamma concentration

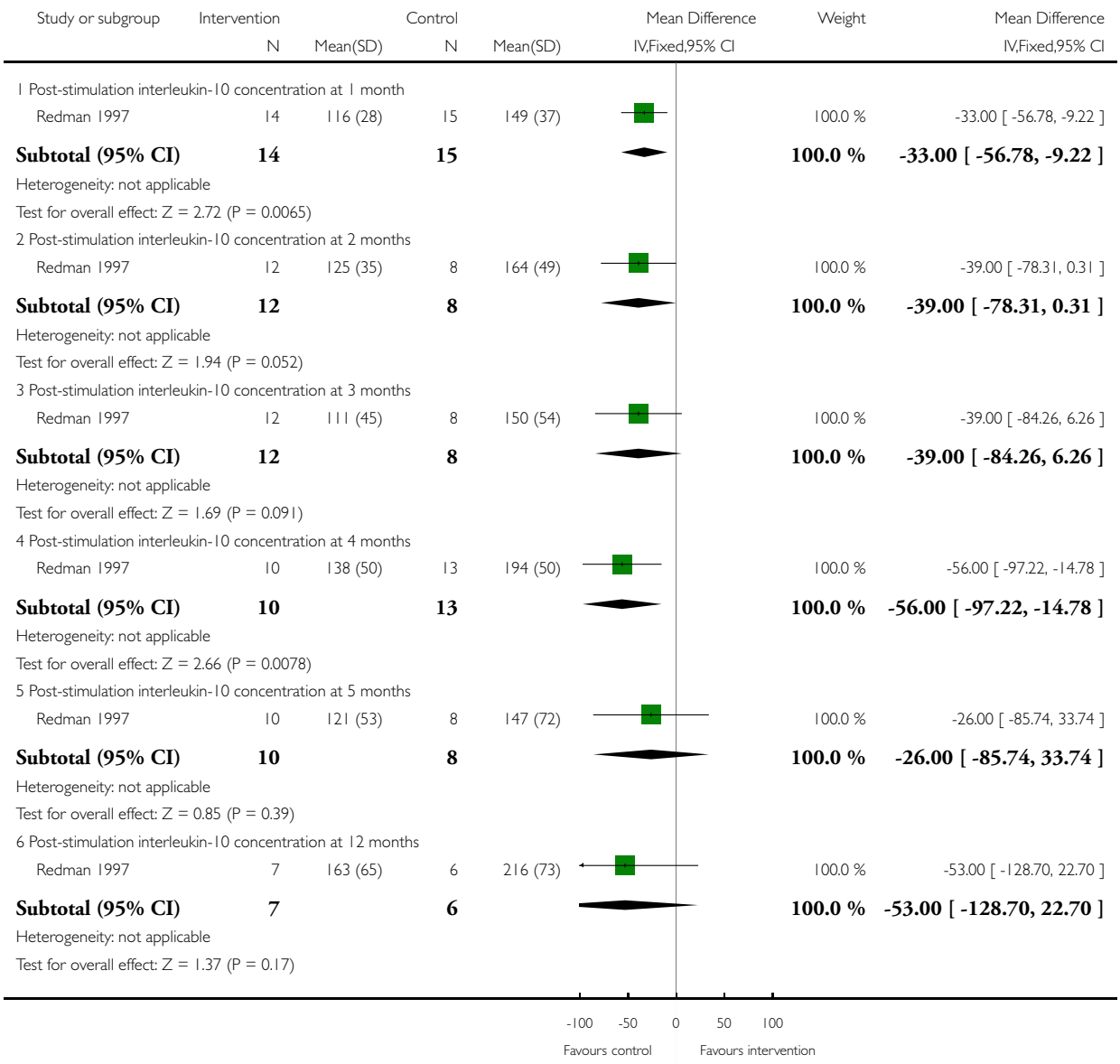


Analysis 1.9. Comparison 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine, Outcome 9 Post-stimulation interleukin-10 concentration.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine

Outcome: 9 Post-stimulation interleukin-10 concentration

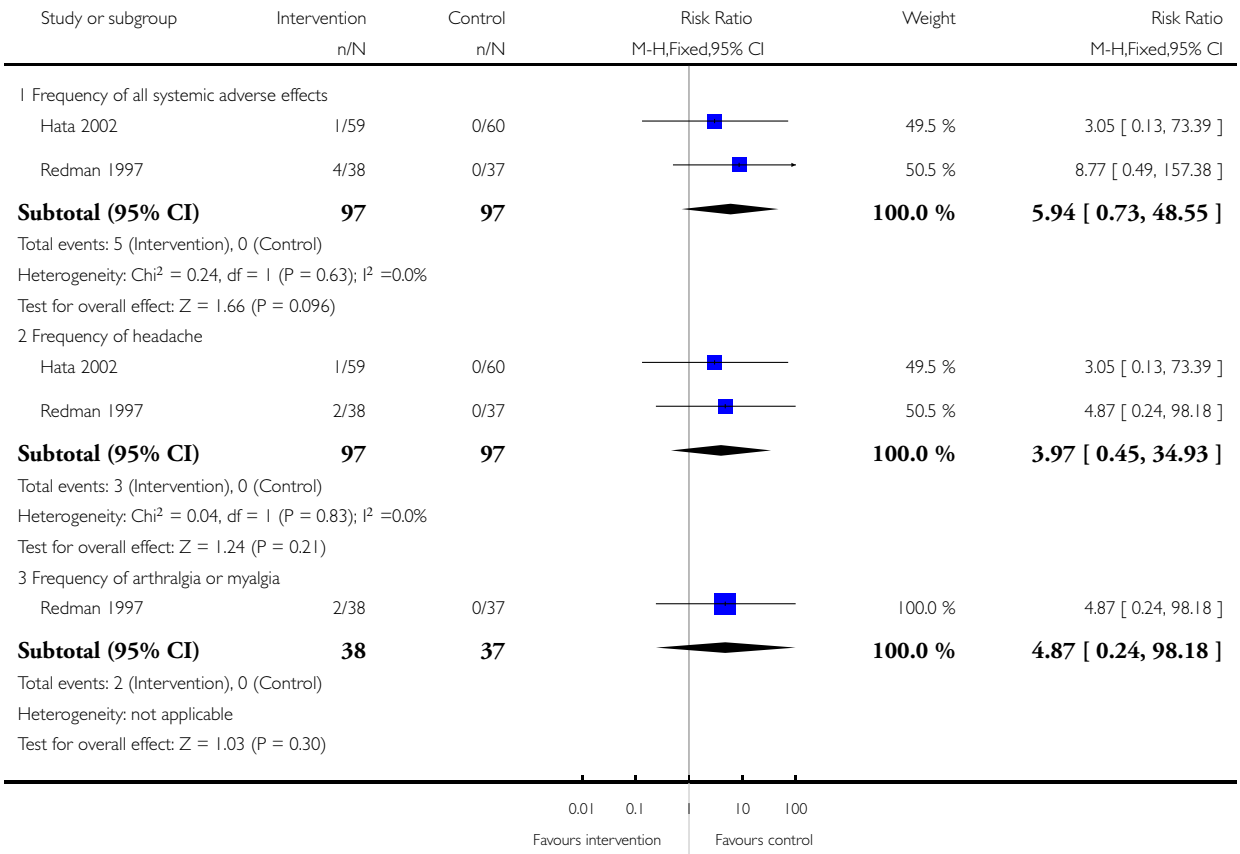


Analysis 1.10. Comparison 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine, Outcome 10 Frequency of systemic adverse effects.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine

Outcome: 10 Frequency of systemic adverse effects



Analysis 1.11. Comparison 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine, Outcome 11 Frequency of local adverse effects.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine

Outcome: 11 Frequency of local adverse effects

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hata 2002	12/59	0/60		49.5 %	25.42 [1.54, 419.70]
Redman 1997	8/38	0/37		50.5 %	16.56 [0.99, 277.05]
Total (95% CI)	**97**	**97**		**100.0 %**	**20.94 [2.88, 152.36]**

Total events: 20 (Intervention), 0 (Control)

Heterogeneity: $Chi^2 = 0.04$, df = 1 (P = 0.83); $I^2 = 0.0\%$

Test for overall effect: Z = 3.00 (P = 0.0027)

Test for subgroup differences: Not applicable

Analysis 1.12. Comparison 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine, Outcome 12 Severity score of herpes zoster.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 1 Varicella zoster vaccine (VZV) vaccine versus no vaccine

Outcome: 12 Severity score of herpes zoster

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Redman 1997	5	11 (1.8)	5	8.4 (0.6)		100.0 %	2.60 [0.94, 4.26]
Total (95% CI)	**5**		**5**			**100.0 %**	**2.60 [0.94, 4.26]**

Heterogeneity: not applicable

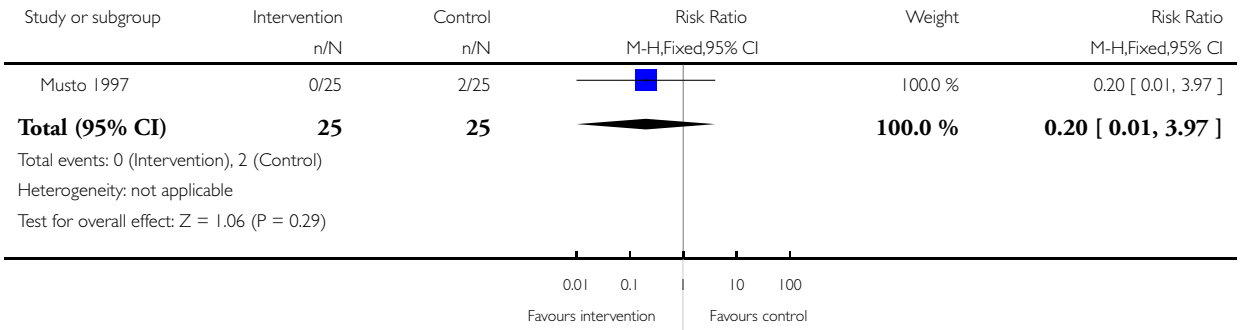
Test for overall effect: Z = 3.06 (P = 0.0022)

Analysis 2.1. Comparison 2 Influenza vaccine versus no vaccine, Outcome 1 Mortality due to infection (pneumonia).

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 2 Influenza vaccine versus no vaccine

Outcome: 1 Mortality due to infection (pneumonia)

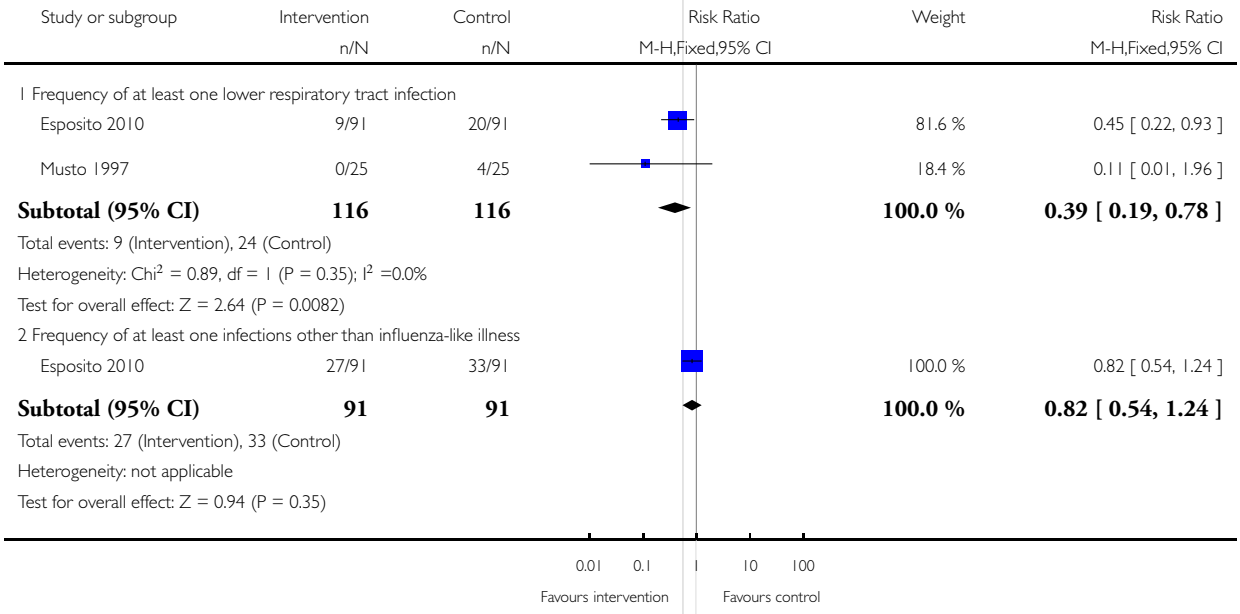


Analysis 2.2. Comparison 2 Influenza vaccine versus no vaccine, Outcome 2 Incidence of complications.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 2 Influenza vaccine versus no vaccine

Outcome: 2 Incidence of complications



Analysis 2.3. Comparison 2 Influenza vaccine versus no vaccine, Outcome 3 Rate of hospitalization.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 2 Influenza vaccine versus no vaccine

Outcome: 3 Rate of hospitalization

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Esposito 2010	8/91	48/91		80.0 %	0.17 [0.08, 0.33]
Musto 1997	2/25	12/25		20.0 %	0.17 [0.04, 0.67]
Total (95% CI)	**116**	**116**		**100.0 %**	**0.17 [0.09, 0.31]**

Total events: 10 (Intervention), 60 (Control)

Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 5.68 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 Influenza vaccine versus no vaccine, Outcome 4 Frequency of at least one adverse effects.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 2 Influenza vaccine versus no vaccine

Outcome: 4 Frequency of at least one adverse effects

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Esposito 2010	19/91	0/91		50.0 %	39.00 [2.39, 636.36]
Musto 1997	15/25	0/25		50.0 %	31.00 [1.96, 491.36]
Total (95% CI)	**116**	**116**		**100.0 %**	**35.00 [4.90, 249.80]**

Total events: 34 (Intervention), 0 (Control)

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 3.55 (P = 0.00039)

Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 Influenza vaccine versus no vaccine, Outcome 5 Frequency of systemic adverse effects.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 2 Influenza vaccine versus no vaccine

Outcome: 5 Frequency of systemic adverse effects

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Frequency of fever					
Esposito 2010	7/91	0/91		100.0 %	15.00 [0.87, 258.82]
Subtotal (95% CI)	**91**	**91**		**100.0 %**	**15.00 [0.87, 258.82]**
Total events: 7 (Intervention), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.86 (P = 0.062)					
2 Frequency of irritability					
Esposito 2010	9/91	0/91		100.0 %	19.00 [1.12, 321.67]
Subtotal (95% CI)	**91**	**91**		**100.0 %**	**19.00 [1.12, 321.67]**
Total events: 9 (Intervention), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.04 (P = 0.041)					
3 Frequency of decreased appetite					
Esposito 2010	6/91	0/91		100.0 %	13.00 [0.74, 227.43]
Subtotal (95% CI)	**91**	**91**		**100.0 %**	**13.00 [0.74, 227.43]**
Total events: 6 (Intervention), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.76 (P = 0.079)					
4 Frequency of rhinitis					
Esposito 2010	4/91	0/91		100.0 %	9.00 [0.49, 164.78]
Subtotal (95% CI)	**91**	**91**		**100.0 %**	**9.00 [0.49, 164.78]**
Total events: 4 (Intervention), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.48 (P = 0.14)					
5 Frequency of cough					
Esposito 2010	7/91	0/91		100.0 %	15.00 [0.87, 258.82]
Subtotal (95% CI)	**91**	**91**		**100.0 %**	**15.00 [0.87, 258.82]**
Total events: 7 (Intervention), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.86 (P = 0.062)					
6 Frequency of vomiting					
Esposito 2010	2/91	0/91		100.0 %	5.00 [0.24, 102.72]
Subtotal (95% CI)	**91**	**91**		**100.0 %**	**5.00 [0.24, 102.72]**

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Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 2 (Intervention), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					

Analysis 2.6. Comparison 2 Influenza vaccine versus no vaccine, Outcome 6 Frequency of local adverse effects.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 2 Influenza vaccine versus no vaccine

Outcome: 6 Frequency of local adverse effects

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Frequency of at least one local adverse events					
Esposito 2010	6/91	0/91		50.0 %	13.00 [0.74, 227.43]
Musto 1997	15/25	0/25		50.0 %	31.00 [1.96, 491.36]
Subtotal (95% CI)	**116**	**116**		**100.0 %**	**22.00 [3.05, 158.51]**
Total events: 21 (Intervention), 0 (Control)					
Heterogeneity: Chi^2 = 0.19, df = 1 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 3.07 (P = 0.0022)					
2 Frequency of redness					
Esposito 2010	3/91	0/91		100.0 %	7.00 [0.37, 133.62]
Subtotal (95% CI)	**91**	**91**		**100.0 %**	**7.00 [0.37, 133.62]**
Total events: 3 (Intervention), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.29 (P = 0.20)					
3 Frequency of swelling or induration					
Esposito 2010	3/91	0/91		100.0 %	7.00 [0.37, 133.62]
Subtotal (95% CI)	**91**	**91**		**100.0 %**	**7.00 [0.37, 133.62]**
Total events: 3 (Intervention), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.29 (P = 0.20)					

Analysis 2.7. Comparison 2 Influenza vaccine versus no vaccine, Outcome 7 Frequency of at least one upper respiratory infections.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 2 Influenza vaccine versus no vaccine

Outcome: 7 Frequency of at least one upper respiratory infections

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Esposito 2010	39/91	66/91		78.6 %	0.59 [0.45, 0.77]
Musto 1997	8/25	18/25		21.4 %	0.44 [0.24, 0.83]
Total (95% CI)	**116**	**116**		**100.0 %**	**0.56 [0.44, 0.72]**

Total events: 47 (Intervention), 84 (Control)

Heterogeneity: Chi^2 = 0.69, df = 1 (P = 0.41); I^2 =0.0%

Test for overall effect: Z = 4.60 (P < 0.00001)

Analysis 2.8. Comparison 2 Influenza vaccine versus no vaccine, Outcome 8 Number of upper respiratory tract infections.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 2 Influenza vaccine versus no vaccine

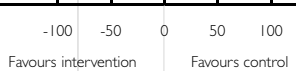
Outcome: 8 Number of upper respiratory tract infections

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Esposito 2010	91	0.49 (0.76)	91	1.72 (1.18)		100.0 %	-1.23 [-1.52, -0.94]
Total (95% CI)	**91**		**91**			**100.0 %**	**-1.23 [-1.52, -0.94]**

Heterogeneity: not applicable

Test for overall effect: Z = 8.36 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 2.9. Comparison 2 Influenza vaccine versus no vaccine, Outcome 9 Number of lower respiratory tract infections.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 2 Influenza vaccine versus no vaccine

Outcome: 9 Number of lower respiratory tract infections

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Esposito 2010	91	0.12 (0.23)	91	0.42 (0.62)		100.0 %	-0.30 [-0.44, -0.16]
Total (95% CI)	**91**		**91**			**100.0 %**	**-0.30 [-0.44, -0.16]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.33 (P = 0.000015)

Test for subgroup differences: Not applicable

Analysis 2.10. Comparison 2 Influenza vaccine versus no vaccine, Outcome 10 Number of infections other than influenza-like illness.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 2 Influenza vaccine versus no vaccine

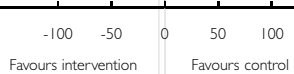
Outcome: 10 Number of infections other than influenza-like illness

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Esposito 2010	91	0.45 (0.77)	91	0.55 (0.92)		100.0 %	-0.10 [-0.35, 0.15]
Total (95% CI)	**91**		**91**			**100.0 %**	**-0.10 [-0.35, 0.15]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.80 (P = 0.43)

Test for subgroup differences: Not applicable



Analysis 2.11. Comparison 2 Influenza vaccine versus no vaccine, Outcome 11 Number of days with fever.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 2 Influenza vaccine versus no vaccine

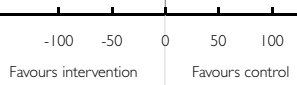
Outcome: 11 Number of days with fever

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Esposito 2010	91	1.52 (1.78)	91	3.22 (1.97)		100.0 %	-1.70 [-2.25, -1.15]
Total (95% CI)	**91**		**91**			**100.0 %**	**-1.70 [-2.25, -1.15]**

Heterogeneity: not applicable

Test for overall effect: Z = 6.11 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 2.12. Comparison 2 Influenza vaccine versus no vaccine, Outcome 12 Number of antibiotics courses.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 2 Influenza vaccine versus no vaccine

Outcome: 12 Number of antibiotics courses

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Esposito 2010	91	0.45 (0.99)	91	2.3 (1.93)		100.0 %	-1.85 [-2.30, -1.40]
Total (95% CI)	**91**		**91**			**100.0 %**	**-1.85 [-2.30, -1.40]**

Heterogeneity: not applicable

Test for overall effect: Z = 8.14 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.13. Comparison 2 Influenza vaccine versus no vaccine, Outcome 13 Number of days lost from school.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 2 Influenza vaccine versus no vaccine

Outcome: 13 Number of days lost from school

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Esposito 2010	91	1.35 (1.71)	91	6.29 (2.98)		100.0 %	-4.94 [-5.65, -4.23]
Total (95% CI)	**91**		**91**			**100.0 %**	**-4.94 [-5.65, -4.23]**

Heterogeneity: not applicable

Test for overall effect: Z = 13.72 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Influenza vaccine, two doses versus single dose, Outcome 1 4-fold rise in influenza antibody titre.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 3 Influenza vaccine, two doses versus single dose

Outcome: 1 4-fold rise in influenza antibody titre

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 4-fold rise in influenza A/H3 antibody titre					
Ljungman 2005	9/34	5/36		100.0 %	1.91 [0.71, 5.12]
Subtotal (95% CI)	**34**	**36**		**100.0 %**	**1.91 [0.71, 5.12]**
Total events: 9 (Intervention), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.28 (P = 0.20)					
2 4-fold rise in influenza A/H1 antibody titre					
Ljungman 2005	6/34	8/36		100.0 %	0.79 [0.31, 2.05]
Subtotal (95% CI)	**34**	**36**		**100.0 %**	**0.79 [0.31, 2.05]**
Total events: 6 (Intervention), 8 (Control)					
Heterogeneity: not applicable					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.48 (P = 0.63)					
3 4-fold rise in influenza B antibody titre					
Ljungman 2005	9/34	8/36		100.0 %	1.19 [0.52, 2.73]
Subtotal (95% CI)	**34**	**36**		**100.0 %**	**1.19 [0.52, 2.73]**
Total events: 9 (Intervention), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.41 (P = 0.68)					

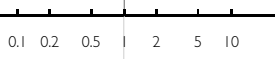
Analysis 3.2. Comparison 3 Influenza vaccine, two doses versus single dose, Outcome 2 Antibody titre above 1:40.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 3 Influenza vaccine, two doses versus single dose

Outcome: 2 Antibody titre above 1:40

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Antibody titre above 1:40 for influenza A/H3					
Ljungman 2005	7/34	8/36		100.0 %	0.93 [0.38, 2.28]
Subtotal (95% CI)	**34**	**36**		**100.0 %**	**0.93 [0.38, 2.28]**
Total events: 7 (Intervention), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.17 (P = 0.87)					
2 Antibody titre above 1:40 for influenza A/H1					
Ljungman 2005	9/34	9/36		100.0 %	1.06 [0.48, 2.35]
Subtotal (95% CI)	**34**	**36**		**100.0 %**	**1.06 [0.48, 2.35]**
Total events: 9 (Intervention), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.14 (P = 0.89)					
3 Antibody titre above 1:40 for influenza B					
Ljungman 2005	5/34	6/36		100.0 %	0.88 [0.30, 2.63]
Subtotal (95% CI)	**34**	**36**		**100.0 %**	**0.88 [0.30, 2.63]**
Total events: 5 (Intervention), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.22 (P = 0.82)					



Analysis 4.1. Comparison 4 Recombinant influenza vaccine 15 ug versus standard influenza vaccine, Outcome 1 4-fold rise in influenza hemoagglutination inhibiting antibody titre.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 4 Recombinant influenza vaccine 15 ug versus standard influenza vaccine

Outcome: 1 4-fold rise in influenza hemoagglutination inhibiting antibody titre

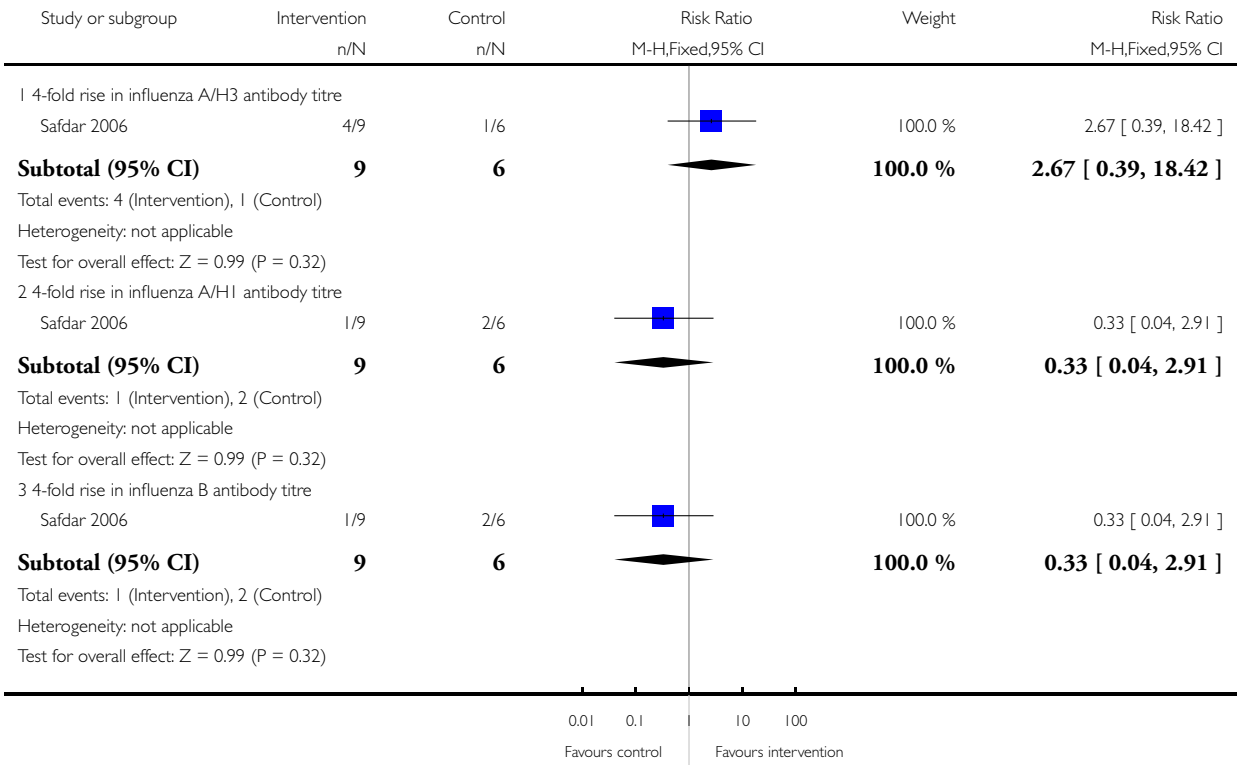
Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 4-fold rise in influenza A/H3 antibody titre					
Safdar 2006	3/9	2/6		100.0 %	1.00 [0.23, 4.31]
Subtotal (95% CI)	**9**	**6**		**100.0 %**	**1.00 [0.23, 4.31]**
Total events: 3 (Intervention), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 4-fold rise in influenza A/H1 antibody titre					
Safdar 2006	0/9	1/6		100.0 %	0.23 [0.01, 4.93]
Subtotal (95% CI)	**9**	**6**		**100.0 %**	**0.23 [0.01, 4.93]**
Total events: 0 (Intervention), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.93 (P = 0.35)					
3 4-fold rise in influenza B antibody titre					
Safdar 2006	1/9	2/6		100.0 %	0.33 [0.04, 2.91]
Subtotal (95% CI)	**9**	**6**		**100.0 %**	**0.33 [0.04, 2.91]**
Total events: 1 (Intervention), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.99 (P = 0.32)					

Analysis 4.2. Comparison 4 Recombinant influenza vaccine 15 ug versus standard influenza vaccine, Outcome 2 4-fold rise in influenza neutralizing antibody titre.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 4 Recombinant influenza vaccine 15 ug versus standard influenza vaccine

Outcome: 2 4-fold rise in influenza neutralizing antibody titre

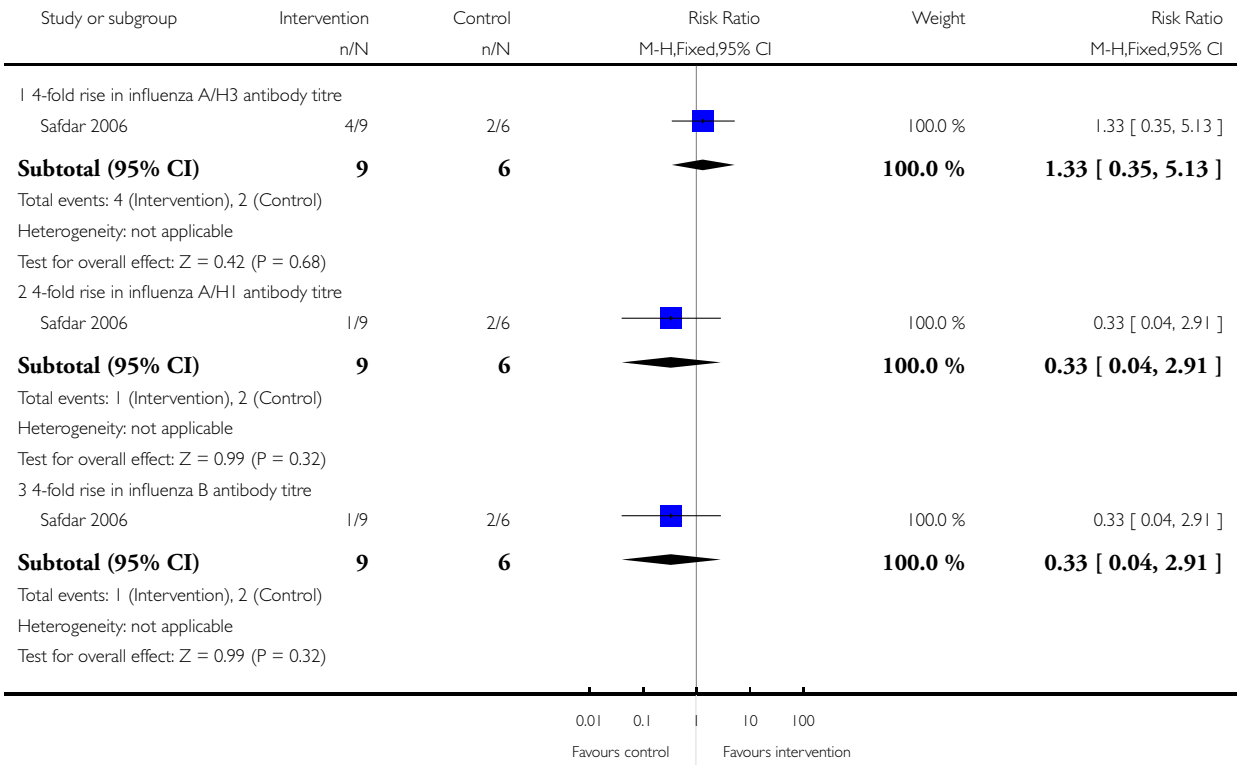


Analysis 4.3. Comparison 4 Recombinant influenza vaccine 15 ug versus standard influenza vaccine, Outcome 3 4-fold rise in influenza antibody titre (either hemoagglutination inhibiting or neutralizing).

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 4 Recombinant influenza vaccine 15 ug versus standard influenza vaccine

Outcome: 3 4-fold rise in influenza antibody titre (either hemoagglutination inhibiting or neutralizing)

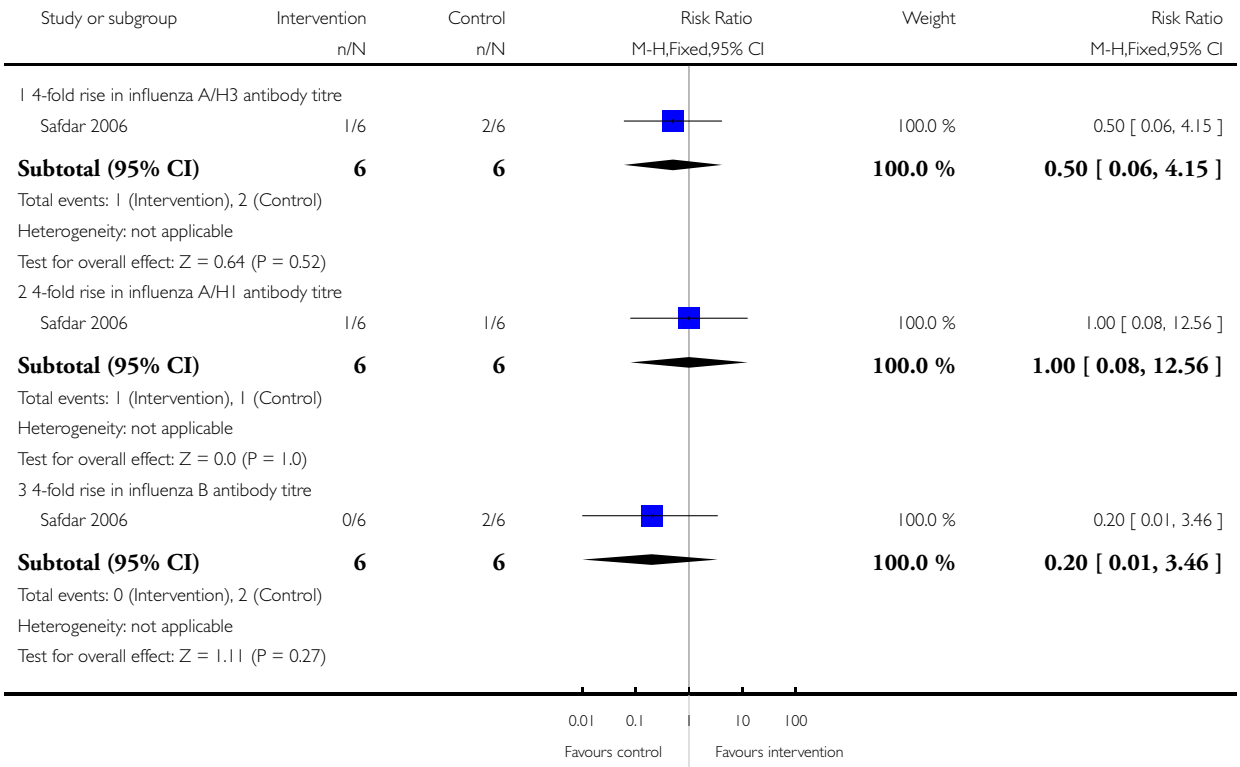


Analysis 5.1. Comparison 5 Recombinant influenza vaccine 45 ug versus standard influenza vaccine, Outcome 1 4-fold rise in influenza hemoagglutination inhibiting antibody titre.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 5 Recombinant influenza vaccine 45 ug versus standard influenza vaccine

Outcome: 1 4-fold rise in influenza hemoagglutination inhibiting antibody titre

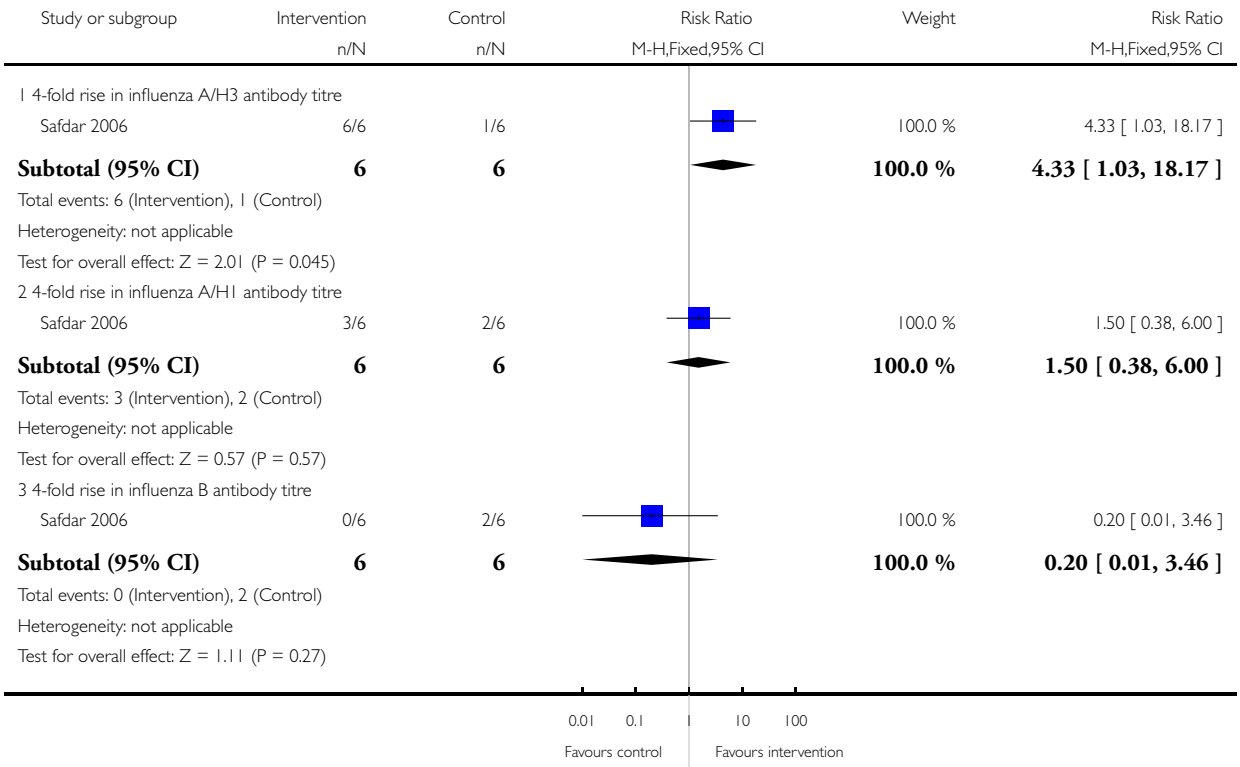


Analysis 5.2. Comparison 5 Recombinant influenza vaccine 45 ug versus standard influenza vaccine, Outcome 2 4-fold rise in influenza neutralizing antibody titre.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 5 Recombinant influenza vaccine 45 ug versus standard influenza vaccine

Outcome: 2 4-fold rise in influenza neutralizing antibody titre

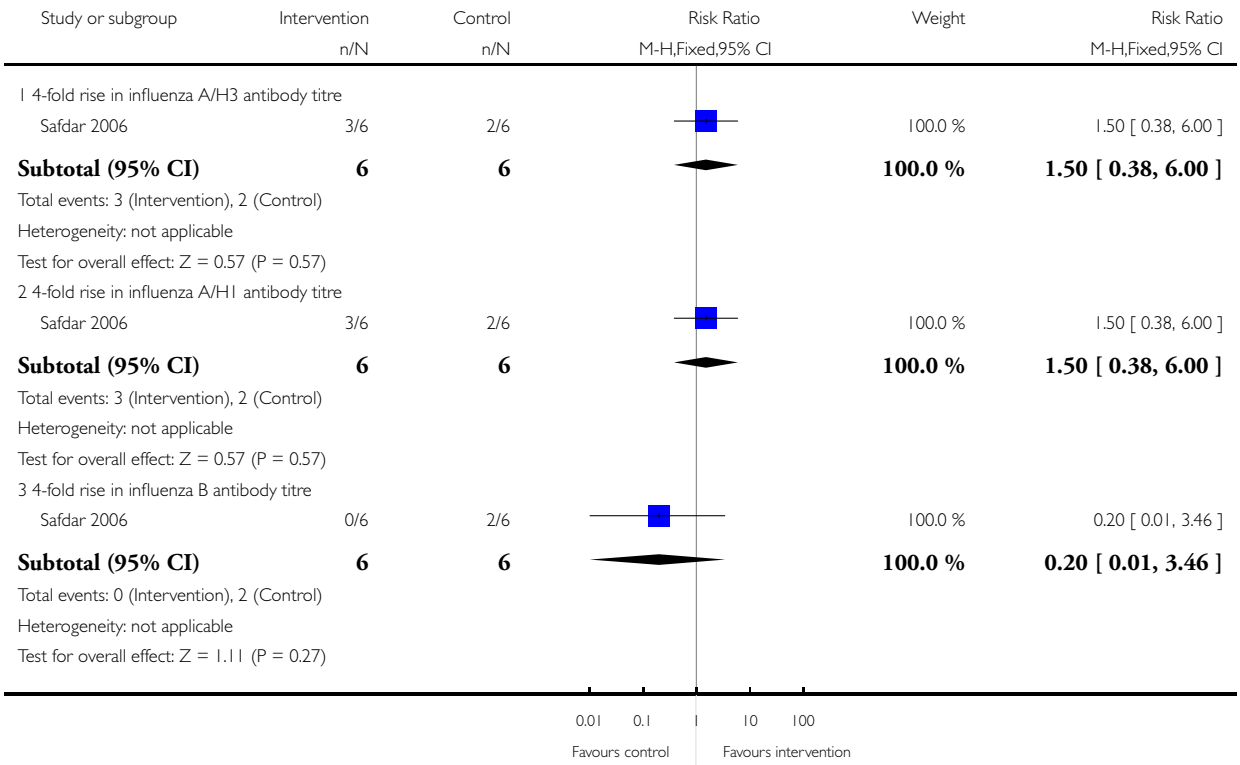


Analysis 5.3. Comparison 5 Recombinant influenza vaccine 45 ug versus standard influenza vaccine, Outcome 3 4-fold rise in influenza antibody titre (either hemoagglutination inhibiting or neutralizing).

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 5 Recombinant influenza vaccine 45 ug versus standard influenza vaccine

Outcome: 3 4-fold rise in influenza antibody titre (either hemoagglutination inhibiting or neutralizing)

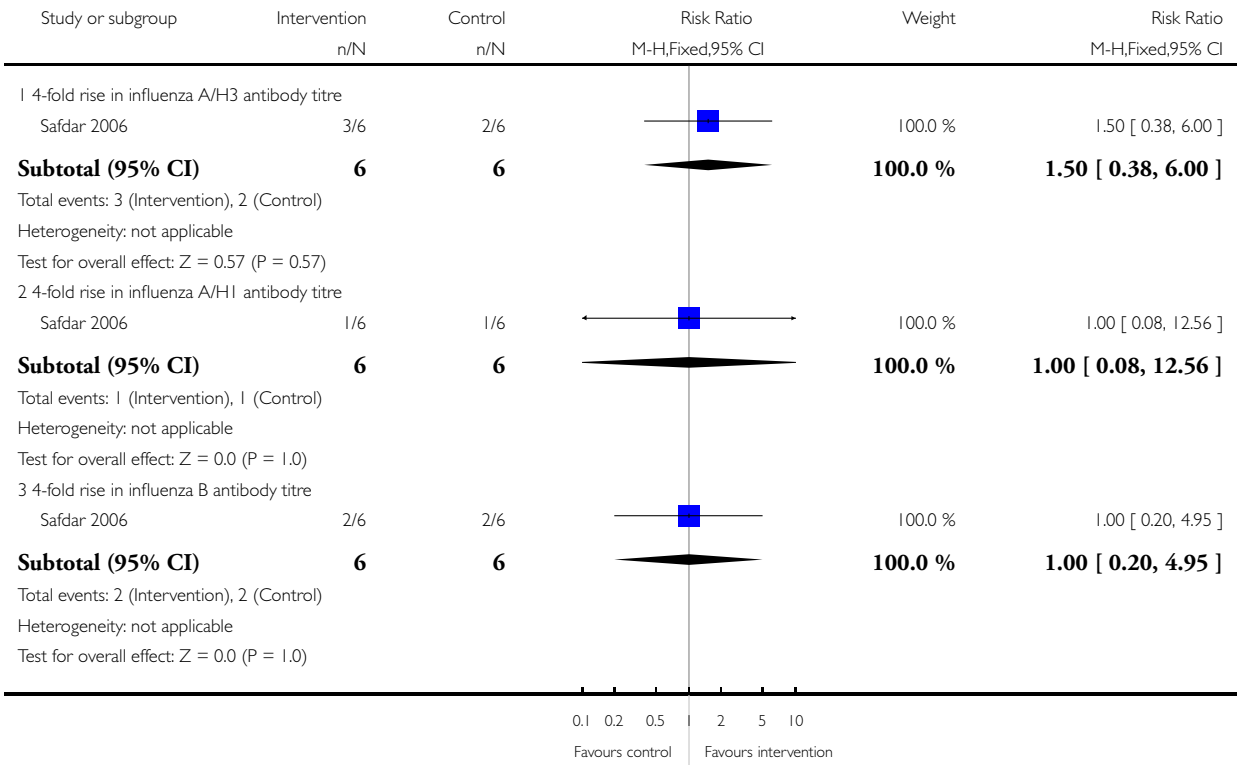


Analysis 6.1. Comparison 6 Recombinant influenza vaccine 135 ug versus standard influenza vaccine, Outcome 1 4-fold rise in influenza hemoagglutination inhibiting antibody titre.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 6 Recombinant influenza vaccine 135 ug versus standard influenza vaccine

Outcome: 1 4-fold rise in influenza hemoagglutination inhibiting antibody titre

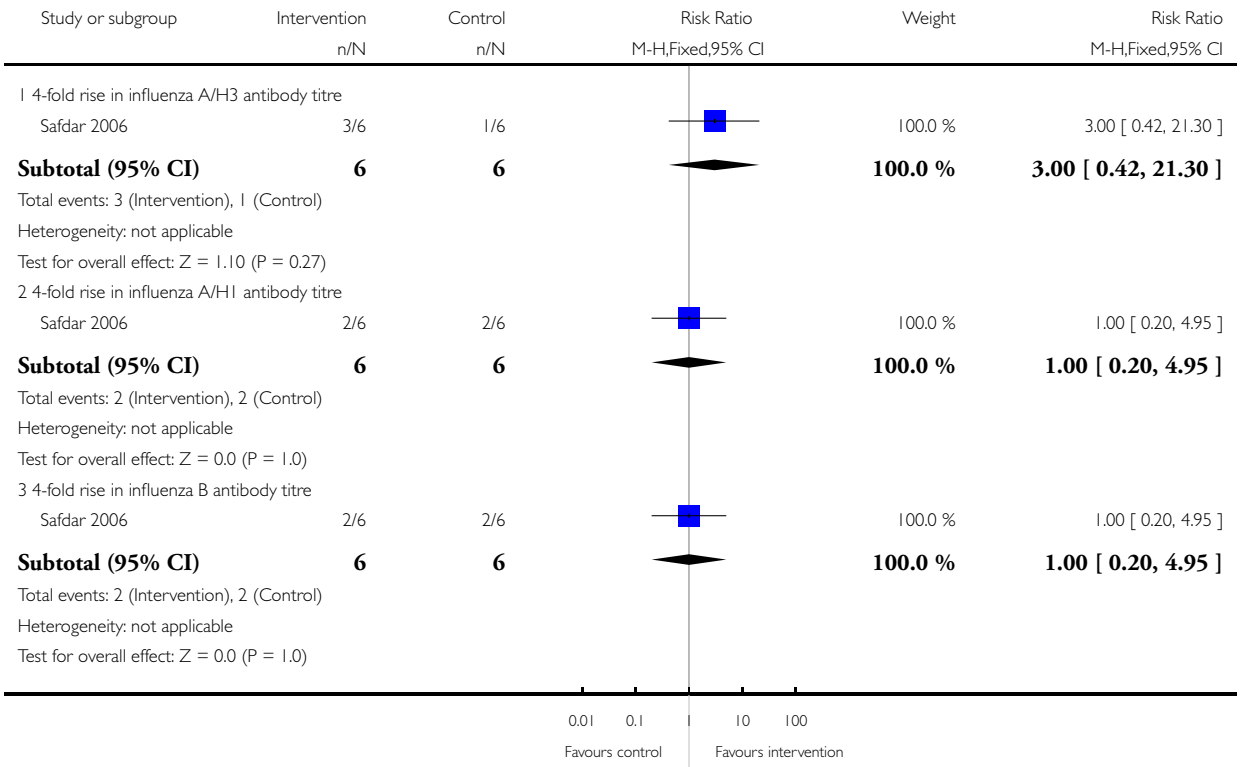


Analysis 6.2. Comparison 6 Recombinant influenza vaccine 135 ug versus standard influenza vaccine, Outcome 2 4-fold rise in influenza neutralizing antibody titre.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 6 Recombinant influenza vaccine 135 ug versus standard influenza vaccine

Outcome: 2 4-fold rise in influenza neutralizing antibody titre

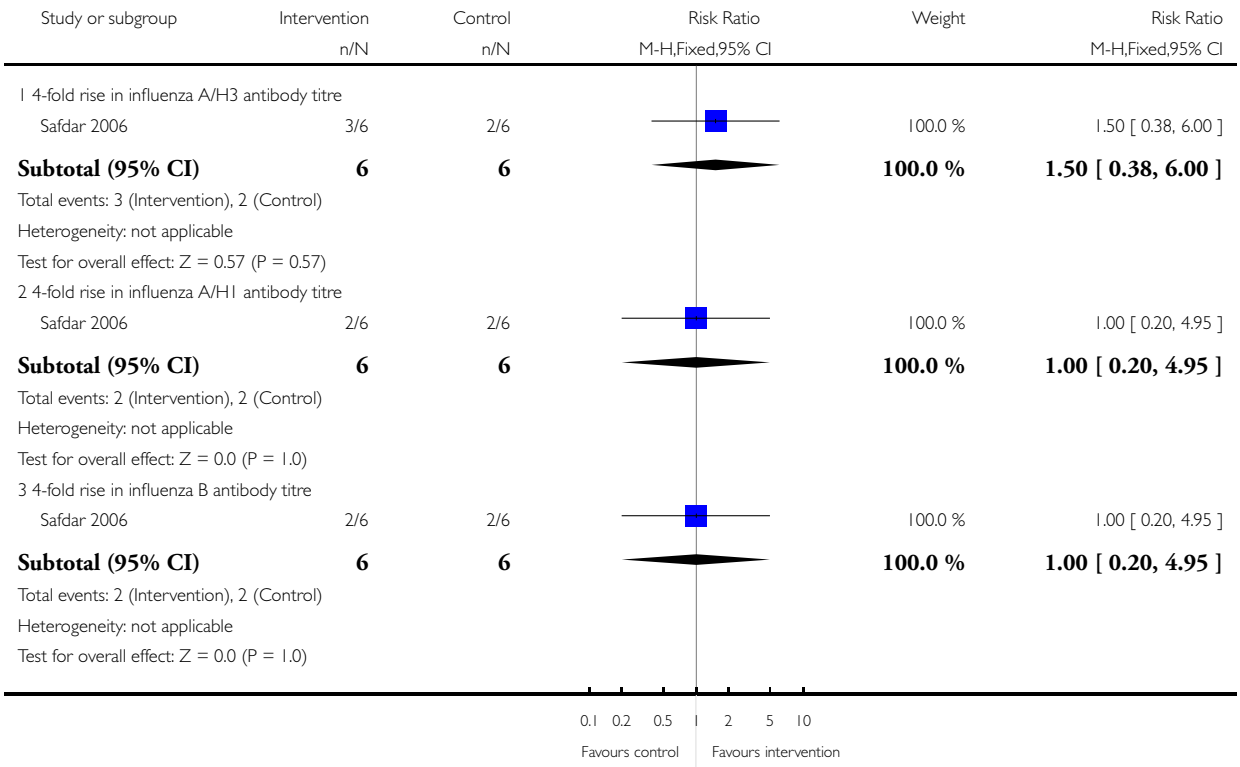


Analysis 6.3. Comparison 6 Recombinant influenza vaccine 135 ug versus standard influenza vaccine, Outcome 3 4-fold rise in influenza antibody titre (either hemoagglutination inhibiting or neutralizing).

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 6 Recombinant influenza vaccine 135 ug versus standard influenza vaccine

Outcome: 3 4-fold rise in influenza antibody titre (either hemoagglutination inhibiting or neutralizing)

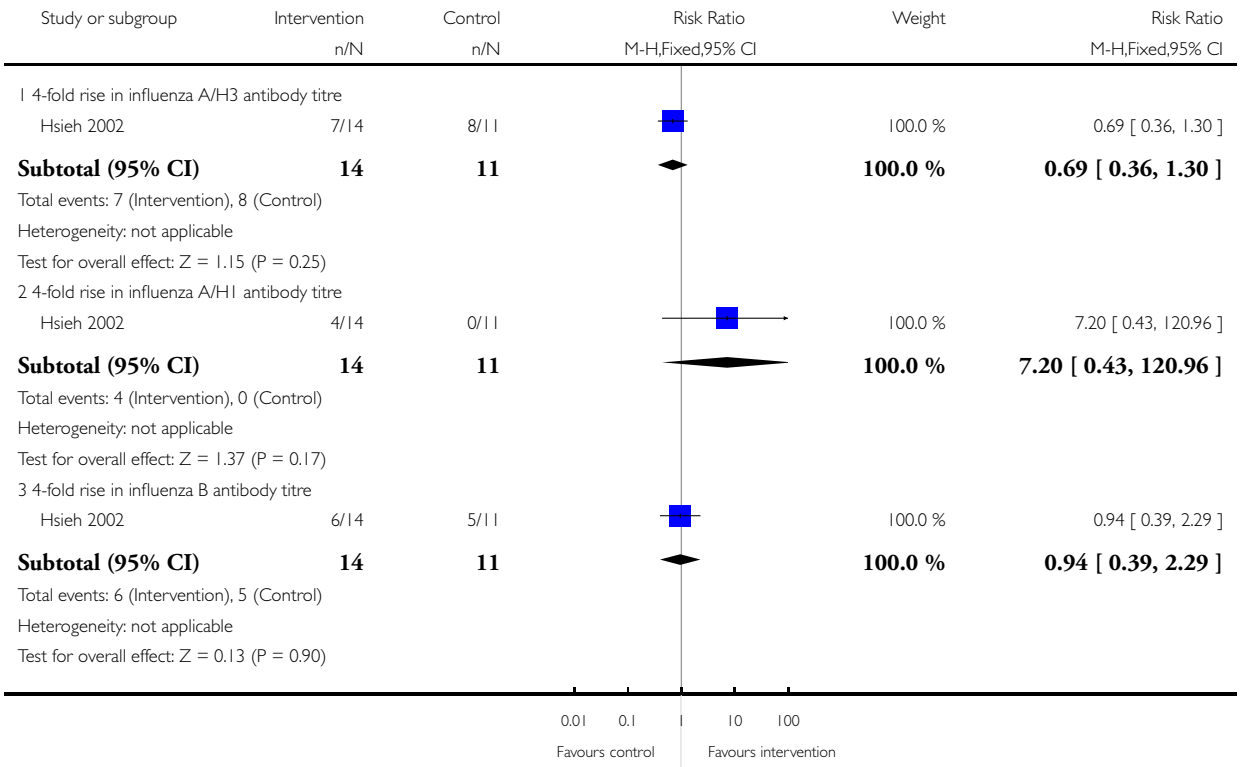


Analysis 7.1. Comparison 7 Comparison of different influenza vaccine schedules: first dose versus second dose given with re-induction, Outcome 1 4-fold rise in influenza antibody titre after first vaccine dose.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 7 Comparison of different influenza vaccine schedules: first dose versus second dose given with re-induction

Outcome: 1 4-fold rise in influenza antibody titre after first vaccine dose

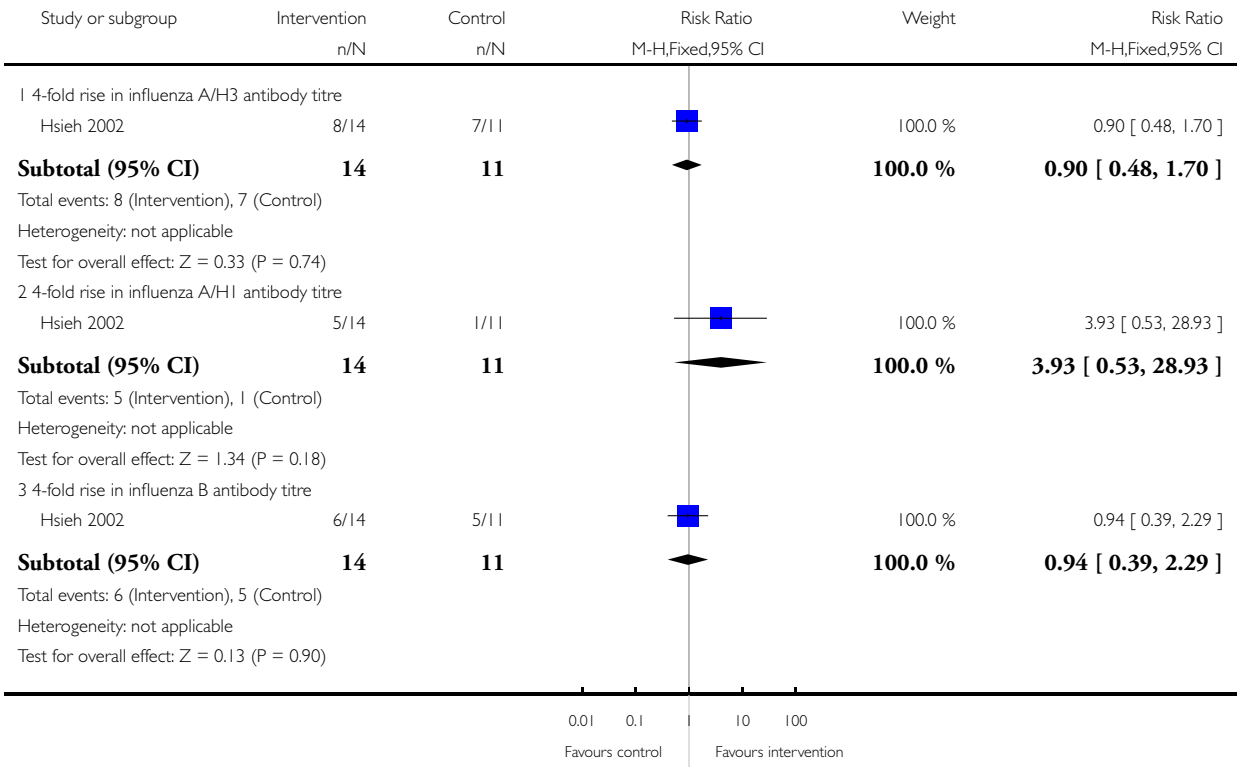


Analysis 7.2. Comparison 7 Comparison of different influenza vaccine schedules: first dose versus second dose given with re-induction, Outcome 2 4-fold rise in influenza antibody titre after second vaccine dose.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 7 Comparison of different influenza vaccine schedules: first dose versus second dose given with re-induction

Outcome: 2 4-fold rise in influenza antibody titre after second vaccine dose

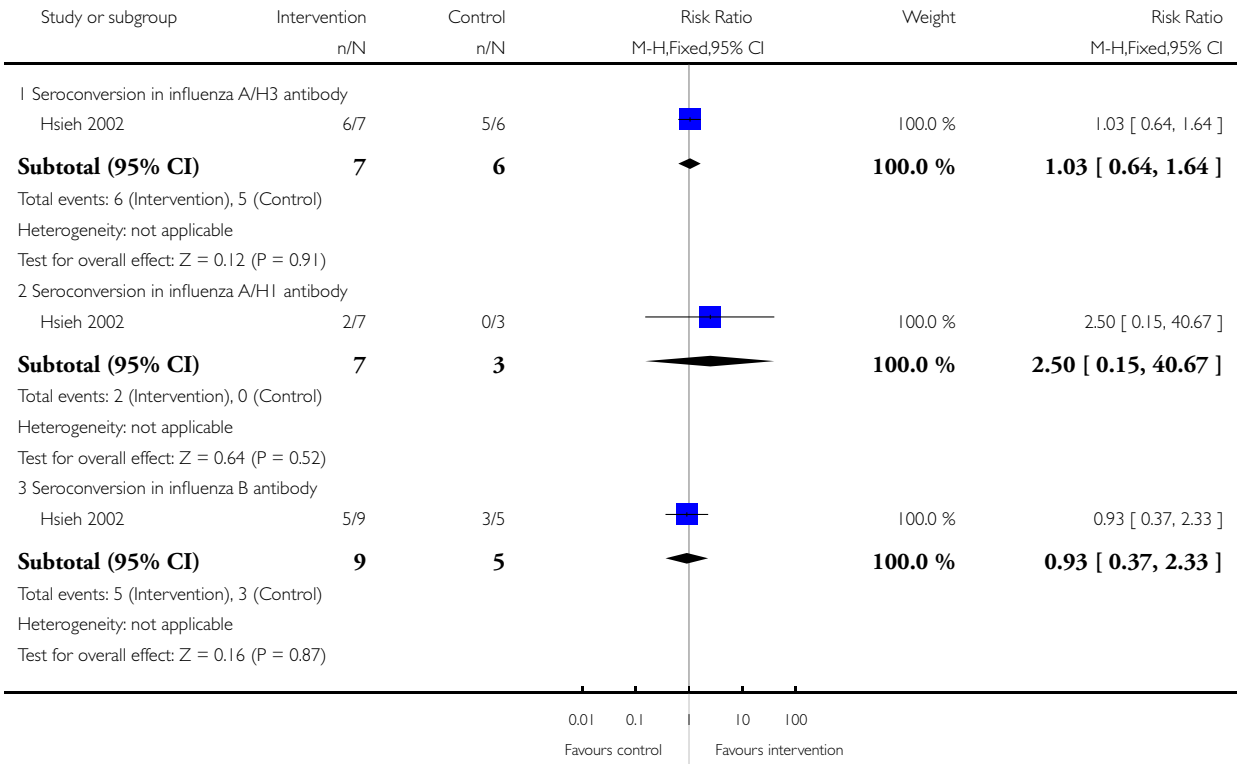


Analysis 7.3. Comparison 7 Comparison of different influenza vaccine schedules: first dose versus second dose given with re-induction, Outcome 3 Seroconversion after first vaccine dose (increase of antibody titre from <40 to >=40).

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 7 Comparison of different influenza vaccine schedules: first dose versus second dose given with re-induction

Outcome: 3 Seroconversion after first vaccine dose (increase of antibody titre from <40 to >=40)

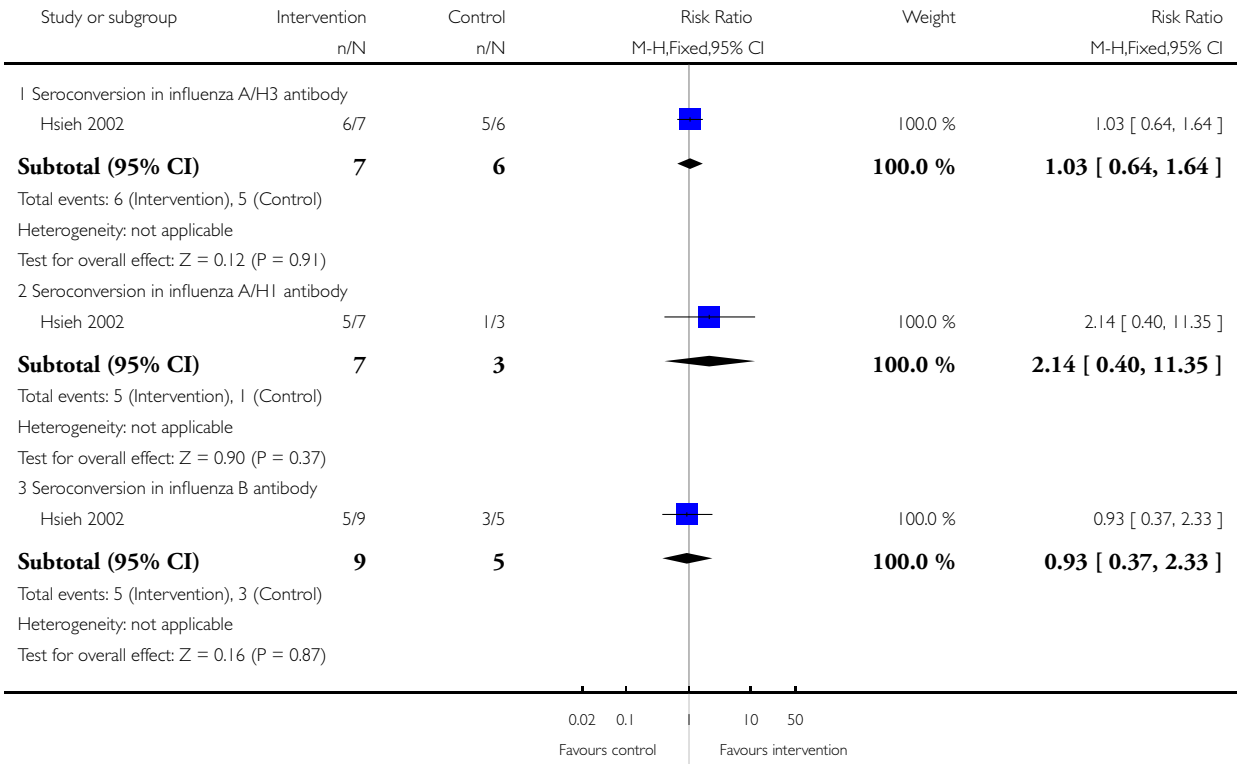


Analysis 7.4. Comparison 7 Comparison of different influenza vaccine schedules: first dose versus second dose given with re-induction, Outcome 4 Seroconversion after second vaccine dose (increase of antibody titre from <40 to >=40).

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 7 Comparison of different influenza vaccine schedules: first dose versus second dose given with re-induction

Outcome: 4 Seroconversion after second vaccine dose (increase of antibody titre from <40 to >=40)



Analysis 8.1. Comparison 8 Inactivated poliovirus vaccine early schedule versus late schedule, Outcome 1 4-fold rise in poliovirus antibody titre after first vaccine dose.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 8 Inactivated poliovirus vaccine early schedule versus late schedule

Outcome: 1 4-fold rise in poliovirus antibody titre after first vaccine dose

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 4-fold rise in poliovirus type 1 antibody titre					
Parkkali 1997	6/22	9/15		100.0 %	0.45 [0.20, 1.01]
Subtotal (95% CI)	**22**	**15**		**100.0 %**	**0.45 [0.20, 1.01]**
Total events: 6 (Intervention), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.94 (P = 0.053)					
2 4-fold rise in poliovirus type 2 antibody titre					
Parkkali 1997	5/22	10/15		100.0 %	0.34 [0.15, 0.80]
Subtotal (95% CI)	**22**	**15**		**100.0 %**	**0.34 [0.15, 0.80]**
Total events: 5 (Intervention), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.48 (P = 0.013)					
3 4-fold rise in poliovirus type 3 antibody titre					
Parkkali 1997	10/22	12/15		100.0 %	0.57 [0.34, 0.96]
Subtotal (95% CI)	**22**	**15**		**100.0 %**	**0.57 [0.34, 0.96]**
Total events: 10 (Intervention), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.12 (P = 0.034)					

Analysis 8.2. Comparison 8 Inactivated poliovirus vaccine early schedule versus late schedule, Outcome 2 4-fold rise in poliovirus antibody titre after second vaccine dose.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 8 Inactivated poliovirus vaccine early schedule versus late schedule

Outcome: 2 4-fold rise in poliovirus antibody titre after second vaccine dose

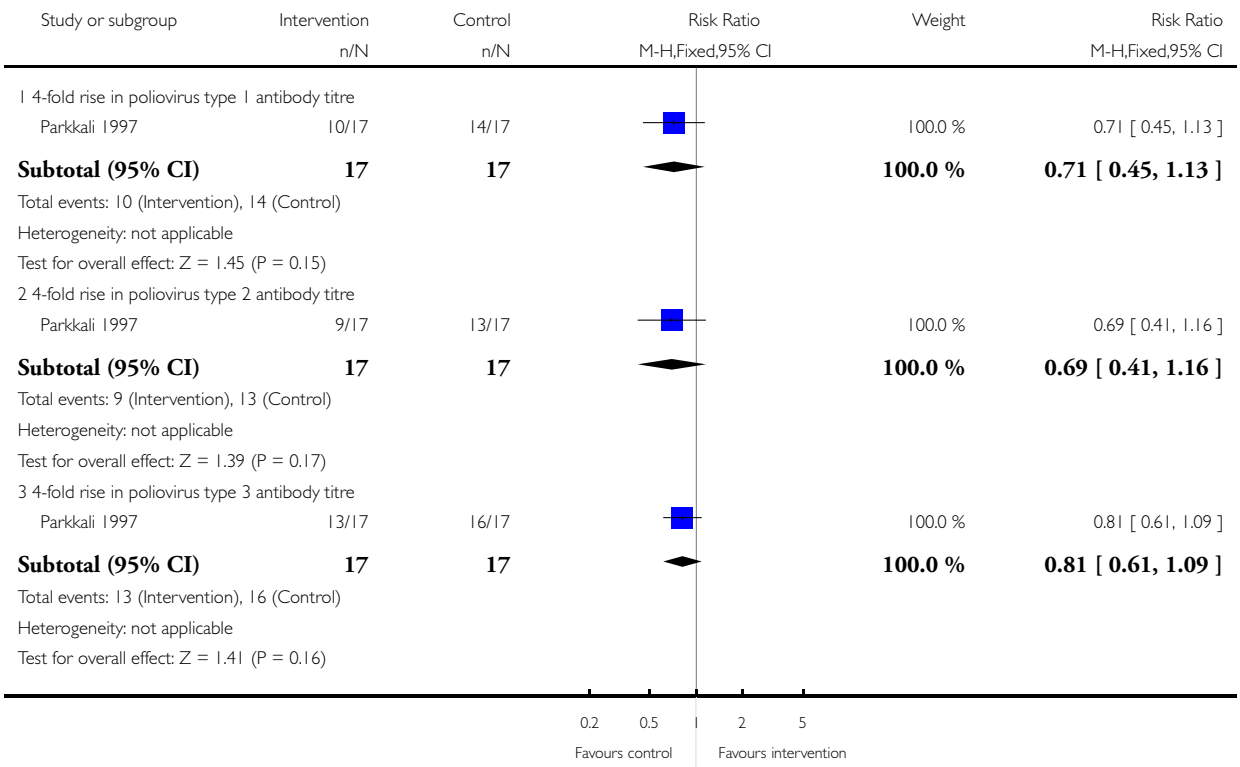
Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 4-fold rise in poliovirus type 1 antibody titre					
Parkkali 1997	9/21	13/18		100.0 %	0.59 [0.34, 1.05]
Subtotal (95% CI)	**21**	**18**		**100.0 %**	**0.59 [0.34, 1.05]**
Total events: 9 (Intervention), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.79 (P = 0.073)					
2 4-fold rise in poliovirus type 2 antibody titre					
Parkkali 1997	9/21	13/18		100.0 %	0.59 [0.34, 1.05]
Subtotal (95% CI)	**21**	**18**		**100.0 %**	**0.59 [0.34, 1.05]**
Total events: 9 (Intervention), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.79 (P = 0.073)					
3 4-fold rise in poliovirus type 3 antibody titre					
Parkkali 1997	13/21	16/18		100.0 %	0.70 [0.48, 1.01]
Subtotal (95% CI)	**21**	**18**		**100.0 %**	**0.70 [0.48, 1.01]**
Total events: 13 (Intervention), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.90 (P = 0.057)					

Analysis 8.3. Comparison 8 Inactivated poliovirus vaccine early schedule versus late schedule, Outcome 3 4-fold rise in poliovirus antibody titre after third vaccine dose.

Review: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Comparison: 8 Inactivated poliovirus vaccine early schedule versus late schedule

Outcome: 3 4-fold rise in poliovirus antibody titre after third vaccine dose



ADDITIONAL TABLES

Table 1. PRISMA flow chart

Identification	Number of records through database searching and other sources = 650
Screening	number of records after duplicates removed = 565 Number of records screened = 575 Number of records excluded = 557
Eligibility	Number of full text articles assessed for eligibility = 8 Number of full text articles excluded = 0
Included	Number of studies included in qualitative and quantitative analyses = 8

APPENDICES

Appendix 1. MEDLINE search strategy

1. Hematologic Diseases/
2. exp Hematologic Neoplasms/
3. (h?ematolog$ adj1 malignan$).tw,kf,ot.
4. (h?ematolog$ adj1 neoplas$).tw,kf,ot.
5. exp Bone Marrow Diseases/
6. exp Lymphoma/
7. exp Leukemia/
8. hodgkin$.tw,kf,ot.
9. lymphogranulomato$.tw,kf,ot.
10. lymphom$.tw,kf,ot.
11. histiocy$.tw,kf,ot.
12. granulom$.tw,kf,ot.
13. non-hodgkin$.tw,kf,ot.
14. nonhodgkin$.tw,kf,ot.
15. reticulosis.tw,kf,ot.
16. reticulosarcom$.tw,kf,ot.
17. (burkitt$ adj (lymphom$ or tumo?r$)).tw,kf,ot.
18. lymphosarcom$.tw,kf,ot.
19. brill-symmer$.tw,kf,ot.
20. plasm##ytom$.tw,kf,ot.
21. myelom$.tw,kf,ot.
22. sezary.tw,kf,ot.
23. leuk?em$.tw,kf,ot.
24. myelodysplas$.tw,kf,ot.
25. aplast$ an?em$.tw,kf,ot.
26. or/1-25
27. randomized controlled trial.pt.
28. controlled clinical trial.pt.
29. Randomized Controlled Trials/
30. Random Allocation/
31. Double Blind Method/
32. Single Blind Method/
33. or/27-32
34. (Animals not Humans).sh.
35. 33 not 34
36. clinical trial.pt.
37. exp Clinical Trial/
38. (clin$ adj25 trial$).ti,ab.
39. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
40. Placebos/
41. placebo$.ti,ab.
42. random$.ti,ab.
43. Research Design/
44. or/36-43
45. 44 not 34
46. 35 or 45
47. exp Viral Vaccines/
48. vaccines.sh
49. vaccin$.tw, kf, ot.

50. immunization.sh
51. prophylaxis.tw,kf,ot.
52. or/47-51
53. exp Chickenpox/
54. exp Varicellovirus/
55. exp Herpes Zoster/
56. exp Influenza/
57. exp Measles/
58. exp Mumps/
59. exp Rubella/
60. exp Poliomyelitis/
61. exp Hepatitis/
62. exp Rotavirus/
63. exp Yellow fever/
64. exp Rabies/
65. exp Encephalitis/
66. varicell$.tw,kf,ot.
67. chickenpox.tw,kf,ot.
68. zoster.tw,kf,ot.
69. flu.tw,kf,ot.
70. measles.tw,kf,ot.
71. mumps.tw,kf,ot.
72. rubella.tw,kf,ot.
73. MMR.tw,kf,ot.
74. polio$.tw,kf,ot.
75. hepatitis.tw,kf,ot.
76. rotavir$.tw,kf,ot.
77. (yellow adj1 fever).tw,kf,ot.
78. rabies.tw,kf,ot.
79. encephalitis.tw,kf,ot.
80. Or/53-79
81. 26 and 46 and 52 and 80

Appendix 2. EMBASE search strategy

1. Hematologic disease/
2. Hematologic neoplasm/
3. Bone marrow disease/
4. Lymphoma/
5. Leukemia/
6. hematolog$ malignan$.mp
7. hematolog$ neoplas$.mp
8. hodgkin$.mp
9. lymphogranulomato$.mp
10. lymphom$.mp
11. histiocy$.mp
12. granulom$.mp
13. non-hodgkin$.mp
14. nonhodgkin$.mp
15. reticulosis.mp
16. reticulosarcom$.mp
17. (burkitt$ lymphom$ or burkitt$ tumor$).mp

18. lymphosarcom$.mp
19. brill-symmer$.mp
20. plasmacytom$.mp
21. myelom$.mp
22. sezary.mp
23. leukem$.mp
24. myelodysplas$.mp
25. aplast$ anem$.mp
26. or/1-25
27. Controlled Clinical Trial/
28. Randomized Controlled Trial/
29. Double Blind Method/
30. Single Blind Method/
31. Randomization/
32. Placebo/
33. blind$.mp.
34. placebo$.mp.
35. prospectiv$.mp.
36. random$.mp.
37. ((singl$ or doubl$ or trebl$ or tripl$) and (blind$ or mask$)).mp.
38. (randomized controlled trial$ or randomised controlled trial$).mp.
39. controlled clinical trial$.mp.
40. or/27-39
41. Human/
42. Nonhuman/
43. Animal/
44. Animal Experiment/
45. or/42-44
46. 45 not 41
47. 40 not 46
48. Viral vaccine/
49. vaccin$.mp
50. (immuniz$ or immunis$).mp
51. prophyla$.mp
52. or/48-51
53. Chickenpox/
54. Varicellovirus/
55. Herpes Zoster/
56. Influenza/
57. Measles/
58. Mumps/
59. Rubella/
60. Poliomyelitis/
61. Hepatitis/
62. Rotavirus/
63. Yellow fever/
64. Rabies/
65. Encephalitis/
66. varicell$.mp
67. chickenpox.mp
68. zoster.mp
69. flu.mp
70. measles.mp

71. mumps.mp
72. rubella.mp
73. MMR.mp
74. polio$.mp
75. hepatitis.mp
76. rotavir$.mp
77. yellow fever.mp
78. rabies.mp
79. encephalitis.mp
80. or/53-79
81. 26 and 47 and 52 and 80

Appendix 3. CINAHL search strategy

(hematolog* malignan* or hematolog* neoplas* or lymphom* or leukem* or hodgkin* or lymphogranulomato* or histiocy* or granulom* or non-hodgkin* or nonhodgkin* or reticulosis or reticulosarcom* or lymphosarcom* or brill-symmer* or plasmacytom* or myelom* or sezary or myelodysplas* or aplastic anem*) and (randomized controlled trial or controlled clinical trial or random* or double blind or single blind or treble blind or triple blind or placebo*) and (vaccin* or immuniz* or immunis* or prophyla*) and (chickenpox or varicell* or zoster or influenza or flu or measles or mumps or rubella or MMR or polio* or hepatitis or rotavir* or yellow fever or rabies or encephalitis)

Appendix 4. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

(hematolog* malignan* or hematolog* neoplas* or lymphom* or leukem* or hodgkin* or lymphogranulomato* or histiocy* or granulom* or non-hodgkin* or nonhodgkin* or reticulosis or reticulosarcom* or lymphosarcom* or brill-symmer* or plasmacytom* or myelom* or sezary or myelodysplas* or aplastic anem*) and (chickenpox or varicell* or zoster or influenza or flu or measles or mumps or rubella or MMR or polio* or hepatitis or rotavir* or yellow fever or rabies or encephalitis)

HISTORY

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CONTRIBUTIONS OF AUTHORS

Cheuk DKL: protocol development, searching for trials, quality assessment of trials, data extraction, data input, data analyses, development of final review, corresponding author.

Chiang AKS: protocol development, searching for trials, quality assessment of trials, data extraction, data analyses, development of final review.

Lee TL: protocol development, development of final review.

Chan GCF: protocol development, development of final review.

Ha SY: protocol development, development of final review.

DECLARATIONS OF INTEREST

There is no potential conflict of interests.

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- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Outcomes that were not pre-defined in the protocol were added.

INDEX TERMS

Medical Subject Headings (MeSH)

Chickenpox Vaccine [*therapeutic use]; Hematologic Neoplasms [*complications]; Influenza Vaccines [*therapeutic use]; Poliovirus Vaccines [*therapeutic use]; Randomized Controlled Trials as Topic; Vaccines, Inactivated [therapeutic use]; Virus Diseases [*prevention & control]

MeSH check words

Humans