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[Intervention Review]

Influenza vaccines in immunosuppressed adults with cancer

Roni Bitterman¹, Noa Eliakim-Raz², Inbal Vinograd³, Anca Zalmanovici Trestioreanu⁴, Leonard Leibovici⁵, Mical Paul¹

¹Division of Infectious Diseases, Rambam Health Care Campus, Haifa, Israel. ²Department of Medicine E; and Sackler Faculty of Medicine, Tel-Aviv University, Israel, Beilinson Hospital, Rabin Medical Center, Petah Tikva, Israel. ³Pharmacy, Schneider Children's Medical Centre of Israel, Petah-Tikva, Israel. ⁴Department of Family Medicine, Beilinson Hospital, Rabin Medical Center, Petah Tikva, Israel. ⁵Department of Medicine E, Beilinson Hospital, Rabin Medical Center, Petah Tikva, Israel

Contact address: Roni Bitterman, Division of Infectious Diseases, Rambam Health Care Campus, Haifa, Israel.
ro_oren@rambam.health.gov.il.

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ABSTRACT

Background

This is an update of the Cochrane review published in 2013, Issue 10.

Immunosuppressed cancer patients are at increased risk of serious influenza-related complications. Guidelines, therefore, recommend influenza vaccination for these patients. However, data on vaccine effectiveness in this population are lacking, and the value of vaccination in this population remains unclear.

Objectives

To assess the effectiveness of influenza vaccine in immunosuppressed adults with malignancies. The primary review outcome is all-cause mortality, preferably at the end of the influenza season. Influenza-like illness (ILI, a clinical definition), confirmed influenza, pneumonia, any hospitalisations, influenza-related mortality and immunogenicity were defined as secondary outcomes.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and LILACS databases up to May 2017. We searched the following conference proceedings: ICAAC, ECCMID, IDSA (infectious disease conferences), ASH, ASBMT, EBMT (haematological), and ASCO (oncological) between the years 2006 to 2017. In addition, we scanned the references of all identified studies and pertinent reviews. We searched the websites of the manufacturers of influenza vaccine. Finally, we searched for ongoing or unpublished trials in clinical trial registry databases.

Selection criteria

Randomised controlled trials (RCTs), prospective and retrospective cohort studies and case-control studies were considered, comparing inactivated influenza vaccines versus placebo, no vaccination or a different vaccine, in adults (16 years and over) with cancer. We considered solid malignancies treated with chemotherapy, haematological cancer patients treated or not treated with chemotherapy, cancer patients post-autologous (up to six months after transplantation) or allogeneic (at any time) haematopoietic stem cell transplantation (HSCT).

Data collection and analysis

Two review authors independently assessed the risk of bias and extracted data from included studies adhering to Cochrane methodology. Meta-analysis could not be performed because of different outcome and denominator definitions in the included studies.

Main results

We identified six studies with a total of 2275 participants: five studies comparing vaccination with no vaccination, and one comparing adjuvanted vaccine with non-adjuvanted vaccine. Three studies were RCTs, one was a prospective observational cohort study and two were retrospective cohort studies.

For the comparison of vaccination with no vaccination we included two RCTs and three observational studies, including 2202 participants. One study reported results in person-years while the others reported results per person. The five studies were performed between 1993 and 2015 and included adults with haematological diseases (three studies), patients following bone marrow transplantation (BMT) (two studies) and solid malignancies (three studies).

One RCT and two observational studies reported all-cause mortality; the RCT showed similar mortality rates in both arms (odds ratio (OR) 1.25 (95% CI 0.43 to 3.62; 1 study, 78 participants, low-certainty evidence)); and the observational studies demonstrated a significant association between vaccine receipt and lower risk of death, adjusted hazard ratio 0.88 (95% CI 0.78 to 1; 1 study, 1577 participants, very low-certainty evidence) in one study and OR 0.42 (95% CI 0.24 to 0.75; 1 study, 806 participants, very low-certainty evidence) in the other. One RCT reported a reduction in ILI with vaccination, while no difference was observed in one observational study. Confirmed influenza rates were lower with vaccination in one RCT and the three observational studies, the difference reaching statistical significance in one. Pneumonia was observed significantly less frequently with vaccination in one observational study, but no difference was detected in another or in the RCT. One RCT showed a reduction in hospitalisations following vaccination, while an observational study found no difference. No life-threatening or persistent adverse effects from vaccination were reported. The strength of evidence was limited by the low number of included studies and by their low methodological quality and the certainty of the evidence for the mortality outcome according to GRADE was low to very low.

For the comparison of adjuvanted vaccine with non-adjuvanted vaccine, we identified one RCT, including 73 patients. No differences were found for the primary and all secondary outcomes assessed. Mortality risk ratio was 0.54 (95% CI 0.05 to 5.73; low-certainty evidence) in the adjuvanted vaccine group. The quality of evidence was low due to the small sample size and the large confidence intervals for all outcomes.

Authors' conclusions

Observational data suggest lower mortality and infection-related outcomes with influenza vaccination. The strength of evidence is limited by the small number of studies and low grade of evidence. It seems that the evidence, although weak, shows that the benefits outweigh the potential risks when vaccinating adults with cancer against influenza. However, additional placebo or no-treatment controlled RCTs of influenza vaccination among adults with cancer is ethically questionable. There is no conclusive evidence regarding the use of adjuvanted versus non-adjuvanted influenza vaccine in this population.

PLAIN LANGUAGE SUMMARY

Influenza (flu) vaccination for preventing influenza in adults with cancer

Background

Adults with cancer are prone to serious complications from influenza, more than healthy adults. The influenza vaccine protects against influenza and its complications. However, its effectiveness among people with cancer is unclear, as immune dysfunction that accompanies cancer as a result of chemotherapy might lower immune response to the vaccine. People with cancer, therefore, do not have clear information on the importance and effectiveness of the vaccine.

The aim of the review

This review focused on the effectiveness of influenza vaccination in adults with cancer who have a suppressed immune system because of cancer or chemotherapy. We searched the literature up to May 2017.

What are the main findings?

We identified six clinical studies (2275 participants) addressing this question, half of which were randomised controlled trials, where patients were randomly selected to get or not to get the vaccine. Two other studies showed that adults with cancer who were vaccinated were found to have lower rates of death, but these studies were not randomised. One small randomised study showed a similar mortality rate in vaccinated and non-vaccinated patients. Pooling (combining) results from the different studies was not possible because of different methods or different ways the results were reported. There was a lower rate of influenza-like illness (any febrile respiratory illness), pneumonia, confirmed influenza and hospitalisation for any reason, among vaccinated people in at least one study. No side effects to the vaccine were reported in these studies. The review also included a trial comparing the regular vaccine to a vaccine containing an adjuvant that is supposed to increase the immune response. This randomised trial was small and did not find differences in all clinical outcomes examined.

Quality of the evidence

The strength of evidence is limited by the low number of studies and by their low methodological quality (high risk of bias).

What are the conclusions?

It is unlikely that there will be any future large-scale controlled trials to investigate this issue. The current evidence, although weak, suggests a benefit for influenza vaccination amongst adults with cancer and the vaccine was not found to be harmful. Influenza vaccines given to adults with cancer contain an inactivated virus that cannot cause influenza or other viral infection.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Influenza vaccine compared to no vaccine for immunosuppressed adults with cancer

Influenza vaccine compared to no vaccine for immunosuppressed adults with cancer

Patient or population: immunosuppressed adults with cancer

Setting: outpatients

Intervention: influenza vaccine

Comparison: no vaccine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no vaccine	Risk with influenza vaccine				
All-cause mortality, solid cancers Follow-up: range 4 months to 12 months	Study population		OR 0.88 (0.78 to 1.00)	1577 (1 observational study)	⊕⊕⊕⊕ VERY LOW ^{1 2 3}	Earle 2003
	417 per 1,000	387 per 1,000 (359 to 417)				
All-cause mortality, solid and haematological malignancies Follow-up: range 5 months to 7 months	Study population		OR 0.42 (0.24 to 0.75)	806 (1 observational study)	⊕⊕⊕⊕ VERY LOW ^{3 4}	Vinograd 2013
	456 per 1,000	260 per 1,000 (167 to 386)				
All-cause mortality, allogeneic BMT Follow-up: mean 6 months	Study population		OR 1.25 (0.43 to 3.62)	78 (1 RCT)	⊕⊕⊕⊕ LOW ^{5 6}	Ambati 2015
	211 per 1,000	250 per 1,000 (103 to 491)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BMT: bone marrow transplantation; **CI:** Confidence interval; **OR:** Odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- 1 observational study, low Newcastle Ottawa score
- 2 confidence interval up to 1
- 3 observational study
- 4 observational study, high Newcastle Ottawa score
- 5 reporting bias- no trial registry, vague description of outcomes in methods, small numbers
- 6 wide confidence interval crossing 1

Summary of findings 2. Adjuvanted influenza vaccine compared to non-adjuvanted influenza vaccine in immunosuppressed adults with cancer

Adjuvanted influenza vaccine compared to non-adjuvanted influenza vaccine in immunosuppressed adults with cancer

Patient or population: immunosuppressed adults with cancer

Setting: outpatients

Intervention: adjuvanted influenza vaccine

Comparison: non-adjuvanted influenza vaccine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non-adjuvanted influenza vaccine	Risk with adjuvanted influenza vaccine				
All-cause mortality, allogeneic BMT, Follow-up: mean 6 months	Study population		RR 0.54 (0.05 to 5.73)	73 (1 RCT)	⊕⊕⊕⊕ LOW ¹	Natori 2017
	53 per 1,000	28 per 1,000 (3 to 302)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RCT:** randomised controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Small sample size, large confidence intervals

BACKGROUND

This is an update of the Cochrane review published in 2013, Issue 10 (Eliakim-Raz 2013).

Influenza is an acute respiratory illness caused by infection with influenza viruses. The illness affects the upper, lower or entire respiratory tract and is often accompanied by systemic signs. There are three types of seasonal influenza viruses: A, B and C. Human influenza A and B viruses cause seasonal epidemics of the disease almost every winter. Influenza C causes mild respiratory illness and occurs much less frequently than A and B. Type A influenza viruses are further categorised into subtypes according to different kinds and combinations of virus surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA) (UpToDate 2017).

Symptoms of influenza include fever, myalgia (muscle pain), headache, cough, chills, nasal congestion and sore throat (Kamps 2006). The major complication of influenza is pneumonia, with secondary bacterial pneumonia being the most common form. Primary influenza pneumonia is a rare but severe condition. Other complications include otitis media (ear infections), bronchiolitis in infants and young children and exacerbations of chronic respiratory disease. There are also non-respiratory complications, including febrile convulsions, Reye's syndrome (a rare, acute encephalopathy characterised by fever, vomiting, fatty infiltration of the liver, disorientation, and coma, occurring mainly in children and usually following a viral infection), neurological sequelae and myocarditis (Angelo 2004; Wiselka 1994). The major morbidity associated with influenza is probably worsening of chronic health problems. Complications occur most frequently in certain groups of people with underlying chronic illnesses who are classified as at 'high risk' for this infection (Glezen 2008; WHO Influenza 2016). These high-risk groups include those with illnesses that involve the cardiovascular or pulmonary systems; people with diabetes mellitus, renal disease or immunosuppression; residents of nursing homes or chronic care facilities; healthy individuals over the age of 65, children aged 6 to 23 months; and pregnant women. Influenza-related death rates differ remarkably between high-risk and low-risk populations. For example, influenza-related annual mortality among persons under the age of 19 are 0.2 per 100,000 persons compared to 66.1 per 100,000 adults among those aged 65 years or more (CDC MMWR 2010). Estimates from the 2015 to 2016 flu season in the USA reveal an influenza-related mortality rate of 12,000 to 56,000 and a hospitalisation rate of 140,000 to 710,000 (CDC Surveillance 2016).

Description of the condition

Influenza among adults with cancer

People with haematological or solid cancers undergoing chemotherapy and bone marrow transplant (BMT) recipients are at increased risk of influenza-related complications (CDC Cancer prevention 2017; Engelhard 2013; Kunisaki 2009). People at highest risk include those with impaired cell-mediated and antibody-mediated immunity, as reflected by a decrease in the number or function of T and B lymphocytes (Pirofski 1998). Highest-risk people include those following allogeneic BMT (or haematopoietic stem cell transplant, hereafter referred to collectively as haematopoietic stem cell transplantation (HSCT) recipients), especially during episodes of graft-versus-host disease (GVHD). Low-risk people with impaired lymphocyte function include adults with chronic

lymphocytic leukaemia (CLL), multiple myeloma, and probably those treated with specific anti-lymphocyte antibodies such as rituximab, alemtuzumab and others (Issa 2009). The main immune deficit affecting other people with cancer is neutropenia (abnormally low concentration of specific white blood cells (neutrophils)), which is associated mainly with higher risk for bacterial infections rather than viral infections. However, influenza-related complications are more common among these patients compared to the general population (Chemaly 2012). Different studies report a wide range of influenza rates and influenza-related pneumonia and deaths rates among people with malignancies admitted to hospital with respiratory symptoms (Table 1). Overall, influenza-related hospitalisation rates are four times higher and mortality 10 times higher among people with cancer compared with the general population (Cooksley 2005; Yousuf 1997). Influenza and its complications may also trigger delays or cancellation of chemotherapy treatment, with possible consequences for cancer disease control.

Due to paucity of data, it is difficult to estimate the differences in influenza and influenza-related complications rates for specific risk-groups among all people with cancer. Although data are limited, allogeneic HSCT recipients seem to be more susceptible to influenza than autologous HSCT recipients. In one study, absolute lymphocyte count of less than 200 cells/mL (indicating severe immune dysfunction) was an independent predictor of progression to influenza-related pneumonia (Chemaly 2006). Among patients with solid cancers data are scarce, however, one study demonstrated that lymphopenia below 200 cells/mL, neutropenia below 500 cells/mL and immunosuppressive treatments were associated with influenza-related complications (Chemaly 2012).

Description of the intervention

Influenza vaccines contain antigens of the circulating influenza viruses and are intended to trigger antibody-mediated protection. Influenza A viruses undergo continual changes in the hemagglutinin (HA) and neuraminidase (NA) proteins, which necessitate annual updating of the influenza vaccine components (Glezen 2008). Current influenza vaccines are available as inactivated vaccine (IV), trivalent (TIV) or quadrivalent (QIV), usually A/H1N1, A/H3N2, and either one or two strains of B, as recombinant vaccine (which may be TIV or QIV) or as a nasal spray of live attenuated influenza vaccine (LAIV) (CDC Flu Vaccination 2017). There are three types of IV: (1) whole virion vaccines, which consist of complete viruses which have been inactivated, so that they are not infectious but retain their strain-specific antigenic properties; (2) subunit virion vaccines, which are made of surface antigens (HA and NA) only; (3) split virion vaccines in which the viral structure is broken up by a disrupting agent. These vaccines contain both surface and internal antigens. The subunit or split vaccines are those used routinely for seasonal vaccination in adults. Currently, both IV and the nasal spray are manufactured using chicken eggs. IV is indicated for all individuals aged six months and older. LAIV has been approved by the United States Food and Drug Administration (FDA) for healthy persons aged two to 49 years and is contra-indicated in immunosuppressed individuals (Fiore 2009). Recent publications have demonstrated very poor efficacy for the LAIV (Jackson 2017), thus they are rarely used nowadays. The protective efficacy of the vaccine is largely determined by the relationship (closeness of 'fit' or

'match') between the strains in the vaccine and the viruses that circulate in the season. Vaccine effectiveness may also be lower among persons with chronic medical conditions (see immune suppression below) and among the elderly, compared with healthy young adults and children (Domnich 2017; Engelhard 2013). A review of vaccine immunogenicity among patients with cancer (both solid cancer and haematologic malignancies) demonstrated decreased seroconversion rate among cancer patients receiving chemotherapy (17% to 52%) compared to cancer patients not receiving chemotherapy (50% to 83%) and compared to healthy controls (67% to 100%) (Shehata 2014). Efforts were made to increase vaccine immunogenicity and efficacy among these populations. One method is the use of adjuvanted influenza vaccines. Currently, there are two adjuvants used in commercially-available influenza vaccines: AS03 and MF59. Both are oil-in-water squalene-based emulsions, and have been tested mainly in children and elderly, where they have demonstrated increased immunogenicity and effectiveness (Black 2015; Domnich 2017). One study has been carried out in immunosuppressed individuals (Natori 2017).

How the intervention might work

Inactivated influenza vaccines probably have a protective effect among people with cancer, despite immunosuppression. On one hand, immunosuppression might attenuate the response to influenza vaccine (Engelhard 2013; Kunisaki 2009). People with cancer with cell-mediated immune dysfunction are likely to have lower responses to influenza vaccination. Some degree of lymphopenia and cellular dysfunction also accompany the neutropenia that follows chemotherapy, and thus most people with cancer will have a poor response to the vaccine. On the other hand, people with cancer have more to gain from any degree of protection because influenza is more severe among immunosuppressed patients. Inactivated vaccine cannot cause influenza, because the inactivated virus is non-pathogenic, thus there is no danger in administering it even to the most immune compromised patients.

Why it is important to do this review

Given an increased risk for complications combined with the expected lower immunogenicity of the vaccine among people with cancer, data on vaccine effectiveness is needed for this population. Furthermore, as people with cancer are heterogeneous with respect to chemotherapy regimens and underlying malignant disease, data are needed for specific subgroups. One systematic review on influenza vaccine in immunosuppressed individuals included a subgroup of patients with cancer. In this subgroup, a meta-analysis of two studies showed a significant decrease in influenza-like illness among those who received influenza vaccination (odds ratio (OR) 0.26, 95% confidence interval (CI) 0.15 to 0.46) (Beck 2012). Other narrative reviews have attempted to summarise the evidence (Alistair 2002; Arrowood 2002; Casper 2010; Engelhard 2013; Kunisaki 2009; Melcher 2005; Pedrazzoli 2014; Vollaard 2017). All recommend giving the seasonal inactivated influenza vaccine. Optimal timing of vaccination is unknown, however most recommend giving the vaccine at least seven days after chemotherapy cycle and at least three months after HSCT (Arrowood 2002; Casper 2010; Engelhard 2013; Kunisaki 2009; Melcher 2005). An accurate assessment of the existing evidence on influenza vaccine effects (death, serological response, clinical outcome and adverse effects) in adults with cancer is

essential to support comprehensive, rational decisions concerning influenza vaccination.

OBJECTIVES

To assess the effectiveness of influenza vaccine in immunosuppressed adults with malignancies. The primary review outcome is all-cause mortality, preferably at the end of the influenza season. Influenza-like illness (ILI, a clinical definition), confirmed influenza, pneumonia, any hospitalisations, influenza-related mortality and immunogenicity were defined as secondary outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We include randomised controlled trials (RCTs), cohort studies and case-control studies. We also consider observational studies to fully examine the empirical data on vaccine trials and their use in adults with cancer.

Types of participants

Adults (16 years and over) with cancer, including:

- solid malignancies treated with chemotherapy;
- haematological cancers treated or not treated with chemotherapy (since people might be immunosuppressed even without chemotherapy);
- adults with cancer, post-autologous (up to six months after transplantation) or allogeneic (at any time) haematopoietic stem cell transplantation (HSCT).

Studies that included a mixed population of children and adults were excluded if the children population comprised more than 30% of the study cohort.

Types of interventions

We considered for inclusion studies comparing inactivated or recombinant influenza vaccines versus placebo, versus no vaccination or versus a different vaccine. We included inactivated influenza vaccine of any type, any dose and any schedule:.

- Trivalent or other
- Whole, subunit or split virion vaccine
- Adjuvanted or non-adjuvanted

Vaccines could be matched or unmatched to circulating strains, and vaccine fit was recorded if reported. Comparisons of the same or different vaccines given during different influenza seasons or to different cancer populations were excluded. We did not include studies comparing vaccine effects in adults with cancer versus healthy adults. We excluded studies comparing vaccine dosing regimens among patients with cancer.

Types of outcome measures

Clinical outcomes were collected for a maximum follow-up period until the end of the influenza season following vaccination. We documented the duration of follow-up in each study. We assessed immunological response up to three months after vaccination, as

defined in each study. We assessed adverse events up to two weeks after vaccination. We included studies reporting on at least one of the review-defined outcomes (primary or secondary).

Primary outcomes

All-cause mortality, preferably at the end of the influenza season. We selected all-cause mortality as the primary outcome, since this is the ultimate goal of influenza vaccination, and the composite outcome of infections, hospitalisations, chemotherapy delays and other effects of influenza.

Secondary outcomes

- Influenza-like illness (ILI): a clinical definition of febrile respiratory illness. We accepted the definitions of ILI used in the study.
- Confirmed influenza using the methods defined in the study.
- Pneumonia from any cause.
- Any hospitalisation and number of hospital days.
- Chemotherapy interruptions.
- Influenza-related mortality.
- Immunological: seroconversion or rise in titre as defined in the study.
- Adverse events (AEs): local events on injection site (tenderness/soreness, erythema, arm stiffness), systemic events (myalgia, fever, headache, fatigue, rash).

Search methods for identification of studies

Electronic searches

For the original review we searched the Cochrane Central Register of Controlled Trials (CENTRAL, Aug 2013; [Appendix 1](#)), MEDLINE (1948 to Aug week 3 2013; [Appendix 2](#)), Embase (1980 to 2013; [Appendix 3](#)), LILACS (to Aug 2013; [Appendix 4](#)) databases. We also searched PubMed (1948 to Aug week 3 2013), combining search terms in PubMed with a highly sensitive search filter for identifying randomised controlled trials (RCTs) as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Cochrane Handbook](#)) and with the SIGN search strategy for identifying observational studies ([SIGN 2010](#); [Appendix 5](#)).

For this update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 4), MEDLINE (2013 to May week 2, 2017), Embase (2013 to 2017 week 21), LILACS (2013 to May 2017) databases.

We contacted the first or corresponding author of each included study for additional information, and researchers active in the field for information on unpublished studies. There were no language or publication type restrictions.

Searching other resources

We searched the following conference proceedings: Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), European Society of Clinical Microbiology and Infectious Diseases (ECCMID), Infectious Disease Conferences (IDSA), American Society of Hematology (ASH), American Society for Blood and Marrow Transplantation (ASBMT), European Group for Blood and Marrow Transplantation (EBMT), and American Society of Clinical Oncology (ASCO) between the years 2006 and 2017. We also scanned the references of all identified studies and pertinent reviews.

We searched the websites of the manufacturers of influenza vaccines (May 2017). Finally, we searched for ongoing or unpublished studies in clinical trials registry databases using the <https://clinicaltrials.gov/> and <https://www.clinicaltrialsregister.eu/ctr-search/search> websites.

Data collection and analysis

Selection of studies

We included all studies fulfilling the eligibility criteria for design, participants and interventions. We did not restrict inclusion by outcomes reported in the abstract, but obtained the full text and attempted to identify at least one of the review-defined outcomes from the text or from author correspondence. Two review authors independently applied the inclusion criteria to all identified and retrieved articles. We documented reasons for excluding studies from the review ([Characteristics of excluded studies](#)).

Data extraction and management

Two review authors independently performed data extraction using a data extraction form. We extracted data on the following study characteristics:

- study design;
- length of the follow-up;
- dates of study;
- location of study;
- risk of bias;
- description of vaccines (content, timing of vaccination and antigenic match);
- description of viral circulation degree;
- description of outcomes;
- characteristics of participants: age, sex, type of malignancy, haematopoietic stem cell transplantation (HSCT), anti-cancer treatment, expected baseline immune suppression: primarily cellular immune dysfunction, severe; primarily cellular immune dysfunction, moderate; primarily neutropenia, severe.

Assessment of risk of bias in included studies

Two review authors (RB, MP) independently assessed the risks of bias in studies fulfilling the review inclusion criteria. We contacted authors for additional information where necessary.

Randomised controlled trials (RCTs)

Assessment of the methodological quality of the RCTs was according to the guidelines of Cochrane's tool for assessing risk of bias ([Higgins 2011](#); see [Appendix 6](#)). We assessed studies according to the following criteria: allocation sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other possible sources of bias. Under other sources of bias we addressed baseline imbalances, sample size calculation and funding.

Cohort studies

For quality assessment of cohort studies we used the Newcastle-Ottawa Scale adapted for our review ([NOS 2010](#); see [Appendix 7](#)). We assessed the following items.

- Selection: including representativeness of the exposed cohort, selection of the non-exposed cohort, and ascertainment of exposure.
- Comparability of cohorts.
- Outcome: including assessment of outcome (independent blind assessment/record linkage/self-report/no description), length of follow-up for outcomes to occur, adequacy of follow-up of cohorts.

We recorded whether an adjusted analysis was reported in the studies. Under other sources of bias we addressed baseline comparability of study groups, sample size calculation and funding.

Measures of treatment effect

We calculated unadjusted odds ratios (ORs) with 95% confidence interval (CI) from RCTs and non-RCTs (cohort and case-control studies) for dichotomous data and rates (events per person-years). For non-RCTs, we extracted adjusted ORs with 95% CI, as available.

Unit of analysis issues

We expected that the studies might report influenza-like illness (ILI) as episodes that occur more than once per person. In this case, we tried to extract the number of adults experiencing at least one event, however these data were not available and studies reporting on events per person-time were analysed as rates.

Dealing with missing data

Whenever data were missing, we attempted to contact the authors of the study and request the information.

Assessment of heterogeneity

The I^2 statistic was calculated for each pooled estimate, in order to assess the impact of statistical heterogeneity. I^2 may be interpreted as the proportion of total variation among effect estimates that is due to heterogeneity rather than to sampling error, and it is intrinsically independent of the number of studies. An I^2 less than 30% would suggest there is little concern about statistical heterogeneity (Higgins 2002; Higgins 2003).

Assessment of reporting biases

Given the paucity of studies in each analysis we were not able to formally assess reporting biases.

Data synthesis

Due to the paucity of trials, different study designs and heterogeneous reporting of events per person or per person-time a meta-analysis could not be performed. We present trial results in the first plots without compiling results. We had planned to stratify the analysis by the following factors, however, due to the paucity of data we could not conduct the stratified analyses:

- participant's type of malignancy and expected degree of immune dysfunction;
- degree of viral circulation;
- vaccine matching with the seasonal circulating strains.

We created 'Summary of findings' tables for the primary outcome of mortality.

We have presented the overall quality of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2013). We created Summary of findings' tables based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and using GRADEpro GDT. We used the GRADE checklist and GRADE Working Group quality of evidence definitions (Meader 2014). We downgraded the evidence from 'high' quality by one level for serious (or by two for 'very serious') concerns for each limitation.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses by the expected severity of immune suppression:

- primarily cellular immune dysfunction, severe: participants post-allogeneic haematopoietic stem cell transplantation (HSCT);
- primarily cellular immune dysfunction, moderate: chronic lymphocytic leukaemia (CLL) treated with alkylating agents, multiple myeloma (MM) treated with monoclonal antibodies;
- primarily neutropenia, severe: participants with severe neutrophil dysfunction: administration of vaccine during neutropenia (e.g. acute leukaemias, autologous HSCT, sarcoma).

Due to the paucity of data we could not perform subgroup analyses. As data accumulate in future updates we will reconsider these analyses.

Sensitivity analysis

We had planned sensitivity analyses based on studies' risk of bias for the primary outcome, but restricting the analysis to RCTs with adequate allocation generation and concealment methods, and to cohort studies at low risk of bias according to the Newcastle-Ottawa Scale adapted for our review (NOS 2010). As previously, data did not permit such analyses.

RESULTS

Description of studies

Results of the search

In the previous version of this review 4439 records were retrieved from the electronic database searches. The CENTRAL search identified 155 records, MEDLINE identified 2798 records and Embase identified 1486 records. Three hundred and seven records were identified from conference proceedings. All records were inspected. Forty-five publications were retrieved for full-text inspection, of which 41 were excluded, and four studies were eventually included in the original review.

In this update, we retrieved 1801 records from the electronic database searches. The CENTRAL search identified 123 records, MEDLINE identified 423 records and Embase identified 1255 records. We identified 274 records in conference proceedings. We inspected all records. We did not evaluate studies in which the abstract suggested a patient population or vaccine incompatible with our inclusion criteria. We also excluded studies in which all

participants were vaccinated, studies comparing vaccinated adults with cancer with the healthy population or studies comparing different doses of influenza vaccine. We retrieved 14 publications for full-text inspection, of which 12 were excluded, mainly because all participants were vaccinated, or different doses of influenza

vaccine were compared. Two randomised controlled trials (RCTs) were added in this update; one comparing vaccine versus no vaccine and one comparing adjuvanted with non-adjuvanted vaccine. See [Figure 1](#) for a flow diagram of studies identified.

Figure 1. Study flow diagram.

Figure 1. (Continued)

Included studies

Six studies fulfilled the inclusion criteria: five studies compared adults with cancer receiving influenza vaccination versus a group that did not receive the vaccine and one RCT compared adjuvanted with non-adjuvanted influenza vaccine among patients after haematopoietic stem cell transplantation (HSCT) (Natori 2017). The studies comparing vaccine with no vaccine included: one case-control study (Machado 2005), two cohort studies (Earle 2003; Vinograd 2013) and two RCTs (Ambati 2015; Musto 1997). The six studies were conducted between 1993 and 2016, and encompassed 2275 participants, with haematological diseases, including patients with multiple myeloma (MM) and patients following HSCT and solid malignancies. The influenza trivalent vaccine (TIV) was used in all studies, in a single dose. There was a good fit with seasonal strains in the three studies providing this information. In the three studies that did not provide information, the fit of the vaccine with seasonal strains was variable according to published data from the Centers for Disease Control and Prevention site and according to data from previous publications (<https://www.cdc.gov/flu/about/season/index.html>, De Jong 2000). In one study, influenza vaccine was given prior to allogeneic HSCT (Ambati 2015), and in another study it was given after allogeneic HSCT (Natori 2017). Other studies did not provide information regarding timing of influenza vaccination. Study details can be found in the [Characteristics of included studies](#).

Excluded studies

Reasons for exclusion are detailed in the [Characteristics of excluded studies](#) table. The main reasons were that all participants were vaccinated (30 studies), comparison was made with a healthy population (16 studies) or the comparison was between different doses of influenza vaccine (7 studies), or trials were excluded for more than one reason, e.g. all participants vaccinated or compared with healthy participants or different doses.

Risk of bias in included studies

The two recent RCTs (Ambati 2015; Natori 2017) had relatively low risk of bias as both had good methods for random sequence generation and allocation concealment. Though both were not blinded the outcomes reported were objective thus the open design probably did not introduce much bias. In the older RCT (Musto 1997), the method of randomisation was not stated, allocation concealment was unclear, and there was no blinding. Attempts to obtain additional information from the author concerning methodological quality were unsuccessful.

The three cohort/case-control studies scored between 5 to 10 (out of a maximum of 13 points) on the Newcastle-Ottawa Scale adapted for our review. (Appendix 7; Table 2). Two of the studies focusing on a specific cancer population were regarded as not representative of the average cancer population. Only Vinograd 2013 controlled for

cancer stage and functional status, although only in the mortality outcome assessment.

Earle 2003 reported results in person-years and results per person were not available. Two cohort studies reported an adjusted

analysis for mortality, using multivariable analysis (Earle 2003; Vinograd 2013); all other outcomes were non-adjusted.

We summarised the results in a 'Risk of bias' summary figure and graph (Figure 2; Figure 3)

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
Ambati 2015	+	+	+	-	+	+	+
Earle 2003	-	-	-	+	-	-	-
Machado 2005	-	-	-	-	-	-	-
Musto 1997	?	?	+	?	?	-	-
Natori 2017	+	+	+	+	+	+	+
Vinograd 2013	-	-	+	+	+	-	-

Allocation

See above text.

Blinding

None of the RCTs were blinded. In one RCT (Natori 2017) only assessors of adverse events and laboratory workers were blinded. In Natori 2017 and Ambati 2015 the outcomes reported were objective therefore we believe that no significant performance or detection bias were introduced.

Incomplete outcome data

In Natori 2017, 6/73 patients did not have data on immunogenicity and in Ambati 2015 data on immunogenicity decreased with duration of follow-up, making them susceptible to attrition bias. In Musto 1997 there was no mention of an intention-to-treat analysis, and the number of dropouts per study arm was not reported. Therefore, analysis by evaluated patients only was possible, making it susceptible to attrition bias.

In one cohort study (Earle 2003), follow-up until death was completed in 86% of participants, making it susceptible to attrition bias. Mortality data were given only for 697 of 1054 patients.

Selective reporting

In Ambati 2015, we had some concerns over selective reporting as the trial was not registered; there was no primary outcome reported in the methods section and seroconversion rates were reported at multiple time points.

Other potential sources of bias

The sponsors of two RCTs (Musto 1997; Natori 2017) and one of the cohorts (Machado 2005) were not mentioned. The National Cancer Institute sponsored Earle 2003, Vinograd 2013 was supported by an internal grant, and Ambati 2015 was sponsored by academic grants.

There was no mention of sample size calculations, except for two studies (Natori 2017; Vinograd 2013).

Effects of interventions

See: [Summary of findings for the main comparison](#) Influenza vaccine compared to no vaccine for immunosuppressed adults with cancer; [Summary of findings 2](#) Adjuvanted influenza vaccine compared to non-adjuvanted influenza vaccine in immunosuppressed adults with cancer

Vaccination versus no vaccination among cancer patients

Three studies reported on all-cause mortality. Two reported on influenza-like illnesses (ILIs), four reported confirmed influenza, three reported on pneumonia, three reported any hospitalisation and one reported on serological results.

Primary outcome

All-cause mortality

One RCT and two cohort studies addressed our primary outcome of all-cause mortality (Analysis 1.1). Both cohort studies reported on adjusted results. The results could not be combined since one cohort study reported results per person-years (Earle 2003) and the other two studies reported results per person, with the RCT (Ambati 2015) showing different results from the cohort study (Vinograd 2013). The three studies assessed different patient populations: Ambati 2015 assessed patients before HSCT, Earle 2003 assessed patients with colorectal carcinoma and Vinograd 2013 assessed a mixed cancer population. The Influenza vaccination in Earle 2003 was associated with an adjusted OR for death of 0.88 (95% CI 0.78 to 1.00; 1 study, 1577 participants, very low-certainty evidence). In Vinograd 2013, influenza vaccination was associated with an adjusted OR for death of 0.42 (95% CI 0.24 to 0.75). A propensity-matched analysis was also reported in this study and the association with mortality remained significant (adjusted OR 0.42, 95% CI 0.24 to 0.76; 1 study, 806 participants, very low-certainty evidence). In Ambati 2015, mortality was similar among those vaccinated and those not vaccinated with very wide confidence intervals due to its small sample size (OR for death 1.25 (95%CI 0.43 to 3.62; 1 RCT, 78 participants, low-certainty evidence) among vaccinated).

The evidence was graded separately per study and population, as low-quality or very low-quality evidence due to the high risk of bias

in the all studies and imprecision ([Summary of findings for the main comparison](#)).

Secondary outcomes

Influenza-like illness

Two studies (856 participants) reported on clinically-defined ILI; one RCT (Musto 1997) and one cohort study (Vinograd 2013). The RCT showed a significant reduction in ILI with vaccination and the cohort study showed no association between influenza vaccination and ILI (Analysis 1.2).

Confirmed influenza

Among studies reporting on confirmed influenza there was one RCT and three non-randomised studies (NRS) (2152 participants) (Analysis 1.3) that could not be combined: Vinograd 2013 and Ambati 2015 reported results per person; Machado 2005 reported results per person with ILI; and Earle 2003 reported events/ person-year. The event rate was low and lower with vaccination in all four studies, reaching statistical significance in one case-control study only (Machado 2005).

Pneumonia

Three studies (2081 participants) reported on pneumonia, which could not be combined: one RCT (Musto 1997) and two cohort studies (Earle 2003; Vinograd 2013). Two of the studies separately showed a reduction in pneumonia rates in vaccinated patients, one significant and one non-significant (Analysis 1.4).

Any hospitalisation

Two studies, one RCT (Musto 1997) and one cohort study (Vinograd 2013), reported on hospitalisations. The RCT showed a significantly lower rate of hospitalisations in vaccinated participants, while in the cohort study there was no difference (Analysis 1.5). Two cohort studies reported on hospitalisation duration (Earle 2003; Vinograd 2013), both showing no significant associations, but a mean duration shorter by 0.9 to 1.8 days with vaccination.

Influenza-related mortality

Three studies (1353 participants) reported on influenza-related deaths, of which one (Musto 1997), reported only deaths due to influenza pneumonia and one (Earle 2003), reported results per person years. Earle 2003 and Musto 1997 showed a statistically non-significant decrease in influenza-related deaths with vaccination, whereas Ambati 2015, a RCT, showed similar rates of influenza-related mortality in both groups (Analysis 1.6). The results could not be pooled.

Serological outcomes

Only one study (Ambati 2015), a RCT, reported on serological response to influenza vaccine. The vaccinated group had significantly higher geometric mean titres (GMTs) for influenza A/H1N1 and A/H3N2 viruses and non significantly higher GMTs for influenza B virus (Table 3).

Given the paucity of the studies, the results of each study are described separately. The main outcomes are summarised also in Table 3.

Ambati 2015

An open-label RCT including 78 patients at least a week before their planned allogeneic bone marrow transplant (BMT), of which 19 were under the age of 16. Patients were recruited during three influenza seasons (2007 to 2010), and were followed up for six months. Odds ratio for all-cause mortality was 1.05 (95% CI 0.4 to 2.77) among those vaccinated. Influenza-related mortality was similar as well between the groups (2/40 among vaccinated versus 2/38 among non vaccinated). Documented influenza infection rate was similar in vaccinated and unvaccinated patients (3/40 versus 4/38, respectively). GMTs at 30 days post-vaccination among the vaccinated population were significantly higher for influenza A/H1N1 and influenza A/H3N2 strains (15 versus 10, $P=0.03$ and 30 versus 12.5, $P<0.001$, respectively).

Earle 2003

A retrospective observational cohort study including adults with advanced colorectal cancer undergoing treatment. A total of 1225 participants (1577 person-years) were observed. Of these person-years, 626 (39.7%) were vaccinated and 951 (60.3%) were not. Follow-up until death was completed in 86% of participants. The one-year survival rate was 60.2% (376 person-years) in the vaccinated group and 55.3% (525 person-years) in those not vaccinated. On multivariate analysis, influenza vaccination treated as a time-dependent variable was associated with a hazard ratio (HR) for death of 0.88 (95% CI 0.77 to 0.99). The number of participants with confirmed influenza was 0/626 person years vaccinated versus 3/951 person years unvaccinated (difference not statistically significant). Vaccinated adults had less pneumonia (7/626 versus 33/951 person years) The mean days of hospitalisation was 15.6, 95% CI 13.3 to 17.8 in the vaccinated group versus 16.4, 95% CI 14.3 to 18.4 among unvaccinated adults, difference non-significant. No deaths due to influenza were observed in the vaccinated group versus two (0.2%) in the unvaccinated. The interval between chemotherapy medical bills was significantly longer for patients who were not vaccinated (unvaccinated versus vaccinated, 6.04 versus 5.06 days).

Musto 1997

A presumably open-label RCT (no placebo used), recruiting 50 adults with multiple myeloma (MM), of which 25 were randomised to receive the vaccine. The follow-up period was four months. ILI occurred in eight out of 25 (32%) vaccine recipients and in 18 out of 25 (72%) controls ($P<0.001$). The mean duration of febrile illness was significantly higher in controls (12 versus five days, $P<0.001$). Pneumonia was observed in four (16%) control and in none of the vaccinated participants (OR 0.09, 95% CI 0.005 to 1.84), and was lethal in two cases. these were the only data on mortality. Twelve unvaccinated participants (48%) required hospitalisation versus two vaccinated (8%, $P<0.001$). Sixty per cent of vaccinated participants complained of mild local symptoms at the site of the injection.

Machado 2005

A retrospective case-control study (cases with confirmed influenza versus controls without influenza). A total of 177 HSCT recipients were followed, mostly (71%) following allogeneic HSCT. One hundred and thirty-four were within the first six months after transplantation and were, therefore, not eligible for influenza vaccination. Of this group, 25 (18.6%) acquired influenza, and are not included in our meta-analysis. Of the remaining 43 participants eligible to receive influenza vaccination, 19 were vaccinated and 24 were not. Two (10%) of the vaccinated participants had confirmed

influenza compared with 12 (50%) unvaccinated ($P=0.015$). No other outcomes were reported in the study.

Vinograd 2013

A prospective observational cohort study, including adults with cancer with solid malignancies undergoing chemotherapy and haematological patients with active disease. A total of 806 patients were observed during a single season (2010 to 11). Of these, 387 (48%) were vaccinated and 419 (52%) were unvaccinated. The only outcome significantly associated with vaccination was all-cause mortality, occurring in 46/387 (11.9%) of vaccinated versus 80/419 (19.1%) of unvaccinated patients ($P=0.005$). On multivariate analysis, influenza vaccination was associated with an OR for death of 0.43 (95% CI 0.26 to 0.71). The association with mortality remained significant in a vaccination propensity-matched analysis (OR 0.41, 95% CI 0.23 to 0.75). ILI was diagnosed in 134/387 (34.6%) of vaccinated versus 137/419 (32.7%) in unvaccinated. Confirmed influenza was reported only in 2/387 versus 4/419 patients, respectively. Pneumonia was reported in 81/387 (20.9%) of vaccinated patients versus 78/419 (18.6%) of unvaccinated. Of the vaccinated patients, 183/387 (47.3%) were hospitalised during follow-up compared to 205/419 (48.9%) of the unvaccinated. The number of hospitalisation days (mean $\pm$ SD) in vaccinated patients was 5.55 ± 11.50 versus 7.39 ± 14.00 in unvaccinated. Chemotherapy interruptions were reported in 97/387 (25.1%) of vaccinated versus 116/419 (27.7%) of unvaccinated. All differences were not statistically significant. Of the 561 patients who were interviewed for adverse events, 267 were vaccinated. Fifty-nine patients (24.6%) reported local and other mild adverse events. Nine patients (3.3%) reported fever related to vaccination.

Adjuvanted versus non-adjuvanted vaccine among cancer patients

The comparison was assessed in a single RCT described below.

Natori 2017

An open-label RCT, enrolling 73 adults after allogeneic HSCT, of which 35 were randomised to receive an adjuvanted influenza vaccine (Fluad) and the rest (38) randomised to a non-adjuvanted influenza vaccine (Influvac). The study was conducted during the 2015 to 2016 flu season and the duration of follow-up was six months. One of 35 patients in the adjuvanted vaccine group died, compared to 2/38 in the non-adjuvanted vaccine group, deaths were not attributed to influenza (RR 0.54, 95% CI 0.05 to 5.73; low-certainty evidence) (Analysis 2.1). There were five cases (14%) of laboratory-confirmed influenza among patients receiving the adjuvanted vaccine compared to three cases (8%) in the non-adjuvanted vaccine group (Analysis 2.2). There was a slightly higher rate of hospitalisations in the non-adjuvanted vaccine group (11/38 versus 8/35, Analysis 2.3), but none were due to influenza infection. Vaccine immunogenicity, reported as seroconversion rate, seroprotection rate and GMTs, was non-significantly higher in the adjuvanted vaccine group. The main outcomes are summarised also in Table 4.

The evidence grade for this comparison, based on a single RCT, was low due to large imprecision (Summary of findings 2).

DISCUSSION

In this review of influenza vaccines for adults with cancer, we identified two open-label randomised trials and

three observational studies comparing vaccination versus no vaccination, encompassing 2202 patients. We also identified one randomised controlled trial (RCT) including 73 patients that compared adjuvanted with non-adjuvanted vaccine in this population. The studied population, the outcomes examined and reporting methods were highly heterogeneous, precluding a meta-analysis for all outcomes.

Summary of main results

Vaccination versus no vaccination

One RCT and two cohort studies assessed all-cause mortality, the primary review outcome. The cohort studies showed that influenza vaccination was associated with significantly lower mortality in an analysis adjusted for other risk factors for death, whereas in the RCT all-cause mortality was unaffected by vaccination status, but with large confidence intervals. For all other outcomes, either no differences were observed or fewer infections occurred among vaccination patients. Confirmed influenza occurred less frequently among vaccinated patients in the four studies that evaluated this, reaching statistical significance in one observational study ([Table 3](#)).

Adjuvanted vaccine versus non-adjuvanted vaccine

There was a trend towards reduced all-cause mortality ([Summary of findings 2](#)) and hospitalisations in the adjuvanted vaccine group, however numbers were small and preclude any conclusions. There were more cases of confirmed influenza among patients who received the adjuvanted vaccine (difference without statistical significance), despite a more robust immunological response ([Table 4](#)).

Overall completeness and applicability of evidence

Despite a thorough search of the literature we found only a few studies that compared vaccinated and unvaccinated adults with cancer and no placebo-controlled RCTs. We also found one study comparing different vaccine types. Each study included different patients - solid cancers, haematologic malignancies and haematopoietic stem cell transplantation (HSCT) recipients. Due to the paucity of data we could not compare between populations and it is questionable whether the results of these studies can be generalised to adults with all malignancies. Data on adverse effects of vaccination and mortality were incomplete.

Quality of the evidence

Observational studies assessing the effects of influenza vaccination have the inherent limitations of selection bias. An adjusted analysis was presented in two studies only and only for the outcome of mortality.

Three RCTs were included in this review. All were open-label. One had unclear methods of randomisation and another had selective reporting. Hence, the quality of the evidence is low. The grade quality of evidence for the outcome of mortality was low to very low ([Summary of findings for the main comparison](#); [Summary of findings 2](#)).

Potential biases in the review process

Inclusion of studies with different methodology and missing data might have introduced bias.

Assessment of the effects of influenza vaccine on mortality is difficult in our review. One can argue that all-cause mortality is not an appropriate outcome in non-RCTs because most deaths are related to the primary cancer rather than to influenza. But since ultimately prevention of mortality is the ultimate goal and reason for vaccination and is the composite outcome of infections, hospitalisations, chemotherapy delays and other effects of influenza, we decided to select mortality as the primary outcome. In the first version of our protocol, we defined a composite primary outcome of influenza-like illness (ILI), pneumonia of any cause or influenza-related death. We realised that obtaining a composite outcome in an aggregate meta-analysis without having access to individual patient data is impossible. Furthermore, influenza-related deaths are difficult to assess because the cause of death is difficult to establish in adults with cancer.

In order to avoid publication bias, we searched the website of the manufacturers of influenza vaccine and tried to obtain information on ongoing studies by correspondence with the authors and in clinical trial registry databases. However, no further studies were identified.

Agreements and disagreements with other studies or reviews

This is the first systematic review trying to compile the clinical evidence on influenza vaccine effects among adults with cancer. A previous systematic review evaluated influenza vaccination among all immunosuppressed patients, however performing a meta-analysis among the subgroup of cancer patients was difficult ([Beck 2012](#)). Previous narrative reviews summarised the evidence, reaching similar conclusions ([Alistair 2002](#); [Arrowood 2002](#); [Casper 2010](#); [Engelhard 2013](#); [Kunisaki 2009](#); [Melcher 2005](#); [Pedrazzoli 2014](#); [Vollaard 2017](#)). A Cochrane review assessed the effectiveness of influenza vaccine among children with cancer ([Goossen 2013](#)). In addition to the interventions and comparisons included in our review, this review included also studies comparing the serological response of children with cancer with that of control groups, including children without cancer. One RCT and eight observational studies were included. In five observational studies, the immune response to trivalent vaccine (TIV) and bivalent vaccine (BIV) in children receiving chemotherapy was weaker than in children off chemotherapy, but not for all influenza virus strains tested. A four-fold rise in antibody titre was observed in 38% to 65% of children receiving chemotherapy compared with 71% to 89% of healthy children (three observational studies). One observational study reported a lower vaccine response in children with acute lymphoid leukaemia on chemotherapy than in children with asthma. None of the studies evaluated clinical influenza or laboratory-confirmed influenza as outcomes. The authors concluded that children with cancer receiving chemotherapy are able to generate an immune response to influenza vaccine, however, the immune response is weaker in children receiving chemotherapy (a four-fold rise of 25% to 52%) than in those children who were off chemotherapy for at least one month (50% to 86%) and in healthy children (71% to 89%). A meta-analysis of four studies (two controlled cohorts, one case-control and one RCT) assessed the effectiveness of influenza vaccine in HIV-positive adults ([Anema 2008](#)). Meta-analysis of the three prospective studies resulted in a 66% reduction in the risk for symptomatic influenza, while the one RCT yielded a 41% reduction.

Multiple guidelines recommend influenza vaccination for adults infected with HIV, who have received solid-organ transplants, who have received haemopoietic stem cell transplants, who have haematologic malignancies, and adults on haemodialysis. The Centers for Disease Control (CDC) guidelines recommend annual vaccination for persons who are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus (HIV)), to adults with cancer or a history of cancer, and to adults who live with or care for those with cancer and survivors ([CDC Cancer prevention 2017](#)). The evidence we showed, though weak, supports influenza vaccination for adults with cancer.

Prior studies evaluating adjuvanted influenza vaccines among patients with cancer, mainly haematologic malignancies and bone marrow transplant (BMT) recipients, showed conflicting results with regard to immunogenicity ([Cherif 2013](#); [Ljungman 2015](#)). Data on clinically relevant endpoints are lacking.

AUTHORS' CONCLUSIONS

Implications for practice

The existing evidence on the effectiveness of influenza vaccine in immune-suppressed adults with malignancies is mostly observational, incomplete and of low quality. It was previously shown that Influenza-related complications are more common among these adults compared to the general population, including hospitalisation and death. Although the data available are sparse and of low quality, there is no harm in the vaccine and possible benefit with regard to survival, confirmed influenza, influenza-like illness, pneumonia and hospitalisations. Data on all-cause mortality from two cohort studies showed significantly lower mortality in vaccinated participants, whereas the one randomised controlled trial (RCT) that evaluated this showed no significant benefit or harm. The evidence (though weak) is in favour of vaccinating this population. The summary of the available evidence should be used to encourage care givers and adults with cancer to accept yearly influenza vaccination.

Unfortunately, no recommendations can be made with regard to the use of adjuvanted influenza vaccine among adults with cancer.

The study included in our review, though an RCT, included few patients and showed no significant improvements in clinical and non-clinical endpoints.

Implications for research

Performing a placebo or no-treatment controlled RCT of influenza vaccination among adults with cancer is ethically questionable. We believe that the vaccine carries some degree of benefit and have no reason to believe that the vaccine is harmful or that adverse events will be different than those observed in the general population. In place of RCTs, we suggest well-conducted observational studies. Such studies should encompass people of a defined age group, and a variety of malignancies treated with different modalities (chemotherapy, immunotherapy, targeted therapy, and especially haematological malignancies, autologous or allogeneic stem cell transplant). These kind of studies should also include many influenza seasons (many years of follow-up) and would allow a better propensity score to be done. Studies should have a minimal risk of bias, the outcomes employed should be clinically important and include all-cause mortality, confirmed influenza, influenza-like illness, pneumonia and influenza-related death. Exact data on immunological response to vaccination, how influenza is confirmed, hospitalisations and hospital days, chemotherapy interruptions, adverse effects of vaccination, should be collected. A retrospective comparison of influenza vaccine effectiveness in years with a good match versus years with a poor match of vaccine and circulating influenza strains could also be useful.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ambati 2015

Methods	Randomised controlled study Location: Brazil
Participants	Patients more than 7 days before allogeneic HSCT 78 patients, of which 19 children. 40 were vaccinated and 38 were unvaccinated Mean age not reported
Interventions	Influenza vaccination versus no vaccination, assigned by randomisation
Outcomes	1. All-cause mortality

UpToDate 2017

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Ambati 2015 (Continued)

2. Influenza-related mortality
3. Vaccine immunogenicity reported as seroconversion rate or geometric mean titres
4. Laboratory-confirmed influenza infections

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	List of random numbers with their respective randomisation group was generated by a website
Allocation concealment (selection bias)	Low risk	Opaque envelopes sequentially numbered and sealed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow up for the mortality outcome.
Selective reporting (reporting bias)	High risk	No primary endpoint defined in methods, no registry. Seroconversion reported at multiple time points
Other bias	Low risk	No baseline imbalances, sponsored by academic grant, no sample size calculation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but outcomes are objective
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcomes are objective

Earle 2003

Methods	Retrospective, observational cohort study Location: USA, Boston
Participants	Stage 4 colorectal adenocarcinoma, with active chemotherapy treatment 1225 adults, 1577 person-years: 626 person-years vaccinated, 951 person-years unvaccinated Mean age 74 year in both groups
Interventions	Yearly influenza vaccination, examined through medical bills
Outcomes	<ol style="list-style-type: none"> 1. Adjusted all-cause mortality 2. Confirmed influenza 3. Pneumonia 4. Hospitalisation duration 5. Chemotherapy interruptions 6. Influenza-related mortality

Earle 2003 (Continued)

7. Mean number of hospital days

Notes	Results given per person-years	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-random
Allocation concealment (selection bias)	High risk	Non-random
Incomplete outcome data (attrition bias) All outcomes	High risk	Mortality data were given only for 697 of 1054 patients.
Selective reporting (reporting bias)	Low risk	None identified
Other bias	High risk	No control for cancer stage and functional capacity, no sample size calculation, funding not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Non-blinded

Machado 2005

Methods	Retrospective case-control study (confirmed influenza versus no influenza) Location and setting: Brazil	
Participants	HSCT recipients (CML, acute leukaemia, severe aplastic anaemia, NHL, MM, other) 43 participants eligible to receive influenza vaccination: 19 vaccinated 24 unvaccinated Mean age not reported	
Interventions	Influenza vaccination, obtained from review of participants' charts	
Outcomes	1. Confirmed influenza by direct immunofluorescence assay 2. Adverse events	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Machado 2005 (Continued)

Random sequence generation (selection bias)	High risk	Non-random
Allocation concealment (selection bias)	High risk	Non-random
Incomplete outcome data (attrition bias) All outcomes	High risk	Mortality - no record
Selective reporting (reporting bias)	High risk	The only outcome reported was documented influenza
Other bias	High risk	No control for cancer stage and functional capacity, funding not mentioned, no sample size calculation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Non-blinded

Musto 1997

Methods	Randomised trial, open-label Location: Italy
Participants	MM, with active chemotherapy treatment 50 adults: 25 vaccinated 25 unvaccinated Mean age not reported
Interventions	Influenza vaccination versus no vaccination, assigned by randomisation
Outcomes	1. Upper respiratory illnesses 2. Pneumonia requiring hospitalisation 3. Any hospitalisation 4. Influenza-related mortality 5. Local adverse events 6. Mean duration of Influenza-like illness 7. Non-programmed visits in haematology day hospital

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

Musto 1997 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow up
Selective reporting (reporting bias)	Unclear risk	Mortality reported only due to influenza pneumonia
Other bias	Unclear risk	No reported baseline imbalances, funding not mentioned, no sample size calculation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Natori 2017

Methods	Randomised controlled trial Location: Canada, Toronto	
Participants	At least 12 weeks post HSCT 73 adults: 35 received adjuvanted vaccine and 38 received non-adjuvanted vaccine Median age 54.5 years in adjuvanted vaccine group versus 52.5 years in non-adjuvanted vaccine group	
Interventions	Adjuvanted influenza vaccination versus non-adjuvanted influenza vaccination, assigned by randomisation	
Outcomes	1. Vaccine immunogenicity reported as seroconversion rate, seroprotection rate or geometric mean titres 2. Laboratory-confirmed influenza infections 3. Mortality related to influenza infections 4. All-cause mortality 5. Hospitalisations attributed to influenza infections 6. Any hospitalisation 7. Adverse events	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement

Natori 2017 (Continued)

Random sequence generation (selection bias)	Low risk	Computer-generated schedule in blocks of four
Allocation concealment (selection bias)	Low risk	Central randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow up for the mortality outcome.
Selective reporting (reporting bias)	Low risk	No significant differences in the secondary outcomes added to the manuscript after registration
Other bias	Low risk	No baseline imbalances, funding not mentioned, sample size achieved
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were not blinded, but low risk because of objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors of adverse events and lab workers were blinded

Vinograd 2013

Methods	Prospective observational cohort study Location: Israel
Participants	Solid malignancies, with active chemotherapy and haematological patients with active disease 806 adults: 387 vaccinated versus 419 unvaccinated Mean age 66 years in vaccinated group versus 60 years in unvaccinated
Interventions	Patients were followed up through medical personal hard copy files and through electronic patients' health records, including inpatient and outpatient records. Telephone or personal interviews were also conducted to collect data on clinical outcomes and assure vaccination status.
Outcomes	1. A composite of hospitalisations for fever or acute respiratory infection; and/or pneumonia necessitating antibiotic treatment; and/or chemotherapy interruptions related to an infectious condition. 2. All-cause mortality 3. Influenza-like illness 4. Laboratory-confirmed influenza 5. Individual components of the primary outcome 6. Any hospitalisation and hospitalisation days 7. Antibiotic treatment necessity in hospitalisation 8. All delays in planned chemotherapy courses
Notes	

Vinograd 2013 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-random
Allocation concealment (selection bias)	High risk	Non-random
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported fully
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Low risk	Controlled for cancer stage and functional capacity, funded by an internal grant, sample size achieved
Blinding of participants and personnel (performance bias) All outcomes	High risk	None blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	None blinded

HSCT: haematopoietic stem cell transplantation; **CML:** chronic myelogenous leukaemia; **MM:** multiple myeloma; **NHL:** non-Hodgkin's lymphoma

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adell 2002	All participants vaccinated
Anderson 1999	All participants vaccinated
Avetisyan 2008	All participants vaccinated
Ayoola 2016	All participants vaccinated
Baluch 2013	All participants vaccinated
Bedognetti 2009	Lymphoma participants compared to healthy participants
Bedognetti 2010	Lymphoma participants compared to healthy participants
Branagan 2015	All participants vaccinated
Branagan 2016	Comparing different doses of influenza vaccine
Branagan 2017	All participants vaccinated

Study	Reason for exclusion
Brydak 1999	All participants vaccinated
Brydak 2001	Healthy participants not vaccinated compared to breast cancer participants vaccinated
Brydak 2006	Lymphoma participants compared to healthy participants
Buccalosi 1995	All participants vaccinated Lymphoma participants compared to healthy participants
Centkowski 2007	All participants vaccinated Lymphoma participants compared to healthy participants
Chadha 2009	All participants vaccinated
De Lavallade 2011	Comparison to healthy participants
Dhedin 2014	Immunogenicity of vaccine compared to infection
Engelhard 1993	All participants vaccinated Comparing different doses of influenza vaccine
Feery 1977	Comparison to healthy participants
Ganz 1978	Comparison to healthy participants
Gribabis 1994	All participants vaccinated
Hahn 2015	Comparing different doses of influenza vaccine
Hodges 1979	Comparison to healthy participants
Issa 2011	All participants vaccinated
Jamshed 2016	Comparing different doses of influenza vaccine
Jo 2009	Comparing different doses of influenza vaccine
Keam 2017	All participants vaccinated
Lachenal 2010	Vaccination rate in haematological participants
Lankes 2009	Association between influenza vaccination and risk of developing Non-Hodgkin lymphoma
Ljungman 2005	Comparing different doses of influenza vaccine
Ljungman 2015	Comparing different types of vaccines in different seasons
Lo 1993	Comparing different doses of influenza vaccine
Mazza 2005	All participants vaccinated Lymphoma participants compared to healthy participants
Mulder 2009	All participants vaccinated

Study	Reason for exclusion
	Comparison to healthy participants
Nakashima 2017	All participants vaccinated, healthy controls
Nordoy 2002	All participants vaccinated
Ortbals 1977	All participants vaccinated
Puthillath 2011	All participants vaccinated Serological outcomes only
Rapezzi 2003	All participants vaccinated Lymphoma participants compared to healthy participants
Robertson 2000	Myeloma participants vaccinated compared to healthy participants' serum
Safdar 2006	Comparing different influenza vaccines in Non-Hodgkin lymphoma patients
Schafer 1979	All participants vaccinated Haematological participants compared to healthy participants
Seidel 2011	All participants vaccinated
Shildt 1979	All participants vaccinated
Spies 2008	No information about control group vaccination prior to study. Mortality is reported in a two-year follow-up, while we stated maximal follow-up period until end of the influenza season following vaccination
Spitaleri 2010	All participants vaccinated
Stiver 1978	All participants vaccinated
Sun 2016	All participants vaccinated
Takata 2009	All participants vaccinated
Van der Velden 2001	All participants vaccinated
Villa 2013	Comparing different doses of influenza vaccine
Wumkes 2013	All participants vaccinated
Xu 2009	All participants vaccinated Comparison to healthy participants
Yalc 2010	All participants vaccinated

DATA AND ANALYSES

Comparison 1. Influenza vaccine versus none

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	3		Odds Ratio (Fixed, 95% CI)	Totals not selected
1.1 Non-randomised, adjusted, events/person-years	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Non-randomised, adjusted, events/person	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Randomised, events/person	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Influenza-like illness	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Randomised, events/person	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Non-randomised, unadjusted, events/person	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Confirmed influenza	4		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Non-randomised, unadjusted, events/person-years	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Non-randomised, unadjusted, events/persons with ILI	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Non-randomised, unadjusted, events/persons	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Randomised, events/person	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Pneumonia	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Randomised, events/person	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Non-randomised, unadjusted, events/person-years	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Non-randomised, unadjusted, events/person	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Any hospitalisation	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Randomised, events/person	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Non-randomised, unadjusted, events/person	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Influenza-related mortality	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Randomised, events/person	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Non-randomised, unadjusted, events/person-years	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Influenza vaccine versus none, Outcome 1 All-cause mortality.

Study or subgroup	Experimental N	Control N	log[Odds Ratio] (SE)	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
1.1.1 Non-randomised, adjusted, events/person-years					
Earle 2003	626	951	-0.1 (0.064)	+	0.88[0.78,1]
1.1.2 Non-randomised, adjusted, events/person					
Vinograd 2013	387	419	-0.9 (0.294)	+	0.42[0.24,0.75]
1.1.3 Randomised, events/person					
Ambati 2015	0	0	0.2 (0.542)	+	1.25[0.43,3.62]
Favours experimental 0.01 0.1 1 10 100 Favours control					

Analysis 1.2. Comparison 1 Influenza vaccine versus none, Outcome 2 Influenza-like illness.

Study or subgroup	Vaccinated n/N	Unvaccinated n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Randomised, events/person				
Musto 1997	8/25	18/25	+	0.18[0.05,0.61]
1.2.2 Non-randomised, unadjusted, events/person				
Vinograd 2013	134/387	137/419	+	1.09[0.81,1.46]
Favours vaccinated 0.01 0.1 1 10 100 Favours unvaccinated				

Analysis 1.3. Comparison 1 Influenza vaccine versus none, Outcome 3 Confirmed influenza.

Study or subgroup	Vaccinated n/N	Unvaccinated n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Non-randomised, unadjusted, events/person-years				
Earle 2003	0/626	3/951	+	0.22[0.01,4.19]
Favours vaccinated 0.01 0.1 1 10 100 Favours unvaccinated

Analysis 1.4. Comparison 1 Influenza vaccine versus none, Outcome 4 Pneumonia.

Analysis 1.5. Comparison 1 Influenza vaccine versus none, Outcome 5 Any hospitalisation.

Analysis 1.6. Comparison 1 Influenza vaccine versus none, Outcome 6 Influenza-related mortality.

Study or subgroup	Vaccine n/N	No vaccine n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Earle 2003	0/626	2/951		0.3[0.01,6.32]
Favours vaccinated				Favours unvaccinated

Comparison 2. Adjuvanted vaccine versus non-adjuvanted vaccine

Outcome or subgroup title	No. of studies	No. of parti- cants	Statistical method	Effect size
1 All-cause mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Confirmed influenza	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Any hospitalisation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Adjuvanted vaccine versus non-adjuvanted vaccine, Outcome 1 All-cause mortality.

Study or subgroup	Adjuvanted vaccine n/N	Non-adjuvanted vaccine n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Natori 2017	1/35	2/38		0.54[0.05,5.73]
Favours adjuvanted				Favours non-adjuvanted

Analysis 2.2. Comparison 2 Adjuvanted vaccine versus non-adjuvanted vaccine, Outcome 2 Confirmed influenza.

Study or subgroup	Adjuvanted vaccine n/N	Non-adjuvanted vaccine n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Natori 2017	5/35	3/38		1.94[0.43,8.82]
Favours adjuvanted				Favours non-adjuvanted

Analysis 2.3. Comparison 2 Adjuvanted vaccine versus non-adjuvanted vaccine, Outcome 3 Any hospitalisation.

Study or subgroup	Adjuvanted vaccine n/N	Non-adjuvanted vaccine n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Natori 2017	8/35	11/38		0.73[0.25,2.09]
Favours adjuvanted				Favours non-adjuvanted

ADDITIONAL TABLES

Table 1. Influenza frequency and related outcomes in HSCT recipients and adults with cancer

Ref.	Type of malignancy (influenza years)	No of cases	Influenza cases	Outcome
Ljungman 2001	Allogeneic BMT/HSCT recipients (1997 to 1998)	819	1.7%	Deaths 29%
	Autologous BMT/HSCT recipients (1997 to 1998)	1154	0.2%	Deaths 0%
	Allogeneic BMT/HSCT recipients (1997 to 2000)	>819		Deaths 23%
	Autologous BMT/HSCT recipients (1997 to 2000)	>1154		Deaths 22%
Hassan 2003	Allogeneic BMT/HSCT recipients (1996 to 2001)	230	2.2%	Deaths 20%
	Autologous BMT/HSCT recipients (1996 to 2001)	396	0%	
Nichols 2004	HSCT recipients (within 120 days after transplantation) (1989 to 2002)	4797	1.3%	Deaths 10% Pneumonia 29%
Machado 2003	HSCT recipients (URTI symptoms present) (2001 to 2002)	179	23%	Deaths 0%
Chemaly 2006	HSCT recipients AND haematologic malignancies (retrospective study of patients with laboratory-confirmed viral respiratory infection) (2000 to 2002)	343	33%	Deaths 4% Pneumonia 30%
	HSCT recipients	230	29%	
	Leukaemia	61	33%	
	Lymphoma	37	51%	
	Multiple myeloma	15	40%	
Yousuf 1997	CLL /acute leukaemia (hospitalised patients) (1993 to 1994)	45	33%	Deaths 27% Pneumonia 80%
Elting 1995	CLL /acute leukaemia (1991 to 1992)	37	11%	Deaths 25% Pneumonia 75%
Redelman-Sidi 2010	Solid cancers (H1N1 2009 pandemic)	226	7%	0% Deaths
	Haematologic malignancies (H1N1 2009 pandemic)	167 (96 HSCT)	17% (22%)	0% Deaths
Ljungman 2011	HSCT recipients (prospective study of patients with laboratory-confirmed H1N1 infection) (H1N1 2009 pandemic)	286		Deaths 6% Pneumonia 33%
Chemaly 2012	Solid cancers (retrospective study of patients with laboratory-confirmed H1N1 infection) (H1N1 2009 pandemic)	115		Deaths 9.5% Pneumonia 23%

BMT: bone marrow transplantation; **CLL:** chronic lymphocytic leukaemia; **HSCT:** haematopoietic stem cell transplantation; **URTI:** upper respiratory tract infection

Table 2. Newcastle-Ottawa Grading

Selection					Comparability	Outcome			Total stars score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability *	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts **	
Earle 2003	c	a	a	a	No	d ***	a	a	5
Machado 2005	c	a	a	a	No	b	a	a	6
Vinograd 2013	b	a	a+b	a	a+b	b+c	a	a	10

* The most important factor to control for was the cancer stage. The second most important factor was functional capacity

** A follow-up rate of $\geq 80\%$ was considered adequate

*** Procedure was described but considered inadequate (through billing accounts and other administrative databases)

Table 3. Summary of Main Outcomes - vaccine versus no vaccine

Outcome	Design	All-cause mortality	Influenza-like illness		Influenza-related mortality		Confirmed influenza		Pneumonia		Any hospitalisation		Chemotherapy interruptions		GMT	
			Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Vaccination status																
Earle 2003	Retrospective observational	Cox adjusted HR 0.88 (95% CI 0.78 to 1), 626 versus 951 py *			0/626 py	2/951 py	10/626 py	3/951 py	7/626 py *	633/951 py *	mean 15.6, 95% CI 13.3 to 17.8 (N = 626 py)	mean 16.4, 95% CI 14.3 to 18.4 (N = 951 py)	mean 5.06 days (N = 626 py) **	mean 6.04 days (N = 951 py) **		

Table 3. Summary of Main Outcomes - vaccine versus no vaccine (Continued)

Machado 2005	Retrospective case-control					2/19 *	12/24 *				
Musto 1997	Randomised, open-label			8/25 *	18/250 *	2/25		0/25	4/25	2/25 *	12/25 *
Vinograd 2013	Prospective observational	MV adjusted OR 0.42 (95% CI 0.24 to 0.75) (387 versus 419p); MV adjusted OR in propensity-matched cohort 0.42 (95% CI 0.24 to 0.76) (218p versus 218p)		134/387	137/419	2/387	4/419	81/387	78/419	183/387	205/419 97/387 116/419
Ambati 2015	Randomised, open-label	OR 1.25 (95%CI 0.43-3.62)				2/40	2/38	3/40	4/38		15*,10*, 12.5*, 30* 60 110*** ***

py= persons years

* denoted statistically significant difference, $P < 0.05$

** mean interval between chemotherapy bills

*** data is for A/H1N1, A/H3N2 and B respectively

CI: confidence interval;**GMT:** geometric mean titre. (Data are for 30 days post vaccination); **HR:** hazard ratio; **OR:** odds ratio;

Table 4. Summary of Main Outcomes - adjuvanted versus non-adjuvanted

Outcome	Design	All-cause mortality		Influenza-related mortality		Confirmed influenza		Any hospitalisation		GMT	
Vaccination status		Adjuvanted	Non-adjuvanted	Adjuvanted	Non-adjuvanted	Adjuvanted	Non-adjuvanted	Adjuvanted	Non-adjuvanted	Adjuvanted	Non-adjuvanted
Natori 2017	Randomised, open-label	1/35	2/38	0/35	0/38	5/35	3/38	8/35	11/38	319.6, 480.7, 298.9 *	195.9, 359.3, 240.5 *

* data is for A/H1N1, A/H3N2 and B respectively

GMT: geometric mean titre. (Data are for 30 days post vaccination).

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Influenza, Human, this term only
 #2 MeSH descriptor Influenza A virus explode all trees
 #3 MeSH descriptor Influenza B virus explode all trees
 #4 MeSH descriptor Influenzavirus C, this term only
 #5 influenza* or gripe or flu or orthomyxovir* or myxovirus*
 #6 (#1 OR #2 OR #3 OR #4 OR #5)
 #7 MeSH descriptor Influenza Vaccines, this term only
 #8 vaccin*
 #9 flumist or CAIV-T or trivalent or LAIV or fluzone or fluarix or fluinsure or fluviral or invivac or influvac or flublok or fluvirin or vaxigrip or mutagrip or flushield or fluogen
 #10 (#7 OR #8 OR #9)
 #11 MeSH descriptor Neoplasms explode all trees
 #12 MeSH descriptor Bone Marrow Transplantation, this term only
 #13 MeSH descriptor Stem Cell Transplantation explode all trees
 #14 cancer* or neoplas* or tumor* or tumour* or malignan* or carcinoma* or metasta* or oncolog* or leukemi* or leukaemi* or lymphoma* or myeloma* or sarcoma*
 #15 MeSH descriptor Antineoplastic Agents explode all trees
 #16 chemotherap* or transplant* or HSCT or BMT
 #17 MeSH descriptor Neutropenia, this term only
 #18 neutropenia
 #19 lymphocyte* near/5 (function* or count* or number*)
 #20 MeSH descriptor Immune Tolerance explode all trees
 #21 (immuno-suppress* or immunosuppress*)
 #22 (immunity or immune) near/5 (suppress* or impair* or dysfunction*)
 #23 immuno-compromise* or immunocompromise*
 #24 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)
 #25 (#6 AND #10 AND #24)

Appendix 2. MEDLINE search strategy

1 Influenza, Human/
 2 exp influenzavirus a/
 3 exp Influenzavirus B/
 4 Influenzavirus C/
 5 (influenza* or gripe or flu or orthomyxovir* or myxovirus*).mp.
 6 1 or 2 or 3 or 4 or 5
 7 Influenza Vaccines/
 8 vaccin*.mp.
 9 (flumist or CAIV-T or trivalent or LAIV or fluzone or fluarix or fluinsure or fluviral or invivac or influvac or flublok or fluvirin or vaxigrip or mutagrip or flushield or fluogen).mp.
 10 7 or 8 or 9
 11 exp Neoplasms/
 12 Bone Marrow Transplantation/
 13 exp Stem Cell Transplantation/
 14 (cancer* or neoplas* or tumor* or tumour* or malignan* or carcinoma* or metasta* or oncolog* or leukemi* or leukaemi* or lymphoma* or myeloma* or sarcoma*).mp.
 15 exp Antineoplastic Agents/
 16 (chemotherap* or transplant* or HSCT or BMT).mp.
 17 Neutropenia/ or neutropenia.mp.
 18 (lymphocyte* adj5 (function* or count* or number*)).mp.
 19 exp Immune Tolerance/
 20 (immuno-suppress* or immunosuppress*).mp.
 21 ((immunity or immune) adj5 (suppress* or impair* or dysfunction*)).mp.
 22 (immuno-compromise* or immunocompromise*).mp.
 23 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
 24 6 and 10 and 23
 25 randomized controlled trial.pt.
 26 controlled clinical trial.pt.

27 randomized.ab.
 28 placebo.ab.
 29 drug therapy.fs.
 30 randomly.ab.
 31 trial.ab.
 32 Epidemiologic studies/
 33 exp case control studies/
 34 exp cohort studies/
 35 case control.tw.
 36 (cohort adj (study or studies)).tw.
 37 cohort analy*.tw.
 38 (follow up adj (study or studies)).tw.
 39 (observational adj (study or studies)).tw.
 40 longitudinal.tw.
 41 retrospective.tw.
 42 cross sectional.tw.
 43 cross-sectional studies/
 44 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
 45 24 and 44

key:

mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier

pt=publication type

tw=textword

ab=abstract

fs=floating subheading

Appendix 3. Embase search strategy

1 exp influenza/
 2 (influenza* or grippe or flu or orthomyxovir* or myxovirus*).mp.
 3 1 or 2
 4 exp influenza vaccine/
 5 vaccin*.mp.
 6 (flumist or CAIV-T or trivalent or LAIV or fluzone or fluarix or fluinsure or fluviral or invivac or influvac or flublok or fluvirin or vaxigrip or mutagrip or flushield or fluogen).mp.
 7 4 or 5 or 6
 8 exp neoplasm/
 9 exp bone marrow transplantation/
 10 stem cell transplantation/
 11 (cancer* or neoplas* or tumor* or tumour* or malignan* or carcinoma* or metasta* or oncolog* or leukemi* or leukaemi* or lymphoma* or myeloma* or sarcoma*).mp.
 12 exp chemotherapy/
 13 exp antineoplastic agent/
 14 (chemotherap* or transplant* or HSCT or BMT).mp.
 15 exp neutropenia/ or neutropenia.mp.
 16 (lymphocyte* adj5 (function* or count* or number*)).mp.
 17 exp Immune Tolerance/
 18 (immuno-suppress* or immunosuppress*).mp.
 19 ((immunity or immune) adj5 (suppress* or impair* or dysfunction*)).mp.
 20 (immuno-compromise* or immunocompromise*).mp.
 21 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
 22 3 and 7 and 21
 23 crossover procedure/
 24 randomized controlled trial/
 25 single blind procedure/
 26 random*.mp.
 27 factorial*.mp.
 28 (crossover* or cross over* or cross-over).mp.
 29 placebo*.mp.
 30 (doubl* adj blind*).mp.

31 (singl* adj blind*).mp.
32 assign*.mp.
33 allocat*.mp.
34 volunteer*.mp.
35 controlled clinical trial/
36 Clinical study/
37 case control study/
38 Family study/
39 Longitudinal study/
40 Retrospective study/
41 Prospective study/
42 Cohort analysis/
43 (cohort adj (study or studies)).mp.
44 (case control adj (study or studies)).tw.
45 (follow up adj (study or studies)).tw.
46 (observational adj (study or studies)).tw.
47 (epidemiologic* adj (study or studies)).tw.
48 (cross sectional adj (study or studies)).tw.
49 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50 22 and 49

key:

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

tw=textword

Appendix 4. LILACS search strategy

influenza AND (vaccine OR vaccination)

Appendix 5. SIGN search strategy for observational studies

Adapted for MEDLINE

1 Epidemiologic studies/
2 Exp case control studies/
3 Exp cohort studies/
4 Case control.tw.
5 (cohort adj (study or studies)).tw.
6 Cohort analy\$.tw.
7 (Follow up adj (study or studies)).tw.
8 (observational adj (study or studies)).tw.
9 Longitudinal.tw.
10 Retrospective.tw.
11 Cross sectional.tw.
12 Cross-sectional studies/
13 Or/1-12

Appendix 6. Assessment of risk of bias in RCTs

Studies were classified according to the following criteria:

Allocation sequence generation:

A = adequate (e.g. a random number table; a computer random number generator)

B = inadequate (e.g. sequence generated by date)

C = unclear or not described

Allocation concealment

A = adequate (e.g. numbered drug containers of identical appearance)

B = inadequate (e.g. using an open-random allocation schedule)

C = unclear or not described

Blinding

A = adequate (e.g. outcome measurement are not likely to be influenced by blinding approach)

B = inadequate (e.g. outcome measurement are likely to be influenced by blinding approach)

C = unclear or not described

Incomplete outcome data addressing (separately for each outcome defined in the study)

A = adequate (e.g. no missing outcome data)

B = inadequate (e.g. reason for missing outcome data likely to be related to true outcome)

C = unclear or not described

Lack of selective outcome reporting (separately for each outcome defined in the study)

A = adequate (e.g. published reports include all expected outcomes)

B = inadequate (e.g. not all of the study's pre-specified primary outcomes have been reported)

C = unclear or not described

Absence of other source of bias

A = adequate (e.g. the study appears to be free of other sources of bias)

B = inadequate (e.g. the study had a potential source of bias related to the specific study design)

Follow-up

Duration of follow-up and percent of participants lost to follow-up.

Appendix 7. Assessment of risk of bias in cohort studies

Adapted Newcastle-Ottawa Scale (NOS)

We classified studies as low risk of bias (up to one inadequate item in the NOS), medium risk of bias (up to three inadequate items) and high risk of bias (more than three inadequate or no description of methods. The following items were assessed.

Selection

1) Representativeness of the exposed cohort (active cancer patients, undergoing chemotherapy, whose immune status is well characterised)

a) truly representative of the exposed cohort #

b) somewhat representative of the exposed cohort #

c) selected group of exposed cancer patients. e.g. nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort #

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record #

b) structured interview #

c) written self-report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes #

b) no

Comparability

1) Comparability of cohorts on the basis of the following items

a) study controls for cancer stage #

b) study controls for functional status #

Outcome

1) Assessment of outcome

a) independent blind assessment #

b) record linkage #

c) self-report

d) no description

2) Was follow-up long enough for outcomes to occur (the end of influenza season)?

a) yes (select an adequate follow-up period for outcome of interest) #

b) no

3) Adequacy of follow-up of cohorts

a) complete follow-up - all participants accounted for #

b) participants lost to follow-up unlikely to introduce bias - small number lost - > 80% (select an adequate %) follow-up, or description provided of those lost) #

c) follow-up rate < 80% (select an adequate %) and no description of those lost

d) no statement

WHAT'S NEW

Date	Event	Description
1 February 2018	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 2011

Review first published: Issue 10, 2013

Date	Event	Description
24 January 2018	New search has been performed	Literature searches re-run May 2017.
24 January 2018	New citation required but conclusions have not changed	Two new randomised controlled trials (RCTs) identified and included but the conclusions remain unchanged. Methods updated to include GRADE assessment of the evidence.

CONTRIBUTIONS OF AUTHORS

Current version

Roni Bitterman (RB) and Noa Eliakim Raz (NER) co-ordinated the review, guided by Mical Paul (MP). Both RB and NER contributed equally to the review.

RB and MP were responsible for undertaking searches and organised retrieval of papers.

RB and MP were responsible for data collection, writing to study authors for additional information.

RB and MP were responsible for screening search results, screening retrieved papers against inclusion criteria and appraising quality of papers and abstracting data from papers (disagreement was settled by discussion).

RB was responsible for entering data into Review Manager 5.

All review authors participated in analysis and interpretation of data.

RB and NER were responsible for writing the review.

Prior version

Inbal Levi-Vinograd (ILV) wrote the original protocol.

Noa Eliakim Raz (NER) co-ordinated the review, guided by Mical Paul (MP).

NER and ILV were responsible for undertaking searches and organised retrieval of papers.

NER and ILV were responsible for data collection, writing to study authors for additional information.

NER, ILV, AZT, LL and MP were responsible for screening search results, screening retrieved papers against inclusion criteria and appraising quality of papers and abstracting data from papers (the latter review author was arbiter in case of disagreement).

NER was responsible for entering data into Review Manager 5.

All review authors participated in analysis and interpretation of data.

NER was responsible for writing the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- Beilinson Young Researcher Foundation, Israel.
- Clalit Foundation, Israel.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The primary protocol-defined outcome was: 'Influenza-like illness defined as: ILI definition in study or Pneumonia of any cause or influenza-related death'. We have changed the primary outcome to 'all-cause mortality' since ultimately this is the goal of influenza vaccination and the composite outcome of infections, hospitalisations, chemotherapy delays and other effects of influenza. All components of the former primary outcome are included as secondary outcomes.

In the previous version of this review it was not stated whether studies conducted on a mixed population of adults and children would be included. Though this is a review on an adult population, we believe mixed population studies should not be omitted. We thus specifically stated that only studies that included more than 30% children were excluded.

When the original review was published adjuvanted influenza vaccines were not commercially available and no studies were conducted on people with cancer. However, as adjuvanted vaccines are now more prevalent we have added them to the updated review.

Though not stated specifically in the original protocol, studies evaluating different dosing regimens were excluded. In this version we stated this clearly.

INDEX TERMS

Medical Subject Headings (MeSH)

Adjuvants, Immunologic [administration & dosage]; Bone Marrow Transplantation [mortality]; Case-Control Studies; Cause of Death; Cohort Studies; Hematologic Neoplasms [immunology] [mortality]; Immunocompromised Host [*immunology]; Influenza Vaccines [*administration & dosage] [immunology]; Influenza, Human [epidemiology] [immunology] [*prevention & control]; Neoplasms [*immunology] [mortality]; Observational Studies as Topic; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans