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Vaccines for the common cold (Review)

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[Intervention Review]

Vaccines for the common cold

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ABSTRACT

Background

The common cold is a spontaneously remitting infection of the upper respiratory tract, characterised by a runny nose, nasal congestion, sneezing, cough, malaise, sore throat, and fever (usually < 37.8° C). The widespread morbidity caused by the common cold worldwide is related to its ubiquitousness rather than its severity. The development of vaccines for the common cold has been difficult because of antigenic variability of the common cold virus and the indistinguishable multiple other viruses and even bacteria acting as infective agents. There is uncertainty regarding the efficacy and safety of interventions for preventing the common cold in healthy people. This is an update of a Cochrane review first published in 2011 and previously updated in 2013.

Objectives

To assess the clinical effectiveness and safety of vaccines for preventing the common cold in healthy people.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (September 2016), MEDLINE (1948 to September 2016), Embase (1974 to September 2016), CINAHL (1981 to September 2016), and LILACS (1982 to September 2016). We also searched three trials registers for ongoing studies and four websites for additional trials (February 2017). We included no language or date restrictions.

Selection criteria

Randomised controlled trials (RCTs) of any virus vaccines compared with placebo to prevent the common cold in healthy people.

Data collection and analysis

Two review authors independently evaluated methodological quality and extracted trial data. We resolved disagreements by discussion or by consulting a third review author.

Main results

We found no additional RCTs for inclusion in this update. This review includes one RCT dating from the 1960s with an overall high risk of bias. The RCT included 2307 healthy participants, all of whom were included in analyses. This trial compared the effect of an adenovirus vaccine against placebo. No statistically significant difference in common cold incidence was found: there were 13 (1.14%) events in 1139 participants in the vaccines group and 14 (1.19%) events in 1168 participants in the placebo group (risk ratio 0.95, 95% confidence interval 0.45 to 2.02; P = 0.90). No adverse events related to the live vaccine were reported. The quality of the evidence was low due to limitations in methodological quality and a wide 95% confidence interval.

Authors' conclusions

This Cochrane Review was based on one study with low-quality evidence. We found no conclusive results to support the use of vaccines for preventing the common cold in healthy people compared with placebo. We identified a need for well-designed, adequately powered RCTs to investigate vaccines for the common cold in healthy people. Any future trials on medical treatments for preventing the common cold should assess a variety of virus vaccines for this condition. Outcome measures should include common cold incidence, vaccine safety, and mortality related to the vaccine.

PLAIN LANGUAGE SUMMARY

Vaccines for preventing the common cold

Review question

We looked at whether vaccines can help to prevent the common cold.

Background

The common cold is caused by viral infection of the upper respiratory tract, and people usually get better when the virus dies. People with common cold feel unwell, have runny noses, nasal congestion, sneezing, and cough with or without sore throat, and slightly elevated temperatures. Treatments are aimed at relieving symptoms.

Globally, the common cold causes widespread illness. It has been difficult to produce vaccines to prevent the common cold due to the many viruses involved. The effect of vaccines on preventing the common cold in healthy people is still unknown.

Search date

For this update we searched the literature up to 2 September 2016.

Study characteristics

We found no new studies in this update. This review includes one previously identified randomised controlled trial performed in 1965. This study involved 2307 healthy people at a training facility for the United States Navy and evaluated the effect of a live weakened (attenuated) adenovirus vaccine compared to a fake vaccine (placebo).

Study funding sources

This study was funded by a government institution.

Key results

There were no differences in the frequency of occurrence of the common cold between those who received the vaccine compared to those who received a fake vaccine. There were no adverse events related to the vaccine. However, due to the low numbers of people included in the study and numbers of colds, as well as flaws in the study design, our confidence in the results is low. Further research may be able to clarify if vaccines can prevent common cold, since the current evidence does not support the use of adenovirus vaccine to prevent common cold in healthy people.

Quality of the evidence

We assessed the quality of the evidence as low due to high risk of bias and low numbers of people included in the study and numbers of colds, which resulted in imprecision.

Summary of findings for the main comparison. Virus vaccines compared to placebo for preventing the common cold in healthy people

Virus vaccines compared to placebo for preventing the common cold in healthy people

Patient or population: healthy people
Settings: outpatients at Great Lakes Naval Training Center
Intervention: virus vaccines for preventing the common cold[1]
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Virus vaccines for preventing the common cold				
Incidence of the common cold Number of participants with common cold by group Follow-up: mean 9 weeks	**Study population**		**RR 0.95** (0.45 to 2.02)	2307 (1 study)[2]	⊕⊕⊝⊝ **low**[3 4]	
	12 per 1000	**11 per 1000** (5 to 24)				
Vaccine safety	The study stated that there were no adverse events related to the vaccine.			2307 (1 study)[2]	⊕⊕⊝⊝ **low**[3 5]	
Mortality related to the vaccine - not reported	See comments	See comments	See comments	See comments	See comments	The included study did not report this outcome.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** risk ratio

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Adenovirus vaccine used for preventing the common cold.
[2] Griffin 1970.

[3]Downgraded one level due to high risk of bias for this outcome.
[4]Downgraded one level due to imprecision: few events (N = 27) and wide 95% confidence interval.
[5]Downgraded one level due to imprecision: zero events reported in a narrative fashion.

BACKGROUND

Description of the condition

There are no standardised definitions for a common cold (see Appendix 1). The common cold is a spontaneously remitting infection of the upper respiratory tract, characterised by a runny nose, nasal congestion, and sneezing, and sometimes cough, malaise, sore throat, and fever (usually < 100° F). A temperature of 100° F (37.8° C) or higher for three to four days is typically associated with influenza and other respiratory diseases (Appendix 2) (DDCP 2010; Heikkinen 2003). While benign in nature, the common cold is the most frequent illness experienced in humans. Children experience six to 11 upper respiratory tract infections per year (Evans 1997; Leder 2003; Nelson 2000), and adults experience two to four episodes per year (Evans 1997; Grüber 2008; Harrison 2008). Because it causes frequent absences from school and work, the common cold has become a significant economic burden (Glezen 2000; Hall 2001; Henrickson 1994; Henrickson 2003); the cost in the United States is estimated at more than USD 60 billion each year (Poland 2009). Furthermore, bacterial complications can lead to morbidity and mortality (Thompson 2003; Wat 2004).

The aetiology of the common cold is diverse (Appendix 3) (Heikkinen 2003). Children, the elderly, and other age groups with comorbidities such as prematurity, chronic lung diseases (chronic obstructive pulmonary disease), congenital heart disease, and asthma are more prone to viral infections that cause the common cold, such as respiratory syncytial virus (RSV), rhinovirus, parainfluenza, coronavirus, and adenovirus (non-polio) (Edlmayr 2009; Jackson 2008; Krasinski 1985; Peltola 2008). Human rhinovirus (HRV) is responsible for 50% to 80% of common colds and is an important cause of morbidity, reduced productivity, and inappropriate use of antibiotics and over-the-counter medications. In humans, the coronavirus (HCoV 229E) causes the common cold by infecting the upper respiratory tract. This is mainly encountered in children, and re-infection occurs in adults (Eriksson 2006). The primary factors that contribute to the spread of this disease are poor hand hygiene, overcrowding, and captive populations (schools and daycare centres) (Harrison 2008).

Description of the intervention

Treatment of the common cold is symptomatic. Studies have shown that simple preventive measures are important but may be difficult to enforce practically (Jefferson 2011). Another method of prevention could be vaccination.

The development of vaccines for the common cold has been challenging because of multiple aetiologies, Poland 2009, and antigenic variability of the common cold viruses (Bembridge 1998; Hussell 1998). In the case of rhinovirus, there are over 167 different rhinoviral serotypes (Ren 2017). For this reason, it is difficult to create a vaccine that can give total protection. However, the future for vaccines for the common cold looks promising, considering the current knowledge of the full genomes of HRV serotypes (Palmemberg 2009). Immune responses are triggered whenever a person is infected with the same virus but with different antigenic molecules (Tobin 2008).

One of the most common causes of respiratory diseases are rhinoviruses. A recombinant vaccine has been reported, produced with rhinovirus-derived VP1, a surface protein that is critically involved in the infection of respiratory cells, and a non-allergenic peptide of the major grass pollen type allergen Ph1 p1 (Edlmayr 2009).

Adenovirus is a commonly recognised pathogen of the upper respiratory tract and has been particularly common in captive populations (Binn 2007). Adenovirus serotype 4 (Ad4) and serotype 7 vaccines were used during immunisation programmes starting in 1971. Unfortunately, their interruption triggered the re-emergence of adenovirus-produced diseases in crowded locations. An example of this reappearance was documented in United States military training sites in 1999, where Ad4 accounted for 98% of all diagnoses (Russell 2006).

Epidemiological and clinical studies have revealed important changes with regard to clinical adenovirus infection, including alterations in its antigenic presentation, geographical distribution, and virulence (Gray 2007). Adenoviral vaccines delivered orally have been used for decades to prevent respiratory illnesses. New studies have concluded that these vaccines are safe and have brought about a good immune response in the studied populations.

Respiratory syncytial virus causes approximately 5% of common colds in adults (Heikkinen 2003). The vaccine development for RSV has had some problems due to antigenic variability, especially in proteins F and G. People who were vaccinated with the formalin-inactivated vaccine displayed X-ray evidence of severe pneumonia and bronchiolitis due to pulmonary Arthus reaction and a process of immunopotentiation. This process was induced by a T helper (Th)-2 and Th17 T cell responses with the enrolment of T cells, neutrophils, and eosinophils causing inflammation and tissue damage (Rey-Jurado 2017). Where an effective vaccine can be offered, it should be administered to children younger than six months of age, when immune systems are still immature. For this reason another approach is the development of a vaccine for maternal immunisation as it has been demonstrated that RSV-neutralising antibodies are transferred efficiently through the placenta from the pregnant woman to the newborn (Munoz 2003). Furthermore, a phase II clinical trial has found that a recombinant F nanoparticle vaccine formulation reduces the incidence of RSV infection when compared to placebo (the incidence was 11% versus 21%, respectively) in healthy women of childbearing age (Glenn 2016).

Vaccines for parainfluenza (HPIV3 cp45) are safe and immunogenic in seronegative children aged between six and 18 months (Belshe 2004a). The vaccine has also demonstrated less risk of transmission than others (wt HPIV3), making it possible to develop more randomised trials. Bovine parainfluenza virus vaccines are also being developed, which have been well-tolerated, effective, and immunogenic in infants (Belshe 2004b).

How the intervention might work

Almost all vaccines work by inducing antibodies in the serum to interfere with microbial invasion of the bloodstream, or in the mucosa, and to block adherence of pathogens to epithelial cells (Pichichero 2009). To protect the body, antibodies must be efficient, neutralising agents or have opsonisation and phagocytosis properties. Correlates of protection after vaccination are sometimes absolute quantities, but are often relative. Most infections are prevented at a particular response level, but some

could occur above that level because of a large challenge dose or deficient host factors. There may be more than one correlate of protection for a disease; authors refer to these as "co-correlates". Either the effector or central memory may co-correlate with protection. Cell-mediated immunity may also operate as a correlate or co-correlate of protection against disease, rather than against infection (Plotkin 2008). Some studies suggest that vaccines that mimic natural infection and take into account the structure of pathogens seem to be effective in inducing long-term protective immunity (Kang 2009).

Why it is important to do this review

1. Common cold vaccines would reduce the prevalence of this disease in more than 25 million people with upper respiratory tract infections each year (Gonzales 2001).
2. The common cold results in an important economic burden with over 189 million missed school days, Roxas 2007, and 8 million to 20 million days of restricted activity (Adams 1999).
3. If randomised controlled trials demonstrate that there is a vaccine providing efficacy and safety to prevent the common cold, scientists could continue research in this area.

OBJECTIVES

To assess the clinical effectiveness and safety of vaccines for preventing the common cold in healthy people.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). We did not apply limits with respect to follow-up periods.

Types of participants

Healthy people aged between 6 months and 90 years.

Types of interventions

Any vaccine that prevents the common cold, which protects against RSV, rhinovirus, parainfluenza, or adenovirus (non-polio), irrespective of dose, schedule, or administration route, versus placebo. We excluded trials on the prevention of influenza A and B because influenza and the common cold are two different diseases (Jefferson 2012). See Appendix 3 for details.

Types of outcome measures

Primary outcomes

1. Incidence of the common cold after vaccination, regardless of the causal agent determined by laboratory or clinical examination.
2. Vaccine safety, i.e. adverse events ("any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment") (Nebeker 2004); and adverse drug reactions ("a response to a drug which is noxious, uninitiated and which occurs at doses normally used in men for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic functions") (Nebeker 2004).
3. Mortality related to the vaccine.

Secondary outcomes

We did not consider secondary outcomes.

Search methods for identification of studies

Electronic searches

We searched the following databases up to 2 September 2016:

- CENTRAL (the Cochrane Central Register of Controlled Trials), which contains the Cochrane Acute Respiratory Infections Specialised Register (CENTRAL; August 2016, Issue 8), in the Cochrane Library (searched 2 September); using the strategy in Appendix 4;
- MEDLINE via Ovid (from 1948 to 2 September 2016) using the strategy in Appendix 5;
- Embase via Elsevier (from 1974 to 2 September 2016) using the strategy in Appendix 6;
- CINAHL via EBSCO (from 1981 to 2 September 2016) using the strategy in Appendix 7; and
- LILACS via BIREME (from 1982 to 2 September 2016) using the strategy in Appendix 8.

We used the Cochrane Highly Sensitive Search Strategy to identify randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy to search Embase, CINAHL, and LILACS.

We searched the following trial registries on 2 February 2017:

- ISRCTN registry (www.isrctn.com);
- ClinicalTrials.gov (clinicaltrials.gov/); and
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/ictrp/search/en/).

We did not restrict the results by language, dates, or publication status (published, unpublished, in press, or in progress).

Searching other resources

We checked the reference lists of all relevant trials and identified reviews. We searched the following websites for trials on 2 February 2017:

1. US Food and Drug Administration (www.fda.gov);
2. European Medicines Agency (www.emea.europa.eu);
3. Medicines & Healthcare Products Regulatory Agency (www.mhra.gov.uk/index.htm);
4. Evidence in Health and Social Care (www.evidence.nhs.uk/).

Data collection and analysis

Selection of studies

Two review authors (MJMZ, JVAF) independently screened the titles and abstracts of studies identified as a result of the search for possible inclusion in the review. We retrieved full-text reports of potentially relevant studies. Two review authors (MJMZ, JVAF) independently screened the full texts to identify studies for inclusion and identified and recorded reasons for exclusion of the ineligible studies. Any disagreements were resolved through discussion or by consulting a third review author (DSR) when needed. We identified and excluded duplicates and collated

multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of included studies table (Moher 2009). We imposed no language restrictions.

Data extraction and management

We used a data collection form for study characteristics and outcome data that we had piloted on at least one study in the review. Two review authors (DSR, CVG) extracted study characteristics from the included studies. We extracted the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (DSR, CVG) independently extracted outcome data from the included studies. We had planned to note in the Characteristics of included studies table if outcome data were not reported in a usable way. We had planned to resolve disagreements by consensus or by involving a third review author (RH). One review author (DSR) transferred data into the Review Manager 5 file (RevMan 2014). We double-checked that the data were entered correctly by comparing the data presented in the systematic review with the study report. A second review author (MJMZ) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Three review authors (DSR, CVG, RH) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another review author (MJMZ). We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low, or unclear and provided quotes from the study report together with a justification for our judgement in the 'Risk of bias' table. Where necessary, we considered blinding separately for different key outcomes.

Measures of treatment effect

We calculated the risk ratio (RR) with 95% confidence intervals (CIs) for incidence of the common cold.

We entered outcome data for the study into a data table in Review Manager 5 to calculate the treatment effects (RevMan 2014). We used RR for dichotomous outcomes.

Unit of analysis issues

The unit of analysis was the participant. We collected and analysed a single measurement for each outcome from each participant.

Dealing with missing data

We had planned to contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study was identified only as an abstract). Where this was not possible, and the missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

If numerical outcome data were missing, such as standard deviations or correlation coefficients, and could not be obtained from the authors, we planned to calculate them from other available statistics such as P values, according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

However, we did not apply these approaches because this update included only one study.

Assessment of heterogeneity

We had planned use the I^2 statistic to measure heterogeneity among the trials in each analysis; however, this update did not include meta-analysis. If in future updates we identify substantial heterogeneity, we will report this and explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

We did not assess publication bias using a funnel plot because we included only one trial. For future updates, we will attempt to assess whether the review is subject to publication bias by using a funnel plot if 10 or more trials are included.

Data synthesis

We carried out statistical analysis using Review Manager 5 software (RevMan 2014). For future updates, we will summarise findings using a fixed-effect model according the *Cochrane Handbook of Systematic Reviews for Interventions* (Higgins 2011).

GRADE and 'Summary of findings' tables

We created a 'Summary of findings' table using the following outcomes: incidence of the common cold, vaccine safety, and mortality. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the evidence as it relates to the study that contributed data (Atkins 2004). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro GDT software (GRADEpro GDT

2014). We justified all decisions to down- or upgrade study quality using footnotes, and made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

In subsequent updates of this review, when sufficient data are available, we plan to carry out the following subgroup analyses:

1. children and adults;
2. country of study; and
3. different responses in relation to different viral agents.

We will explore sources of heterogeneity in the assessment of the primary outcome measure by subgroup analyses and meta-regression analyses. The meta-regression analyses will assess the effect of methodological quality (high versus low), type of virus vaccines, and participant characteristics. We will only conduct meta-regression if 10 or more RCTs are included.

Sensitivity analysis

For future updates, we plan to conduct sensitivity analyses comparing the results using all trials as follows.

1. Trials with high methodological quality (studies classified as having a 'low risk of bias' versus those identified as having a 'high risk of bias') (Higgins 2011).
2. Trials that performed intention-to-treat versus per-protocol analyses.

We will also evaluate the risk of attrition bias, as estimated by the percentage of participants lost. We will exclude trials with a total attrition of more than 30% or where differences between the groups exceeded 10%, or both, from meta-analysis, but will include them in the review.

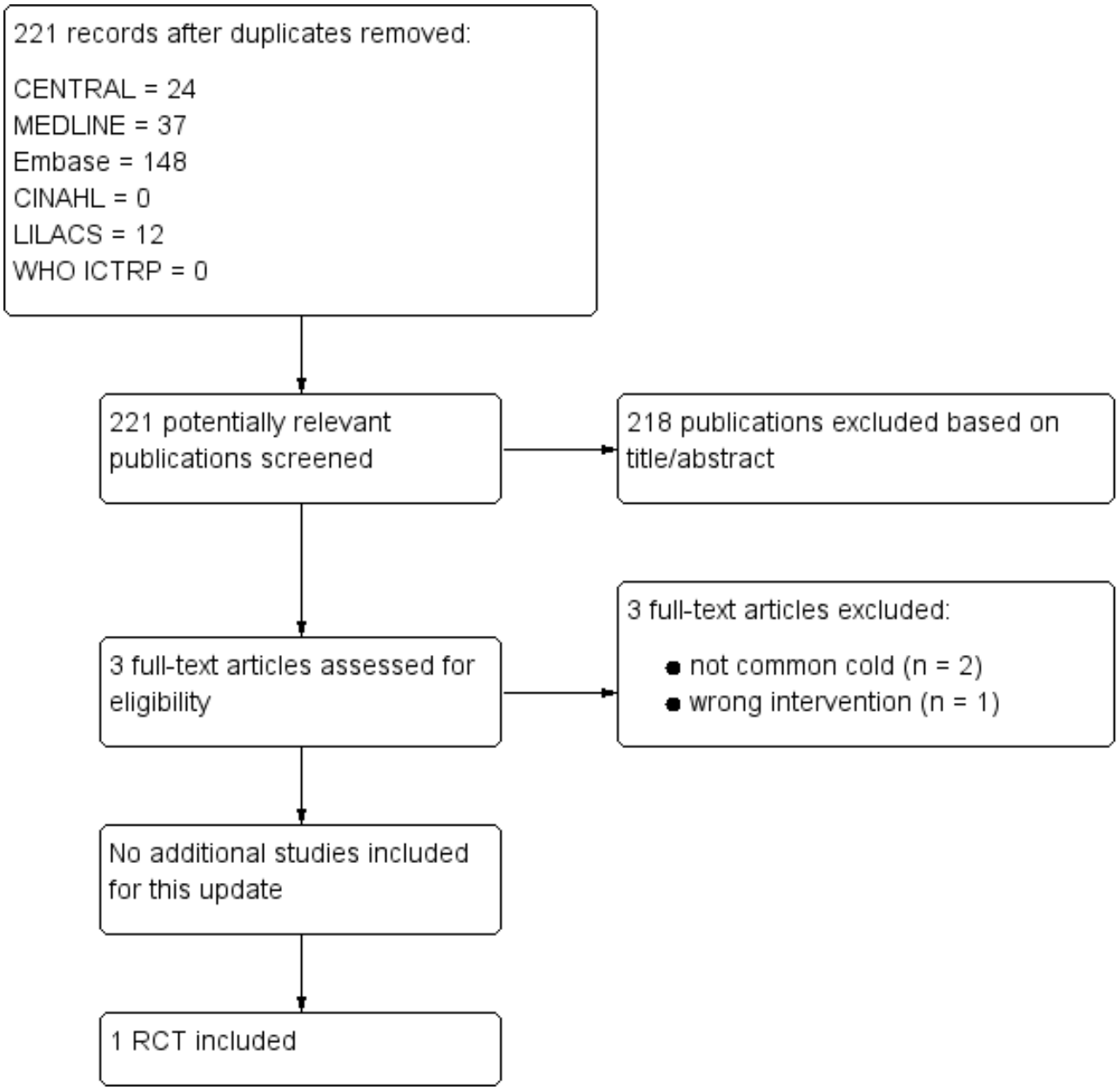
RESULTS

Description of studies

Results of the search

For this 2016 update we assessed 221 results from our electronic searches (Figure 1). We excluded 218 records based on assessment of title and abstract. We obtained three full-text reports, which we excluded after full-text assessment. Consequently, we did not include any new studies for this update. Only one study was included (Griffin 1970).

Figure 1. Study flow diagram



Included studies

This review included one RCT involving 2307 healthy people (Griffin 1970). See the Characteristics of included studies table.

Excluded studies

In the previous review we excluded 41 studies (Belshe 1982; Belshe 1992; Belshe 2004a; Belshe 2004b; Clements 1991; DeVincenzo 2010; Doggett 1963; Dudding 1972; Falsey 1996; Falsey 2008; Fulginiti 1969; Gomez 2009; Gonzalez 2000; Greenberg 2005; Hamory 1975; Karron 1995a; Karron 1995b; Karron 1997; Karron 2003; Karron 2005; Langley 2009; Lee 2001; Lee 2004; Lin 2007; Lyons 2008; Madhi 2006; Munoz 2003; Murphy 1994; Paradiso 1994; Piedra 1995; Pierce 1968; Power 2001; Ritchie 1958; Simoes 2001; Tang 2008; Top 1971; Tristram 1993; Watt 1990; Welliver 1994; Wilson 1960; Wright 1976). In this update, we excluded three new studies: two did not evaluate the common cold as an outcome (Glenn 2016; Karron 2015), and the third study involved an intervention that was not relevant to this review (probiotics) (Kumpu 2015).

See the Characteristics of excluded studies tables.

Risk of bias in included studies

Griffin 1970 had overall low methodological quality. See Figure 2 and Figure 3.

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

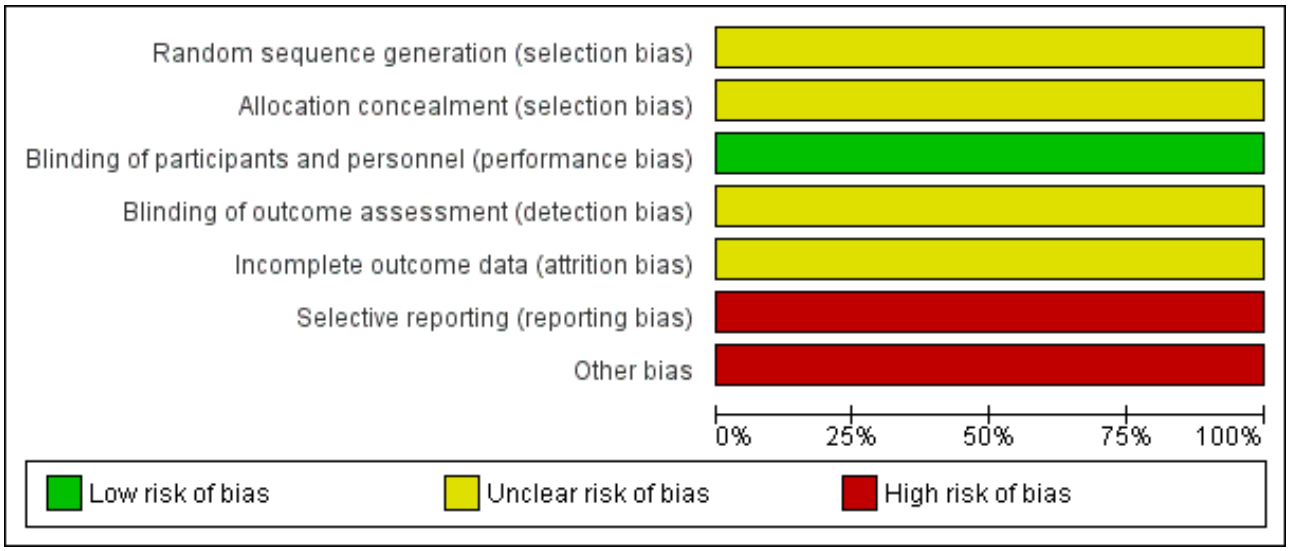
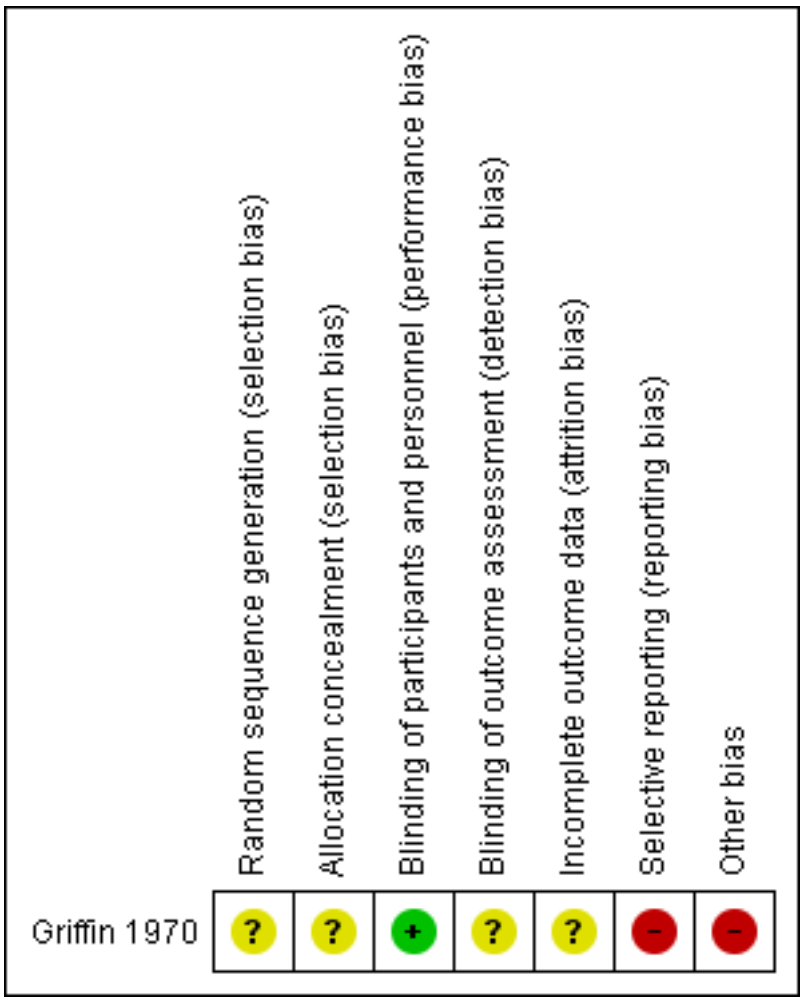


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for the included study



Allocation

We assessed Griffin 1970 as at unclear risk of bias for random sequence generation and allocation concealment since the information provided was inadequate for judgement of this domain.

Blinding

We assessed Griffin 1970 as at low risk of bias for blinding of participants and personnel, but unclear for outcome assessor. Although a placebo was used, there could be a risk of detection bias because common cold does not require hospitalisation.

Incomplete outcome data

We assessed Griffin 1970 as at unclear risk of attrition bias because the information provided was insufficient to enable assessment of this domain.

Selective reporting

Griffin 1970 was at high risk of bias for selective reporting. The study protocol was not available, but it was clear that the published reports include all expected outcomes. However, some of the outcomes were described in a narrative fashion and did not specify incidence for each group.

Other potential sources of bias

Griffin 1970 had a high risk for other sources of bias. Participants' base characteristics were not described, and because there was no detailed information relating to assessment of selection bias, information was insufficient to evaluate if both groups were comparable.

Effects of interventions

See: **Summary of findings for the main comparison** Virus vaccines compared to placebo for preventing the common cold in healthy people

Results were based on one RCT (Griffin 1970, N = 2307 healthy people), which we assessed as providing low-quality evidence. See Summary of findings for the main comparison.

Primary outcomes

1. Incidence of the common cold

Griffin 1970 (2307 participants, 27 events) showed that adenovirus vaccine was associated with a non-statistically significant reduction in the incidence of the common cold compared with placebo (RR 0.95, 95% CI 0.45 to 2.02; P = 0.90; Analysis 1.1). We downgraded the quality of the evidence to low due to high risk of bias and imprecision; there were few events in each group, resulting in imprecision represented by a wide 95% confidence interval.

2. Vaccine safety

Griffin 1970 reported that there were no adverse events related to the live vaccine preparation. We downgraded the quality of the evidence to low due to high risk of bias and imprecision (0 events).

3. Mortality related to vaccine

Griffin 1970 did not assess this outcome.

DISCUSSION

Summary of main results

We included one RCT that met our inclusion criteria. Critical appraisal of Griffin 1970 did not support the use of any virus vaccines for preventing the common cold in healthy people. We did not find significant differences in the incidence of the common cold in people treated with adenovirus vaccines compared with placebo. Griffin 1970 did not evaluate main clinical outcomes such as mortality related to the vaccine. This RCT reported that there were no adverse events related to the vaccine. The relative effect of any of the vaccines for viruses that cause the common cold remains unclear.

Overall completeness and applicability of evidence

The included trial did not detect statistically significant differences between the treatment groups (Griffin 1970).

When dealing with such neutral results, we need to keep in mind that 'absence of evidence' is not 'evidence of absence' (Altman 1995; Fermi Paradox 2012). The fact that this review did not detect any differences between the intervention groups does not imply that placebo and adenovirus vaccine have the same effect on preventing the common cold. The first possible explanation is failure to determine an appropriate sample size (Green 2002; Schulz 1995), in this case resulting in small differences in the incidence of the common cold and few events in the comparison groups. In a remarkable paper from 28 years ago, Freiman 1978 suggested that "many of the therapies labelled as 'no different from control' in trials using inadequate samples, have not received a fair test" and that "concern for the probability of missing an important therapeutic improvement because of small sample sizes deserves more attention in the planning of clinical trials". Moher 1998 emphasised that "most trials with negative results did not have large enough sample sizes to detect a 25% or a 50% relative difference". Moreover, it has been suggested that the most important therapies adopted in clinical practice have shown more modest benefits (Kirby 2002).

Quality of the evidence

The results for the primary outcomes 'incidence of the common cold' and 'vaccine safety' were based on low-quality evidence due to imprecision (low number of events and wide confidence intervals) and methodological limitations. The random sequence generation, allocation, sample size, and base characteristics of participants were not reported. Furthermore, the study may be at high risk of detection bias, since the common cold syndrome rarely requires hospitalisation, and the effect of the intervention could not be adequately evaluated. The report of adverse events was not individualised for each group.

Potential biases in the review process

In the process of performing a systematic review, there is a group of biases known as 'significance-chasing' (Ioannidis 2010). This group includes publication bias, selective outcome reporting bias, selective analysis reporting bias, and fabrication bias (Ioannidis 2010). Publication bias represents a major threat to the validity of systematic reviews, particularly in reviews that include small trials. However, we did an exhaustive search that included many RCTs that did not evaluate common cold outcomes.

Agreements and disagreements with other studies or reviews

We found no other reviews or studies that investigated vaccines for the common cold. We excluded 11 non-RCTs that evaluated vaccines for upper respiratory tract infections (Belshe 1982; Clements 1991; Doggett 1963; Dudding 1972; Fulginiti 1969; Hamory 1975; Karron 1997; Ritchie 1958; Watt 1990; Wilson 1960; Wright 1976). However, only one study evaluated the incidence of common cold (Ritchie 1958), while the others focused on immunologic outcomes. Ritchie 1958 prepared an "autologous vaccine" developed from the nasal secretions of 125 healthy volunteers, who were then inoculated with this product, while 75 served as a control. The results showed a lower incidence of common cold in the vaccine group than in the control group.

AUTHORS' CONCLUSIONS

Implications for practice

This Cochrane Review update found very limited evidence on the effects of vaccines for the common cold in healthy people. We included only one randomised controlled trial, which did not report differences between comparison groups. Review findings were based on only one trial assessed as providing low-quality evidence at high risk of bias and with imprecise estimates. Griffin 1970 involved 2307 participants and assessed adenovirus vaccine compared with placebo.

We found insufficient evidence to support the use of vaccines for the common cold. Prescription of virus vaccines for preventing the common cold in healthy people can neither be supported nor rejected, unless new evidence from large, high-quality trials alters this conclusion. This Cochrane Review does not provide evidence about other virus vaccines for preventing the common cold in healthy people.

Implications for research

This Cochrane Review update highlights the need for well-designed, high-quality randomised trials to assess the effectiveness and safety of virus vaccines to prevent the common cold in healthy people. Future trials should include outcomes such as common cold incidence, vaccine safety, mortality related to the vaccine, and adverse events related to vaccine administration. Future trials should be conducted by independent researchers and reported according to CONSORT guidelines (Ioannidis 2004; Moher 2010), and using the Foundation of Patient-Centered Outcomes Research recommendations (Anonymous 2012; Gabriel 2012).

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CHARACTERISTICS OF STUDIES

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

Griffin 1970

Methods	**Design:** double-blind, RCT (2 arms) **Country:** USA (1 site) **Clinical setting:** Great Lakes Naval Training Center **Follow-up:** 9 weeks' basic-training period **Intention-to-treat:** yes **Randomisation unit:** participant **Analysis unit:** participant
Participants	Great Lakes Naval Training Center, new recruits Randomised: 2307 participants Vaccines group: 1139 (49.3%) Placebo group: 1168 (50.7%) Participants receiving intervention: 1139 Vaccines group: 1139 (49.3%) Placebo group: 1168 (50.7%) Lost post-randomisation: 0% Analysed participants: Vaccines group: 1139 (49.3%) Placebo group: 1168 (50.7%) Age median (mean (SD)): did not report Gender (number of men): did not report Inclusion criteria: 1. Aged 17 to 20 years 2. Great Lakes Naval Training Center, new recruits Exclusion criteria: not reported

Griffin 1970 *(Continued)*

Interventions	Experimental group: the vaccines used were composed of orally administered live adenovirus 4, parenterally administered inactivated adenovirus 4, and parenterally administered inactivated adenovirus 4 and 7 preparations Control group: placebo Co-interventions 1. 1.2 million units of benzathine penicillin G 2. polyvalent influenza vaccine
Outcomes	This RCT did not specify primary or secondary outcomes. Incidence of admissions of participants with respiratory illness (not only hospitalised participants) 1. Acute undifferentiated respiratory disease 2. Common cold syndrome: an acute inflammation of the upper respiratory tract with coryza as a prominent feature and temperature, taken orally, of 100° F or less on admission 3. Exudative pharyngitis 4. Atypical pneumonia 5. Viral exanthem Toxic effects
Notes	1. Trial registration: not reported 2. A priori sample size estimation: not reported 3. Conducted: from 19 February to 16 April, and observations continued to 20 June 1965 4. Funder: "This investigation was supported in part by the Department of the Navy, research project MF 022.03.07-4014, and in part by the Public Health Service Vaccine Development Branch, contract 43-65-1031" (p. 981) 5. Role of funder: "Capt. Robert O. Peckinpaugh, MC, USN; LCDR Wayne E. Frazier, MC, USN; and Willard E. Pierce aided in the design, conduct, and statistical interpretation of this investigation" (p. 981) 6. Declared conflicts of interest: "The opinions and assertions contained here in are those of the authors and are not to be construed as official or as reflecting the views of the Navy Department or the Naval Service at large." (p. 981)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Epidemiologic design of this study consisted of the random assignment of one half of the recruits ..." (p. 982). Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind procedure was followed with paramedical personnel administering the appropriate vaccine or placebo to recruits on their third day after arrival at Great Lakes, just prior to initiation of basic training" (p. 982) Quote: "Placebo for the parenterally administered vaccines consisted of an injection of physiological saline, and that for the orally administered vaccine consisted of an identical appearing inert gelatin capsule" (p. 982) Comment: Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken

Griffin 1970 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Since recruits with the common cold syndrome rarely require hospitalizations, the effect of the adenovirus vaccines on this clinical entity can not be adequately evaluated." Comment: Although placebo was used, there could be a risk of detection bias because common cold does not require hospitalization
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Comment: The study protocol is not available, but it is clear that the published reports include all expected outcomes. However, some are described in a narrative fashion and not per group. Quote: "... there was no observable toxic reaction to this new live vaccine preparation within the study design." (p. 985)
Other bias	High risk	The sample size was not reported. There is no table with basal characteristics of the participants

RCT: randomised controlled trial
SD: standard deviation

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

Study	Reason for exclusion
Belshe 1982	Not RCT
Belshe 1992	RCT. Did not evaluate common cold
Belshe 2004a	RCT. Did not evaluate common cold
Belshe 2004b	RCT. Did not evaluate common cold
Clements 1991	Not RCT
DeVincenzo 2010	RCT. Did not evaluate common cold
Doggett 1963	Not RCT
Dudding 1972	Not RCT
Falsey 1996	RCT. Did not evaluate common cold
Falsey 2008	RCT. Did not include healthy people
Fulginiti 1969	Not RCT
Glenn 2016	RCT. Did not evaluate common cold
Gomez 2009	RCT. Did not evaluate common cold
Gonzalez 2000	RCT. Did not evaluate common cold

Study	Reason for exclusion
Greenberg 2005	RCT. Included participants aged < 6 months
Hamory 1975	Not RCT
Karron 1995a	RCT. Did not evaluate common cold
Karron 1995b	RCT. Did not evaluate common cold
Karron 1997	Not RCT
Karron 2003	RCT. Did not evaluate common cold
Karron 2005	RCT. Did not evaluate common cold
Karron 2015	RCT. Did not evaluate common cold
Kumpu 2015	RCT. Did not evaluate a vaccine (evaluated a probiotic)
Langley 2009	RCT. Did not evaluate common cold
Lee 2001	RCT. Included participants aged < 6 months
Lee 2004	Non-vaccine interventions
Lin 2007	RCT. Did not evaluate common cold
Lyons 2008	RCT. Did not evaluate common cold
Madhi 2006	RCT. Included participants aged < 6 months
Munoz 2003	RCT. Included pregnant women
Murphy 1994	Update on vaccines topic
Paradiso 1994	RCT. Did not evaluate common cold
Piedra 1995	RCT. Did not evaluate common cold
Pierce 1968	RCT. Did not evaluate common cold
Power 2001	RCT. Did not evaluate common cold
Ritchie 1958	Not RCT
Simoes 2001	Meta-analysis
Tang 2008	RCT. Did not evaluate common cold
Top 1971	RCT. Did not evaluate common cold
Tristram 1993	RCT. Did not evaluate common cold
Watt 1990	Not RCT
Welliver 1994	RCT. Did not evaluate common cold

Study	Reason for exclusion
Wilson 1960	Not RCT
Wright 1976	Not RCT

RCT: randomised controlled trial

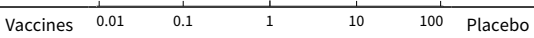
DATA AND ANALYSES

Comparison 1. Adenovirus vaccines versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of the common cold	1	2307	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.45, 2.02]

Analysis 1.1. Comparison 1 Adenovirus vaccines versus placebo, Outcome 1 Incidence of the common cold.

Study or subgroup	Vaccines n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Griffin 1970	13/1139	14/1168		100%	0.95[0.45,2.02]
Total (95% CI)	**1139**	**1168**		**100%**	**0.95[0.45,2.02]**
Total events: 13 (Vaccines), 14 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.13(P=0.9)					



APPENDICES

Appendix 1. Glossary

Term	Definition	Reference
Common cold	The common cold is a self limiting acute upper respiratory tract infection, characterised by rhinorrhoea, nasal congestion, sneezing, cough, sore throat, fever, and malaise.	Heikkinen 2003
Vaccination	Inoculation with a vaccine, i.e. a preparation of microbial antigen often combined with adjuvants administered to an individual in order to induce protective immunity against microbial infections. The antigen may be in the form of live, avirulent micro-organisms or purified macromolecular components of micro-organisms.	Abbas 2001
Immune system	The collection of cells, tissues, and molecules that mediate resistance to infections	Abbas 2001

(Continued)

Cell-mediated immunity	The arm of the adaptative immune response whose role is to combat infections by intracellular microbes. This type of immunity is mediated by T lymphocytes.	Abbas 2001
Antigenical variability	Microbes have evolved mechanisms to evade immunity. Many bacteria and viruses mutate their antigenic surface molecules and can no longer be recognised by antibodies produced in response to previous infection.	Abbas 2001
Serotypes	An antigenically distinct subset of a species of an infectious organism that is distinguished from other subsets by serologic (i.e. serum antibody) tests. Humoral immune response to one serotype of microbes, e.g. influenza virus, may not be protective against another serotypes.	Abbas 2001
Immune responses	Once a foreign organism has been recognised, the immune system enlists the participation of a variety of cells and molecules to mount an appropriate response in order to eliminate or neutralise the organism.	Goldsby 2000
Antigenic molecules	Any molecule capable of being recognised by an antibody or T-cell receptor. Any substance that elicits an immune response.	Goldsby 2000; Roitt 2004
Allergens	An antigen that elicits an immediate hypersensitivity (allergic) reaction. Allergens are proteins, or chemicals bound to proteins, that induce immunoglobulin E antibody production in atopic individuals.	Abbas 2001
Immunopotentiation	Non-specific immunostimulation given by various agents that can stimulate the immune response. It is believed that the mechanism of action is through some modification of local cytokines or growth of innate immune mechanisms. An increase in the functional capacity of the immune response	Gorczynski 2007
Opsonisation	The process by which particulate antigens are rendered more susceptible to phagocytosis The process of attaching opsonins, such as immunoglobulin G or complement fragments, to microbial surfaces to target microbes for phagocytosis	Abbas 2001; Goldsby 2000
Phagocytosis	Macrophages are capable of ingesting and digesting exogenous antigens, such as whole micro-organisms and insoluble particles, and endogenous matter, such as injured or dead host cells, cellular debris, and activated clotting factors. The process by which certain cells of the innate immune system, including macrophages and neutrophils, engulf large particles (> 0.5 µm diameter), such as intact microbes. The cell surrounds the particle by a cytoskeleton-dependent process, leading to formation of an intracellular vesicle called a phagosome, which contains the ingested particle.	Abbas 2001; Goldsby 2000

Appendix 2. Differences between clinical characteristics of the common cold and influenza

Feature	Common cold	Influenza	References
Aetiological agent	> 100 viral strains; rhinovirus most common	3 strains of influenza virus: influenza A, B, C	DDCP 2010; Gwaltney 1967; Gwaltney 2000; Heikkinen 2003;
Site of infection	Upper respiratory tract	Entire respiratory system	
Symptom onset	Gradual: 1 to 3 days	Sudden: within a few hours	

(Continued)

Fever, chills	Occasional, low grade (< 100° F)	Fever is usually present with the flu, in up to 80% of all flu cases. A temperature of 100° F or higher for 3 to 4 days is typically associated with the flu.	Roxas 2007; Thompson 2003
Headache	Frequent, usually mild	Characteristic, more severe	
General aches, pains	Mild, if any	Characteristic, often severe and affecting the entire body	
Cough, chest congestion	Mild to moderate, with hacking cough	Common, may become severe	
Sore throat	Common, usually mild	Sometimes present	
Runny, stuffy nose	Very common, accompanied by bouts of sneezing	Sometimes present	
Fatigue, weakness	Mild, if any	Usual, may be severe and last 2 to 3 weeks	
Extreme exhaustion	Never	Frequent, usually in early stages of illness	
Season	Year around, peaks in winter months	Most cases between November and February	
Antibiotics helpful	No, unless secondary bacterial infection develops	No, unless secondary bacterial infection develops	

Appendix 3. Viral causes of the common cold

Virus	Estimated annual proportion of cases	References
Rhinoviruses	30% to 50%; during autumn 80%. Once considered to be limited to the upper airway, now recognised as an important cause of lower respiratory infections	Arruda 1997; Gwaltney 1985; Heikkinen 2003; Lemanske 2005; Monto 1993; Mäkelä 1998; Regamey 2008
Coronaviruses	7% to 18% in adults with upper respiratory infections. Responsible for 2.1% of hospital admissions for acute respiratory tract infections in all age groups	Larson 1980; Lau 2006; Mäkelä 1998; Nicholson 1997
Influenza viruses	5% to 15%	Heikkinen 2003
Respiratory syncytial virus (RSV)	In low-income countries, 15% to 20% In hospital the proportion of children aged between birth and 5 months with RSV acute lower respiratory tract infections ranged between 9% and 87%. Among children up to at least 5 years of age reported with RSV, on average 39% (range 20% to 62%) were < 6 months old; on average 24% of cases (range 14% to 38%) were children aged 6 to 11 months. An average of 63% of children were thus under 1 year of age. On average 20% (range 13% to 29%) of the children were between 1 and 2 years of age.	Berman 1991; Falsey 2005; Thompson 2003

(Continued)

	Respiratory syncytial virus accounts for approximately 10,000 deaths annually in people over the age of 65 years in the USA. Respiratory syncytial virus in adults, 5% infection annually	
Parainfluenza viruses	Acute respiratory infections cause 3% to 18% of all admissions to paediatric hospitals; 9% to 30% of these patients depending on the time of year. Parainfluenza viruses account for 17% of hospitalised illness-associated virus isolation. In low-income countries 7% to 10% This virus causes 50% to 74.2% of croup cases.	Berman 1991; Denny 1983; Henrickson 2003
Adenoviruses	In low-income countries can be summarised as 2% to 4%	Berman 1991
Metapneumovirus	10% short epidemic	Esper 2003; Kahn 2003; Nissen 2002; Risnes 2005
Unknown	20% to 30%	Monto 1993; Mäkelä 1998

Appendix 4. CENTRAL search strategy

#1 [mh "Common Cold"]
#2 "common cold*":ti,ab
#3 "coryza":ti,ab
#4 (acute near/5 ("upper respiratory infection*" or "upper respiratory tract infection*" or urti or uri)):ti,ab
#5 [mh "Picornaviridae Infections"]
#6 [mh Rhinovirus]
#7 "rhinovir*":ti,ab
#8 "hrv":ti,ab
#9 [mh "Paramyxoviridae Infections"]
#10 [mh "parainfluenza virus 1, human"] or [mh "parainfluenza virus 3, human"]
#11 [mh "parainfluenza virus 2, human"] or [mh "parainfluenza virus 4, human"]
#12 "parainfluenza*":ti,ab
#13 [mh coronavirus] or [mh "coronavirus 229e, human"] or [mh "coronavirus oc43, human"]
#14 [mh "Coronavirus Infections"]
#15 "coronavir*":ti,ab
#16 [mh adenoviridae] or [mh "adenoviruses, human"]
#17 [mh "Adenovirus Infections, Human"]
#18 "adenovir*":ti,ab
#19 [mh "respiratory syncytial viruses"] or [mh "respiratory syncytial virus, human"]
#20 [mh "Respiratory Syncytial Virus Infections"]
#21 ("respiratory syncytial virus*" or rsv):ti,ab
#22 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #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 or #21
#23 [mh Vaccines]
#24 [mh Vaccination]
#25 (vaccin* or inocul* or immuni*):ti,ab
#26 #23 or #24 or #25
#27 #22 and #26

Appendix 5. MEDLINE (Ovid) search strategy

1 Common Cold/
2 common cold*.tw.
3 coryza.tw.
4 (acute adj5 (upper respiratory infection* or upper respiratory tract infection* or urti or uri)).tw.
5 Picornaviridae Infections/

6 Rhinovirus/
7 rhinovir*.tw.
8 hrv.tw.
9 Paramyxoviridae Infections/
10 parainfluenza virus 1, human/ or parainfluenza virus 3, human/
11 parainfluenza virus 2, human/ or parainfluenza virus 4, human/
12 parainfluenza*.tw.
13 coronavirus/ or coronavirus 229e, human/ or coronavirus oc43, human/
14 Coronavirus Infections/
15 coronavir*.tw.
16 exp adenoviridae/ or adenoviruses, human/
17 Adenovirus Infections, Human/
18 adenovir*.tw.
19 respiratory syncytial viruses/ or respiratory syncytial virus, human/
20 Respiratory Syncytial Virus Infections/
21 (respiratory syncytial virus* or rsv).tw.
22 or/1-21
23 exp Vaccines/
24 exp Vaccination/
25 (vaccin* or inocul* or immuni*).tw.
26 or/23-25
27 22 and 26

Appendix 6. Embase (Elsevier) search strategy

#27. #23 AND #26
#26. #24 OR #25
#25. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti
#24. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#23. #18 AND #22
#22. #19 OR #20 OR #21
#21. 'vaccination'/de
#20. vaccin*:ab,ti OR immuni*:ab,ti OR inocul*:ab,ti
#19. 'vaccine'/exp
#18. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#17. 'respiratory syncytial virus':ab,ti OR 'respiratory syncytial viruses':ab,ti OR rsv:ab,ti
#16. 'respiratory syncytial pneumovirus'/de OR 'respiratory syncytial virus infection'/de
#15. adenovir*:ab,ti
#14. 'adenovirus'/exp OR 'human adenovirus infection'/de
#13. coronavir*:ab,ti
#12. 'coronavirus'/de OR 'coronavirus infection'/de
#11. parainfluenza*:ab,ti
#10. 'parainfluenza virus 1'/de OR 'parainfluenza virus 2'/de OR 'parainfluenza virus 3'/de OR 'parainfluenza virus 4'/exp
#9. 'parainfluenza virus'/exp
#8. 'paramyxovirus infection'/de
#7. rhinovir*:ab,ti OR hrv:ab,ti
#6. 'rhinovirus infection'/de OR 'human rhinovirus'/de
#5. coryza:ab,ti
#4. 'acute upper respiratory infection':ab,ti OR 'acute upper respiratory infections':ab,ti OR 'acute upper respiratory tract infection':ab,ti OR 'acute upper respiratory tract infections':ab,ti OR (acute NEAR/5 (urti OR uri)):ab,ti
#3. 'viral upper respiratory tract infection'/de OR 'upper respiratory tract infection'/de
#2. 'common cold':ab,ti OR 'common colds':ab,ti
#1. 'common cold'/de OR 'common cold symptom'/de

Appendix 7. CINAHL (EBSCO) search strategy

S34 S23 and S33
S33 S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32
S32 (MH "Quantitative Studies")
S31 TI placebo* or AB placebo*
S30 (MH "Placebos")
S29 TI random* or AB random*

S28 TI (singl* mask* or doubl* mask* or tripl* mask* or trebl* mask*) or AB (singl* mask* or doubl* mask* or tripl* mask* or trebl* mask*)
S27 TI (singl* blind* or doubl* blind* or trebl* blind* or tripl* blind*) or AB (singl* blind* or doubl* blind* or trebl* blind* or tripl* blind*)
S26 TI clinic* w1 trial* or AB clinic* w1 trial*
S25 PT clinical trial
S24 (MH "Clinical Trials+")
S23 S18 and S22
S22 S19 or S20 or S21
S21 TI (vaccin* or immuni* or inocula*) or AB (vaccin* or immuni* or inocula*)
S20 (MH "Immunization")
S19 (MH "Vaccines+")
S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17
S17 TI (respiratory syncytial virus* or rsv) or AB (respiratory syncytial virus* or rsv)
S16 (MH "Respiratory Syncytial Virus Infections")
S15 (MH "Respiratory Syncytial Viruses")
S14 TI adenovir* or AB adenovir*
S13 TI coronavir* or AB coronavir*
S12 (MH "Coronavirus+")
S11 (MH "Coronavirus Infections")
S10 TI parainfluenza* or AB parainfluenza*
S9 (MH "Paramyxovirus Infections")
S8 (MH "Paramyxoviruses")
S7 TI hrv or AB hrv
S6 TI rhinovir* or AB rhinovir*
S5 (MH "Picornavirus Infections")
S4 TI (upper respiratory tract infection* or upper respiratory infection*) or AB (upper respiratory tract infection* or upper respiratory infection*)
S3 TI coryza or AB coryza
S2 TI common cold* or AB common cold*
S1 (MH "Common Cold")

Appendix 8. LILACS (BIREME) search strategy

(mh:"Common Cold" OR "common cold" OR "common colds" OR coryza OR "Resfriado Común" OR "Resfriado Comum" OR "Coriza Aguda" OR "Upper Respiratory Tract Infections" OR "upper respiratory tract infection" OR "Infecciones del Tracto Respiratorio Superior" OR "Infecciones de las Vías Respiratorias Superiores" OR "Infecções do Trato Respiratório Superior" OR "Infecções das Vias Respiratórias Superiores" OR "Infecções das Vias Aéreas Superiores" OR "Infecções do Sistema Respiratório Superior" OR mh:"Picornaviridae Infections" OR "Infecciones por Picornaviridae" OR "Infecções por Picornaviridae" OR "Picornavirus Infections" OR mh:rhinovirus OR rhinovir* OR "Virus de la Coriza" OR "Virus del Resfriado Común" OR "Vírus da Coriza" OR "Vírus do Resfriado Comum" OR hrv OR mh:"Paramyxoviridae Infections" OR parainfluenza* OR mh:"Parainfluenza Virus 1, Human" OR mh:"Parainfluenza Virus 2, Human" OR mh:"Parainfluenza Virus 3, Human" OR mh:"Parainfluenza Virus 4, Human" OR mh:"Coronavirus Infections" OR coronavir* OR mh:coronavirus OR mh:"Coronavirus 229E, Human" OR mh:"Coronavirus OC43, Human" OR mh:"Coronavirus NL63, Human" OR mh:adenoviridae OR mh:"Adenoviruses, Human" OR mh:"Adenovirus Infections, Human" OR adenovir* OR mh:"Respiratory Syncytial Viruses" OR "Virus Sincitiales Respiratorios" OR "Vírus Sinciciais Respiratórios" OR "Virus Sincitial Respiratorio" OR "Vírus Sincicial Respiratório" OR mh:"Respiratory Syncytial Virus, Human" OR "respiratory syncytial virus" OR "Virus Humano Respiratorio Sincitial" OR mh:"Respiratory Syncytial Virus Infections" OR "Infecciones por Virus Sincitial Respiratorio" OR "Infecções por Vírus Respiratório Sincicial" OR rsv) AND (mh:vaccines OR vaccin* OR vacunas OR vacinas OR mh:d20.215.894* OR mh:vaccination OR vacunación OR vacinação OR mh:"Mass Vaccination" OR mh:immunization OR inmunización OR imunização OR mh:e02.095.465.425.400* OR mh:e05.478.550* OR mh:n02.421.726.758.310* OR mh:n06.850.780.200.425* OR mh:n06.850.780.680.310* OR mh:sp2.026.182.113* OR mh:sp8.946.819.838* OR immuni* OR inmuni* OR imuni*) AND db:("LILACS") AND type_of_study:("clinical_trials")

WHAT'S NEW

Date	Event	Description
2 September 2016	New citation required but conclusions have not changed	We recruited three new authors to update this review.
2 September 2016	New search has been performed	We updated our searches and excluded three new trials (Glenn 2016; Karron 2015; Kumpu 2015).

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 6, 2013

Date	Event	Description
22 January 2015	New search has been performed	Searches conducted
16 March 2011	New citation required and major changes	Protocol taken over by a new team of review authors
26 February 2009	Amended	Protocol withdrawn Issue 3, 2009

CONTRIBUTIONS OF AUTHORS

- Conceiving the review: DSR
- Designing the review: DSR, CVG, MLF, RH
- Co-ordinating the review: DSR
- Data collection for the review: DSR
- Screening search results: JVAF, MJMZ
- Appraising quality of papers: DSR, CVG, RH, JVAF, MJMZ
- Extracting data from papers: DSR
- Writing to authors of papers for additional information: DSR
- Obtaining and screening data on unpublished studies: JVAF, MJMZ
- Data management for the review: DSR
- Entering data into Review Manager 5: DSR, JVAF, MJMZ
- Interpretation of data: All authors
- Providing a methodological perspective: MJMZ
- Providing a clinical perspective: CVG, MLF, RH
- Writing the review: DSR, JVAF, MJMZ
- All authors contributed to the improvement of this updated review and approved the final version of the review.

DECLARATIONS OF INTEREST

Daniel Simancas-Racines: None known.
Juan VA Franco: None known.
Claudia V Guerra: None known.
Maria L Felix: None known.
Ricardo Hidalgo: None known.
Maria José Martinez-Zapata: None known.

SOURCES OF SUPPORT

Internal sources

- Universidad Tecnológica Equinoccial, Ecuador.

  Methodological
- Centro de Investigación en Salud Pública y Epidemiología Clínica (CISPEC). Facultad de Ciencias de la Salud Eugenio Espejo, Ecuador.

  Methodological
- Instituto Universitario Hospital Italiano, Argentina.

  Methodological

External sources

- Instituto de Salud Carlos III, Spain.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Three new authors contributed to this update: Juan VA Franco, Maria L Felix, and Maria José Martinez-Zapata.

We considered risk of bias as unclear for blinding in the previous version of this review. For this update, we reassessed this as low because the study used a placebo.

We added two additional primary outcomes, vaccine safety and mortality related to the vaccine, to Summary of findings for the main comparison.

We did not search Scirus for this update since this service became unavailable in 2014.

INDEX TERMS

Medical Subject Headings (MeSH)

Adenovirus Vaccines [*administration & dosage]; Common Cold [*prevention & control]; Health Status; Randomized Controlled Trials as Topic; Vaccines, Attenuated [administration & dosage]

MeSH check words

Humans