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[Intervention Review]

Vaccines for post-exposure prophylaxis against varicella (chickenpox) in children and adults

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ABSTRACT

Background

The prevention of varicella (chickenpox) using live attenuated varicella vaccines has been demonstrated both in randomised controlled trials (RCTs) and in population-based immunisation programmes in countries such as the United States and Australia. Many countries do not routinely immunise children against varicella and exposures continue to occur. Although the disease is often mild, complications such as secondary bacterial infection, pneumonitis and encephalitis occur in about 1% of cases, usually leading to hospitalisation. The use of varicella vaccine in persons who have recently been exposed to the varicella zoster virus has been studied as a form of post-exposure prophylaxis (PEP).

Objectives

To assess the efficacy and safety of vaccines for use as PEP for the prevention of varicella in children and adults.

Search methods

We searched CENTRAL (2014, Issue 1), MEDLINE (1966 to March week 1, 2014), EMBASE (January 1990 to March 2014) and LILACS (1982 to March 2014). We searched for unpublished trials registered on the clinicaltrials.gov and WHO ICTRP websites.

Selection criteria

RCTs and quasi-RCTs of varicella vaccine for PEP compared with placebo or no intervention. The outcome measures were efficacy in prevention of clinical cases and/or laboratory-confirmed clinical cases and adverse events following vaccination.

Data collection and analysis

Two review authors independently extracted and analysed data using Review Manager software.

Main results

We identified three trials involving 110 healthy children who were siblings of household contacts. The included trials varied in study quality, vaccine used, length of follow-up and outcomes measured and, as such, were not suitable for meta-analysis. We identified high or unclear risk of bias in two of the three included studies. Overall, 13 out of 56 vaccine recipients (23%) developed varicella compared with 42 out of 54 placebo (or no vaccine) recipients (78%). Of the vaccine recipients who developed varicella, the majority only had mild disease (with fewer than 50 skin lesions). In the three trials, most participants received PEP within three days following exposure; too few participants

were vaccinated four to five days post-exposure to ascertain the efficacy of vaccine given more than three days after exposure. No included trial reported on adverse events following immunisation.

Authors' conclusions

These small trials suggest varicella vaccine administered within three days to children following household contact with a varicella case reduces infection rates and severity of cases. We identified no RCTs for adolescents or adults. Safety was not adequately addressed.

PLAIN LANGUAGE SUMMARY

Post-exposure prophylaxis vaccine to prevent varicella (chickenpox)

Review question

This review assessed how useful the varicella (also known as chickenpox) vaccine is in preventing chickenpox when given to children or adults who have never been immunised or previously had chickenpox, but who receive the vaccine within a short time following exposure to a person infectious with chickenpox. Varicella is a highly contagious viral infection characterised by a widespread pustular rash, fever and generally feeling unwell. We identified three trials involving 110 healthy children who were siblings of household contacts.

Background

Although many cases of chickenpox are mild, complications such as secondary bacterial infection, neurological complications and other problems occur in at least 1% of cases, usually resulting in hospitalisation. The virus that causes chickenpox also remains dormant in sensory nerve roots after infection and can reactivate later in life as a painful blistering rash known as herpes zoster or shingles.

Chickenpox can be prevented by vaccination with live attenuated varicella vaccine. However, many countries have not yet funded routine population-based immunisation programmes and exposure to chickenpox remains commonplace. Even in highly vaccinated populations, outbreaks can occur, particularly in childcare and school settings.

Key results

The question of how to prevent chickenpox occurring in an adult or child who has been in contact with a person with the disease has led to trials of varicella vaccines in this setting. This review assessed published studies up to March 2014 and found that three separate trials investigated the effectiveness of giving varicella vaccine as post-exposure prophylaxis following household exposure of non-immune children to siblings with varicella compared to a placebo. Overall, 13 of 56 (18%) vaccine recipients developed varicella compared with 42 of 54 (78%) placebo (or no vaccine) recipients. These studies support giving varicella vaccine to a child, particularly if given within three days of contact with a chickenpox case. Although mild chickenpox may still occur in some cases, the vaccine is likely to prevent moderate to severe cases of chickenpox.

Quality of the evidence

The number of participants in these three trials was small and is a limitation of this review. The quality of the included studies varied, which also limits confidence in the results. There have been no trials of this type undertaken in adults, and none of the trials commented on adverse events following immunisation, such as fever or injection site reactions.

BACKGROUND

Description of the condition

Varicella (chickenpox) is an acute, highly infectious disease, caused by the varicella zoster virus (VZV). In healthy children varicella is usually self limiting and manifests as a vesicular rash, fever and constitutional symptoms. The most common complication in children is secondary bacterial infection. However, other serious complications are well recognised and include pneumonia, dehydration, hepatitis, ataxia and encephalitis (Gershon 2013; Preblud 1984). The estimated rate of cerebellar ataxia among children is 1 in 4000 cases (Guess 1986), and for encephalitis 1.7 per 100,000 varicella cases (Preblud 1984).

Women who contract varicella in the first 20 weeks of pregnancy have a 2% risk of their fetus developing congenital varicella syndrome and pregnant women who contract varicella in the last trimester are at an increased risk of pneumonia (Gershon 2013; Pastuszac 1994). The onset of varicella in a pregnant woman from five days prior to delivery to two days after delivery can result in severe neonatal varicella in 17% to 30% of cases (Enders 1994). Following primary infection, VZV remains dormant in the sensory nerve ganglia of individuals and can reactivate to cause herpes zoster. Herpes zoster is especially associated with increasing age and is responsible for significant population morbidity (Gnann 2002). Immunocompromised patients are at risk from either primary VZV infection or reactivation, both of which can be associated with substantial morbidity (Gershon 2013).

Transmission of VZV is spread from person-to-person either by direct contact with vesicle fluid or through aerosolised respiratory secretions. The incubation period ranges from 7 to 21 days, during which time infected persons are asymptomatic. Secondary attack rates may reach 90% for susceptible household contacts of varicella cases (Simpson 1952). In temperate climates, varicella is typically a disease of childhood with more than 90% of adults being immune (Gershon 2013). Primary infection usually provides lifetime immunity to varicella but second infections, although unusual, are well recognised (Hambleton 2005). Persistence of immunity (VZV-specific immunoglobulin (Ig) G) following natural infection is reliably measured using commercially available antibody tests. However, commercially available tests are not sufficiently sensitive to detect vaccine-induced antibodies reliably. Numerous laboratory methods, including neutralisation assays (NA), enzyme-linked immunosorbent assay (ELISA), fluorescent antibody membrane antigen (FAMA) techniques, glycoprotein-based ELISA (gpELISA) and measures of cell-mediated immunity, have been employed in clinical trials of varicella vaccines. However, these assays have inherent variability, making comparison of vaccine-induced immunologic responses challenging (Gershon 2013).

Description of the intervention

Live attenuated varicella vaccines are available for use in several countries. All varicella-containing vaccines use the attenuated Oka strain of VZV, first developed in Japan from the virus of an infected child (Takahashi 1974). The Oka vaccine virus has been further modified through passage in cell culture by varicella vaccine manufacturers: Merck and Co. (Varivax), GlaxoSmithKline (GSK) (Varilrix) and the Biken Institute (BIKEN). Two vaccines are also available in China from the Changchun and Shanghai

Institutes of Biologic Products (Fu 2010). The first trials of live attenuated varicella vaccine were conducted in Japan in the 1970s, predominantly in hospitalised children. Many of the earliest clinical trials of varicella vaccine in the USA and elsewhere were in immunocompromised children, predominantly those with malignancies (Brunell 1982; Gershon 1982; Iwaza 1977). Large-scale randomised clinical trials of the use of live attenuated varicella vaccine in healthy children were conducted in the following two decades (Kuter 1991; Varis 1996; Weibel 1984), and in 1995 the USA was the first country to begin universal varicella vaccination of children from 12 months of age (MMWR 1996). Recently, quadrivalent vaccines, which include measles, mumps, rubella and varicella vaccine viruses (MMRV), have been developed by two manufacturers, Merck and Co. (ProQuad) and GSK (Priorix Tetra) and are used in a number of countries.

How the intervention might work

Many of the early data concerning the efficacy and safety of varicella vaccines were in the form of uncontrolled, prospective cohort studies. In addition, many studies of the post-licensure effectiveness and safety of varicella vaccination, mostly from the United States, add to the body of knowledge regarding the vaccines (Hambleton 2005; Marin 2007). A number of narrative reviews of the safety and efficacy of varicella vaccines are also available (Breuer 2001; Hambleton 2005; Skull 2001; Takahashi 1996). One review of post-exposure prophylaxis (PEP) studies by Ferson suggested that varicella vaccine may be effective when used as a PEP (Ferson 2001). Many of the studies of the efficacy of varicella vaccines include clinically diagnosed disease as an outcome measure. This is often characterised as either mild, moderate or severe, most commonly depending on the number of skin lesions present.

Why it is important to do this review

Although varicella vaccines are licensed and recommended for use in many countries, few countries, including the USA, Canada, Germany, Uruguay and Australia, have adopted publicly funded, national, population-based varicella vaccination programmes (Macartney 2005; MMWR 1996; NACI 2004; Quian 2008; Sadzot-Delvaux 2008). In populations where universal immunisation does not occur, or in the case of unimmunised susceptible contacts, the use of varicella vaccine as a PEP is a potential strategy for the prevention of morbidity from varicella infection. The objectives of this review were to examine the efficacy and safety of varicella vaccine when used as a PEP. This review has systematically identified RCTs of varicella vaccination and considered the evidence available from these studies. The purpose of this exercise was to add to the evidence base for this intervention and to highlight deficiencies in our knowledge that should be addressed by further research.

OBJECTIVES

To assess the efficacy and safety of vaccines for use as PEP for the prevention of varicella in children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs.

Types of participants

Healthy children and adults susceptible to VZV infection. We assumed susceptibility if there was no past history of chickenpox or varicella vaccination and serological evidence of no past infection.

Types of interventions

Vaccination with live attenuated varicella vaccine within seven days following known exposure to VZV, with comparison to placebo or no intervention.

Types of outcome measures

The outcome measure for this study was interruption of transmission of VZV to contacts of a varicella case. This included comparison of secondary attack rates in those given either vaccine or placebo (or no intervention) within seven days of a documented exposure to VZV.

We defined varicella cases using clinical criteria with a case definition of an illness characterised by fever, malaise and a generalised vesicular rash (typically with 250 to 500 lesions) lasting four to five days. We included the severity of cases, as either mild, moderate or severe, depending upon the number of skin lesions present. We also included clinically diagnosed disease, with the additional use of laboratory assays to detect seroconversion to VZV in previously non-immune participants.

Primary outcomes

1. Prevention of varicella in contacts of a varicella case.
2. Vaccine adverse events including local injection site adverse events, fever and systemic adverse events.

Secondary outcomes

1. Prevention of moderate to severe varicella in contacts of a varicella case.

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 1) (accessed 18 March 2014), MEDLINE (May 2010 to March week 1, 2014), EMBASE (June 2010 to March 2014) and LILACS (2010 to March 2014). We also reviewed the clinical trials registers www.clinicaltrials.gov and <http://www.who.int/ictpr> (to March 2014) for unpublished studies. Details of the original search are in [Appendix 1](#).

We used the following search terms to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format ([Lefebvre 2011](#)). We adapted the search strategy for EMBASE ([Appendix 2](#)).

MEDLINE (OVID)

- 1 Chickenpox/
- 2 (chicken pox or chickenpox).tw.
- 3 Herpesvirus 3, Human/
- 4 Varicellovirus/
- 5 varicell*.tw.
- 6 vzv.tw.

- 7 or/1-6
- 8 exp Vaccines/
- 9 exp Vaccination/
- 10 Immunization/
- 11 (vaccin* or immuni* or inocul*).tw.
- 12 or/8-11
- 13 7 and 12
- 14 exp Chickenpox Vaccine/
- 15 13 or 14

Searching other resources

We did not apply any language or publication restrictions. We searched the reference lists of studies and reviews identified during the updating of the review. We identified published articles that cite the previously included studies using Scopus. In addition, we consulted content experts and, where necessary, attempted contact with trial authors of studies considered for inclusion.

Data collection and analysis

Selection of studies

In the original review, one review author (KM) made initial exclusions of irrelevant studies based on the abstracts obtained from the literature searches. Two review authors (KM, PM) independently assessed the remaining studies to determine whether they fulfilled the inclusion criteria. In this updated review, one review author (AH) made initial exclusions of irrelevant studies based on the abstracts obtained from the updated literature searches. Two review authors (AH, KM) independently assessed potentially relevant studies from the updated search results to determine inclusion eligibility.

Data extraction and management

Two review authors (KM, PM) independently extracted data from the included studies by using a data extraction form. The review authors (KM, PM) attempted to contact trial authors for clarification of study content where necessary. No further trial data or information was subsequently made available.

We extracted and entered the following data into the Review Manager software ([RevMan 2012](#)).

1. Date and location of trials.
2. Methodological quality of trials.
3. Characteristics of participants.
4. Characteristics of interventions.
5. Characteristics of outcome measures.
6. Data on outcome measures.
7. Publication status.

Assessment of risk of bias in included studies

We did not consider blinding of the review authors for assessment of the included studies to be feasible given the limited number of relevant studies. Two review authors (KM, PM) independently graded the methodological quality of the included studies and we resolved any disagreements through discussion.

We used The Cochrane Collaboration's domain-based evaluation tool for assessing the risk of bias ([Higgins 2011](#)). The domains included sequence generation, allocation concealment, blinding,

completeness of outcome data, non-selective reporting of outcomes and other potential sources of bias. Of particular importance was the assessment of data completeness in the reporting of outcomes. The findings are included in the 'Risk of bias' tables below.

Measures of treatment effect

Vaccine efficacy was measured in a number of ways: efficacy within three days post-exposure; efficacy within five days post-exposure; efficacy in the prevention of varicella of any severity; and the prevention of moderate/severe varicella. Measures of treatment effect extracted included vaccine efficacy (VE) and risk ratio (RR), if reported. VE is calculated as $VE = (ARU - ARV)/ARU \times 100$, where ARU = attack rate in the unvaccinated and ARV = attack rate in vaccinated participants. We included reporting of any adverse event as a treatment effect. Adverse events that we sought were injection site reactions, fever, other systemic adverse events and serious adverse events.

Unit of analysis issues

Not applicable.

Dealing with missing data

In studies estimating vaccine efficacy, missing outcome data can lead to a biased estimate of effect size. We assessed studies for reporting of loss to follow-up.

Assessment of heterogeneity

There was considerable heterogeneity between the results of the trials and we explored the reasons for this. We assessed methodological heterogeneity by comparing the 'Risk of bias' tables. We assessed statistical heterogeneity by comparing the statistical tests employed by the study authors and the adequacy of the reporting of statistical results.

Assessment of reporting biases

We assessed for each study in the review whether all expected outcomes of interest were included and reported, including pre-specified outcomes.

Data synthesis

The two review authors (KM, PM) assessed the homogeneity of participants, intervention and outcomes in each study before deciding whether to combine the data. The synthesis of data was also dependent on the overall quality of trials.

Subgroup analysis and investigation of heterogeneity

We planned assessment of efficacy outcomes by disease severity and length of time between exposure and vaccination.

Sensitivity analysis

We did not subject the results of the included studies to meta-analysis and we did not undertake a sensitivity analysis.

RESULTS

Description of studies

Results of the search

The original search identified 780 studies. After eliminating duplicate reports and studies not concerned with varicella vaccine, we examined the abstracts of 144 studies identified from the original searches and an additional 18 publications identified from reference lists.

In the updated searches we identified 222 articles, excluding duplicates, published since the original review. Additionally, we identified 25 potential studies published since the original review from the reference lists or citation reports of previously included studies. After eliminating duplicates and studies not concerned with varicella vaccine, we examined 108 abstracts.

Included studies

Three studies from the original review were eligible for inclusion. We identified no further eligible studies in this updated review. All included studies reported on the use of varicella vaccine as a PEP following household exposure of non-immune children to siblings with varicella ([Arbeter 1986a](#); [Asano 1977a](#); [Mor 2004](#)). These studies were conducted over a 27-year time period in Japan, the United States and Israel, respectively. The three studies used three different live attenuated varicella vaccines that varied substantially in viral titre. One of these PEP studies was reported in a publication that reviewed a number of clinical trials on the use of varicella vaccine in different settings ([Arbeter 1986a](#)). See [Characteristics of included studies](#).

Excluded studies

We excluded a total of 267 studies: 107 from the updated review and 160 from the original review. See [Characteristics of excluded studies](#).

Eight uncontrolled studies or observational studies reported on the use of varicella vaccine as a PEP in non-hospital settings ([Asano 1982](#); [Brotons 2010](#); [Getaz 2010](#); [Naganuma 1984](#); [Ma 2009a](#); [Pinochet 2012](#); [Salzman 1998](#); [Watson 2000](#)). We also identified a number of placebo-controlled RCTs of varicella vaccines. However, these studies did not examine the use of the vaccine as a PEP. These included placebo-controlled RCTs on the use of varicella vaccine in healthy children for the prevention of varicella ([Ferrera 2009](#); [Kuter 1991](#); [Meurice 1996](#); [Varis 1996](#); [Weibel 1984](#)), and placebo-controlled RCTs of the use of varicella vaccine (either live attenuated or heat-inactivated) for the prevention of any VZV disease in oncology patients undergoing chemotherapy or bone marrow transplantation ([Cristofani 1991](#); [Hardy 1991](#); [Hata 2002](#); [Redman 1997](#); [Yeung 1992](#)). We excluded placebo-controlled RCTs and other studies examining high-titre VZV vaccines for the prevention of herpes zoster in healthy adults ([Gilderman 2008](#); [Macaladad 2007](#); [Mills 2010](#); [Oxman 2005](#); [Oxman 2008](#); [Simberkoff 2010](#); [Trannoy 2000](#)). Many of the other clinical trials on the use of varicella vaccine did not have a prospective RCT design; if controls were reported, they were often non-randomised and historical. A number of studies reported long-term follow-up of vaccinees in terms of immunogenicity, vaccine effectiveness or safety, without control subjects. Other studies not eligible for this review were designed to examine the immunogenicity and

safety of varicella vaccine when used concomitantly with other routinely administered vaccines, were dose-ranging studies of varicella vaccine or reported on the immunogenicity and safety of combination measles-mumps-rubella vaccine (MMRV) compared with use of MMR and monovalent varicella vaccine.

Risk of bias in included studies

Two review authors (KM, PM) independently assessed allocation method, allocation concealment, blinding and completeness of follow-up. We did not perform synthesis of results from these three studies as the overall quality was low and bias could not be excluded.

Allocation

The study by [Asano 1977a](#) was not blinded and the method of randomisation and completeness of follow-up was unclear. Similarly, the method of randomisation and allocation concealment in the study by [Arbeter 1986a](#) was unclear. The study by [Mor 2004](#) stated the method of sequence allocation and concealment and was triple-blinded with no further information included.

Blinding

The study by [Arbeter 1986a](#) was reported to be double-blinded and completeness of follow-up was stated. However, the duration of follow-up was not specified. The most recent study included more complete follow-up and adequate data with regards to methodological quality ([Mor 2004](#)).

Incomplete outcome data

For the studies [Arbeter 1986a](#) and [Mor 2004](#) there were no missing outcome data. However, for [Asano 1977a](#) there was insufficient reporting to permit judgement.

Selective reporting

The published reports included all expected outcomes, including those that were pre-specified.

Other potential sources of bias

No other potential sources of bias were identified.

Effects of interventions

Primary outcomes

1. Prevention of varicella in contacts of a varicella case

The efficacy of varicella vaccine (given within five days post-exposure) as prophylaxis for the prevention of varicella was assessed in a total of 110 healthy children in the three included studies ([Arbeter 1986a](#); [Asano 1977a](#); [Mor 2004](#)). Overall, 13 of 56 vaccine recipients developed varicella (23%) compared with 42 of 54 placebo (or no vaccine) recipients (78%). [Table 1](#) summarises the results of the studies by 'no disease' and 'mild disease'. The quality of the studies varied, therefore the vaccine used in each study differed (particularly in viral titre) and as there was diversity in the study design and outcome measures chosen we did not deem it appropriate to subject the combined results to a meta-analysis.

The majority of all study participants who received varicella vaccine did so within three days post-exposure: 10/13 participants in

[Arbeter 1986a](#); 20/21 participants in [Asano 1977a](#); and 41% of vaccine recipients compared with 45% of placebo recipients in [Mor 2004](#). However, in the study by [Mor 2004](#), outcomes limited to those who received vaccine within three days were not separately described. Thus, the efficacy of varicella vaccine in preventing varicella when given within three days post-exposure could only be assessed in 64 healthy children from two studies ([Arbeter 1986a](#); [Asano 1977a](#)).

Comparison of the efficacy of post-exposure prophylaxis (PEP) administered on days four and five post-exposure, with vaccination administered within three days of exposure, was not possible due to the low number of participants who were known to have received vaccine on days four or five. However, in the study by [Arbeter 1986a](#), the three participants who received vaccine on days four or five all developed clinical disease, although of mild severity. In the study by [Asano 1977a](#), the single participant who received vaccine beyond three days (five days) did not develop the disease. In the study by [Mor 2004](#), 59% of vaccine recipients were immunised more than 72 hours after their household exposure, which may have contributed to a decrease in vaccine efficacy seen in comparison to the other studies ([Table 1](#)). The study by [Mor 2004](#) was also notable for a low secondary attack rate in the control participants (9/20 cases of varicella, 45%) in comparison to that seen in the earlier studies, where 100% and 92%, respectively, of control participants developed varicella. Varicella in a household member usually results in infection in almost all susceptible people in that household in the absence of any intervention, with secondary attack rates of more than 90% reported ([Gershon 2013](#); [Simpson 1952](#)). The reason for the low rate of varicella in placebo recipients in the [Mor 2004](#) study is unclear.

2. Vaccine adverse events including local injection site adverse events, fever and systemic adverse events

The pre-determined safety outcomes of the review, such as local injection site reactions, fever and other systemic and serious adverse events were not reported in any of the three studies included in this review.

Secondary outcomes

1. Prevention of moderate to severe varicella in contacts of a varicella case

As shown in [Table 1](#), all vaccine recipients experienced either no disease or only mild disease, with the exception of one participant in the study of [Mor 2004](#) who had moderate to severe varicella. All three studies showed an effect individually in the prevention of moderate to severe disease. Of the 34 recipients in the two studies in which efficacy of post-exposure vaccination within three days could be assessed ([Arbeter 1986a](#); [Asano 1977a](#)), none developed moderate to severe disease compared with 33 of 34 in the control groups.

DISCUSSION

This review was limited by the small number of studies eligible for inclusion. In addition, the methodological quality of the studies varied and the number of participants in each study was small. The studies identified only included children who were household contacts of varicella cases.

The varicella vaccines used in the studies examined were produced in three different laboratories over a long period of time and were of different titres. Although the parent vaccine strain of all varicella vaccines was the Oka strain, originally adapted by [Takahashi 1974](#), subsequent adaptation has occurred by the different vaccine manufacturers. For example, the Oka/Merck vaccine lot used in the [Arbeter 1986a](#) trial was of the highest dose (4350 plaque-forming units (pfu)), whereas the Oka/GlaxoSmithKline vaccine (Varilrix) contained more than 2000 pfu/dose and the Oka/Biken vaccine contained between 800 to 1000 pfu/dose. The variation in vaccine titre in these studies does not appear to correlate with the results obtained. However, it is worth noting that only the most recent study used a commercially available vaccine ([Mor 2004](#)).

The results of this review provide limited support for the use of varicella vaccine as a post-exposure prophylaxis (PEP) within three days post-exposure, based on the small number of participants in the studies examined and the variations between the studies described above. Given the incubation period for varicella, it is biologically plausible that varicella vaccine given four to five days after exposure results in some protection against the disease. However, the studies included in this review contain too few participants documented as having received PEP on days four to five to make any conclusions.

The conclusions of this review are supported by a number of observational studies that did not meet the inclusion criteria. In two early Japanese studies (without control participants) vaccine (Oka/Biken, at more than 800 pfu/dose), given as a PEP within three days of exposure, protected all recipients against varicella, whereas children vaccinated more than three days post-exposure were likely to develop the disease ([Asano 1982](#); [Naganuma 1984](#)). Five additional uncontrolled or observational studies showed similar findings. The first, conducted during a disease outbreak in a homeless shelter, found that PEP with the licensed Oka/Merck vaccine (more than 1350 pfu/dose) at 36 hours post-exposure had a vaccine effectiveness of 95.2% (95% confidence interval (CI) 81.6% to 91.8%) for children under 13 years of age ([Watson 2000](#)). Three prospective studies report PEP provided to sibling household contacts. One used the Oka/Merck vaccine, with seven families reporting no disease (50%) or mild disease (50%) in household contact vaccine recipients ([Salzman 1998](#)). The other study found PEP with either the Oka/Merck vaccine or the Oka/GSK vaccine was 62.3% effective in preventing any varicella and 79.4% effective in preventing moderate to severe varicella when administered to household contacts within five days after exposure ([Brotans 2010](#)). The third, a small cohort study of 33 children, reported a vaccine effectiveness of 40% (95% CI 1% to 64%) against any disease and 77% (95% CI 14% to 94%) against severe disease when the vaccine was received within three days ([Pinochet 2012](#)). A prospective study of PEP in four large primary schools in Beijing, China reported varicella vaccine effectiveness of 85.3% in susceptible children within the same classrooms, floors or school buildings ([Ma 2009a](#)). A number of other studies in Japan, conducted without control participants in hospital settings, also suggested that vaccines used as PEP were efficacious ([Asano 1977b](#); [Asano 1983](#); [Katsushima 1982](#); [Katsushima 1984](#); [Naganuma 1984](#); [Takahashi 1974](#)).

Unfortunately, the trials in this review do not provide information on the safety of varicella vaccines when used as a PEP. Information regarding adverse events following varicella vaccination is available from other randomised controlled trials (RCTs) identified

but not included in this review ([Varis 1996](#); [Weibel 1984](#)), and from post-licensure studies of the safety of varicella vaccine, particularly from the USA where a population-based varicella vaccination programme has been in place for more than 15 years and has demonstrated that the vaccine has a good safety profile. Safety of varicella vaccines used as a PEP would be expected to be similar to data from these population-based studies ([Black 1999](#); [Sharrar 2000](#); [Wise 2000](#)).

The use of antiviral medication (acyclovir) in immunocompetent contacts of varicella cases has been suggested to be effective as PEP by a few small, uncontrolled observational studies and isolated case reports. However, this option is not currently recommended, based on the lack of data supporting its use ([Kesson 1996](#); [Marin 2007](#); [Ogilvie 1998](#)). In summary, the conclusions of this review provide some limited support for the use of varicella vaccine as the method of choice for PEP in healthy children, particularly when administered within three days following exposure in the household setting.

Summary of main results

There is limited evidence from RCTs to support the effectiveness of varicella vaccine as a PEP in preventing varicella. Overall, 18% of vaccine recipients developed varicella compared with 78% of placebo (or no vaccine) recipients. Varicella vaccine as a PEP was effective in preventing moderate to severe disease. Overall, only one vaccine recipient developed moderate to severe disease (2%) compared to 41 (29%) placebo recipients.

Overall completeness and applicability of evidence

The studies included in this review are relevant to the question of the efficacy of varicella vaccine for use as a post-exposure intervention. However, the studies are limited to contacts with household exposure and this restricts the generalisability of PEP to settings where a known contact is present and secondary transmission rates are high. No studies in outbreak settings, such as childcare or primary school settings, were included in this review. We identified no studies of PEP in adolescents and adults.

Quality of the evidence

The body of evidence identified here provides limited evidence to support the review objectives. Only three RCTs of varying methodological quality were included in this review, with a total of 110 healthy children, randomised to receive the varicella vaccine (56 children) or placebo/no vaccine (54 children).

While study quality varied, these three studies were consistently in support of the use of varicella vaccine as PEP.

Potential biases in the review process

It is likely that all relevant RCTs were identified for this review. This study is limited to RCTs of the use of varicella vaccine as PEP.

Agreements and disagreements with other studies or reviews

The RCTs in this review are supported by observational studies reporting the use of varicella vaccine as PEP ([Asano 1982](#); [Asano 1983](#); [Brotans 2010](#); [Katsushima 1982](#); [Katsushima 1984](#); [Ma 2009a](#); [Naganuma 1984](#); [Pinochet 2012](#); [Salzman 1998](#); [Takahashi 1974](#); [Watson 2000](#)).

AUTHORS' CONCLUSIONS

Implications for practice

This review provides information relevant to immunisation policy makers. Routine childhood varicella vaccination has been provided through publicly funded immunisation programmes in few countries. Experience indicates that varicella zoster virus (VZV) circulation persists, despite moderately high vaccine coverage and therefore the risk of exposure of unimmunised individuals to those with varicella also persists. In countries that do not recommend the routine use of varicella vaccine, it may be recommended for susceptible adolescents and adults or certain high-risk groups. In countries without routine childhood immunisation, post-exposure prophylaxis (PEP) is relevant for those at high risk of severe varicella or at high risk of transmission. This study provides limited support for the use of varicella vaccine as PEP in settings where a known contact is present and secondary transmission rates are high. The findings of this review are particularly applicable to young children in the household or other close contact settings. However, safety data are not available.

Many countries recommend or suggest consideration of the use of varicella vaccine in PEP ([ATAGI 2013](#); [Marin 2007](#); [NACI 2004](#)). This review found some evidence to support that recommendation in children. This may be particularly relevant for the control of outbreaks in settings with low to moderate varicella vaccine coverage. Additional studies are required of the use of PEP in adolescents and adults who, by virtue of their age, experience higher rates of complications from varicella and have lower seroconversion rates following one dose of vaccine. It is possible that the efficacy of PEP may be reduced in people older than

13 years of age, who require two doses of the varicella vaccine schedule to generate a sufficient primary immune response.

Implications for research

The focus of this review has been the use of live attenuated varicella vaccine for PEP in healthy participants. In immunocompetent people, there is qualified evidence for the effectiveness of varicella vaccine within three to five days of exposure. People who are significantly immunocompromised are generally not considered eligible to receive live viral vaccines but are known to experience the highest morbidity from varicella. The use of inactivated VZV vaccines for the prevention of varicella, herpes zoster or both has been the subject of studies in immunocompromised people ([Hata 2002](#); [Redman 1997](#)) and should be the topic of further study and review. There is very limited evidence for the value (if any) of the alternative use of chemoprophylaxis with antiviral agents for PEP ([Gershon 2013](#)). A head-to-head trial of varicella vaccine compared with chemoprophylaxis within five days of a varicella exposure may be justified.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Arbeter 1986a

Methods	Double-blinded, placebo-controlled, randomised trial of post-exposure prophylaxis
Participants	Healthy exposed siblings Aged 18 months to 16 years n = 13 vaccine n = 13 placebo
Interventions	Oka/Merck vaccine lot 867 4350 pfu frozen versus placebo (not stated)
Outcomes	Clinical varicella Varicella severity
Notes	Length of follow-up not stated

Vaccines for post-exposure prophylaxis against varicella (chickenpox) in children and adults (Review)

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Arbeter 1986a (Continued)

Serologic testing not discussed or reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. Insufficient information to permit judgement
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement. "Double blinding" stated but no additional details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Asano 1977a

Methods	Controlled trial of post-exposure prophylaxis
Participants	Healthy exposed siblings, aged 1 month to 11 years, with a negative history of varicella n = 24 vaccine n = 19 unvaccinated
Interventions	Oka/BIKEN vaccine versus no vaccine
Outcomes	Clinical varicella Post-vaccination serology (in index cases and vaccine recipients only) Follow-up period ranged from 4 to 8 weeks
Notes	No discussion of randomisation All participants had serology performed at enrolment and those found to be seropositive for varicella IgG were excluded from analysis of results

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-random allocation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias)	Low risk	Unblinded study but we judged that the outcome and the outcome measurement are not likely to be influenced by lack of blinding

Asano 1977a (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Mor 2004

Methods	Double-blinded, placebo-controlled trial of post-exposure prophylaxis
Participants	Healthy exposed siblings, aged 1 to 13 years, with a negative history of varicella n = 22 vaccine (mean age 40 months) n = 20 placebo (mean age 53 months)
Interventions	Varilix, GSK, (Oka/RIT) 2000 pfu versus placebo (vaccine diluent)
Outcomes	Clinical varicella. Varicella severity Follow-up period was 28 days
Notes	Serologic testing not discussed or reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "children were assigned the next available study number on the basis of a randomised number table with a block size of eight."
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The placebo vial and diluent container were identical to the varicella vaccine vial and the same injection procedure was followed." "Statistical analysis was done blindly, with the statistician being unaware of which code referred to the placebo or the vaccine."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. However, no laboratory confirmation was performed
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appears to be free of other sources of bias

pfu: plaque-forming units

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Akazawa 2013	Non-RCT/VV non-PEP
Alpay 2002	No non-treatment group
Ampofo 2002	No non-treatment group; duration of immunity
Andrei 2011	Non-RCT/review non-PEP
Arbeter 1982	Non-RCT/no non-treatment group
Arbeter 1983	No non-treatment group
Arbeter 1984	Summary of 10 comparative clinical trials, no original data
Arbeter 1986	No non-treatment group (MMRV vaccine)
Arbeter 1990	No non-treatment group
Arent 2009	Non-RCT
Asano 1975	Non-RCT/no non-treatment group
Asano 1977b	No non-treatment group; cohort study
Asano 1977c	No non-treatment group; cohort study
Asano 1982	Non-RCT/no non-treatment group; PEP of family contacts
Asano 1983	No non-treatment group
Asano 1984	No non-treatment group; prospective cohort follow-up
Asano 1985	No non-treatment group; prospective cohort follow-up
Asano 1994	Non-RCT
Asano 2008	Non-RCT
Bai 2011	RCT; VV non-PEP
Baldacci 2008	Non-RCT
Bancillon 1991	Non-RCT
Banz 2009	Non-RCT
Barbosa 2009	RCT; VV non-PEP
Barbosa 2012	RCT; VV non-PEP
Bate 2011	PEP; non-RCT; no non-treatment group
Bednarek 2004	Non-RCT; no non-treatment group
Bekker 2006	Non-RCT

Study	Reason for exclusion
Bergen 1990	No non-treatment group
Berger 1984	Non-RCT
Berger 1985	Non-RCT
Berger 1998	Non-PEP RCT; immunologic outcomes in elderly participants
Berghella 2010	Non-RCT
Bernstein 1993	Non-RCT
Black 2006	Non-PEP RCT
Black 2008	Non-RCT
Blatter 2012	RCT; WV non-PEP
Bogger-Goren 1982	Non-RCT
Brotons 2010	Non-RCT; no non-treatment group; PEP of household contacts
Broyer 1985	Non-RCT; no non-treatment group
Brunell 1982	Non-RCT; no non-treatment group
Brunell 1986	Non-RCT; no non-treatment group
Brunell 1988	No non-treatment group
Bryant 2012	RCT; WV non-PEP
Bryant 2013	RCT; WV non-PEP
Burgess 1999	No non-treatment group
Ceyhan 2009	Non-RCT
Chao 2012	Non-RCT/WV non-PEP
Chlibek 2014	RCT; WV non-PEP
Chui 2014	Non-RCT/WV non-PEP
Clements 1995	Non-RCT; no non-treatment group
Contopoulos-Ioannidis 2012	RCT; WV non-PEP
Cristofani 1991	Non-PEP; RCT; vaccine versus placebo in immunocompromised children
Czajka 2009	Non-RCT
D'Angio 2007	Non-RCT; no non-treatment group
Davies 1994	Non-RCT

Study	Reason for exclusion
de Soárez 2009	Non-RCT
Dennehy 1991	No non-treatment group
Dennehy 1994	No non-treatment group
Diaz 1991	Non-RCT; no non-treatment group
Diaz 2006	No non-treatment group
Dube 2012	Non-RCT/review non-PEP
Duchateau 1985	No non-treatment group
El-Darouti 2012	RCT; VV non-PEP
Englund 1989	Non-PEP RCT
Enright 2006	Non-RCT
Fadrowski 2004	Non-RCT; review
Ferrera 2009	Non-PEP RCT
Ferrera 2012	RCT; VV non-PEP
Fridman 2011	Non-RCT/VV non-PEP
Fu 2010	Non-RCT
Furth 2003a	Non-RCT; no non-treatment group
Furth 2003b	Non-RCT; no non-treatment group
Gatchalian 2003	No non-treatment group
Gatchalian 2004	No non-treatment group
Gershon 1982	No non-treatment group
Gershon 1984	Non-RCT; no non-treatment group
Gershon 1985	Non-RCT
Gershon 1986	Non-RCT; cohort study
Gershon 1988	No non-treatment group
Gershon 1989	No non-treatment group
Gershon 1990	Non-RCT
Getaz 2010	Non-RCT; no non-treatment group; PEP of susceptible prison contacts
Giacchino 1995	Non-RCT

Study	Reason for exclusion
Gilderman 2008	Non-PEP RCT
Gillet 2009a	Non-PEP RCT
Gillet 2009b	Non-PEP RCT
Glanz 2010	Non-RCT
Gnann 2008	Non-RCT
Gonzaga 2008	Non-RCT
Groves 2010	Non-RCT
Guerra 2006	Non-PEP RCT
Ha 1980	Non-RCT
Habermehl 1999	No non-treatment group
Halperin 2009	Non-PEP RCT
Hambleton 2008	Non-RCT
Hardy 1991	Non-PEP RCT
Hartung 2013	RCT; VW non-PEP
Hata 2002	Non-PEP RCT
Hayward 1992	Non-RCT
Hayward 1994	Non-RCT
Hayward 1996	Non-RCT
Heller 1985	Non-RCT
Hesley 2004	Non-PEP RCT
Holcomb 2008	Non-RCT
Horiuchi 1984	Non-RCT
Huang 2013	RCT; VW non-PEP
Iovlev 1969	Non-RCT
Iwaza 1977	Non-RCT
Johnson 1988	Non-RCT
Johnson 1989	Non-RCT
Jones 2009	Non-RCT

Study	Reason for exclusion
Just 1985	Non-RCT
Just 1986	Non-RCT; no non-treatment group
Kanra 2000	Non-RCT; no non-treatment group
Katsushima 1982	Non-RCT
Katsushima 1984	Non-RCT
Klein 2012a	RCT; VV non-PEP
Klein 2012b	RCT; VV non-PEP
Knuf 2006	Non-PEP RCT
Knuf 2010	Non-PEP RCT
Knuf 2012	Non-RCT/VV non-PEP
Konno 1984	Non-RCT; no non-treatment group
Kosuwon 2004	No non-treatment group
Krah 1997	Non-RCT
Krause 1995	Non-RCT
Kreth 1994	No non-treatment group
Kreth 2006	Non-RCT
Kreth 2008	Non-RCT
Kumagai 1980	Non-RCT
Kuter 1991	Non-PEP RCT
Kuter 1995	No non-treatment group
Kuter 2004	No non-treatment group
Kuter 2006	No non-treatment group
Lau 2002	No non-treatment group
Lawrence 1988	Non-RCT
Leonardi 2011	RCT; VV non-PEP
Leroux-Roels 2012	RCT; VV non-PEP
Leung 2004	Non-RCT; no non-treatment group
Levin 1992	Non-RCT; no non-treatment group

Study	Reason for exclusion
Levin 2000	No non-treatment group
Levin 2001	Non-RCT/no placebo; immunisation of HIV-infected children
Levin 2003	No non-treatment group
Levin 2008a	Non-PEP RCT
Levin 2008b	Non-RCT
Li 2012	Non-RCT/VV non-PEP
Lieberman 2006	No non-treatment group
Lim 1998	No non-treatment group
Lin 1981	Non-RCT
Liu 2009	Non-RCT
Lopez 2011	Non-RCT/VV non-PEP
Lou 1996	No non-treatment group
Loulergue 2013	Non-RCT/VV non-PEP
Lu 1998	No non-treatment group
Ma 2009a	Non-RCT; no non-treatment group; PEP of primary school contacts
Ma 2009b	Non-RCT
Macaladad 2007	Non-PEP RCT
Macartney 2012	Non-RCT; PEP review
Marin 2008	Non-RCT
Marquez-Pelaez 2009	Non-RCT
Marshall 2009	Non-RCT
McAdam 2013	RCT; VV non-PEP
Meurice 1996	Non-PEP RCT
Mick 2010	Non-RCT
Mills 2010	Non-PEP RCT
Morales 2000	No non-treatment group
Mustafa 2009	Non-RCT
Nader 1995	No non-treatment group

Study	Reason for exclusion
Naganuma 1984	Use as PEP but non-RCT
Ndumbe 1985	Non-RCT
Neff 1981	Non-RCT
Ngai 1996	No non-treatment group
Nithichaiyo 2001	Non-RCT
Nolan 2002	No non-treatment group
Nolan 2008	Non-PEP RCT
Novadzki 2010	Non-RCT
Oxman 2005	Non-PEP RCT
Oxman 2008	Non-PEP RCT
Oxman 2009	Non-RCT
Oxman 2010	Non-RCT
Ozaki 1978	Non-RCT
Ozaki 1984	Non-RCT
Parment 2003	Non-RCT
Pileggi 2010	Non-RCT/VV non-PEP
Pinochet 2012	Non-RCT
Prelog 2010	Non-RCT
Prymula 2014	RCT; VV non-PEP
Quian 2010	Non-RCT
Quien 1977	Non-RCT
Ramkissoon 1995	No non-treatment group
Redman 1997	Non-PEP RCT
Reisinger 2006	Non-PEP RCT
Reuman 1997	No non-treatment group
Riera 2012	Non-RCT; PEP review
Rinderknecht 2011	RCT; VV non-PEP
Rios 2009	Non-RCT

Study	Reason for exclusion
Ross 1997	Non-RCT
Rothstein 1997	No non-treatment group
Rozenbaum 2008	Non-RCT
Ruger 2012	Non-RCT/VV non-PEP
Rumke 2011	RCT; VV non-PEP
Sadaoka 2008	Non-RCT
Saiman 2001	No non-treatment group
Salleras 2009	Non-RCT
Salleras Sanmarti 2008	Non-RCT
Salzman 1998	PEP; non-RCT
Sanford 2010	Non-RCT
Schmid 2010	Non-RCT
Schuster 2008	Non-PEP RCT
Seward 2008	Non-RCT
Shapiro 2011	Non-RCT/VV non-PEP
Sharp 1992	Non-RCT
Shinefield 1998	No non-treatment group
Shinefield 2002	No non-treatment group
Shinefield 2005a	No non-treatment group
Shinefield 2005b	No non-treatment group
Shinefield 2006	No non-treatment group
Shinefield 2008	Non-RCT
Simberkoff 2010	Non-PEP RCT
Smith 2003	Non-RCT
Sperber 1992	No non-treatment group
Stadtmauer 2013	RCT; VV non-PEP
Streng 2010	Non-RCT/VV non-PEP
Stuck 2002	No non-treatment group

Study	Reason for exclusion
Sutradhar 2009	Non-RCT
Takahashi 1974	Non-RCT; no non-treatment group
Takahashi 1985	Non-RCT
Takahashi 2001	Non-RCT
Takahashi 2003	Non-RCT
Takahashi 2008	Non-RCT
Takayama 1992	Non-RCT
Tan 1996	No non-treatment group
Tang 2012	RCT; VW non-PEP
Terada 2002	Non-RCT
Tillieux 2008	Non-RCT
Trannoy 2000	Non-PEP RCT
Ueda 1977	Non-PEP clinical trial
Varis 1996	Non-PEP RCT
Vazquez 2004	Non-RCT
Vesikari 1991	No non-treatment group
Vesikari 2007	Non-PEP RCT
Vesikari 2010	Non-PEP RCT
Vesikari 2012	RCT; VW non-PEP
Vessey 2001	No non-treatment group
Wang 2013	Non-RCT/VW non-PEP
Watson 1993a	Non-RCT
Watson 1993b	No non-treatment group
Watson 1994	Non-RCT
Watson 1995	No non-treatment group
Watson 1996	No non-treatment group
Watson 2000	PEP; but non-RCT
Watson 2008	Non-RCT

Study	Reason for exclusion
Webb 2000	Non-RCT
Weibel 1984	Non-PEP RCT
Weibel 1985	No non-treatment group
Weinberg 2009	Non-RCT
Weinberg 2010	RCT; VV non-PEP
White 1991	Non-RCT; review
White 1992	Non-RCT
White 1997	No placebo; MMRV, MMR and varicella and concomitant vaccines
Wise 2000	Non-RCT
Wu 2010	Non-RCT/review non-PEP
Yamaguti 2008	Non-RCT
Yerkovich 2007	Non-PEP RCT
Yetman 2013	RCT; VV non-PEP
Yeung 1992	Non-PEP RCT
Zerboni 1998	Non-RCT

MMR: measles, mumps and rubella vaccine

MMRV: measles, mumps, rubella and varicella vaccine

PEP: post-exposure prophylaxis

RCT: randomised controlled trial

VV: varicella vaccine

ADDITIONAL TABLES

Table 1. Cases of varicella in three clinical trials of the use of varicella vaccine as post-exposure prophylaxis (compared with placebo or no vaccine) when given within five days of varicella exposure

	Vaccine recipients				Placebo (or no vaccine) recipients				Statistical significance (moderate-severe disease versus no disease)*
	No disease (%)	Mild disease	Moderate to severe disease	Total number	No disease (%)	Mild disease	Moderate to severe disease	Total number	
Arbeter	9 (69.2%)	4 (30.8%)	0	13	1 (7.7%)	0	12 (92.3%)	13	P value < 0.000003
Asano	21 (100%)	0	0	21	0 (0%)	0	21 (100%)	21	Not done
Mor	13 (59.1%)	8 (36.4%)	1 (4.5%)	22	11 (55.0%)	1 (5.0%)	8 (40.0%)	20	Risk ratio (RR) 8 (95% confidence interval (CI) 1.2 to 51.5) P = 0.003
Total	43 (76.8%)	12 (21.4%)	1 (1.8%)	56	12 (22.2%)	1 (1.9%)	41 (75.9%)	54	

*Statistical test as stated in source publication.

APPENDICES

Appendix 1. Previous searches

The search strategy was updated to the current search strategy when the review was updated in June 2010. We searched *The Cochrane Library*, Cochrane Central Register of Controlled Trials (CENTRAL Issue 2, 2010); MEDLINE (February 2008 to June week 2, 2010); and EMBASE.com (March 2008 to June 2010). The clinical trials register www.clinicaltrials.gov was also reviewed (to June 2010) for unpublished studies. Details of the original search are in Appendix 1.

Previously we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2008, Issue 1); MEDLINE (1966 to February 2008); and EMBASE (January 1990 to March 2008). The following search terms were used in MEDLINE and CENTRAL and adapted for EMBASE.

MEDLINE (OVID)

- 1 exp CHICKENPOX/
- 2 (chickenpox or chicken pox).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 3 exp Varicellovirus/
- 4 varicella.mp.
- 5 or/1-4
- 6 exp VACCINES/
- 7 (vaccin\$ or inoculat\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 8 or/6-7
- 9 5 and 8
- 10 exp CHICKENPOX VACCINE/
- 11 or/9-10
- 12 randomized controlled trial.pt.
- 13 controlled clinical trial.pt.
- 14 randomized.ab.
- 15 placebo.ab.
- 16 drug therapy.fs.
- 17 randomly.ab.
- 18 trial.ab.
- 19 groups.ab.
- 20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
- 21 humans.sh.
- 22 20 and 21
- 23 11 and 22

EMBASE (Webspurs)

- #25 (((explode 'chickenpox-' / all subheadings in DEM,DER,DRM,DRR) or ((chickenpox in ti) or (chickenpox in ab)) or ((chicken pox in ti) or (chicken pox in ab)) or (explode 'Varicella-zoster-virus' / all subheadings in DEM,DER,DRM,DRR) or ((varicella in ti) or (varicella in ab)))) and (((explode 'vaccine-' / all subheadings in DEM,DER,DRM,DRR) or ((vaccine* in ti) or (vaccine* in ab)))) or (explode 'chickenpox-vaccine' / all subheadings in DEM,DER,DRM,DRR)) and (((explode 'randomized-controlled-trial' / all subheadings) or (explode 'controlled-study' / all subheadings) or (explode 'single-blind-procedure' / all subheadings) or (explode 'double-blind-procedure' / all subheadings) or (explode 'crossover-procedure' / all subheadings) or (explode 'phase-3-clinical-trial' / all subheadings) or ((randomi?ed controlled trial in ti) or (randomi?ed controlled trial in ab)) or (((random* or placebo* or double-blind*)in ti) or ((random* or placebo* or double-blind*)in ab)) or ((controlled clinical trial* in ti) or (controlled clinical trial* in ab))) not ((nonhuman in der) not ((human in der)and (nonhuman in der))))
- #24 ((explode 'randomized-controlled-trial' / all subheadings) or (explode 'controlled-study' / all subheadings) or (explode 'single-blind-procedure' / all subheadings) or (explode 'double-blind-procedure' / all subheadings) or (explode 'crossover-procedure' / all subheadings) or (explode 'phase-3-clinical-trial' / all subheadings) or ((randomi?ed controlled trial in ti) or (randomi?ed controlled trial in ab)) or (((random* or placebo* or double-blind*)in ti) or ((random* or placebo* or double-blind*)in ab)) or ((controlled clinical trial* in ti) or (controlled clinical trial* in ab))) not ((nonhuman in der) not ((human in der)and (nonhuman in der))))
- #23 (nonhuman in der) not ((human in der)and (nonhuman in der))
- #22 (explode 'randomized-controlled-trial' / all subheadings) or (explode 'controlled-study' / all subheadings) or (explode 'single-blind-procedure' / all subheadings) or (explode 'double-blind-procedure' / all subheadings) or (explode 'crossover-procedure' / all subheadings) or (explode 'phase-3-clinical-trial' / all subheadings) or ((randomi?ed controlled trial in ti) or (randomi?ed controlled trial in ab)) or (((random* or placebo* or double-blind*)in ti) or ((random* or placebo* or double-blind*)in ab)) or ((controlled clinical trial* in ti) or (controlled clinical trial* in ab))
- #21 (controlled clinical trial* in ti) or (controlled clinical trial* in ab)
- #20 ((random* or placebo* or double-blind*)in ti) or ((random* or placebo* or double-blind*)in ab)
- #19 (randomi?ed controlled trial in ti) or (randomi?ed controlled trial in ab)

#18 explode 'phase-3-clinical-trial' / all subheadings
 #17 explode 'crossover-procedure' / all subheadings
 #16 explode 'double-blind-procedure' / all subheadings
 #15 explode 'single-blind-procedure' / all subheadings
 #14 explode 'controlled-study' / all subheadings
 #13 explode 'randomized-controlled-trial' / all subheadings
 #12 (((explode 'chickenpox-' / all subheadings in DEM,DER,DRM,DRR) or ((chickenpox in ti) or (chickenpox in ab)) or ((chicken pox in ti) or (chicken pox in ab)) or (explode 'Varicella-zoster-virus' / all subheadings in DEM,DER,DRM,DRR) or ((varicella in ti) or (varicella in ab))) and ((explode 'vaccine-' / all subheadings in DEM,DER,DRM,DRR) or ((vaccine* in ti) or (vaccine* in ab)))) or (explode 'chickenpox-vaccine' / all subheadings in DEM,DER,DRM,DRR)
 #11 explode 'chickenpox-vaccine' / all subheadings in DEM,DER,DRM,DRR
 #10 ((explode 'chickenpox-' / all subheadings in DEM,DER,DRM,DRR) or ((chickenpox in ti) or (chickenpox in ab)) or ((chicken pox in ti) or (chicken pox in ab)) or (explode 'Varicella-zoster-virus' / all subheadings in DEM,DER,DRM,DRR) or ((varicella in ti) or (varicella in ab))) and ((explode 'vaccine-' / all subheadings in DEM,DER,DRM,DRR) or ((vaccine* in ti) or (vaccine* in ab)))
 #9 (explode 'vaccine-' / all subheadings in DEM,DER,DRM,DRR) or ((vaccine* in ti) or (vaccine* in ab))
 #8 (vaccine* in ti) or (vaccine* in ab)
 #7 explode 'vaccine-' / all subheadings in DEM,DER,DRM,DRR
 #6 (explode 'chickenpox-' / all subheadings in DEM,DER,DRM,DRR) or ((chickenpox in ti) or (chickenpox in ab)) or ((chicken pox in ti) or (chicken pox in ab)) or (explode 'Varicella-zoster-virus' / all subheadings in DEM,DER,DRM,DRR) or ((varicella in ti) or (varicella in ab))
 #5 (varicella in ti) or (varicella in ab)
 #4 explode 'Varicella-zoster-virus' / all subheadings in DEM,DER,DRM,DRR
 #3 (chicken pox in ti) or (chicken pox in ab)
 #2 (chickenpox in ti) or (chickenpox in ab)
 #1 explode 'chickenpox-' / all subheadings in DEM,DER,DRM,DRR

Appendix 2. Embase.com

#20. #16 AND #19
 #19. #17 OR #18
 #18. 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 allocat*:ab,ti OR assign*:ab,ti OR ((singl* OR doubl*) NEAR/2 (blind* OR mask*)):ab,ti
 #17. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
 #16. #14 OR #15
 #15. 'chickenpox vaccine'/exp 0
 #14. #8 AND #13
 #13. #9 OR #10 OR #11 OR #12
 #12. vaccin*:ab,ti OR immuni*:ab,ti OR inocul*:ab,ti
 #11. 'immunization'/de
 #10. 'vaccination'/de
 #9. 'vaccine'/exp
 #8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 1
 #7. vzv:ab,ti
 #6. varicell*:ab,ti
 #5. 'varicellovirus'/de
 #4. 'human herpesvirus 3':ab,ti OR 'human herpes virus 3':ab,ti
 #3. 'varicella zoster virus'/de
 #2. chickenpox:ab,ti OR 'chicken pox':ab,ti
 #1. 'chickenpox'/de

Appendix 3. LILACS (BIREME) search strategy

((mh:chickenpox OR "chicken pox" OR chickenpox OR varicela OR varicella OR catapora OR mh:"Herpesvirus 3,Human" OR "Herpesvirus Humano 3" OR "Virus da Varicela" OR "Virus do Herpes Zoster" OR "Herpesvirus varicellae" OR "Herpesvirus Humano Tipo 3" OR "Virus VZ" OR "Virus da Varicela-Zoster" OR mh:varicellovirus OR varicel* OR vzv) AND (mh:vaccines OR vacunas OR vacinas OR mh:d20.215.894* OR vacina OR mh:vaccination OR vacunación OR vacinação OR mh:e02.095.465.425.400.530.890* OR mh:e05.478.550.600.890* OR mh:n02.421.726.758.310.890* OR mh:n06.850.780.200.425.900* OR mh:n06.850.780.680.310.890* OR mh:sp4.001.012.178* OR mh:sp8.946.819.838.803* OR mh:immunization OR inmunización OR imunização OR vaccin* OR immuni* OR inocul*)) OR (mh:"Chickenpox Vaccine" OR "Vacuna contra la Varicela" OR "Vacina contra Varicela" OR "Varicella Vaccine" OR "Vacuna contra la Varicella" OR "Vacuna Chickenpox" OR "Vacina contra Varicela" OR "Vacina Antivaricela")) AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("clinical_trials"))

WHAT'S NEW

Date	Event	Description
30 June 2014	Amended	Updated percentage of vaccine recipients developing varicella in Abstract and Results of main text.

HISTORY

Protocol first published: Issue 4, 1999

Review first published: Issue 3, 2008

Date	Event	Description
18 March 2014	New citation required but conclusions have not changed	No new studies are included in the updated review. New excluded studies are cited in the conclusions.
18 March 2014	New search has been performed	Updated searches conducted. We excluded 45 new studies (Andreï 2011 ; Akazawa 2013 ; Bai 2011 ; Barbosa 2012 ; Barbosa 2009 ; Blatter 2012 ; Bate 2011 ; Bryant 2012 ; Bryant 2013 ; Contopoulos-Ioannidis 2012 ; Chlibek 2014 ; Chui 2014 ; Chao 2012 ; Dube 2012 ; El-Darouti 2012 ; Ferrera 2012 ; Fridman 2011 ; Klein 2012a ; Klein 2012b ; Knuf 2012 ; Hartung 2013 ; Huang 2013 ; Leonardi 2011 ; Leroux-Roels 2012 ; Li 2012 ; Lopez 2011 ; Loulergue 2013 ; McAdam 2013 ; Macartney 2012 ; Pileggi 2010 ; Pinochet 2012 ; Prymula 2014 ; Riera 2012 ; Rinderknecht 2011 ; Ruger 2012 ; Rumke 2011 ; Shapiro 2011 ; Stadtmauer 2013 ; Streng 2010 ; Tang 2012 ; Vesikari 2012 ; Wang 2013 ; Weinberg 2010 ; Wu 2010 ; Yetman 2013). We did not identify any new trials suitable for inclusion in this update.
18 June 2010	New citation required but conclusions have not changed	A new review author joined the team to update this review.
18 June 2010	New search has been performed	Updated searches conducted. We excluded 63 new studies (Arnt 2009 ; Asano 2008 ; Baldacci 2008 ; Banz 2009 ; Berghella 2010 ; Black 2008 ; Brotons 2010 ; Ceyhan 2009 ; Czajka 2009 ; de Soárez 2009 ; Ferrera 2009 ; Fu 2010 ; Getaz 2010 ; Gilderman 2008 ; Gillet 2009a ; Gillet 2009b ; Glanz 2010 ; Gnann 2008 ; Gonzaga 2008 ; Groves 2010 ; Halperin 2009 ; Hambleton 2008 ; Holcomb 2008 ; Jones 2009 ; Knuf 2010 ; Kreth 2008 ; Levin 2008a ; Levin 2008b ; Liu 2009 ; Ma 2009a ; Ma 2009b ; Marin 2008 ; Marquez-Pelaez 2009 ; Marshall 2009 ; Mick 2010 ; Mills 2010 ; Mustafa 2009 ; Nolan 2008 ; Novadzki 2010 ; Oxman 2008 ; Oxman 2009 ; Oxman 2010 ; Prelog 2010 ; Quian 2010 ; Rios 2009 ; Rozenbaum 2008 ; Sadaoka 2008 ; Salleras 2009 ; Salleras Sanmarti 2008 ; Sanford 2010 ; Schmid 2010 ; Schuster 2008 ; Seward 2008 ; Shinefield 2008 ; Simberkoff 2010 ; Sutradhar 2009 ; Takahashi 2008 ; Tillieux 2008 ; Vesikari 2010 ; Watson 2008 ; Weinberg 2009 ; Yamaguti 2008). We did not identify any new trials suitable for inclusion in this update.
27 February 2008	New search has been performed	Searches conducted.
24 January 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Kristine Macartney (KM) was the primary author of this review. Anita Heywood (AH) updated the review and contributed to revisions. Peter McIntyre (PM) contributed revisions and gave additional input as co-author.

DECLARATIONS OF INTEREST

Peter McIntyre is a member of the Australian Technical Advisory Group on Immunisation (ATAGI) in Australia, which provides advice on the clinical use of vaccines.

Kristine Macartney is the Deputy Director of Policy Support at the National Centre for Immunisation Research and Surveillance and also provides advice on policy related to immunisation in Australia.

Anita Hayward has received funding to conduct investigator-driven research from GSK and Sanofi Pasteur.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original published protocol for this review was broad-ranging and included the objectives of reviewing varicella vaccine efficacy and safety in the context of its use as a population-based preventative measure against varicella zoster virus infection. The review authors now feel that the original aims of the protocol, particularly regarding the use of vaccine in healthy children, may have been superseded by the considerable evidence on vaccine effectiveness that has come from the United States. The review authors decided to modify the review and focus on looking at vaccine use in post-exposure prophylaxis, as this is probably the most pertinent information currently available.

INDEX TERMS

Medical Subject Headings (MeSH)

*Herpesvirus 3, Human; Chickenpox [*prevention & control] [transmission]; Chickenpox Vaccine [*administration & dosage]; Post-Exposure Prophylaxis [*methods]; Randomized Controlled Trials as Topic; Vaccines, Attenuated [administration & dosage]

MeSH check words

Adult; Child; Humans