ClinicalEvidence

Chickenpox

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ABSTRACT

INTRODUCTION: Chickenpox is extremely contagious. Over 90% of unvaccinated people become infected, but infection occurs at different ages in different parts of the world — over 80% of people have been infected by the age of 10 years in the USA, the UK, and Japan, and by the age of 20–30 years in India, South East Asia, and the West Indies. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent chickenpox in healthy adults and children? What are the effects of interventions to prevent chickenpox in children exposed prenatally? What are the effects of interventions to prevent chickenpox in immunocompromised adults and children? What are the effects of treatments for chickenpox in healthy adults and children? What are the effects of treatments for chickenpox in immunocompromised adults and children? We searched: Medline, Embase, The Cochrane Library and other important databases up to March 2007 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 13 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: acyclovir, famciclovir, live attenuated vaccine, valaciclovir, varicella zoster immunoglobulin, and zoster immunoglobulin.

QUESTIONS

What are the effects of interventions to prevent chickenpox in healthy adults and children? . . . 3

What are the effects of interventions to prevent chickenpox in children exposed prenatally? . . . 4

What are the effects of interventions to prevent chickenpox in immunocompromised adults and children? . . . 5

What are the effects of treatments for chickenpox in healthy adults and children? . . . 8

What are the effects of treatments for chickenpox in immunocompromised adults and children? . . . 10

INTERVENTIONS

PREVENTION IN HEALTHY ADULTS AND CHILDREN

Beneficial

Live attenuated vaccine in healthy children . . . 3

Unknown effectiveness

Live attenuated vaccine in healthy adults . . . 4

PREVENTION IN PRENATALLY EXPOSED CHILDREN

Unknown effectiveness

Aciclovir in children exposed prenatally . . . 4

Famciclovir in children exposed prenatally New . . . 4

Valaciclovir in children exposed prenatally New . . . 4

Varicella zoster immunoglobulin in children exposed prenatally New . . . 5

Zoster immunoglobulin in children exposed prenatally . . . 5

PREVENTION IN IMMUNOCOMPROMISED ADULTS AND CHILDREN

Beneficial

Aciclovir, high dose (> 3200 mg/day) prevention in people with HIV infection . . . 5

Unknown effectiveness

Aciclovir prevention in people with immunocompromise other than HIV . . . 6

Famciclovir (prevention in immunocompromised people) New . . . 6

Live attenuated vaccine in immunocompromised people . . . 5

Valaciclovir (prevention in immunocompromised people) New . . . 6

Varicella zoster immunoglobulin(prevention in immunocompromised people) New . . . 6

Zoster immunoglobulin(prevention in immunocompromised people) . . . 7

TREATMENT IN HEALTHY ADULTS AND CHILDREN

Likely to be beneficial

Aciclovir (oral) in healthy people (given less than 24 hours after onset of rash) . . . 8

Unknown effectiveness

Aciclovir (oral) treatment in healthy people (given more than 24 hours after onset of rash) . . . 9

Famciclovir (treatment in healthy people) New . . . 9

Valaciclovir (treatment in healthy people) New . . . 9

TREATMENT IN IMMUNOCOMPROMISED ADULTS AND CHILDREN

Likely to be beneficial

Aciclovir (intravenous) for treatment of chickenpox in children with malignancy . . . 10

Unknown effectiveness

Famciclovir (treatment in immunocompromised people) New . . . 10

Valaciclovir (treatment in immunocompromised people) New . . . 11

Key points

- Chickenpox is caused by primary infection with varicella zoster virus. In healthy people, it is usually a mild, self-limiting illness, characterised by low-grade fever, malaise, and a generalised, itchy, vesicular rash.

  Chickenpox is very contagious — in the UK, USA and Japan, over 80% of people have been infected by the age of 10 years.

  The most common complications are bacterial skin sepsis in children under 5, acute cerebellar ataxia in older children, and varicella pneumonia in adults (which causes 20–30 hospital admissions per 10 000 adults).

- Live attenuated varicella vaccine is effective at preventing chickenpox in healthy children.

  The vaccine does not appear to reduce the incidence of chickenpox in postexposed children, although it does reduce severity of symptoms.

- We haven't found any evidence that looks at the effect of the vaccine in healthy adults.

- Newborns whose mothers' rashes appear in the last 5 days of pregnancy or within 2 days of birth have been reported, in small case series, to have a very high risk of severe chickenpox.

  In these cases, the general consensus is to administer zoster immunoglobulin.

  We haven't found any evidence assessing aciclovir, famciclovir, or valaciclovir for preventing chickenpox in prenatally exposed children.

- Overall, there is sparse evidence examining the effects of vaccines in immunocompromised adults and children.

  We don't know how effective famciclovir, valaciclovir, live attenuated varicella virus, or zoster immunoglobulin are in preventing chickenpox in immunocompromised adults or children.

  Aciclovir (high dose) has been shown to be beneficial in reducing clinical chickenpox in people with HIV infection. We don't know how effective it is in other immunocompromised people to prevent chickenpox.

- Oral aciclovir also seems to effectively treat chickenpox if administered within 24 hours of onset of rash.

  When given later than 24 hours after onset of rash, aciclovir doesn't appear to be so effective, although the evidence is sparse.

  We haven't found any evidence assessing famciclovir or valaciclovir for treating chickenpox in healthy people.

- In children with malignancy, intravenous aciclovir appears to reduce clinical deterioration from chickenpox.

  We couldn't find any evidence assessing how effective aciclovir, famciclovir, or valaciclovir are in treating immunocompromised adults with chickenpox.

DEFINITION

Chickenpox is caused by primary infection with varicella zoster virus. In healthy people, it is usually a mild, self limiting illness, characterised by low grade fever, malaise, and a generalised, itchy, vesicular rash. [1]

INCIDENCE/ PREVALENCE

Chickenpox is extremely contagious. Over 90% of unvaccinated people become infected, but infection occurs at different ages in different parts of the world — over 80% of people have been infected by the age of 10 years in the USA, the UK, and Japan, and by the age of 20–30 years in India, South East Asia, and the West Indies. [2] [3] [4]

AETIOLOGY/ RISK FACTORS

Chickenpox is caused by exposure to varicella zoster virus.

PROGNOSIS

Infants and children: In healthy children the illness is usually mild and self limiting. In the USA, mortality in infants and children (aged 1–14 years) with chickenpox is about 7/100,000 in infants, and 1.4/100,000 in children. [5] In Australia, mortality from chickenpox is about 0.5–0.6/100 000 in children aged 1–11 years, and about 1.2/100,000 in infants. [6] Bacterial skin sepsis is the most common complication in children under 5 years of age, and acute cerebellar ataxia is the most common complication in older children; both cause hospital admission in 2–3/10 000 children. [1] **Adults:** Mortality in adults is higher, at about 31/100,000. [5] Varicella pneumonia is the most common complication, causing 20–30 hospital admissions/10 000 adults. [1] Activation of latent varicella zoster virus infection can cause herpes zoster, also known as shingles (see review on postherpetic neuralgia). **Cancer chemotherapy:** One case series (77 children with both cancer and chickenpox; 1 child received zoster immune globulin within 72 hours of exposure) found that more children receiving chemotherapy developed progressive chickenpox with multiple organ involvement compared with those in remission (19/60 [32%] of children receiving chemotherapy *v* 0/17 [0%] of children in remission), and more children died (4/60 [7%] of children receiving chemotherapy *v* 0/17 [0%] of children in remission). [7] **HIV infection:** One retrospective case series (45 children with AIDS; no treatment reported) found that 1/4 (25%) children with AIDS who acquired chickenpox in hospital developed pneumonia, and 5% died. [8] In a retrospective cohort study (73 children with HIV and chickenpox; 83% with symptomatic HIV; 14 children received varicella zoster

immune globulin, 9 within 48 hours of exposure), infection beyond 2 months occurred in 10 children (14%), and recurrent varicella zoster virus infections occurred in 38 (55%). There was a strong association between an increasing number of recurrences and low CD4 cell counts. [9] Half of recurrent infections involved generalised rashes, and the other half had zoster. **Newborns:** We found no cohort studies of untreated children with perinatal exposure to chickenpox. One cohort study (281 neonates receiving varicella zoster immune globulin because their mothers had developed a chickenpox rash during the month before or after delivery) found that 134 (48%) developed a chickenpox rash and 19 (14%) developed severe chickenpox. [10] Sixteen (84%) of the 19 cases of severe chickenpox occurred in neonates of mothers whose rash had started between 4 days before and 2 days after delivery.

AIMS OF INTERVENTION To prevent clinical chickenpox (characterised by a rash); to reduce the duration of illness and complications of chickenpox.

OUTCOMES Development of clinical chickenpox; duration of illness (time to no new lesions, disappearance of fever); complications of chickenpox; mortality.

METHODS *BMJ Clinical Evidence* search and appraisal March 2007. The following databases were used to identify studies for this review: Medline 1966 to March 2007, Embase 1980 to March 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 1. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow up required to include studies. We excluded all studies described as "open", "open label", or not blinded, unless blinding was impossible. We also searched for cohort studies on specific harms of named interventions. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 13).

QUESTION What are the effects of interventions to prevent chickenpox in healthy adults and children?

OPTION LIVE ATTENUATED VARICELLA VACCINE IN HEALTHY CHILDREN

Incidence of chicken pox

Compared with placebo Live attenuated varicella vaccine reduces the incidence of chickenpox in healthy children after 9 months to 2 years (high-quality evidence).

For GRADE evaluation of interventions for chickenpox, see table, p 13 .

Benefits:

Live attenuated varicella vaccine in healthy children:
We found one systematic review (search date 2000, 2 RCTs), [11] and one subsequent RCT. [12] The first RCT identified by the review (914 healthy children aged 1–14 years, reported over 2 publications) found that live attenuated varicella vaccine significantly reduced clinical chickenpox at 9 months (0/468 [0%] with vaccine *v* 38/446 [9%] with placebo; ARR 8.5%, 95% CI 6.1% to 11.5%; protection level 100%) [13] and at 2 years (1/163 [< 1%] with vaccine *v* 21/161 [13%] with placebo; OR 0.05, 95% CI 0.01 to 0.35). [14] The second RCT identified by the review (327 healthy children aged 10–30 months) also found that live attenuated varicella vaccine significantly reduced clinical chickenpox after a mean of 29 months (AR: 5/166 [3%] with vaccine *v* 41/161 [25%] with placebo; RR 0.12, 95% CI 0.05 to 0.29). [15] The subsequent RCT (42 children aged 12 months to 13 years, immunised within 72 hours of the first skin lesion appearing in a sibling) found no significant difference in the incidence of clinical chickenpox between live attenuated varicella vaccine and placebo at 28 days (AR: 9/22 [41%] with vaccine *v* 9/20 [45%] with placebo; RR 1.10, 95% CI 0.55 to 2.21). It found that significantly more children receiving placebo developed moderate or severe disease (1/9 [11%] with vaccine *v* 8/9 [89%] with placebo; RR of moderate to severe disease 8.00, 95% CI 1.21 to 51.51). [12]

Harms:

The systematic review found that the only reported adverse effect with varicella vaccine was a non-significant increase in varicella-like papules or vesicles (AR: 5.4% with vaccine *v* 3.7% with placebo;

RR 1.45, 95% CI 0.53 to 4.0). [11] No children had fever or constitutional symptoms. The subsequent RCT found no adverse effects with varicella vaccine. [12] One postmarketing analysis of a database of 89,753 vaccinated adults and children found no associations with any rare serious adverse events. [16] Another analysis found that the rate of serious adverse events was 2.9/100,000 doses. [17]

Comment: **Clinical guide**:
Chickenpox vaccine is a safe and effective vaccine against a usually mild disease in healthy children. The decision to use the vaccine depends on a trade-off between the potential benefits, harms, and cost. This trade-off will vary with the context.

OPTION LIVE ATTENUATED VACCINE IN HEALTHY ADULTS

We found no clinically important results about the effects of live attenuated varicella vaccine in healthy adults.

For GRADE evaluation of interventions for chickenpox, **see table, p 13 .**

Benefits: **Live attenuated varicella vaccine in healthy adults:**
We found one systematic review. [11] It found no RCTs assessing clinical outcomes in healthy adults.

Harms: We found no RCTs.

Comment: **Clinical guide**:
Chickenpox vaccine is a safe and effective vaccine against a disease that is usually mild, at least in healthy children. The decision to use the vaccine depends on a trade-off between the potential benefits, harms, and cost. This trade-off will vary with the context.

QUESTION What are the effects of interventions to prevent chickenpox in children exposed prenatally?

OPTION ACICLOVIR IN CHILDREN EXPOSED PRENATALLY

We found no clinically important results about the effects of aciclovir in prenatally exposed children.

For GRADE evaluation of interventions for chickenpox, **see table, p 13 .**

Benefits: We found no systematic review or RCTs on the effects of aciclovir in prenatally exposed children.

Harms: We found no RCTs.

Comment: **Clinical guide:**
Newborns whose mothers' rashes appear in the last 5 days of pregnancy, or within 2 days of birth, have been reported in small case series to have a very high risk of severe chickenpox. On the basis of observational evidence and experience, most clinicians use varicella immunoglobulin in preference to aciclovir.

OPTION FAMCICLOVIR IN CHILDREN EXPOSED PRENATALLY New

We found no clinically important results about the effects of famciclovir for preventing chickenpox in prenatally exposed children.

For GRADE evaluation of interventions for chickenpox, **see table, p 13 .**

Benefits: We found no systematic review or RCTs assessing famciclovir for preventing chickenpox in prenatally exposed children.

Harms: We found no RCTs.

Comment: None.

OPTION VALACICLOVIR IN CHILDREN EXPOSED PRENATALLY New

We found no clinically important results about the effects of valaciclovir for preventing chickenpox in prenatally exposed children.

For GRADE evaluation of interventions for chickenpox, see table, p 13 .

Benefits: We found no systematic review or RCTs assessing valaciclovir for preventing chickenpox in prenatally exposed children.

Harms: We found no RCTs.

Comment: None.

OPTION VARICELLA ZOSTER IMMUNOGLOBULIN IN CHILDREN EXPOSED PRENATALLY New

We found no clinically important results about the effects of varicella zoster immunoglobulin in prenatally exposed children.

For GRADE evaluation of interventions for chickenpox, see table, p 13 .

Benefits: We found no systematic review or RCTs assessing varicella zoster immunoglobulin (VZIG) in prenatally exposed children.

Harms: We found no RCTs.

Comment: None.

OPTION ZOSTER IMMUNOGLOBULIN IN CHILDREN EXPOSED PRENATALLY

We found no clinically important results about the effects of zoster immunoglobulin in prenatally exposed children.

For GRADE evaluation of interventions for chickenpox, see table, p 13 .

Benefits: We found no systematic review or RCTs on the effects of zoster immunoglobulin (ZIG) in prenatally exposed children.

Harms: We found no RCTs.

Comment: **Clinical guide:**
Newborns whose mothers' rashes appear in the last 5 days of pregnancy, or within 2 days of birth, have been reported in small case series to have a very high risk of severe chickenpox. Studies into the effects of zoster immunoglobulin have not been, and are unlikely to be, undertaken. Based on observational evidence and experience, most clinicians regard it as effective.

QUESTION What are the effects of interventions to prevent chickenpox in immunocompromised adults and children?

OPTION LIVE ATTENUATED VARICELLA VACCINE IN IMMUNOCOMPROMISED PEOPLE

We found no clinically important results about the effects of live attenuated varicella vaccine in immunocompromised adults or children.

For GRADE evaluation of interventions for chickenpox, see table, p 13 .

Benefits: We found no systematic review or RCTs assessing clinical outcomes in people receiving cancer chemotherapy, or in people with HIV.

Harms: We found no RCTs.

Comment: The single antigen vaccine is licensed for use in the USA for HIV-infected children with CD4 counts greater than 15%, and in Europe for HIV-infected children with CD4 greater than 25%, and for immunocompromised people with more than 1200 lymphocytes per uL blood.

OPTION ACICLOVIR, HIGH DOSE (> 3200 MG/DAY) PREVENTION IN PEOPLE WITH HIV INFECTION

Mortality
Compared with placebo Aciclovir at doses of at least 3200 mg/day may reduce all-cause mortality over 22 months' treatment compared with placebo in people with HIV infection (moderate-quality evidence).

Incidence of chickenpox
Compared with placebo Aciclovir at doses of at least 3200 mg/day reduces the incidence of chickenpox compared with placebo in people with HIV infection (high-quality evidence).

Benefits: We found one systematic review (search date not reported, 8 RCTs, 1792 people with different stages of HIV, median CD4 count 34–607/mm^3) comparing high dose aciclovir versus placebo. [18] Three of the RCTs were unpublished, including two pharmaceutical company trials. The review found that aciclovir (at least 3200 mg/day for up to 22 months) significantly reduced clinical chickenpox (AR: 14/895 [2%] with aciclovir *v* 54/897 [6%] with placebo; OR 0.29, 95% CI 0.13 to 0.63; NNT 23, 95% CI 17 to 39). All cause mortality was also reduced (HR 0.78, 95% CI 0.65 to 0.93; OR 0.75, 95% CI 0.57 to 1.00). The treatment effect did not vary significantly with CD4 count. We found no RCTs of lower doses of aciclovir in people with HIV.

Harms: The systematic review gave no information on adverse effects (see harms under aciclovir for treatment, p 8).

Comment: None.

OPTION ACICLOVIR PREVENTION IN PEOPLE WITH IMMUNOCOMPROMISE OTHER THAN HIV

We found no clinically important results about the effects of aciclovir in people with immunocompromise other than HIV.

For GRADE evaluation of interventions for chickenpox, see table, p 13 .

Benefits: We found no systematic review or RCTs assessing aciclovir in adults or children with immunocompromise other than HIV.

Harms: We found no RCTs.

Comment: None.

OPTION FAMCICLOVIR (PREVENTION IN IMMUNOCOMPROMISED PEOPLE) New

We found no clinically important results about the effects of famciclovir for chickenpox in immunocompromised people.

For GRADE evaluation of interventions for chickenpox, see table, p 13 .

Benefits: We found no systematic review or RCTs assessing famciclovir for chickenpox in immunocompromised people.

Harms: We found no RCTs.

Comment: None.

OPTION VALACICLOVIR (PREVENTION IN IMMUNOCOMPROMISED PEOPLE) New

We found no clinically important results about the effects of valaciclovir to prevent chickenpox in immunocompromised people.

For GRADE evaluation of interventions for chickenpox, see table, p 13 .

Benefits: We found no systematic review or RCTs assessing valaciclovir to prevent chickenpox in immunocompromised people.

Harms: We found no RCTs.

Comment: None.

OPTION VARICELLA ZOSTER IMMUNOGLOBULIN (PREVENTION IN IMMUNOCOMPROMISED PEOPLE) New

Incidence of chickenpox
Compared with zoster immunoglobulin (ZIG) Varicella zoster immunoglobulin is as effective as zoster immunoglobulin at preventing chickenpox in immunocompromised children (moderate-quality evidence).

Note
We found no direct information about whether varicella zoster immunoglobulin is better than no active treatment in immunocompromised children. We found no clinically important results about the effects of varicella zoster immunoglobulin compared with immune serum globulin in immunocompromised children or adults, or compared with zoster immunoglobulin in immunocompromised adults.

For GRADE evaluation of interventions for chickenpox, **see table, p 13 .**

Benefits:

Varicella zoster immunoglobulin versus placebo:
We found no systematic review or RCTs.

Varicella zoster immunoglobulin versus immune serum globulin in immunocompromised adults:
We found no systematic review or RCTs.

Varicella zoster immunoglobulin versus immune serum globulin in immunocompromised children:
We found no systematic review or RCTs.

Varicella zoster immunoglobulin versus zoster immunoglobulin in immunocompromised adults:
We found no systematic review or RCTs.

Varicella zoster immunoglobulin versus zoster immunoglobulin in immunocompromised children:
We found no systematic review. We found one RCT (164 immunocompromised children, mostly with leukaemia, exposed to a sibling with chickenpox) comparing varicella zoster immunoglobulin (VZIG) 1.25 mL/10 kg versus zoster immunoglobulin (ZIG) 1.25 mL/10 kg. [19] It found no significant difference between VZIG and ZIG in the proportion of children with clinical chickenpox at 12 weeks (AR: 31/88 [37%] with ZIG *v* 36/81 [44%] with VZIG; RR 0.84, 95% CI 0.58 to 1.22).

Harms: The RCT gave no information on adverse effects. [19]

Comment:

Clinical guide:
Zoster immunoglobulin and varicella zoster immunoglobulin are frequently used to prevent chickenpox in exposed susceptible immunocompromised children, and sometimes in exposed pregnant women, preterm babies, adolescents, and adults.

OPTION ZOSTER IMMUNOGLOBULIN (PREVENTION IN IMMUNOCOMPROMISED PEOPLE)

Incidence of chickenpox
Compared with varicella zoster immunoglobulin (VZIG) Zoster immunoglobulin is as effective as VZIG at preventing chickenpox in immunocompromised children (moderate-quality evidence).

Compared with immune serum globulin Zoster immunoglobulin may reduce the risk of developing chickenpox in healthy children after 20 days compared with immune serum globulin (moderate-quality evidence), but we found no clinically important information about their comparative effects in immunocompromised children.

Note
We found no direct information about whether or not zoster immunoglobulin is better than no active treatment in immunocompromised children. We found no clinically important results about the effects of zoster immunoglobulin compared with immune serum globulin or compared with varicella zoster immunoglobulin in immunocompromised adults.

For GRADE evaluation of interventions for chickenpox, **see table, p 13 .**

Benefits:

Zoster immunoglobulin versus placebo:
We found no systematic review or RCTs.

Zoster immunoglobulin versus immune serum globulin in immunocompromised adults:
We found no systematic review or RCTs.

Zoster immunoglobulin versus immune serum globulin in immunocompromised children:
We found no systematic review or RCTs.

Zoster immunoglobulin versus varicella zoster immunoglobulin in immunocompromised adults:
We found no systematic review or RCTs.

Zoster immunoglobulin versus varicella zoster immunoglobulin in immunocompromised children:
We found no systematic review. We found one RCT, see benefits of varicella zoster immunoglobulin, p 6 .

Harms: The RCT gave no information on adverse effects. [19]

Comment:

Zoster immunoglobulin versus immune serum globulin in healthy children:
We found one small RCT (12 healthy susceptible children exposed to a sibling with recent onset of chickenpox) comparing ZIG (2 mL/10 kg) versus immune serum globulin (ISG) (2 mL/10 kg). [20] It found that ZIG reduced the proportion of children with clinical chickenpox at 20 days (AR: 0/6 [0%] with ISG *v* 6/6 [100%] with ZIG). The RCT did not assess adverse effects. [20] In the absence of evidence in immunocompromised people, data on effects in healthy people may be of some use, but the applicability of the findings to immunocompromised people is questionable.

Clinical guide:
Zoster immunoglobulin and varicella zoster immunoglobulin are frequently used to prevent chickenpox in exposed susceptible immunocompromised children, and sometimes in exposed pregnant women, preterm babies, adolescents, and adults.

QUESTION What are the effects of treatments for chickenpox in healthy adults and children?

OPTION ACICLOVIR GIVEN WITHIN 24 HOURS AFTER ONSET OF RASH IN HEALTHY PEOPLE

Duration of fever
Compared with placebo Aciclovir given within 24 hours of onset of rash reduces the duration of fever compared with placebo in healthy children (high-quality evidence).

Duration of rash
Compared with placebo Aciclovir given within 24 hours of onset of rash does not reduce the duration of rash compared with placebo in healthy children (high-quality evidence). Aciclovir reduces the duration of rash in healthy adults if given within the first 24 hours of onset of rash compared with placebo (moderate-quality evidence).

For GRADE evaluation of interventions for chickenpox, see table, p 13 .

Benefits:

Aciclovir in healthy children:
We found one systematic review in children and adolescents (search date 2005, 3 RCTs, 979 children). [21] The systematic review compared aciclovir versus placebo given within 24 hours of onset of rash in otherwise healthy children aged 0–18 years. [21] It found no significant difference in time to no new lesions between aciclovir and placebo (WMD –0.8 days, 95% CI –1.6 days to +0.02 days). It found that aciclovir significantly reduced duration of fever compared with placebo (weighted mean reduction in duration of fever: 1.1 days, 95% CI 1.3 days to 0.9 days). [21]

Aciclovir in healthy adults:
We found one systematic review (search date 1997, 3 RCTs). [22] It did not perform a meta-analysis. The first RCT identified by the review (148 adults) compared early and late administration of aciclovir (800 mg 5 times/day) versus placebo. It found that aciclovir given within 24 hours of the onset of rash significantly reduced the maximum number of lesions ($P < 0.01$) and the time to full crusting of lesions ($P = 0.001$) compared with placebo. The two remaining RCTs (total of 168 healthy adults) only compared aciclovir given more than 24 hours after the onset of rash versus placebo.

Harms: The systematic review in children found no significant differences between treatment and control groups, or unfavourable trends in children taking aciclovir. [21]

Comment: In healthy people who make an uneventful recovery without treatment, the effect on the measured outcomes was small and of questionable clinical importance.

Clinical guide:
Evidence is sparse, but symptomatic treatments are commonly used in practice, and may be beneficial. Paracetamol is used to reduce fever, topical calamine or crotamiton to soothe the skin and possibly relieve itching, and a sedating anithistamine at night to help sleep, and possibly break the itch-scratch-itch cycle. Should viral complications of chickenpox (e.g. pneumnia or encephalitis) develop in healthy people, aciclovir is indicated.

OPTION ACICLOVIR TREATMENT IN HEALTHY PEOPLE GIVEN MORE THAN 24 HOURS AFTER ONSET OF RASH

Duration of rash
Compared with placebo Aciclovir may reduce the duration of rash in healthy children if started on the second day compared with the third day (low-quality evidence). Aciclovir does not reduce the duration of rash in healthy adults compared with placebo if started more than 24 hours after the onset of rash (moderate-quality evidence).

For GRADE evaluation of interventions for chickenpox, see table, p 13 .

Benefits:

Aciclovir in healthy children or adults:
We found one RCT that included children, adolescents, and adults (77 people). [23] The RCT found that aciclovir started on the second day of the rash significantly reduced the time to no new lesions in children compared with starting on the third day (median: 4 days when started on second day *v* 5 days when started on third day; P < 0.04). [23] It found no significant difference in time to new lesions between adolescents and adults. Earlier treatment significantly reduced the time to lowering of fever in adolescents (median: 2–3 days when started on second day *v* 3–4 days when started on third day; P < 0.02), but not in children and adults.

Aciclovir in healthy adults alone:
We found one systematic review (search date 1997, 3 RCTs). [22] It did not perform a meta-analysis. The first RCT identified by the review (148 adults) compared early and late administration of aciclovir (800 mg 5 times/day) versus placebo. It found no significant difference in time to full crusting of lesions if aciclovir was given 24–72 hours after the rash (P > 0.2). The two remaining RCTs (total of 168 healthy adults) compared aciclovir given more than 24 hours after the onset of rash versus placebo. Neither found a significant difference in the time to no new lesions (P = 0.55 in 1 RCT, P values reported separately for different severities of eruption in the other RCT, all P > 0.05). They did not provide numerical information on the time to lowering of fever.

Harms:
The systematic review in children found no significant differences between treatment and control groups, or unfavourable trends in children taking aciclovir. [21]

Comment:

Clinical guide:
Evidence is sparse, but symptomatic treatments are commonly used in practice, and may be beneficial. Paracetamol is used to reduce fever, topical calamine or crotamiton to soothe the skin and possibly relieve itching, and a sedating anithistamine at night to help sleep, and possibly break the itch-scratch-itch cycle. Should viral complications of chickenpox (e.g. pneumnia or encephalitis) develop in healthy people, aciclovir is indicated.

OPTION FAMCICLOVIR (TREATMENT IN HEALTHY PEOPLE) New

We found no clinically important results about the effects of famciclovir for treating chickenpox in healthy people.

For GRADE evaluation of interventions for chickenpox, see table, p 13 .

Benefits: We found no systematic review or RCTs assessing famciclovir for treating chickenpox in healthy people.

Harms: We found no RCTs.

Comment: None.

OPTION VALACICLOVIR (TREATMENT IN HEALTHY PEOPLE) New

We found no clinically important results about the effects of valaciclovir for treating chickenpox in healthy people.

For GRADE evaluation of interventions for chickenpox, see table, p 13 .

Benefits: We found no systematic review or RCTs assessing valaciclovir for treating chickenpox in healthy people.

Harms: We found no RCTs.

Comment: None.

QUESTION **What are the effects of treatments for chickenpox in immunocompromised adults and children?**

OPTION ACICLOVIR TREATMENT IN IMMUNOCOMPROMISED ADULTS

We found no clinically important results about the effects of aciclovir to treat chickenpox in immunocompromised adults.

For GRADE evaluation of interventions for chickenpox, **see table, p 13** **.**

Benefits: We found no systematic review or RCTs on the effects of aciclovir in immunocompromised adults.

Harms: We found no RCTs.

Comment: Despite scarce evidence, aciclovir is indicated in immunocompromised people, because of the poor prognosis without treatment, and the relatively minor harmful effects of the drug.

OPTION ACICLOVIR (INTRAVENOUS) FOR TREATMENT OF CHICKENPOX IN CHILDREN WITH MALIGNANCY

Severity of illness
Compared with placebo Intravenous aciclovir may reduce the severity of illness compared with placebo in immunocompromised children (low-quality evidence) effective.

For GRADE evaluation of interventions for chickenpox, **see table, p 13** **.**

Benefits: We found two placebo controlled RCTs of intravenous aciclovir in children with cancer receiving chemotherapy. [24] [25] The largest RCT (50 children aged 1–14 years with chickenpox, 60% of whom had a rash for > 24 hours) found that significantly fewer children receiving aciclovir (500 mg/m^2 of body surface area) deteriorated clinically and were transferred to open label aciclovir compared with placebo (1/25 [4%] with aciclovir *v* 12/25 [48%] with placebo; RR 0.08, 95% CI 0.01 to 0.59; NNT 3, 95% CI 2 to 4). [24] Analysis of the remaining children not moved to open label aciclovir found that aciclovir significantly reduced the time to full crusting of lesions (mean: 5.7 days with aciclovir *v* 7.1 days with placebo; P < 0.013). It found no significant difference in lowering of fever. However, the exclusion from the subsequent analysis of children taking placebo who deteriorated clinically means that the effect of placebo may have been overestimated. [24] The second RCT (20 children, mean age 6.4 years) comparing aciclovir (500 mg/m^2 of body surface area) versus placebo found no significant difference in the proportion of children who deteriorated clinically and were moved to open label aciclovir (AR: 1/8 [12%] with aciclovir *v* 5/12 [42%] with placebo; RR 0.30, 95% CI 0.04 to 2.10). [25] However, the RCT was too small to exclude a clinically important difference.

Harms: In the first RCT, 2/25 (8%) children on aciclovir developed transient elevated blood urea nitrogen levels, compared with two children with other transient minor adverse effects on placebo. [24] In the second RCT, no adverse events were observed in the eight children receiving aciclovir, except one child with a self limiting maculopapular rash lasting 1 day. [25]

Comment: Despite scarce evidence, aciclovir is indicated in immunocompromised people, because of the poor prognosis without treatment, and the relatively minor harmful effects of the drug.

OPTION FAMCICLOVIR (TREATMENT IN IMMUNOCOMPROMISED PEOPLE) New

We found no clinically important results about the effects of famciclovir for treating chickenpox in immunocompromised people.

For GRADE evaluation of interventions for chickenpox, **see table, p 13** **.**

Benefits: We found no systematic review or RCTs assessing famciclovir for treating chickenpox in immunocompromised people.

Harms: We found no RCTs.

Comment: None.

OPTION VALACICLOVIR (TREATMENT IN IMMUNOCOMPROMISED PEOPLE) New

We found no clinically important results about the effects of valaciclovir for treating chickenpox in immunocompromised people.

For GRADE evaluation of interventions for chickenpox, **see table, p 13 .**

Benefits: We found no systematic review or RCTs assessing valaciclovir for treating chickenpox in immunocompromised people.

Harms: We found no RCTs.

Comment: None.

GLOSSARY

Immune serum globulin (ISG) Immunoglobulin prepared from pooled human plasma.
Varicella zoster immune globulin (VZIG) Prepared from units of donor plasma selected for high titres of antibodies to varicella zoster virus.
Zoster immune globulin (ZIG) Prepared from the plasma of donors convalescing from herpes zoster (sustainable supplies are difficult to obtain).
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect
Low-quality evidence 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
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

SUBSTANTIVE CHANGES

Famciclovir for preventing chickenpox in prenatally exposed children New option. No systematic review or RCTs found. Categorisation: Unknown effectiveness
Valaciclovir for preventing chickenpox in prenatally exposed children New option. No systematic review or RCTs found. Categorisation: Unknown effectiveness
Varicella zoster for preventing chickenpox in prenatally exposed children New option. No systematic review or RCTs found. Categorisation: Unknown effectiveness
Famciclovir to prevent chickenpox in immunocompromised people New option. No systematic review or RCTs found. Categorisation: Unknown effectiveness
Valaciclovir to prevent chickenpox in immunocompromised people New option. No systematic review or RCTs found. Categorisation: Unknown effectiveness
Varicella zoster immunoglobulin to prevent chickenpox in immunocompromised people New option. One RCT [19] found no significant difference in clinical chickenpox with zoster immunoglobulin compared with varicella zoster immunoglobulin. Categorisation: Unknown effectiveness
Famciclovir for treating chickenpox in healthy people New option. No systematic review or RCTs found. Categorisation: Unknown effectiveness.
Valaciclovir for treating chickenpox in healthy people New option. No systematic review or RCTs found. Categorisation: Unknown effectiveness.
Famciclovir for treating chickenpox in immunocompromised people New option. No systematic review or RCTs found. Categorisation: Unknown effectiveness.
Valaciclovir for treating chickenpox in immunocompromised people New option. No systematic review or RCTs found. Categorisation: Unknown effectiveness.

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Disclaimer

TABLE **GRADE evaluation of interventions for chickenpox**

Important outcomes	Incidence of chickenpox, duration of illness, complications, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions to prevent chickenpox in healthy adults and children?									
3 (1283) [13] [26] [27]	Incidence of chicken pox	Live attenuated varicella vaccine *v* placebo (healthy children)	4	0	–1	0	+2	High	Consistency point deducted for conflicting results. Effect size points added for OR less than 0.2
What are the effects of interventions to prevent chickenpox in children exposed prenatally?									
No studies found									
What are the effects of interventions to prevent chickenpox in immunocompromised adults and children?									
8 (1792) [18]	Mortality	Aciclovir *v* placebo (in HIV infection)	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
8 (1792) [18]	Incidence of chickenpox	Aciclovir *v* placebo (in HIV infection)	4	–1	0	0	+1	High	Quality point deducted for incomplete reporting of results. Effect size point added for OR less than 0.5
1 (164) [19]	Incidence of chickenpox	Varicella zoster immunoglobulin *v* zoster immunoglobulin	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (12) [20]	Incidence of chickenpox	Zoster immunoglobulin *v* immune serum globulin (healthy children)	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (979) [21]	Duration of fever	Aciclovir *v* placebo (healthy children with chickenpox)	4	0	0	0	0	High	
3 (979) [21]	Duration of rash	Aciclovir *v* placebo (healthy children with chickenpox)	4	0	0	0	0	High	
1 (148) [22]	Duration of rash	Aciclovir *v* placebo (healthy adults, first 24 hours of onset of rash)	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
4 (393) [22] [23]	Duration of rash	Aciclovir *v* placebo (healthy adults, started 24–72 hours after rash)	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
1 (77) [23]	Duration of rash	Aciclovir od second day *v* aciclovir started on third day	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results in children and adolescents
2 (70) [24] [25]	Severity of illness	Intravenous aciclovir *v* placebo (immunocompromised children with chickenpox)	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.