CURRENT TOPIC

Varicella vaccination—a critical review of the evidence

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Varicella (chickenpox) is an universal, highly infectious disease characterised by a pruritic vesicular eruption associated with fever and malaise caused by varicella zoster virus (VZV). In children, the illness is usually self limiting, lasting four to five days, but at least 1% of children under 15 years experience a complication.² These include secondary bacterial infection (particularly with group A beta haemolytic streptococcus),³ pneumonia, encephalitis, haemorrhagic complications, hepatitis, arthritis, and Reye syndrome.⁴ Furthermore, 10–50% of all children will visit a physician with an infection.⁵ The mortality rate of varicella in children under 14 years in the United States is estimated at 2 per 100 000 cases,⁶ and 90% of these have no risk factors for severe disease.⁷

Adults experience only 5% of all varicella cases, but experience more severe disease (hospitalisations 18 per 1000) and deaths (50 per 100 000).⁸ Herpes zoster (shingles), a painful, dermatomal, vesicular rash occurs with reactivation of the virus in approximately 15% of the population.¹² The likelihood of developing herpes zoster increases with advancing age: the incidence is approximately 74 per 100 000 children aged under 10 years,⁹ 300 per 100 000 adults aged 35–44 years,¹⁰ and 1200 per 100 000 adults over 75 years.¹¹

In temperate climates, 95% of varicella cases occur among persons less than 20 years of age.¹¹ ¹⁴ Seropositivity is lower in adults from tropical and subtropical areas.¹¹ ¹⁵ Seronegativity in adults may be increasing in temperate populations, as shown by a significant upward trend in age distribution of chickenpox cases in England and Wales,¹¹ and increasing varicella susceptibility in young US adults.¹⁶

A live attenuated varicella vaccine was first developed in 1974 in Japan by Takahashi and colleagues.¹⁹ As this Oka strain virus is heat sensitive, Biken/Oka vaccine (Japan) and Varivax (Oka/Merck) require storage at −15°C and administration within 30 minutes of reconstitution to retain potency (product monograph). Oka strain vaccines were first licensed for use in high risk children in Europe in 1984 and Japan in 1986. Licensure for use in healthy children commenced in 1986 in Japan, 1988 in Korea, and most recently in the USA, Sweden, and Germany (1995).²⁰ ²¹ and Canada (December 1998).²² Many millions of doses have been given in total.

Aims of review

The purpose of this review was to evaluate the evidence that bears on the various options for use of vaccine to prevent varicella in healthy individuals. These include universal vaccination of healthy infants, catch up vaccination of older children, and vaccination of susceptible adolescents and adults. Models of cost effectiveness and epidemiological change suggest that implementation of routine varicella vaccination for infants and children could reduce total number of cases and case severity, and generate cost savings.³³ Potential harm that may occur as a result of vaccination includes immediate adverse reactions, transmission of varicella from vaccinees, an increased risk of zoster, and a shift in varicella cases to an older age group (and hence more severe disease).³³ In evaluating varicella vaccine it is important that these issues are considered in addition to vaccine effectiveness.

Methodology of search

MEDLINE was searched from 1966 to December 2000 using the MeSH subheadings chickenpox, vaccination, and human (search date 19 January 2001). There was no language restriction. Methodological search terms included: random allocation, placebo, double-blind method, comparative study, epidemiologic methods, research design, clinical trials, controlled clinical trials, meta-analysis, drug evaluation, prospective studies, and evaluation studies. EMBASE was searched using a similar strategy. To identify other studies, we searched reference lists of located studies; the Internet for position papers and summaries from health organisations such as the World Health Organisation and the Centers for Disease Control and Prevention; vaccine product information; and the Cochrane Library.

Published studies were included if they: (1) considered healthy, human subjects vaccinated with VZV vaccine; and (2) were controlled trials addressing the incidence of varicella, zoster, or adverse outcomes. Prospective cohort studies were considered only for longer term outcomes of varicella and zoster following vaccination. To limit the analysis to studies with the highest methodological quality, prospective cohort studies were excluded if: (a) they contained less than 50 subjects; (b) loss to follow up was not described; or (c) duration of follow up was less than one year. All eligible
Table 1 Randomised control trials of VZV vaccination effectiveness

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Study population(s)</th>
<th>Varicella cases</th>
<th>Effect size</th>
<th>Cases with known exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weibel et al&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Vaccine x1 dose</td>
<td>956 (1–14 y) (v) 0/468</td>
<td>PE = 100% NNT = 11.8</td>
<td>(v) 0/33 (p) 4/9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow up 9 mth</td>
<td>(p) 39/446</td>
<td>PE = 100% NNT = 2.3</td>
<td>At 20 months</td>
<td></td>
</tr>
<tr>
<td>Kuter et al&lt;sup&gt;41&lt;/sup&gt;</td>
<td>7 year follow up of Weibel et al cohort</td>
<td>956 (1–14 y) (v) 23/468</td>
<td>PE = 95% at 7 years</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(v) 163 (p) 161</td>
<td>Mean lesions 56</td>
<td>(v) 1/19 (p) 5/8</td>
<td></td>
</tr>
<tr>
<td>Kuter et al&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Vaccine x2 dose</td>
<td>757 (13–54 y) 1. 384 2. 373</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow up 1 yr</td>
<td>Varicella self reported</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Varis and Vesikari&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Vaccine x1 dose</td>
<td>493 (10–30 mth) (v) 24/7%</td>
<td>PE = 72%, NNT = 5.5</td>
<td>High dose PE = 88%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose titration study</td>
<td>(v) 332 (p) 161 (g) 41 25%</td>
<td>1–2 vs 30 lesions</td>
<td>p &gt; 0.05 Close contact &gt;4 h</td>
<td></td>
</tr>
<tr>
<td>Tan et al&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Vaccine x1 dose</td>
<td>191 (9–24 mth)</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose titration study</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Watson et al&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Vaccine x1 dose</td>
<td>111 (12–19 mth) (v) vs MMRV</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow up 1 year</td>
<td>—</td>
<td>—</td>
<td>Close contact &gt;4 h</td>
<td></td>
</tr>
<tr>
<td>Rothstein et al&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Level II-2 evidence</td>
<td>Vaccine x1 dose</td>
<td>150 (1–6 y) 15/150 10%</td>
<td>p &gt; 0.05 —</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose titration study</td>
<td>Varicella self reported</td>
<td>Median lesions 25</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>White et al&lt;sup&gt;46&lt;/sup&gt; (1st study)</td>
<td>Vaccine x1 dose MMRV + (v)</td>
<td>494 (1–2.5 y) Varicella self reported</td>
<td>Unrelated to dose 2% vs 0.8% Mean lesions 30 vs 29</td>
<td>p &gt; 0.05 —</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow up 1 year</td>
<td>Varicella self reported</td>
<td>1/318</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>White et al&lt;sup&gt;46&lt;/sup&gt; (2nd study)</td>
<td>Vaccine x1 dose</td>
<td>318 (1–3.5 y)</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MMRV vs MMR + (v) Follow up 1 year</td>
<td>Varicella self reported</td>
<td>20 lesions</td>
<td>p &gt; 0.05 —</td>
<td></td>
</tr>
<tr>
<td>Lim et al&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Vaccine x1 dose</td>
<td>181 (9–24 mth) 18/168</td>
<td>—</td>
<td>Close contact &gt;4 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose titration study</td>
<td>7% loss to follow up</td>
<td>&lt;50 lesions in 15 —</td>
<td>Total = 18/82</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low titre vs high titre Follow up mean 35 mth</td>
<td>Related to dose</td>
<td>&gt;50 in 3 low titre</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

(v), varicella vaccine group; (p), placebo group; (c), control group; MMR, measles, mumps, rubella vaccine; PE, protective efficacy; NNT, number needed to treat; HH, household.

Studies were systematically reviewed using the methodology of the Canadian Task Force on Preventive Health Care. The quality of evidence in each study was rated from I (well designed randomised controlled trials [RCTs]) to III (descriptive studies or consensus reports) using the Task Force's established methodological hierarchy (see Appendix).

Identified studies meeting inclusion criteria

A total of 26 controlled trials and 50 cohort studies were identified using the described search strategy. After application of exclusion criteria, 24 controlled trials and 18 cohort studies remained for review. For each of the criteria evaluated, we describe the best available level of evidence along with key supporting studies. Summaries of RCTs are presented in the tables.

Vaccine effectiveness

Two randomised, placebo controlled trials in children (aged 10 months to 14 years) provide level I evidence that a single dose of VZV vaccine is effective in preventing varicella for up to seven years (table 1). Although data beyond three years are subject to a large loss to follow up of study subjects. Supportive evidence is provided by three RCTs randomising to different vaccine doses and 12 prospective cohort studies with follow up of 1–19.6 years. Three of these trials (each with over 2000 subjects) also studied adolescents (aged 13–17 years, followed for 1–8 years). Some methodological issues were noted in these studies: an increasing loss of subjects occurred with longer follow up (up to 62%), and self reported illness was used to determine effectiveness. In adults, effectiveness is shown by one non-randomised controlled trial and two prospective cohort studies with maximum duration of follow up of six years. Further level II-2 evidence is provided by one RCT providing combined data from both arms of a two dose adult trial. All but one adult study calculated effectiveness based on self reporting of disease. Adult and child vaccinees experiencing close contact with varicella are also protected.

Although controlled trials confirm approximately 100% relative risk reduction for severe disease, no deaths have been reported for subjects in either vaccine or placebo groups. No trial to date has had sufficient power to examine this outcome. A post-licensure report (level III evidence) found 14 deaths temporally related to 9.7 million doses of varicella vaccine; of the five presented case reports, none had proven vaccine strain VZV. There is therefore no direct evidence to support or refute a risk reduction in varicella mortality consequent to use of varicella vaccine, although available evidence suggests a reduction is likely. Data for differences in hospitalisation rates are similarly lacking.

The protective efficacy of varicella vaccine has been determined in two placebo controlled RCTs in children. Weibel et al estimated a protective efficacy of 100% over nine months and 98% over seven years, while Varis et al found a protective efficacy of 72% over a mean of 29 months. A cohort study of vaccinated and unvaccinated children under 5 years found a vaccine effectiveness of 83%. For the RCTs,
Varicella vaccination

attack rates were 0–3% per year compared with 7–11% per year in placebo recipients, giving the number needed to treat (the number needed to vaccinate to prevent one case of varicella) as 5.5–11.8. Assuming complications occur in 1% of varicella cases, the number needed to vaccinate to prevent one complicated case of varicella is therefore 550–1180. Supportive evidence of a low annual attack rate in vaccinees is provided by other RCTs to four years (0.3–3.6%),29 30 40 and prospective cohort studies to 19.6 years (0.3–2.8%),31 32 34–41 44 45 including adolescents and adults to eight and six years respectively.38 37 44 45 Breakthrough disease may be more common in individuals who are seronegative prior to vaccination.74 51 Exposure to varicella and age less than 14 months at time of vaccination have also been shown to be risk factors for breakthrough disease.50

Tetravalent vaccines for prevention of measles, mumps, rubella, and varicella appear to have similar effectiveness against varicella to varicella vaccine given separately from measles/mumps/rubella vaccine (MMR) at 12–15 months (level of evidence: I,49 II-1,52-54 and II-247).

A wide range of vaccine doses have been utilised in studies examining vaccine effectiveness (table 1). One RCT showed no difference in vaccine effectiveness between doses varying from 439 to 3625 PFU,29 while another showed decreased effectiveness below 1260 PFU.33 The study showing no difference had a longer duration of follow up (mean 4.3 years compared to 29 and 35 months), but relied on self reporting of disease.29 Lim et al more recently showed that doses less of 501–631 PFU resulted in less of 501–631 PFU resulted in breakthrough disease more commonly than doses of 7943–10 000 PFU.50

Protection against chickenpox is provided by a single injection in children, without further increase in protection with more doses (table 1). A direct comparison of vaccine effectiveness for one versus two injection regimens has not been performed in adolescents or adults. Available data in adolescents come from three prospective cohort studies using a single injection,26 28 29 and one RCT using two injections in all participants (at different intervals and doses).46 All three studies found evidence of protection (all level II-2 evidence). Similarly in adults, one small controlled trial indicates that a single injection offers protection (level II-1 evidence),43 while three prospective studies providing level II-1 and II-2 evidence suggest two injections given four or eight weeks apart are effective.44–46

The level of VZV antibody six weeks after vaccination appears to be correlated with effectiveness in preventing subsequent varicella to 10 years in children and adolescents (level II-2 evidence).32 34 High seroconversion rates of 94–100% have been shown six to eight weeks after a single VZV vaccination in children29 34 and two doses in adolescents and adults (level I evidence).36 51 A trial by Ndumbe et al suggests a single vaccination may result in less frequent seroconversion in adults (level II-2 evidence).43 This is supported by two prospective cohort studies which found 79–82% seroconversion after one dose in subjects older than 12 years compared with 94–100% after two doses.37 44 Duration of seroconversion has been shown to approach 100% for up to six years in children following a single dose of vaccine27 29 and for two years in adolescents and adults following two doses (level I evidence).46

ADVERSE REACTIONS TO VACCINATION

RCTs in children show no increase in rates of fever or varicella-like rash with varicella vaccination over placebo (table 2).26 28 46 One RCT found an increase in local reactions (mild and well tolerated) in vaccine recipients,26 while another smaller trial found no difference.26 Rates of fever varied from 0% to 36% depending on the definition of fever and the duration of follow up. Injection site reactions occurred in 7–30%, and less than 5% of vaccine and placebo recipients experienced a mild varicella-like rash. RCTs in adults give similar results.50 55 57 A higher dose in PFU appears not to result in a greater frequency of adverse reactions.74 29 58 Controlled trials comparing VZV vaccine alone with tetravalent MMR-VZV also show no increase in adverse reactions.49 52 56 Finally, a second dose of vaccine appears to cause fewer reactions than the first.31 36 57 No serious adverse reactions have been reported in controlled trials. Post licensure level III evidence is conflicting, with one review of 89 000 vaccinees belonging to a health maintenance organisation finding no serious reactions,51 while Wise et al found a temporally related serious adverse event rate of 2.9/100 000 doses.46

TRANSMISSION OF VARICELLA FROM VACCINATED INDIVIDUALS TO OTHERS

No clinical trials have shown transmission of vaccine related VZV between immunocompetent individuals. One placebo controlled RCT found seroconversion, but no disease in 3/439 placebo vaccinated siblings of 465 VZV vaccine recipients.26 Natural infection or subclinical spread of vaccine virus may have occurred. In a small controlled trial, Asano et al found no evidence of transmission or boosting in unvaccinated seronegative and seropositive close contacts.65 Finally, a prospective study of 37 vaccinated siblings of 30 cancer patients also found no evidence of varicella transmission.41 However, case reports of transmission have been reported rarely from adults and children with varicella like rash following vaccination.62 64 Brunell and Argaw recently reported transmission of vaccine strain virus from a vaccinated child with zoster to their vaccinated sibling, resulting in mild chickenpox.8 A post-licensure report using passive surveillance methods has also found very few cases of possible vaccine strain transmission ("mostly unconfirmed by PCR") (level III evidence).46 While not a complication of vaccination, transmission of wild type virus (non-vaccine related) breakthrough disease has been reported between vaccinated siblings (rate...
### Table 2  Randomised control trials of adverse reactions following VZV vaccination (<8 weeks)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population(s)</th>
<th>Fever</th>
<th>Local reaction</th>
<th>Varicella like rash</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weibel et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>956 (1-14 y)</td>
<td>&gt;38.9°C oral (v) = (p) = 2% per wk</td>
<td>(v) 27% at 48 h (p) 19% at 48 h</td>
<td>(v) 4% at 8 wk (p) 2% at 8 wk</td>
</tr>
<tr>
<td>Englund et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>111 (15-18 mth)</td>
<td>&gt;37.8°C oral (v) 35% (p) 36%</td>
<td>7% at 48 h (p) 4% at 48 h</td>
<td>(v) = (p) = 2% at 8 wk</td>
</tr>
<tr>
<td>Levin et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>202 (55-87 y)</td>
<td>&lt;1%</td>
<td>1st injection 6%</td>
<td>6/202 3%</td>
</tr>
<tr>
<td>Kuter et al&lt;sup&gt;32&lt;/sup&gt;</td>
<td>757 (13-54 y)</td>
<td>&gt;37.8°C oral</td>
<td>1st injection 19%</td>
<td>Post 1st: 8%</td>
</tr>
<tr>
<td>Ramiksissoon et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>200 (9-24 mth)</td>
<td>—</td>
<td>2nd 7%</td>
<td>Total 2/200 1%</td>
</tr>
<tr>
<td>Tan et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>191 (9-24 mth)</td>
<td>—</td>
<td>Total 23%</td>
<td>Total 6/191 3%</td>
</tr>
<tr>
<td>Watson et al&lt;sup&gt;35&lt;/sup&gt;</td>
<td>111 (12-19 mth)</td>
<td>&gt;38.9°C oral</td>
<td>Total 6%</td>
<td>Total 5/111 4.5%</td>
</tr>
<tr>
<td>Varis and Vesikari&lt;sup&gt;36&lt;/sup&gt;</td>
<td>493 (10-30 mth)</td>
<td>—</td>
<td>Not defined</td>
<td>3.5% vs 5.6%</td>
</tr>
<tr>
<td>Ngai et al&lt;sup&gt;37&lt;/sup&gt;</td>
<td>2186 (1-12 y)</td>
<td>&gt;38.9°C oral</td>
<td>24% vs 26%</td>
<td>4% vs 1%</td>
</tr>
<tr>
<td>Rotstein et al&lt;sup&gt;38&lt;/sup&gt;</td>
<td>150 (1-6 y)</td>
<td>&gt;38.9°C oral</td>
<td>1 dose 15%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>White et al&lt;sup&gt;39&lt;/sup&gt;</td>
<td>494 (1-2.5 y)</td>
<td>&gt;38.9°C oral</td>
<td>To 6 weeks</td>
<td>To 6 weeks</td>
</tr>
<tr>
<td>White et al&lt;sup&gt;40&lt;/sup&gt;</td>
<td>318 (1-3.5 y)</td>
<td>&gt;38.9°C oral</td>
<td>To 6 weeks</td>
<td>To 6 weeks</td>
</tr>
<tr>
<td>Berget et al&lt;sup&gt;41&lt;/sup&gt;</td>
<td>200 (55-88 y)</td>
<td>—</td>
<td>Not defined</td>
<td>To 6 weeks</td>
</tr>
</tbody>
</table>

(v), varicella vaccine group; (p), placebo group; (c), control group.

Disease was mild in both primary and secondary cases.

There have been no clinical trials of VZV vaccination during pregnancy. One report of inadvertent administration in seven pregnant women (6–31 weeks gestation) describes delivery of two healthy infants of two completed pregnancies. As of March 2000, the Varivax in pregnancy registry had reports of 21 occurrences of inadvertent vaccination during pregnancy including these seven women. Of the 20 prospectively enrolled pregnancies, 16 have had birth outcomes: 14 pregnancies have resulted in normal infants and two have had spontaneous abortions (personal communication, Dr J Seward, Centers for Disease Control and Prevention, March 2000). Wise et al reported no cases of congenital varicella among infants of 87 women inadvertently vaccinated during pregnancy using a passive surveillance system (level III evidence). Although it is likely that the rate of vaccine VZV transmission in pregnancy is lower than that for wild type VZV, there are insufficient clinical data at this time to confirm whether the risks of vaccination are less than those of congenital varicella syndrome, zoster, and varicella from wild type VZV infection in pregnancy.

### Risk of Herpes Zoster Following Vaccination

Only one placebo controlled RCT has commented on the risk of zoster following vaccination: no cases were noted in either placebo or vaccine recipients after nine months (732 person years). A single prospective cohort study of children has reported a mild case of zoster in one of 854 children (duration of follow up unknown). Other cohort studies report no zoster for as much as 19 years 7 months, or 3277 person years after vaccination. However, isolated case reports in children have occurred. Two mild cases of zoster (no virus isolated) were reported in healthy children (aged 2 and 4 years) following vaccination with Oka/Merck vaccine, and a rate of 21 cases per 100 000 person-years was estimated for Oka/Merck recipients to that time, compared with an expected rate of 77 per 100 000 person-years in school aged children following natural chickenpox. In 1992, White estimated that 14 cases per 100 000 vaccinees (all mild) had occurred over nine years of Oka/Merck vaccination in the USA. A population based study over a longer period found a rate of 42 per 100 000 in unvaccinated children (20 per 100 000 in children under 5 years). Most recently, the US post-licensure Vaccine Adverse Event Reporting System suggests a rate of 2.6/100 000 vaccine doses distributed.

Two adult cohort studies have described the occurrence of zoster six years after vaccination. Gershon et al vaccinated 187 varicella susceptible adults and reported one case of zoster caused by wild type virus after six years (1/1122 person years). Levin et al reported a rate similar to that expected in an unvaccinated population for persons over 55 years of age who had previously had varicella and received varicella immunisation (10/130 vaccinees or 1/100 person years). In all cases the disease was mild.

Of interest, a recent paper using mathematical modelling predicted a short to medium term increase in zoster after vaccination if exposure to varicella is important for preventing reactivation, although a reduction was likely in the longer term (level III evidence). Thus, there is fair evidence to suggest that there is a reduced incidence of herpes zoster in vaccinees. Evidence from studies of leukemic vaccinees support this statement.
SHIFT IN AGE OF VARICELLA

There has been a trend towards increasing age of varicella infections over the 20 years preceding use of VZV vaccine. A theoretical risk of varicella vaccination in children may increase this trend; that is an upward shift in remaining varicella cases resulting in more adult varicella with higher complication rates, particularly if immunity in vaccinees is not long lasting. Mathematical models that assume exposure to varicella plays a role in maintaining immunity and preventing reactivation of VZV, suggest that under certain conditions, widespread vaccination of children could result in increased zoster in adults. Although the model of Halloran et al predicted a shift in age of remaining varicella cases towards older individuals (with higher complication rates), an overall reduction in the number of adult cases with decreased total morbidity and hospitalisations was predicted.

A more extended model developed by Brisson et al also predicted a reduction in incidence and morbidity of varicella. However, clinical evidence is currently lacking to support some of the assumptions of these models, including the role of exposure to wild type varicella and of varicella vaccination in maintenance of long term protection against varicella and zoster in adults. Furthermore, several studies have shown that administration of varicella vaccine boosts cell mediated immunity to varicella in the elderly, including a recent RCT by Berger and colleagues. If widespread vaccine use results in decreased risk of exposure to varicella, vaccination of adults could be useful by boosting immunity. This view is supported by Krause and Klinman, who showed reactivation with decrease in falling antibody titres after vaccination.

COST EFFECTIVENESS DATA FOR VARICELLA VACCINE

No clinical trials have examined the cost effectiveness of VZV vaccination in healthy populations. Simulation studies examining both societal and health care costs associated with varicella have all found net cost savings with programmes for routine VZV vaccination directed at children aged 15 months. Lieu and colleagues, in a cost effectiveness study using morbidity and mortality data as well as projected data for vaccine impact, found a saving of $US5.40 for every dollar spent on routine vaccination of preschool children. Scuffham et al found a return of NZ$2.67 and $0.67 for each dollar invested, with and without inclusion of societal costs respectively. Simultaneous administration with MMR vaccine and additional catch up vaccination in children under 12 years may be even more cost effective.

Accuracy of history in those with uncertain or negative history of varicella is an important determinant of cost effectiveness for VZV vaccination in older subjects. In a cross sectional survey of children whose clinicians had ordered varicella sero testing, Lieu et al found that for all children aged 7–8 years, and for 9–12 year olds with a negative or probable negative history of varicella (determined by parental telephone interview), presumptive vaccination was the most cost effective approach. However, for 9–12 year olds with an uncertain history of varicella, sero testing followed by vaccination of those negative for VZV was the most cost effective approach. Sero testing regardless of history was also found to be the most cost effective strategy for adolescents, although clinical effectiveness was somewhat less than with a presumptive vaccination strategy.

Evidence of rising seronegativity in adults independent of country of origin suggests potential cost benefit from adult vaccination programmes in susceptible populations. Gray et al found sero testing of adult health care workers with a negative or uncertain history of varicella was the most cost effective approach to vaccination. This approach is also supported by mathematical models and a 1998 cohort study of American soldiers. Routine prenatal screening with postpartum vaccination of susceptible women may also be cost saving.

METHODOLOGICAL QUALITY OF STUDIES

The quality of evidence in studies included in this analysis was generally good. However, a number of methodological issues were identified. Loss of subjects from analysis was sometimes considerable, particularly where the duration of follow up was seven years or more. This occurred in one RCT and several prospective cohort studies. Other trials relied on self reporting of VZV disease to investigators while occasional studies followed only vaccinees who initially seroconverted. The only RCT examining the rate of herpes zoster in vaccinees was based on a very short period of follow up. These biases could potentially result in an over estimation of vaccine effectiveness by underestimating the true number of cases. However, outcomes across studies were consistent regardless of study design or duration of follow up, suggesting a true effect.

Study subjects were generally from upper middle class socioeconomic backgrounds. As varicella affects approximately 95% of individuals under 20 years living in a temperate climate, the generalisability of results is unlikely to be affected.

All cost effectiveness studies were based on simulations. Collection of data from clinical trials and from centres where vaccine use is now licensed would be needed to confirm basic assumptions of proposed models for vaccine and wild type VZV epidemiology and estimated costs of vaccination programmes. No clinical trials have examined hospitalisation rates or mortality as outcomes.

Conclusions

Because of the universality of infection, despite a relatively low complication rate, varicella is an important contributor to hospitalisations and mortality. This critical review has found strong evidence for the effectiveness of VZV vaccination in the prevention of varicella in children. Furthermore, vaccination appears to be cost effective, particularly when taken from a...
societal perspective. The quality of evidence in support of vaccination in adults is weaker, but in sum is also supportive of two injection regimens in susceptible individuals, who may be identified after confirmatory serological testing. Effectiveness data are required in adolescents and adults to clarify the optimal number of doses. The results of studies do not support the theoretical concerns that vaccination may lead to an increased incidence of herpes zoster or an unacceptable rate of transmission of infection from vaccinees. Although vaccination may increase the mean age of varicella, the overall reduction in the numbers of cases of adult varicella will probably offset this phenomenon. However, it will be important to monitor the epidemiology of varicella infection after introduction of widespread vaccination. Our findings support current recommendations from the United States, Canada, and the World Health Organisation (WHO) (see table 3). The American Academy of Pediatrics and Immunization Practices Advisory Committee (ACIP) of the Centers for Disease Control and Prevention recommends that all children should be routinely vaccinated at 12–18 months of age; that children under 13 years should receive one vaccination; and that older individuals susceptible to varicella should be offered two vaccinations 4–8 weeks apart. The National Advisory Committee on Immunisation (Canada) recommends immunisation of all susceptible persons aged 12 months or greater, with similar dose regimens. A 1998 WHO position paper recommends that routine childhood immunisation against varicella be considered in countries where the disease is a relatively important public health and socioeconomic problem, where the vaccine is affordable, and where high (85–95%) sustained vaccine coverage can be achieved. Additionally, vaccine may be offered to adolescents and adults without a history of varicella.

We acknowledge the contribution of the members of the Canadian Task Force on Preventive Health Care in providing guidance and feedback during the evidence review process. We thank also the following independent experts for reviewing a draft form of this report: Dr. Anne Gershon, Division of Pediatric Infectious Diseases, Columbia Medical Center, New York; Dr. Barbara Law, Department of Medical Microbiology, University of Manitoba, Winnipeg, MB; and Dr. Tracy Lue, Department of Ambulatory Care and Prevention, Harvard Pilgrim Health Centre and Harvard Medical School, Boston, Massachusetts. The views expressed in this report are those of the authors and do not necessarily reflect the position of the Canadian Task Force, nor those of the independent reviewers. Dr. Wang now works at Aventis Pasteur, a vaccine manufacturer. The work was completed when Dr. Wang’s primary appointment was at The Hospital for Sick Children. The discussed vaccines are not produced by Dr. Wang’s employer.

### Table 3: Summary of recommendations for use of VZV vaccine

<table>
<thead>
<tr>
<th>Maneuver</th>
<th>Effectiveness</th>
<th>Level of evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunisation of 12–15 mth old children with varicella vaccine</td>
<td>Effective in preventing varicella infection and secondary cases in household contacts</td>
<td>Randomised control trials/II-2**</td>
<td>Good evidence to include in routine health care (A)*</td>
</tr>
<tr>
<td>Catch up immunisation of children to 12 years with varicella vaccine</td>
<td>Effective in preventing varicella infection and secondary cases in household contacts</td>
<td>Randomised control trials/II-2**</td>
<td>Good evidence to include in routine health care (A)</td>
</tr>
<tr>
<td>Immunisation of susceptible adolescents with varicella vaccine</td>
<td>Effective in preventing varicella infection and secondary cases in household contacts</td>
<td>Propective cohort studies/II-2**</td>
<td>Fair evidence to include in routine health care (B)</td>
</tr>
<tr>
<td>Immunisation of susceptible adults with varicella vaccine</td>
<td>Effective in preventing varicella infection and secondary cases in household contacts</td>
<td>Controlled trials/II-1**</td>
<td>Fair evidence to include in routine health care (B)</td>
</tr>
</tbody>
</table>

*Good evidence also exists for simultaneous administration with MMR vaccine at separate sites.

### Appendix: Levels of evidence

Quality of published evidence:

- I—Evidence from at least one well designed, randomised controlled trial
- II—Evidence from well designed, controlled trials without randomisation
- III—Evidence from comparisons between times and places with or without the intervention; dramatic results from uncontrolled studies could also be included here
- IV—Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees.

Physiotherapy for cerebral palsy

Therapies can make people feel better and/or they can have specific measurable effects on the condition treated. The two effects do much to explain the conventional versus complementary or alternative medicine schism. A problem for conventional practitioners is that complementary/alternative practitioners often claim that their methods have the second type of effect when there is little or no evidence to show it and little or no sensible theory to suggest it possible. Nevertheless it can not be denied that making people feel better is a perfectly valid and necessary aim.

Physiotherapy for children with cerebral palsy is conventional and parents want it. Professionals promote it to the extent of describing “certain services or facilities” (including physiotherapy) as a “basic right” without “having to meet a strict test of effectiveness”. That is where we lie. It can not be denied that making people feel better is a perfectly valid and necessary aim.

A total of 56 children aged 3–12 years with bilateral cerebral palsy (Gross Motor Function Classification System grade III, IV, or V) each had six months of study treatment from their own physiotherapist (56 physiotherapists: 54 “eclectic” and 2 Bobath). They were randomised to four groups: usual physiotherapy with general aims, usual physiotherapy with specific goals, intensive (1 hour/day Monday to Friday) physiotherapy with general aims, and intensive physiotherapy with specific goals. The main outcome measures were function (Gross Motor Function Measure) and performance (Gross Motor Performance Measure). Neither extra physiotherapy nor goal setting significantly influenced these outcomes although there was a trend towards better function after six months in the intensively treated children, which declined over the six months following the end of trial therapy. Almost all of the physiotherapists, and many of the parents, considered the intensive physiotherapy too tiring for themselves and the children.

It seems that this degree and type of intensive physiotherapy gives no measured advantage over standard provision and may be unacceptable. (The “routine” group received some 2 or 3 hours of physiotherapy a month and the “intensive” group around 15 hours a month; perhaps something in between would be better). A comparison of routine and intensive physiotherapy tells us nothing about the value of routine therapy but the question remains, is it the physiotherapy or the physiotherapist that patients and parents need? Martin Bax in an editorial (Ibid: 3) reasserts that “we must try and see provision of services and facilities as basic rights for children with disabilities”. It is difficult to disagree with that, but we are still free to ask, which services? which facilities?, and the answer must be, those that best provide for the needs of the children and their parents.

Present decisions must depend on present knowledge and present circumstances but it ill behoves us to turn our backs on the principle of “strict tests of effectiveness”. That is where we (at least, those of us who haven’t yet joined the bandwagon) part company with much of complementary or alternative medicine.

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