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LES SOINS DE SANTÉ PRÉVENTIFS

Use of Varicella Vaccine in Healthy Populations

Systematic Review & Recommendations

TECHNICAL REPORT

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Use of Varicella Vaccine in Healthy Populations
Systematic Review & Recommendations

Technical Report #01-1, April 2000

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The Canadian Task Force on Preventive Health Care

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ABSTRACT

Objectives: 1) To evaluate the evidence relating to the effectiveness and potential harms of varicella-zoster virus (VZV) vaccine for the prevention of varicella in healthy individuals, and 2) To make recommendations regarding administration of VZV vaccine in healthy populations.

Options: Universal vaccination of healthy infants, catch up vaccination of older children and vaccination of susceptible adolescents and adults are options for the prevention of varicella.
Outcomes: Incidence of varicella, zoster or adverse outcomes following vaccination.

Evidence: MEDLINE and EMBASE were searched for trials of VZV vaccine in healthy populations published from 1966 to December 1998. Additional articles were identified using the reference lists of these publications, position statements from health organizations; vaccine product information and the Cochrane Library. Selection criteria were used to limit the review to randomised controlled trials or cohort studies of at least one year's duration with loss to follow-up described.

Benefits, harms and costs: Health benefits of VZV vaccine were evaluated in terms of prevention of VZV morbidity. The risks of vaccination were evaluated by examining immediate side effects and long-term risk for varicella and herpes zoster.

Values: The strength of evidence was evaluated using the methods of the Canadian Task Force on Preventive Health Care.

Recommendations: There is good evidence based on effectiveness data to recommend in favour of routine vaccination of children aged 12-15 months and catch-up vaccination of children to 12 years for the prevention of VZV illness (Grade A recommendation). There is fair evidence for the vaccination of susceptible adolescents and adults (Grade B recommendation). Further clinical trials would be needed to provide better data on cost-effectiveness, mortality and hospitalization; long-term effectiveness in adults and to compare effectiveness of one- versus two-dose regimens in adolescents and adults.

Validation: The findings of this analysis were reviewed through an iterative process by the members of the Canadian Task Force on Preventive Health Care and peer reviewed by three independent experts.

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Background

Varicella (chicken-pox) is a common, highly infectious disease caused by varicella zoster virus (VZV). Primary subclinical infection is rare. On days 10-14 after exposure, a vesicular eruption occurs associated with fever and malaise. A mean of 250-500 lesions occurs.[1, 2] These are pruritic and can scar if secondarily infected. The illness is usually self-limiting, lasting 4 to 5 days in children, but is more severe in adults. Secondary attack rates in susceptible household contacts are approximately 87%.[1] VZV infection usually results in lifelong immunity, although re-exposure results in boosting of antibody titer.[3, 4] Clinical illness after re-exposure is more likely in immunocompromised individuals.[3, 4] Herpes zoster (shingles), a painful, dermatomal, vesicular rash occurs with reactivation of the virus in approximately 15% of the population.[5]

Burden of suffering and populations at risk

In temperate climates, 95% of varicella cases occur among persons less than 20 years of age [6, 7] Seropositivity is lower in adults from tropical and subtropical areas[8, 9] for reasons that remain unclear,[9, 10] although reduced transmission in rural areas may be important.[11] Seronegativity in adults may be increasing in temperate populations, as shown by a significant upward trend in age distribution of chicken-pox cases in England and Wales,[12] and increasing varicella susceptibility in young U.S. adults.[13]

Before the introduction of VZV vaccine in the U.S. in 1995, approximately 4 million cases were reported annually (1,500 per 100,000 population), resulting in 10,000 hospitalizations and 100 deaths (43 child deaths) per year.[3, 14] Reporting greatly underestimates actual burden of disease with reporting efficiency as low as 5%.[3, 6] Despite the availability of vaccination, varicella is the most common cause of vaccine-preventable deaths in the U.S., with approximately 100 deaths continuing to occur annually.[3, 14-16] Forty five percent of varicella-related deaths and 66% of hospitalizations occur in persons less than 20 years of age.[6] The mortality rate of varicella in children under 14 years is estimated at 2 per 100,000 cases.[17] Approximately one child per week dies from varicella in the U.S.,[16] and 90% have no risk factors for severe disease.[14] Choo et al report at least one complication in approximately 1% of children under 15 years with varicella.[18], while others have found a somewhat higher rate.[19]

Complications include secondary bacterial infection (particularly with group A beta hemolytic streptococcus),[20] pneumonia, encephalitis, hemorrhagic complications, hepatitis, arthritis, and Reye syndrome.[21] Although uncommon, complications lead to a significant burden due to universality of disease. Furthermore, while only a small proportion of children experience complications, 10-50% of all children will visit a physician.[22-24]

Adults experience only 5% of all varicella cases, however, severe disease (hospitalizations 18 per 1000) and death (50 per 100,000) are more common than in children.[25] Complications occur in just over 1%.[18] The likelihood of developing herpes zoster increases with advancing age, occurring in approximately 1200 per 100,000 cases in adults > 75 years,[26] 300 per 100,000 aged 35-44 years[26] and 74 per 100,000 < 10 years.[5]

Although most women of child-bearing age will have immunity to VZV, infection in pregnancy can cause congenital varicella syndrome, neonatal varicella and zoster in infancy or early childhood. Congenital varicella syndrome occurs in approximately 2% of babies born to mothers infected in the first half of pregnancy, with the majority of cases occurring between 13 and 20 weeks.[27, 28] Severe varicella occurs in 15-30% of neonates when maternal infection develops from five days before to two days after delivery,[3] although this risk is markedly reduced by administration of varicella zoster immune globulin.[29] Zoster occurs in approximately 2% of children born to mothers infected after the first trimester of pregnancy.[27]

In 1999, Law et al estimated the yearly overall economic impact of chickenpox in Canada to be $122.4 million.[30] Costs due to varicella are mostly attributable to lost parental work days and hospitalization.[22, 30-32] Although societal costs for uncomplicated varicella in healthy children are less than for complicated cases ($CA236-$370 vs $CA7060-$8398 respectively), uncomplicated cases are responsible for approximately 90% of overall economic burden.[30, 32] A cost-benefit analysis suggests that routine use of varicella vaccine at one year of age would result in a savings of $384 million per year in the U.S.[31]

Manoeuvre

A live attenuated varicella vaccine was first developed in 1974 in Japan by Takahashi.[33] Similar vaccines developed from this Oka-strain vary in their level of attenuation, dose in plaque forming units (PFU) and stabiliser content. As the 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). Dry ice is preferable for transport between sites. This contributes immensely to the complexity and cost of vaccine distribution. Pasteur-Merieux-Connaught have developed a vaccine with stability at +5°C for two years.[34] Varilrix (SmithKline Beecham) also appears relatively stable at +4°C for two years.[35, 36]

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 U.S., Sweden and Germany (1995),[36, 37] and Canada (Dec 1998).[38] Several million doses have been given in total.

Rationale for this update

Options for the use of vaccine to prevent varicella in healthy individuals include universal vaccination of healthy infants, catch up vaccination of older children and vaccination of susceptible adolescents and adults. Models of cost-effectiveness and epidemiologic change suggest that implementation of routine varicella vaccination for infants and children could reduce total cases, case severity and generate cost savings.[39] Potential harms that may occur as a result of vaccination include 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) [40]. Recommendations for use of varicella vaccine must consider these factors as well as vaccine effectiveness.

Hence, the objectives of this first review by the Canadian Task Force on Preventive Health Care of varicella-zoster virus (VZV) vaccine for the prevention of varicella in healthy individuals are (a) to evaluate the evidence relating to effectiveness and potential harms and (b) to make recommendations regarding administration.

Methods

Extraction of evidence

MEDLINE was searched from 1966 to December 1998 using the MeSH subheadings chicken-pox, vaccination and human. 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 organizations 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. Trials of "emergency" vaccination following known exposure were excluded. 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 methodologic 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 studies were reviewed and data extraction performed by the main reviewer (S.S.). The grading of the quality of evidence and recommendations of this report was based on the grading system established by the Canadian Task Force on Preventive Health Care (Appendix 1).

Critical appraisal and consensus development

This evidence was systematically reviewed using the methodology of the Canadian Task Force on Preventive Health Care (CTF). Critical appraisal of key studies and ratings of the quality of this evidence was performed using the CTF's established methodological hierarchy (Appendix 1). Recommendations are based upon the best level of evidence available and consideration of gaps in evidence. They result from an iterative process involving CTF member and expert reviewer input. The full methodology is described in Woolf et al.[41] and in the CTF's 1994 Canadian Guide to Clinical Preventive Health Care.[42]

Results

25 controlled trials and 49 cohort studies were identified using the described search strategy. After application of exclusion criteria, a total of 23 controlled trials and 17 cohort

studies remained for review. For each of the following sections presented in Results, we describe the best available level of evidence along with key supporting studies. Randomised controlled trials are presented in the tables.

Vaccine effectiveness

Two randomized, placebo-controlled trials in children (aged 10 months-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)[35, 43, 44] although data beyond 3 years are subject to a large loss to follow-up of study subjects.[44] Supportive evidence is provided by two RCTs randomizing to different vaccine doses[36, 45] and 11 prospective cohort studies with follow-up of 1-19.6 years.[46-56] Three of these trials (each with over 2000 subjects) also studied adolescents (aged 13-17 years followed for 1-8 years).[51-53] Some methodologic issues were noted in included paediatric effectiveness studies. In some, increasing loss of subjects from analysis was noted with increasing duration of follow-up (up to 62%), and others used self-reporting of illness to determine effectiveness.[46, 51-53] In adults, effectiveness is demonstrated by one non-randomized controlled trial[57] and two prospective cohort studies[58, 59] 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.[60] This study also included adolescents. All but one adult study[57] calculated effectiveness based upon self-reporting of disease. Adult and child vaccinees experiencing close contact with varicella are also protected.[36, 43, 44, 60, 61]

All studies have found breakthrough varicella in vaccinees to be mild compared with natural varicella in terms of the mean number of vesicular lesions (1-56 lesions) and systemic symptoms (Table 1). However, occasional children have been noted to have typical varicella: two prospective cohort studies each describe one case.[49, 55] 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. 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 hospitalization rates are similarly lacking.

The protective efficacy (PE) of varicella vaccine has been determined in two placebo-controlled RCTs in children. Weibel et al estimated a PE of 100% over 9 months and 98% over 7 years,[43, 44] while Varis et al found a PE of 72% over a mean of 29 months.[35] Attack rates were 0-3% per year compared with 7-11% per year in placebo recipients, giving the number needed to treat (NNT) (the number needed to vaccinate to prevent one case of varicella) as 5.5-11.8. Assuming complications occur in 1% of varicella cases,[18] 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 4 years (0.3-2.3%)[45, 62] and prospective cohort studies to 19.6 years (0.3-2.8%),[46, 47, 49-56, 58, 59] including adolescents and adults to eight and six years respectively.[51, 52, 58, 59]

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,[62] II-1[63-65] and II-2[61]).

A wide range of vaccine doses have been utilized in studies examining vaccine effectiveness (Table 1) One randomized control trial (RCT) showed no difference in vaccine effectiveness between doses varying from 439 to 3625 PFU,[45] while another showed decreased effectiveness below 1260 PFU.[35] The study showing no difference had a longer duration of follow-up (mean 4.3 years compared to 29 months), but relied on self-reporting of disease.[45]

Protection against chicken-pox 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 comes from three prospective cohort studies using a single injection,[51-53] and one RCT using two injections in all participants (at different intervals and doses).[60] 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),[57] while 3 prospective studies providing level II-1 and II-2 evidence suggest two injections given 4 or 8 weeks apart are effective.[58-60]

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).[47, 53] High seroconversion rates of 94-100% have been demonstrated 6-8 weeks after a single VZV vaccination in children[35, 43] and two doses in adolescents and adults (level I evidence).[60, 66] A trial by Ndumbe et al suggests a single vaccination may result in less frequent seroconversion in adults (level II-2 evidence).[57] 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.[52, 58] Duration of seroconversion has been shown to approach 100% for up to six years in children following a single dose of vaccine[44, 45] and for two years in adolescents and adults following two doses. (level I evidence)[60]

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).[35, 43, 67] One RCT found an increase in local reactions (mild and well-tolerated) in vaccine recipients,[43] while another smaller trial found no difference.[67] Rates of fever varied from 0-36% depending on the definition of fever and the duration of follow-up. Injection site reactions occurred in 7% to 30% and less than 5% of vaccine and placebo recipients experienced a mild, varicella-like rash. RCTs in adults give similar results.[60, 66, 68] A higher dose in PFU appears not to result in a greater frequency of adverse reactions.[36, 45, 69] Controlled trials comparing VZV vaccine alone with tetravalent MMR-VZV also show no increase in adverse reactions.[61-63, 67] Finally, a second dose of vaccine appears to cause fewer reactions than the first.[46, 60, 68] No serious adverse reactions have been reported in controlled trials.

Transmission of varicella from vaccinated individuals to others

No clinical trials have demonstrated 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.[43] 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.[70] Finally, a prospective study of 37 vaccinated siblings of 30 cancer patients also found no evidence of varicella transmission.[71] However, case reports of transmission have been

reported rarely from adults and children with varicella-like rash following vaccination.[72-74] Whilst not a complication of vaccination, transmission of wild-type virus (non-vaccine related) breakthrough disease has been reported between vaccinated siblings (rate 12.2%).[51] 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.[75] Since this publication, the Varivax in pregnancy registry has 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 Jane Seward, Centers for Disease Control and Prevention, March 2000). 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).[43] A single prospective cohort study of children has reported a mild case of zoster in one of 854 children (duration of follow-up unknown).[76] Other cohort studies report no zoster for as much as 19 years 7 months, or 3277 person years after vaccination.[48-50, 54, 56, 77, 78] 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,[79] and a rate of 21 cases per100,000 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 chicken-pox. In 1992, White estimated that 14 cases per 100,000 vaccinees (all mild) had occurred over 9 years of Oka/Merck vaccination in the U.S.[80] 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 five years).[81] Most recently, the U.S.

post-licensure Vaccine Adverse Event Reporting System suggests a rate of 2.6/100,000 vaccine doses distributed.[82]

Two adult cohort studies have described the occurrence of zoster six years after vaccination. Gershon et al vaccinated 187 varicella-susceptible adults and reported 1 case of zoster due to wild-type virus after six years (1/1122 person years).[58, 83] 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).[84] In all cases the disease was mild.

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.[85-87]

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.[12, 88] A theoretical risk of varicella vaccination is that routine VZV 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.[89] 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 hospitalizations was predicted.[39] 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, administration of varicella vaccine has been shown to boost cell-mediated immunity to varicella in the elderly.[90] If widespread vaccine use results in decreased risk of exposure to varicella, vaccination of adults could be useful by boosting immunity.

Cost-effectiveness data for varicella vaccine

There have been no clinical trials examining 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 programs for routine VZV vaccination directed at children aged 15 months.[31, 91-93] Lieu et al,[31] in a cost-effectiveness study using recent morbidity and mortality data as well as projected data for vaccine impact,[39] found a saving of $US 5.40 for every dollar spent on routine vaccination of preschool children. Simultaneous administration with MMR vaccine[91, 92] and additional catch-up vaccination in children under 12 years may be even more cost-effective.[93, 94]

Accuracy of history in those with uncertain or negative history for varicella is an important determinant of cost-effectiveness for VZV vaccination in older subjects.[94] In a cross-sectional survey of children whose clinicians had ordered varicella serotesting, 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.[95] However, for 9-12 year olds with an uncertain history of varicella, serotesting followed by vaccination of those negative for VZV was the most cost-effective approach. Serotesting 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.[94] Evidence of rising seronegativity in adults independent of country of origin suggests potential cost benefit from adult vaccination programs in susceptible populations.[13] Gray et al found serotesting of adult health care workers with a negative or uncertain history of varicella was the most cost-effective approach to vaccination.[96]

Methodologic quality of studies

The quality of evidence in studies included in this analysis was generally good. However, a number of methodologic 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[44] and several prospective cohort studies.[49, 50, 77, 78] Other trials relied on reporting of VZV disease to investigators,[45, 60, 62, 63] while occasional studies followed only vaccinees who initially seroconverted.[44] The only RCT examining the rate of herpes zoster in vaccinees was based on a very short period of follow-up.[43] 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. However, since varicella affects approximately 95% of individuals under 20 years living in a temperate climate,[7] 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 centers 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 programs. No clinical trials have examined hospitalization rates or mortality as outcomes.

Interpretation

Canadian Task Force Recommendations

Recommendations from this evidence-based review of VZV vaccine use appear in Table 3.

There is good evidence to recommend implementing single dose, routine childhood vaccination for 12-15 month old children (Grade A recommendation), and catch-up vaccination for children aged one to 12 years based on effectiveness and immunogenicity data (Grade A recommendation). This could prevent most severe morbidity from varicella in children and in adults. Simultaneous administration with MMR vaccine at a separate site is also safe and effective.[62, 67] Vaccination of susceptible adults (Grade B recommendation) and adolescents (Grade B recommendation) can also be recommended on the basis of effectiveness and immunogenicity data. Two doses given 4-8 weeks apart appear more effective than a single dose based on immunogenicity data in subjects over 12 years. However, effectiveness data are required in adolescents and adults to clarify the optimal number of doses. Until this becomes available, it is reasonable to adopt a two-dose regimen for susceptible adolescents and adults. There is insufficient evidence documenting safety of VZV in pregnancy to recommend vaccination in susceptible pregnant women, although risk is likely to be less than for naturally acquired VZV.

OKA-strain vaccines from different manufacturers have similar effectiveness. Duration of protection has been shown to 7 years in RCTs and 20 years in prospective cohort studies. Vaccines with greater thermal stability could potentially simplify distribution and reduce costs.

Vaccination is likely to be cost-effective. In children under 12 years, vaccination regardless of a previous history of varicella appears the most cost-effective approach. The exception is 9-12 year olds with an uncertain history of varicella who should have serotesting prior to vaccination. For adolescents and adults, prior serotesting is likely to be the most cost-effective.

Immediate side effects of VZV vaccination appear minimal in both adults and children. Breakthrough varicella and zoster are mild and occur at a lower rate than after natural infection. While transmission of vaccine VZV has been reported, these incidents appear much less frequently than for natural varicella. Although models of varicella epidemiology following widespread childhood vaccination predict an increased proportion of remaining cases in adults, overall adult cases and morbidity should decrease. However, data on the effects of lack of exposure to wild-type VZV on both varicella and zoster epidemiology are currently lacking and require further study.

Data are also required for cost-effectiveness following vaccination. Given the rarity of hospitalizations and mortality following vaccination, it may be difficult to collect data on these outcomes in clinical trials. It will be important to measure these during post-marketing surveillance. RCTs comparing the effectiveness of one- and two- dose regimens in adults and adolescents would help clarify an optimal approach to vaccination in older subjects.

Potential barriers to implementation of widespread varicella vaccination should be identified and addressed. Following licensure in May 1995, U.S. coverage was only 25% in March-June 1997[16] and mortality due to varicella continued at a similar rate to that of the pre-vaccination era.[15] Adequate resourcing for staff, education, surveillance, vaccine and appropriate refrigeration devices will be key to strategies for vaccine implementation. Education of consumers and health practitioners about VZV vaccination should include clinical and cost-effectiveness messages; advice regarding possible adverse reactions; teaching in administration, handling and maintenance of the cold chain; and reporting requirements for varicella, zoster and vaccine side effects. It should also address common misconceptions such as that of varicella

being seen as a mild disease. Ongoing, adequately resourced surveillance will be necessary to monitor changes in seroprevalence, and disease susceptibility, age distribution and severity for varicella and zoster as well as vaccine side effects. Implementation can be aided by licensing VZV vaccine for use in healthy children, adolescents and adults, incorporating VZV vaccine into the Canadian routine paediatric immunization schedule, and including VZV serology in the adult periodic examination for those with a negative history of varicella. Timing of vaccination with the visit for MMR vaccine would obviate an extra health care visit.

Recommendations of others

The American Academy of Pediatrics and Immunization Practices Advisory Committee (ACIP) of the Centers for Disease Control and Prevention recommended in 1995 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.[3, 97] The National Advisory Committee on Immunization (Canada) recommends immunization of all susceptible persons aged 12 months or greater, with similar dose regimens.[38]

Research priorities

1. To study longer-term effectiveness following vaccination of adults.
2. To compare effectiveness of single- and two-dose regimens in adults and adolescents.
3. To study the effect of decreasing re-exposure to VZV on long-term protection against varicella
4. Further development of effective combination vaccines incorporating MMR and VZV.
5. Clinical trials for cost-effectiveness of varicella vaccination, including hospitalization and mortality data where feasible, including post-marketing surveillance for hospitalization and mortality data.
6. Ongoing surveillance of varicella and herpes zoster epidemiology.

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Table 1. Randomized control trials of VZV vaccination effectiveness

Study	Study design	Study Population(s)	Varicella cases	Effect size	Cases with known exposure
Weibel et al[43]	Vaccine x1 dose Follow-up 9 months	956 (1-14years) (v) 491 (p) 465	(v) 0/468 (p) 39/446	PE=100% NNT = 11.8	(v) 0/33 (p) 4/9 PE=100% NNT= 2.3
Kuter et al[44]	7 year follow up of Weibel et al cohort	956 (1-14years) (v) 163 (p) 161 92% loss to follow-up	(v) 23/468 mean lesions 56	PE = 95% at 7 years	At 20 months (v) 1/19 (p) 5/8 PE 92% NNT = 1.1
Kuter et al[60]	Vaccine x 2 dose 4 vs 8 weeks apart Follow-up 1 yr Level II-2 evidence	757 (13-54 years) 1. 384 2. 373 varicella self reported	-	-	Close contact>=4h Total = 2/46 Mean 29 lesions
Varis et al[35]	Vaccine x1 dose Dose titration study Follow-up mean 29m	493 (10-30m) (v) 332 (p) 161	(v) 24 7% (p) 41 25% 1-2 vs 30 lesions	PE=72% NNT=5.5 High dose PE 88%	-
Tan et al[36]	Vaccine x1 dose Dose titration study Follow-up 6 months	191 (9 -24 months) 13% loss to follow-up	-	p>0.05	Close contact >4h Total=6/52 Unrelated to dose
Watson et al[61]	Vaccine x1 dose (v) vs MMRV Follow-up 1 year Level II-2 evidence	111 (12-19 months) 13% loss to follow-up	-	-	Close contact >4h Total = 0/17
Rothstein et al[45]	Vaccine x1 dose Dose titration study Follow-up 4.3 years	150 (1-6 years) varicella self reported	15/150 10% median lesions 25 Unrelated to dose	p>0.05	-
White et al[62] (First study)	Vaccine x1 dose MMRV + (p) vs MMR+ (v) Follow-up 1 year	494 (1 - 2.5 years) varicella self reported	2% vs 0.8% mean lesions 30 vs 29	p>0.05	-
White et al[62] (2nd study)	Vaccine x1 dose MMRV vs MMR + (v) Follow-up 1 year	318 (1 - 3.5 years) varicella self reported	1/318 20 lesions	p>0.05	-

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

Table 2. Randomized control trials of adverse reactions following VZV vaccination (< 8 weeks)

Study	Population(s)	Fever	Local reaction	Varicella-like rash
Weibel et al[43]	956 (1-14years)	>38.9 oral (v) = (p) = 2% per week	(v) 27% at 48h (p) 19% at 48h	(v) 4% at 8 weeks (p) 2% at 8 weeks
Englund et al[67]	111 (15-18m) 4 lost to follow-up	>37.8^{o} oral (v) 35% (p) 36%	(v) 7% at 48h (p) 4% at 48h	(v) = (p) = 2% at 6 weeks
Levin et al[68]	202 (55-87 years)	>38^{o}C <1%	1st injection 6% 2nd - 0%	6/202 3% Level II evidence
Kuter et al[60]	757 (13-54 years) 57 lost to follow-up	>37.8 ^{o}C oral 1st injection10% 2nd:7%	1st injection 19% 2nd 31% p>0.05	Post 1st: 8% Post 2nd:<1%
Ramiksissoon et al[69]	200 (9 -24 months) 18 lost to follow-up Dose titration study	-	Zero all groups	Total 2/200 1%
Tan et al[36]	191 (9 -24 months) Dose titration study	Total 23% p>0.05	Total 24%	Total 6/191 3%
Watson et al[61]	111 (12-19 months) MMRV + (p) vs MMR + (v)	Total 6%	-	Total 5/111 4.5% 3.5% vs 5.6%
Varis et al[35]	493 (10-30m)	Not defined Zero	Not noted	To 4 weeks (v) 4.5% (p) 3.7%
Ngai et al[46]	2196 (1 -12 years) 238 lost to follow-up	>=38.9^{0}C oral 1 dose 15% 2 doses 11%	24% vs 26%	4% vs 1% p<0.001
Rothstein et al[45]	150 (1-6 years) Dose titration study	>38.9 oral 10-16% p>0.05	To 6 weeks 12-18%	To 6 weeks 2-4%
White et al[62] (First study)	494 (1 - 2.5 years) MMRV + (p) MMR + (v)	>=38.9^{0}C oral 25% vs 22%	To 6 weeks 14% vs 12%	To 6 weeks 7% both groups
White et al[62] (2nd study)	318 (1 - 3.5 years) 2 lost to follow-up MMRV vs MMR + (v)	>=38.9^{0}C oral 23% vs 15%	To 6 weeks 2.5% vs 2%	To 6 weeks 17% vs 16%
Berger et al[66]	200 (55-88yrs)	Not defined Zero at 72h	To 6 weeks (v) 36% (c) 66%	To 6 weeks 1/200

(v) varicella vaccine group
(p) placebo group
(c) control group

Table 3. Summary of recommendations for use of VZV vaccine

Manoeuvre	Effectiveness	Level of Evidence	Recommendation
Immunization of 12-15 month old children with varicella vaccine	Effective in preventing varicella infection and secondary cases in household contacts.	Randomized control trials/I [35, 36, 43-45] Prospective cohort studies/II-2 [46-48, 50-56]	Good evidence to include in routine health care (A)*
Catch-up immunization of children to 12 years with varicella vaccine	Effective in preventing varicella infection and secondary cases in household contacts	Randomized control trials/I [35, 36, 43-45] Prospective cohort studies/II-2 [46-49, 51-56, 78]	Good evidence to include in routine health care (A)
Immunization of susceptible adolescents with varicella vaccine	Effective in preventing varicella infection and secondary cases in household contacts	Prospective cohort studies/II-2 [51-53, 60]	Fair evidence to include in routine health care (B)
Immunization of susceptible adults with varicella vaccine	Effective in preventing varicella infection and secondary cases in household contacts	Controlled trials/II-1 [57] Prospective cohort studies/II-2 [58-60]	Fair evidence to include in routine health care (B)

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

Appendix 1: Methodology of the Canadian Task Force on Preventive Health Care

Critical appraisal

A manuscript providing critical appraisal of the evidence for this topic was prepared by the lead author. This included identification and critical appraisal of key studies, and ratings of the quality of this evidence using the task force's established methodological hierarchy (sidebar), which resulted in a summary of proposed conclusions and recommendations for consideration by the task force.

Consensus development

Evidence for this topic was presented by the lead author and deliberated upon during a task force meetings in June 1999. Expert panelists addressed critical issues, clarified ambiguous concepts and analyzed the synthesis of the evidence. At the end of this process, the specific clinical recommendations proposed by the lead author were discussed, as were issues related to clarification of the recommendations for clinical application and any gaps in evidence. The results of this process are reflected in the description of the decision criteria presented with the specific recommendations. The group and lead author arrived at final decisions on recommendations unanimously.

Subsequent to the meetings, the lead author revised the manuscript accordingly. After final revision, the task force sent the manuscript to three experts in the field (identified by task force members at the meeting). Feedback from these experts was incorporated into the final technical report.

Procedures to achieve adequate documentation, consistency, comprehensiveness, objectivity and adherence to the task force methodology were maintained at all stages during review development, the consensus process and beyond to ensure uniformity and impartiality throughout.

Levels of evidence

I Evidence from at least one well-designed randomized controlled trial

II-1 Evidence from well-designed controlled trials without randomization

II-2 Evidence from well-designed cohort or case–control analytic studies, preferably from more than one centre or research group

II-3 Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here

III Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

Grades of recommendations

A Good evidence to support the recommendation that the condition or manoeuvre be specifically considered in a periodic health examination (PHE)

B Fair evidence to support the recommendation that the condition or manoeuvre be specifically considered in a PHE

C Insufficient evidence regarding inclusion or exclusion of the condition or manoeuvre in a PHE, but recommendations may be made on other grounds

D Fair evidence to support the recommendation that the condition or manoeuvre be specifically excluded from a PHE

E Good evidence to support the recommendation that the condition or manoeuvre be specifically excluded from a PHE