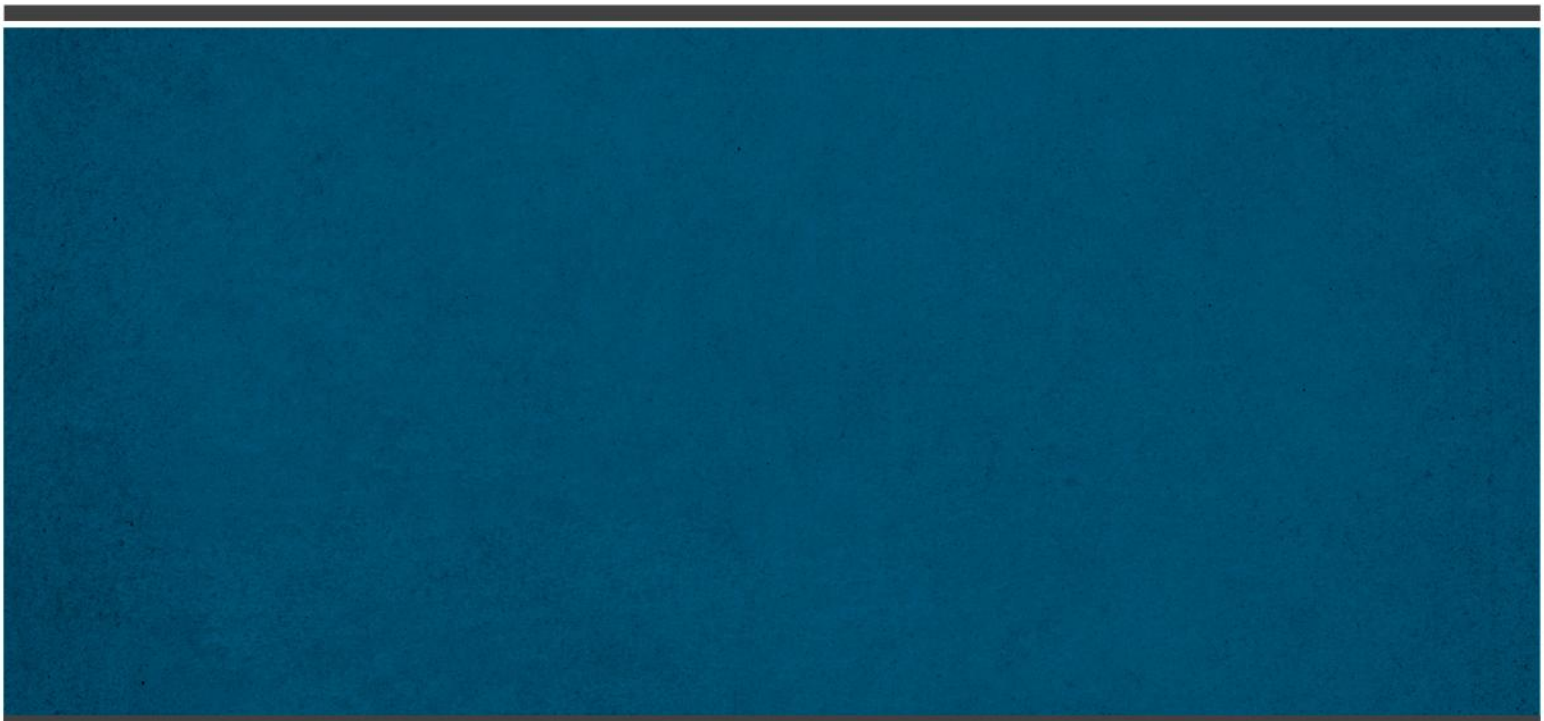
RECOMMENDATIONS FOR VARICELLA TWO-DOSE IMMUNIZATION PROGRAMS

CANADIAN IMMUNIZATION COMMITTEE



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FOREWORD

The purpose of this statement is for the Canadian Immunization Committee (CIC) to provide recommendations on the implementation of a two-dose varicella immunization program. These recommendations are based on a review of the literature, analysis of research data and technical expertise.

Varicella-zoster virus (VZV) is a virus in the herpes virus family. Infection due to the VZV causes varicella (chicken pox) and zoster (shingles). Varicella is mainly a childhood disease that is spread by direct contact with virus shed from characteristic skin lesions, oral secretions or through airborne transmission. Zoster is caused by a reactivation of the virus in the sensory nerve ganglia, leading to neuropathic pain and a skin rash.

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BURDEN OF DISEASE

VARICELLA SURVEILLANCE IN CANADA

Identifying accurate incidence rates of varicella in Canada is challenging for many reasons. There is currently no national active surveillance system across Canada for varicella, other than the hospital based system described below. In the absence of surveillance data, many provinces and territories (P/Ts) rely on administrative data (e.g. physician billing and hospitalization data) to monitor varicella incidence. Administrative data are known to underestimate the true incidence of disease. Additionally, not all affected children will receive medical attention, which further contributes to the under-reporting of varicella cases.

The Canadian Immunization Monitoring Program Active (IMPACT) is a national hospital-based active surveillance system that captures information about varicella admissions. Since 1999, IMPACT has captured varicella cases in children 0 through 16 years of age at twelve pediatric tertiary care centers in eight provinces including referrals from all thirteen Canadian provinces and territories.

Confirmed cases of varicella disease are nationally notifiable; however, confirmation of varicella is not notifiable in all P/Ts. Currently, all P/Ts, with the exception of BC, MB, NS and QC, report cases of varicella to the Canadian Notifiable Disease Surveillance System (CNDSS). This is a passive surveillance system that relies on the case reports from P/Ts on a voluntary basis. Data is available from 1924 to 1959 and from 1986 to 2008. It is thought that less than 10% of the expected cases are being reported through the CNDSS.

AGE AT DISEASE ONSET

A study in Quebec was conducted from 1995 to 1997 among children 10 years of age to assess age-specific incidence of varicella based on parental recall. In this cohort of 2255 children, it was found that 92% of children had acquired varicella before the age of 11 years and nearly 50% developed the disease before starting kindergarten (1).

In the U.S. Varicella Active Surveillance Project (VASP) study, the median age at disease onset shifted upwards for both those with and without a history of immunization. During the ten-year study period from 1995 to 2005, the median age increased from five years to eight years in immunized cases and from five years to 13 years in non-immunized cases in Antelope Valley. In West Philadelphia, the median age at disease onset increased from three to six years in immunized cases and from six to 19 years in non-immunized cases between 1995 and 2005 (2).

MORTALITY

Varicella case fatality rates are highest among adults (30 deaths per 100,000 cases) followed by infants under the age of 1 year (7 deaths per 100,000 cases) and then those aged 1 to 19 years (1-1.5 deaths per 100,000 cases) (3).

IMPACT data from 2000-2008 (4) showed a total of 2,048 varicella-related hospital admissions. There were 333 children < 1 year-of-age (16%), 1,012 children 1-4 years-of-age (49%), 570

children 5-9 years-of-age (28%), and 133 children 10-16 years-of-age (7%). The majority (57%) of hospitalizations occurred in previously healthy children. Since 2000, a total of ten varicella-related pediatric deaths have occurred, with a range of 0-3 each year.

In Alberta, chickenpox was recorded as the cause of 14 deaths between 1983 and 2010 and of these, 5 were between 2000 and 2006. Of the 14 deaths, 8 were under the age of 10 years of which two were under age 1 (5). Mortality is a rare event related to varicella infection.

BURDEN OF VARICELLA PRIOR TO THE INTRODUCTION OF VARICELLA IMMUNIZATION PROGRAMS

The varicella vaccine was first recommended for use by the National Advisory Committee on Immunization (NACI) in 1999 (6). Prior to the introduction of universal varicella immunization programs, varicella was deemed to be primarily a benign disease in healthy children less than 13 years of age. In the pre-vaccine era, there were approximately 350,000 chickenpox cases per year (estimated incidence of 11.7 per 1,000 population) and approximately 50% and 90% of Canadian children were expected to have had an infection by the age of 5 years and 12 years respectively (7). The literature reveals that infection with VZV was responsible for a total of 3,681 paediatric hospitalizations in Canada between 1991-1996 and 1999-2005 (8, 9). Of the 59 deaths attributed to varicella between 1987 and 1997, 70% occurred in individuals over 15 years of age.

A study published in 1999 estimated the total direct costs (i.e. hospitalizations, physician consults, and medical and surgical procedures) and productivity costs (e.g. time missed from work and caregiver activities) related to childhood varicella illness to be approximately $122 million annually in Canada (10). Despite the fact that hospitalization risk was low (approximately 1 in 200 to 400), children accounted for 90% of the annual 1500 to 2000 varicella-related hospitalizations each year; and providing care for children who were ill and lost productivity accounted for 81% of the annual cost of disease prior to 1999 (11). Hospitalized cases of varicella were more likely to have complications, such as some type of neurological complication (nearly 20%) and other life-threatening infections (8%) such as necrotizing fasciitis or septicaemia (11).

An evaluation of IMPACT data for surveillance of herpes zoster admissions was conducted from 1991 to 1996 and reintroduced in 1999. It was found that 648 children were admitted with herpes zoster. Approximately 88% of these cases had a history of varicella zoster virus infection while varicella immunization was documented in 4 children before admission (12).

The burden of varicella prior to universal immunization was examined in British Columbia (BC) between 1994 and 2003 (a varicella immunization program was implemented in 2005 in BC). With the use of administrative data sources, it was found that there was an average of 12,891 varicella-related physician visits per year and the majority of these visits (78%) were for children below 14 years of age. There were 1,548 varicella-related hospitalizations during the 10-year period in BC with the highest rates observed among children 4 years of age and younger. In addition, there were 7 deaths associated with varicella during this period and the highest age-specific mortality rate was reported in children 1 to 4 years of age (0.54 deaths per million population) (13).

Several concerns related to the implementation of routine varicella immunization were considered before immunization programs were put in place. It was thought that, with immunization, there may be a shift in the average age of infection from children to adults, leading to an overall reduction in the health of the adult population due to the greater risk of complication among infected adults. However, mathematical models predicted otherwise with simulation results demonstrating that many of the adult cases occur after vaccine-induced immunity wanes and so cases are mild with few complications. Also, high numbers of varicella cases among immunized individuals in clinical trials raised concerns. In addition, there were concerns that there would be an increase in the incidence of zoster as a result of varicella immunization. Modeling based on epidemiological studies predicted that reducing circulating VZV through universal varicella immunization may lead to a significant increase in zoster (14).

COMMON COMPLICATIONS ASSOCIATED WITH VARICELLA HOSPITALIZATION

A retrospective chart review of 144 patients conducted in a children's hospital in Chicago from 1993 to 2001 reported a significant decrease ($p<0.01$) in the number of varicella-related Invasive Group A Streptococcal (IGAS) infections, one of the most common complications associated with varicella-related hospitalization in their patient population. While varicella infection was the most common predisposing factor to IGAS, as the vaccine coverage increased, the percent of IGAS cases associated with varicella decreased from 27% to 2% (15). Nevertheless, while it should be noted that four studies (16,17,18,19) did not observe significant declines in paediatric IGAS after the introduction of varicella immunization programs, the shorter lengths of follow-up (two to four years) and the fact that changes in IGAS were not exclusively examined may have contributed to the absence of an immunization-induced reduction in IGAS infections.

BURDEN OF VARICELLA AFTER THE INTRODUCTION OF VARICELLA IMMUNIZATION PROGRAMS

Following national recommendations for the use of the varicella vaccine in 1999, varicella immunization programs were subsequently implemented by each province and territory at various times between 2000 and 2007 (see Table 1). With the introduction of the routine one-dose varicella immunization in Canada, the incidence of varicella and related morbidity decreased significantly. Studies have shown that breakthrough varicella (varicella cases in vaccinated individuals) is generally mild and less contagious than varicella in unvaccinated individuals (14).

According to IMPACT (4), since the implementation of publicly-funded varicella immunization programs, the annual average number of varicella-related hospitalizations has decreased from 303 cases (2000 to 2004) to 134 (2005-2008). Breakthrough disease increased from 0.9% of cases in 2000-01 to 9.5% of cases in 2007-08, the majority in immunocompromised children.

Between 1999 and 2005, 55% of the paediatric varicella cases were male, with children ages 1 to 4 years accounting for the largest percentage of hospitalizations (45%), while children aged 5 to 9 years accounted for 30% of hospitalizations. According to the *2006 Canadian National Report on Immunization*, seven deaths due to varicella and one death attributed to herpes zoster were reported in Canada between 1999 and 2005 (8).

The incidence of varicella has been investigated in various provinces, comparing rates prior to immunization program implementation with rates post-implementation. In Alberta, a publicly-funded varicella immunization program began in April 2001. Results from a study by Russell and colleagues found that the introduction of varicella vaccine in Alberta decreased the incidence of varicella and that the effect was greatest in those under age 10, which is expected with the vaccine administered at 12 months of age. The vaccine helped to prevent primary infection which would subsequently decrease the secondary attack rate (i.e. rate of disease among those exposed to cases) (20).

Data from Quebec report similar results when evaluating the burden of varicella over a three year period (2006-2008) after the implementation of a universal varicella immunization program. Rates of varicella-related hospitalizations, medical visits, and deaths were found to decrease in the period after implementation. Varicella-related hospitalizations decreased by 66% (95% CI: 63-70%) and medical visits decreased by 87% (95% CI: 86-87%) after universal program implementation when compared to the pre-vaccine period. No deaths due to varicella were reported in the years after the implementation of the program (21).

An evaluation of the impact of publicly-funded immunization programs for varicella immunization in Ontario demonstrated reduced rates of varicella-related health care outcomes. Prior to the availability of the varicella vaccine, from 1992 to 1998, overall rates of hospitalizations, emergency department use and office visits related to varicella were 4.0 per 100,000 (95% CI: 3.9-4.2), 50.3 per 100,000 (95% CI: 49.8-50.8) and 624.7 per 100,000 (95% CI:622.9-626.4) respectively in Ontario. After implementation of the program, these rates decreased to 1.7 per 100,000 (95% CI: 1.6-1.9), 22.3 per 100,000 (95% CI: 21.7-22.9) and 246.0 per 100,000 (95% CI: 243.9-248.1) (22). This evaluation of health outcomes uses data over the two year period (2005-2006) after the implementation of the publicly funded immunization program in Ontario.

In the United States (U.S.), a large-scale VASP was set up in Antelope Valley (California), West Philadelphia (Pennsylvania), and Travis County (Texas), to assess the impact of universal varicella immunization on varicella epidemiology in these communities. Population-based disease surveillance in three U.S. communities after the introduction of universal varicella vaccination programs between 1995 and 2005 reported a 90% decline in incidence case reports (2) while achieving immunization coverage levels of 74% to 84% in children aged 19 to 35 months (16). Children aged 1 to 4 years experienced the greatest decline in disease incidence.

Also in the U.S., a comprehensive prospective longitudinal study found that overall between 1995 and 2005, varicella-related hospitalization rates per 100,000 population decreased significantly from 2.54 (95% CI: 2.1–3.0) during the early immunization period (1995–1998) to 0.6 (95% CI: 0.4–1.0) during the late immunization period (2002–2005; $p<0.01$). A change in the age distribution of case patients was also observed in addition to the decline in varicella-related hospitalizations. From 1995 to 1998, children less than 10 years of age accounted for 69% of all varicella-related hospitalizations, those 10 to 19 years of age accounted for 7.8% of varicella-related hospitalizations, and those 20 years of age or older accounted for 23.3% of varicella-related hospitalizations. After 1998, children younger than 10 years accounted for 48.8% of varicella-related hospitalizations, while those 10 to 19 years made up 19.5% and adults 20 years or older accounted for 31.7% of varicella-related hospitalizations (23). In addition, the number of deaths where varicella was noted as an underlying cause decreased from 115 to 16 between 1995 and 2003 (23). A similar decreasing trend in varicella-related hospitalization was observed in a large-scale Market-Scan database, which included information from approximately 40 self-insured employers from across the U.S. with about 4 million people. The

reported overall hospitalization rates decreased from 2.3 to 0.3 per 100,000 population between 1994 and 2002 with the greatest declines among infants younger than one year of age (24).

IMMUNIZATION STATUS OF VARICELLA CASES

In the active VASP surveillance sites, between 1995 and 2005, there was an increase in the proportion of varicella cases with a previous history of immunization. This proportion decreased as age increased. By 2005, the proportion of immunized cases 1 year of age or older ranged from 57% to 64%. A history of immunization among cases was observed in approximately 87% to 97% of those aged 5 to 9 years, 38% to 45% for those 10 to 14 years, 17% to 31% for those 15 to 19 years and 7% to 9% for those patients 20 years of age or older (2). The majority of these cases would have received only one dose of the vaccine prior to disease onset. Earlier data from this population revealed that the secondary attack rate was 15% if contacts were immunized and 71.5% if the contact was not immunized (risk ratio 0.21; 95% CI: 0.15–0.30).

To evaluate contagiousness of immunized varicella cases, a population-based study in the U.S. described secondary attack rates within households (the proportion of secondary varicella cases that occurred among household contacts exposed to the primary household varicella case). Overall, individuals with breakthrough disease (persons with varicella despite being immunized) were found to have approximately half the secondary attack rate of non-immunized cases. Nevertheless, immunized cases with 50 lesions or more had a similar secondary attack rate as non-immunized cases with 50 lesions or more (65.2% and 73.8%, respectively) whereas immunized cases with fewer than 50 lesions had one third the secondary attack rate as non-immunized cases with fewer than 50 lesions (23.4% and 67.9% respectively) (16). Specimen analysis using Polymerase Chain Reaction (PCR) from 33 immunized children found that 76% of those with adequate lesion sample were positive for wild-type varicella zoster virus (25). The Oka vaccine virus was not identified in any specimens submitted for analysis.

VARICELLA IN ADULTS

It has been hypothesized that with the implementation of child varicella immunization programs, a shift in the age distribution of varicella cases would result in an increase in incidence and morbidity in adults. However, from 1995 to 2005 varicella incidence rates declined significantly from 0.50 per 100,000 population to 0.13 per 100,000 population ($p<0.0001$). Disease was more severe in non-immunized adults compared with non-immunized children. Adults had a 1.8 and 1.9 times higher risk of more than 500 skin lesions, a 2.0 times greater risk of developing complications and a 6.2 times higher chance of hospitalization compared with non-immunized children. Furthermore, non-specific general symptoms, including nausea, vomiting, headache, fatigue, dizziness and appetite loss, were more prevalent in adults (one in 17 adult cases vs. one in 116 child cases). Dehydration and pneumonia also occurred more frequently in adults than in children (RR 5.4 and 10.6, $p<0.001$) (26).

VACCINE-MODIFIED (OR BREAKTHROUGH) DISEASE

Vaccine-modified (breakthrough) disease is defined as a case of infection with wild-type VZV occurring later than 42 days after immunization. Immunized children typically tend to have milder cases of disease with fewer lesions, shorter duration of illness and lower incidence of

fever. Mild disease is defined as less than 50 lesions, moderate disease as 50 to 500 lesions and severe disease more than 500 lesions or the occurrence of serious complications such as varicella-associated pneumonia, encephalitis, hospitalization or death.

The VASP in the U.S., where universal immunization programs have been in place for more than 10 years, observed that the percentage of cases with vaccine-modified disease increased from 3.5% in 1997 to 24% in 2000 to 72% in 2005 because of increasing immunization coverage rates (27).

IMPACT OF VARICELLA IMMUNIZATION ON ZOSTER

In the U.S., surveillance studies have demonstrated a small increase in zoster incidence following the introduction of routine varicella immunization. However, direct links between these increases and the use of the varicella vaccine cannot be made due to a lack of zoster incidence data prior to implementation of the program. Also, increases in age-specific zoster incidence rates prior to implementation of varicella immunization programs have been observed in other countries (14).

Brisson *et al*. suggest that if the incidence of zoster increases in unimmunized individuals after varicella immunization then zoster immunization may need to be targeted to those 10 to 44 years of age at the time of introduction to routine immunization. This segment of the population is at high risk of developing zoster due to no boosting effect from exposure to circulating varicella disease. Recent research has demonstrated a significant increase in zoster in children 10 to 19 years of age with most of the cohort either too old to receive the varicella vaccine or had previously been infected when immunization began. Further research is required to determine effective VZV vaccine strategies to minimize the potential increase in zoster incidence (14).

VACCINE CHARACTERISTICS

Varivax® III (live attenuated, [Oka/Merck]), produced by Merck Frosst Canada Ltd., Varilrix® (live attenuated, [Oka-strain]), produced by GlaxoSmithKline Inc. and Priorix-Tetra™ (live attenuated, [Oka-strain]), produced by GlaxoSmithKline Inc. are three varicella vaccines authorized for use in Canada.

Varivax® received its first authorization for use in Canada in 1999 and Varilrix® in 2002. Each vaccine consists of lyophilized, live attenuated varicella virus designated the Oka strain, which was developed in Japan in the mid-1970s. Each 0.5 mL dose of Varivax® III contains a minimum of 1,350 Plaque Forming Units (PFU) (28). Each dose of Varilrix® contains a minimum of 1995 PFU (29).

In July 2007, a combination measles-mumps-rubella-varicella vaccine (MMRV, Priorix-Tetra™, GlaxoSmithKline Inc.) was authorized in Canada and is the subject of a separate NACI statement (30).

IMMUNOGENICITY

A study evaluated whether administration of measles-mumps-rubella (MMR II) and varicella (Varivax®) immunization administered concomitantly at separate injection sites with administration of the two vaccines six weeks apart in two separate groups of subjects would yield differences in immune responses, persistence of antibody, and duration of protection against varicella or safety profiles. Seroconversion rates and percent of those with glycoprotein enzyme-linked immunosorbent assay (ELISA) titres ≥ 5.0 units were the same for the two groups (99.5% and 92.5% for the group with co-administered vaccines vs. 100% and 94.8% for the group given the vaccines six weeks apart, respectively ($p>0.05$)). However, while the seroconversion rates were similar, a statistically significant difference was observed in the geometric mean titers (GMTs) between the two groups. GMTs were slightly but significantly lower in the group with concomitant MMR and varicella vaccine administration: 13.2 in the co-administered groups vs. 17.9 in the group given the vaccines six weeks apart ($p<0.05$) (31). Whether this difference in GMTs is clinically significant is not known.
Varicella antibody persistence rates were >98% to 100% during six years of follow-up for the two groups, and vaccine efficacy during five years of follow-up were similar between the two groups: 90.5% (95% CI: 86.2–95.0) and 88.9% (95% CI: 83.7–93.7) respectively (31).

VARIVAX® III

In children 12 months to 12 years of age, a single vaccine dose gave a seroconversion rate of 98% at 4 to 6 weeks after immunization, with antibodies persisting in 98% at 5 years and 96% at 7 years after immunization (32,33,34). In adults and adolescents ≥ 13 years of age, two doses of Varivax® administered 4 to 8 weeks apart gave seroconversion rates of 75% to 95% and 99% at 4 to 6 weeks after the first and second doses respectively. Antibodies persisted in 97% at 2 years and 97% at 5 years after two doses of vaccine (34,35).

VARILRIX®

A single vaccine dose gave a seroconversion rate of > 98% in children 12 to 36 months old and 97% in children 5 to 7 years old at 6 weeks after immunization. Antibodies persisted for at least 7 years after immunization in children immunized at 12 to 15 months of age (36,37,38,39).

PRIORIX-TETRA™ (MMRV)

There have been several studies that have compared MMRV with MMR plus varicella or MMR alone. These are summarized in the NACI statement on MMRV (available at http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-9/index-eng.php). The studies indicate that significant boosting for all vaccine components occurs whether the second MMRV dose is administered six weeks after the first dose at 12 months of age, or at 15 months up to 5 to 6 years of age (30).

EFFECTIVENESS

To date there is one clinical trial that compares the efficacy of a one-dose varicella immunization regimen with a two-dose regimen. With 10 years of follow-up data, it was found that children receiving two doses of varicella vaccine had significantly higher vaccine efficacy rates than children who received one dose [98.3% (95% CI: 97.3-99.0) vs. 94.4% (95% CI: 92.9-95.7), $p<0.001$], and a 3.3-fold lower risk of breakthrough disease than those who received one dose (40).

A 2006 school outbreak study in the U.S assessed vaccine effectiveness of one-dose versus two-dose varicella immunization, and found a lower attack rate (AR) among children who had received two doses of varicella vaccine (AR 10.4%), compared with those who had received one dose (AR 14.6%) (41). This was very early after the U.S. Advisory Committee on Immunization Practices (ACIP) published their recommendation for two-dose catch-up immunization in outbreak management. Varicella vaccine coverage amongst the school children during the outbreak was very high (97%), but only 39% had received two doses while 58% had received one dose. Further studies are needed to determine if the AR will fall further once two-dose coverage increases.

In Quebec, an evaluation of the impact of the universal varicella immunization program used hospital data to report rates of complications found in varicella-related hospitalizations from 1990 to 2008. Among the neurological complications observed in those hospitalized with varicella, seizures were experienced by 4.6% of individuals less than 20 years of age and by 0.5% of those 20 years of age and older (21). In April 2008, Quebec replaced separate MMR and univalent varicella immunization with a single dose of Priorix-Tetra™ for routine immunization of children at 12 months of age.

A model-based analysis of the potential impact of a two-dose varicella immunization program when compared to a one-dose program predicted that a two-dose program would reduce varicella and zoster cases by about 90% and 10% respectively over 80 years. Various two-dose vaccine program scenarios were evaluated (infant, preschool and grade school) providing robust results that such programs would reduce varicella incidence and breakthrough infections. Long-term predictions indicate that zoster incidence would also decline more markedly with the use of a two-dose program since a smaller proportion of the population would have a history of infection (14).

When the first dose for varicella immunization was recommended by NACI in 1999, the objectives of the program were clearly defined to include reduction in hospitalizations and deaths. The burden of illness related to varicella declined after the first dose program and a further reduction of 22% may be attained through a second dose as described in the Immunization Strategies section of this document. This also provides a premise for the 2010 NACI recommendation for a second dose in Canada (37).

SAFETY

Information on the safety of varicella-containing vaccines can be found in the NACI statements on varicella (7,42) and MMRV vaccine (30).

FEBRILE SEIZURES AFTER PRIORIX-TETRA™ (MMRV)

Febrile seizures are reported in 2% to 5% of children between the ages of 3 months and 5 years (43). These seizures are frequently associated with underlying viral infections and may follow other childhood immunization. Febrile seizures that are generalized but short-lived (<15 minutes), that occur at the height of the fever and that do not recur after treating the fever are generally considered benign, with an excellent neurological prognosis (44). A benign febrile seizure occurring after immunization is not considered a contraindication for future immunization with either the same, or other childhood vaccines (3).

In the study by Schuster *et al*., where two doses of MMRV (Priorix-Tetra™), or one dose of MMR (Priorix®) co-administered with one dose of Varicella (Varilrix®) followed by a second dose of MMR were administered six weeks apart in children 10 to 21 months of age, a febrile seizure was uncommon and comparable in both MMRV [three out of 732 (0.4%); only one of the three was deemed to be related to immunization] and MMR+V [one out of 232 (0.4%)] groups (45). Gillet *et al.* also documented febrile seizures occurring in their cohort of 458 children aged 15 months to 6 years previously immunized with MMR, and randomized to receive either MMRV (Priorix-Tetra™), or MMR+V (Priorix® and Varilrix®) followed by a dose of varicella (Varilrix®) six to eight weeks later. Only one patient in the control group had a febrile seizure after both the MMR+V and varicella immunizations (46). While the risk of febrile seizures has been an issue with ProQuad® (a MMRV vaccine formula available in the U.S.), a Canadian study showed that for the 0-43, 5-12 and 0-4 days period, rate ratios for convulsions were 1.5 (CI 95%:0.8-3.0), 1.3 (CI95%:0.4-4.2), and 1.7 (CI 95%:0.6-5.6) after the first dose of MMRV (Priorix-Tetra™) in comparison with MMR+V in children under 2 years of age. The risk difference was of 4.2 (CI95%:-2.8;11.2), 0.9 (CI95%:-3.3;5.1), and 2.5 (CI95%:-2.0;7.0) respectively for the same period. None of these risks were statistically significant (47). Consequently, larger post-licensure studies may be needed to document if there is any increase in febrile seizure rates after Priorix-Tetra™. Further research using vaccine safety data has estimated that vaccination with MMRV(ProQuad®) results in one additional febrile seizure 7 to 10 days after vaccination for every 2300 doses given to 12 to 23 month olds when compared to administering MMR+V vaccine doses (48). More Canadian adverse event surveillance is needed to assess the risk of febrile seizure post-vaccination as this may impact how adverse events following immunization (AEFI) surveillance is done for MMRV when compared to MMR+V.

For surveillance purposes, the IMPACT surveillance system in Canada is designed to include data on children hospitalized for febrile seizures after receiving childhood vaccines (which would include MMRV) in 12 paediatric tertiary care centres. Vaccine providers are also encouraged to report any cases presenting with febrile seizures within 30 days post-MMRV to the Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) at the Public Health Agency of Canada (PHAC). Febrile seizures are typically seen in emergency rooms and are not hospitalized and hence, may not be captured in IMPACT data.

CONCOMITANT VACCINE ADMINISTRATION

Both varicella vaccines (Varivax® III and Varilrix®) may be administered concomitantly with measles-mumps-rubella (MMR), diphtheria-tetanus-acellular pertussis (DTaP), inactivated polio virus (IPV), *Haemophilus influenza* type b (Hib), pneumococcal conjugate-7, meningococcal C-conjugate, and hepatitis B and influenza vaccines, using separate syringes and at separate sites.

IMMUNIZATION STRATEGIES

The overall goal for varicella disease reduction identified at the National Consensus Conference for Vaccine-Preventable Diseases in Canada (NCC-VPD) in June 2005 was to reduce illness and death due to complications from varicella through immunization (49).

Recommendations from the NCC-VPD include:

- Achieve a sustained reduction of 70% and 90% in the incidence of varicella;
- Achieve and maintain age-appropriate immunization coverage with varicella vaccine in 85% of children by their 2nd and 7th birthdays, and 85% of susceptible adolescents by their 17th birthday;
- Decrease varicella-related hospitalization rates and varicella-related deaths by 80%;
- Achieve and maintain a 100% demonstrated varicella immunity in health care workers;
- Screen 100% of pregnant women annually for immunity to varicella.

Evaluation of the achievement of these recommendations is challenging for several reasons: 1) confirmed cases of varicella disease are currently notifiable in Canada, but confirmation of varicella is not notifiable in all provinces and territories; 2) the commencement of varicella programs varied across the country from 2000 to 2007. As a result, national immunization rates currently reported by the Childhood National Immunization Coverage Survey (cNICS) are limited to children 2 years of age, with the 2009 survey results reporting a rate of 86% coverage for 2 year olds. IMPACT reports demonstrate a 65% to 84% reduction in hospitalizations as a result of a single dose of varicella from 1999 to 2004 or 2006 (50).

The recent NACI Statement published in 2010 providing recommendations for two-dose varicella immunization concludes that healthy children 12 months to 12 years of age should receive two doses of varicella-containing vaccine (univalent or MMRV) for primary immunization based on the accumulated evidence to date (42). However, cost-effectiveness data may play a role in the feasibility of two doses, depending on when the second dose is administered. The cost effectiveness section later in this report describes this in further detail.

A second dose of varicella immunization is also recommended by the Canadian Paediatric Society (CPS) to be included in the routine immunization programs for children. The CPS committee recommends the second dose be provided between 4 and 6 years of age in order to minimize the risk of infection resulting from waning immunity (51).

Table 1 illustrates that a one-dose varicella immunization program is part of the immunization schedules of all Canadian provinces and territories. The most common recommendation is immunization at 12 months for 11 of the 13 provinces/territories (P/Ts), with only Nunavut and Ontario recommending immunization at 15 months. Catch-up immunization with variable schedules exists in most jurisdictions.

Table 1: Canadian Provincial and Territorial Childhood Varicella Immunization Programs.

	Month/Year Implemented	Target Population	Catch-Up Programs
NACI recommendation	**N/A**	**12 months-18months (1 dose)**	**-**
Province/ Territory			
British Columbia	Jan 2005	12 mths	- 4-6 year olds - Grade 6 - Susceptible 18-47 months (ended 2007)
Alberta	Mar 2001	12 mths	- 4-6 year olds (ended 2007) Grade 5 (ended 2007)
Saskatchewan	Jan 2005	12 mths	Grade 6 (ongoing until 2015)
Manitoba	Oct 2004	12 mths	- 4-6 year olds - Grade 4
Ontario	Sep 2004	15 mths	- unimmunized, susceptible 5 year olds (remain eligible until immunized)
Quebec	Jan 2006	12 mths	- 4-6 year olds - Grade 4 (completed) - Non-immune health care workers
New Brunswick	Sep 2004	12 mths	- 4 year olds (ended 2007)
Nova Scotia	Sep 2002	12 mths	- 1-6 yrs old - Grade 4 (ended 2007)
Prince Edward Island	Apr 2000	12 mths	-
Newfoundland	Jan 2005	12 mths	- 4-6 year olds
Northwest Territories	Sep 2001	12 mths	- Children <5 year olds
Yukon	Sep 2007	12 mths	-
Nunavut	Sep 2002	15 mths	-

Note: Table 1 is adapted from the NACI statement: Literature Review on One-Dose and Two-Dose Varicella Immunization; Table 3 (52).

If a two-dose varicella vaccine schedule is to be considered, the most effective timing for the second dose is uncertain. Kuter *et al.*'s study of a two-dose schedule reported a 10-year vaccine effectiveness of 98.3% in children immunized three months apart (40). There are currently no other clinical studies which evaluate the long-term epidemiological outcome of other dosing intervals (e.g. at 12 months, 4 to 6 years or grade 4). The Advisory Committee on Immunization Practices (ACIP) in the U.S. has chosen to recommend 4 to 6 years of age for boosting children with waning immunity (23). As referenced in the 2010 NACI statement (42), theoretically this may provide immunity lasting into the adolescent years, although this has not been studied. A disadvantage of a longer interval between doses is that children with primary vaccine failure after the first dose will be unprotected between the scheduled doses, with potential for day care and pre-kindergarten outbreaks (41). If a higher antibody threshold (correlate of seroprotection) is necessary to prevent breakthrough disease, providing the second dose closer to the first dose (e.g. with two routine doses at 12 and 15 months, or at 12 and 18

months of age) should correct the primary vaccine failure and avoid breakthrough cases in children between infancy and the preschool age group (42).

Each province and territory will need to consider local epidemiology, program feasibility, and cost-effectiveness data when deciding on what option fits best with their jurisdiction.

Five options to be considered for continuing or enhancing the varicella immunization program:

Option 1: Second varicella-containing dose at 18 months

- To coincide with the administration of the 4th dose of DTaP-IPV-Hib which is currently administered by all P/T's at 18 months and would possibly provide the highest second dose coverage; may not address concerns of waning immunity.
- Univalent varicella vaccine or MMRV.

Option 2: Second varicella-containing dose at preschool (4-6 years)

- To coincide with the DTaP-IPV dose recommended at 4-6 years providing high coverage and addressing concerns of waning immunity. This option, however, would leave those with primary failure susceptible for several years before receiving the second dose.
- Univalent varicella vaccine or MMRV.

Option 3: Second varicella-containing dose or catch-up dose between grades 4 to 7

- To be administered concurrently with either the hepatitis B vaccine and/or the human papillomavirus school-based programs. However, this may result in the lowest second dose coverage as well as leaving those with primary failures susceptible even longer before they receive their second dose.
- Establish end date for school-based catch-up program.

Option 4: No second dose recommendation

Option 5: Catch-up programs in addition to the options mentioned above

- May be considered at the level of preschool or school-aged students.
- Should be a decision made by each jurisdiction depending on epidemiology of disease and immunization program introductions.
- Establish end date for school-based catch-up program, if implemented.
- Providers should use all clinical opportunities to screen for needed vaccines and, when indicated, to immunize (3).

COST EFFECTIVENESS

Implementation of routine varicella immunization programs has raised certain concerns, such as varicella immunization programs leading to increased incidence of varicella and zoster infection. Policy decisions pertaining to the implementation of a routine varicella immunization program involving two doses require examination of the potential short and long-term impact on the population (14).

Unpublished cost-effectiveness analyses of one- and two- dose varicella immunization by Brisson (November 2010) demonstrate a range from cost saving to producing overall losses in Quality-Adjusted Life-Years (QALYs) for a second dose of varicella vaccine (versus a one-dose program) (14). Under base case assumptions, however, implementing a second dose of varicella at 18 months yields a cost per QALY of $52,833 (90% uncertainty interval: $16,779 to $925,386) while a grade 4 program would cost $7,102 per QALY (90% uncertainty interval: cost-saving to $27,901). A commonly used threshold is that interventions are “very cost effective” if they are less than the per capita gross domestic product (GDP), which for Canada resulted in a threshold of $40,000 being used in Brisson’s papers on this issue. In Brisson’s sensitivity analysis, under many model and parameter assumptions, two-dose immunization (vs. one-dose) yields cost-effectiveness ratios below $40,000 per QALY-gained.

While it is important to understand cost-effectiveness, there is a need for more analysis on the economics of chickenpox and shingles, and to understand the benefits of one approach over another for a two-dose program.

ACCEPTABILITY AND FEASIBILITY

PROGRAM ACCEPTABILITY

Universal measles, mumps, and rubella immunization has been established in many industrialized countries. Safe and effective vaccines have been available for a number of years. There is a general acceptance of the measles, mumps, and rubella vaccines, but less so for the varicella vaccine. In 2009, coverage of measles, mumps and rubella were estimated to be above 90% among 2 year olds in Canada according to the Childhood National Immunization Coverage Survey (cNICS) (53). Similar uptake is expected for the two dose varicella immunization. The first dose of varicella vaccine as introduced in early 2000 was at first not widely accepted by the public and health professionals - many healthcare professionals and parents alike felt that varicella disease was a 'rite of childhood' (i.e. something that all children experience). However, in more recent years, there is a growing acceptance and uptake of this vaccine with more parents agreeing to have their children immunized. In 2009, the cNICS found that 86% of 2 year olds in Canada had received the varicella vaccine (53). According to the National Immunization Survey (NIS) in the U.S., vaccine coverage for one dose of varicella indicates a high level of uptake of a single dose of varicella (54). When the vaccine was introduced in the early 2000s the requirements for a second dose were discussed as a possibility (6).

The introduction of the second dose program in the U.S. was hampered by reports of febrile seizures post first dose with the Merck product ProQuad®, which is not currently authorized in Canada. This occurrence is outlined in the NACI statement (6). Further surveillance is required to determine if a similar scenario would occur with the use of the product currently being used in Canada, Priorix-Tetra™. Coverage estimates for one dose of a varicella-containing vaccine in Quebec among children less than 15 months have steadily increased from 23% before the implementation of a vaccine program, to 52% in 2006 and 89% in 2008, demonstrating acceptability of the program (21). Coverage of varicella immunization also increased in Alberta over time, with 69% coverage in 2002 (one year after program implementation) to 87% in 2007 among one year old children. Similarly, in Manitoba, coverage of the varicella vaccine was 3.2% in 2002 and increased to 64.2% among 2 year olds in 2006, 2 years following implementation of the varicella immunization program. In BC, varicella coverage for children at the 2nd birthday born in 2004 was 78.9% and this coverage increased to 83.6% among two-year olds born in 2006, the year the varicella immunization program was implemented in BC (55).

An important issue determining acceptability/feasibility is the cost of a new program, and the competition for fiscal resources by similar programs. Savings from previous three dose programs being reduced to two dose programs (i.e. HBV) may reduce the vaccine budget and the administration requirements in some jurisdictions. These changes to dosing may allow for an opportunity to introduce a second dose schedule in Canada.

The introduction of new vaccines is planned, operationalized and paid for by P/Ts. How specific new vaccine programs are prioritized may be dependant upon the epidemiology within the jurisdiction, budget availability and level of political support. Not implementing a two-dose program could result in negative public perception of the effectiveness and value of the varicella vaccine due to continued breakthrough disease in those who have received one dose of the vaccine (52).

PROGRAM FEASIBILITY

Varicella vaccine is now available and approved for use in Canada in both univalent (Varivax® and Varilrix®) and combined with MMR (MMRV or Priorix-Tetra™). The most convenient schedule would be a first dose at 12 months, which concurs with current practice, and a second dose at a time that meets the individual P/T schedule. The following table reflects the current vaccine use in the Canadian schedule and a possible catch-up plan (February 2012).

Table 2: Current Provincial and Territorial Childhood Varicella (VZ) Immunization Programs.

Province/ Territory	VZ 1st dose (vaccine update) Date Implemented	VZ 2nd dose Date Implemented	Catch-up program
British Columbia	12 months (MMR+V*) Jan 2005	4-6 yrs (V) January 2012	grade 6 catch-up starting 2012/13 school year
Alberta	12 months (MMRV) Aug 2010	4-6 yrs (MMRV) Summer 2012	no catch-up
Saskatchewan	12 months (MMRV) Oct 2010	18 months (MMRV) April 2011	Grade 6
Manitoba	12 months (MMR + V) Jun 2012	n/a	n/a
Ontario	15 months (V) Jan 2005	4 – 6 years (MMRV) August 2011	Catch-up for children born on or after January 2000
Quebec	12 months (MMRV) Apr 2008	n/a	n/a
New Brunswick	12 months (MMRV) May 2011	18 months (MMRV) May 2011	Limited catch-up for all those born in 2009
Nova Scotia	12 months (MMRV) April 2012	4-6 years (MMRV) April 2012	no catch-up
Newfoundland & Labrador	12 months (MMRV) Jan 2012	n/a	n/a
Prince Edward Island	12 months (MMRV) Aug 2010	18 months (MMRV) October 2011	no catch-up
Northwest Territories	12 months (V) Sept 2001	n/a	< 5 years, Grade 9
Yukon	12 months (V) Jan 2007	4 – 6 years (V) April 2012	no catch-up
Nunavut	15 months (V) Sept 2002	n/a	n/a

* MMR + V are the separate vaccines (measles, mumps, rubella vaccine, and the varicella vaccine)
** MMRV is the combined Measles, Mumps, Rubella and Varicella vaccine

The varicella vaccine has been in production for over 20 years; there has not been a shortage within this time frame. To ensure vaccine supply is available and maintained, manufacturers require approximately 18 months notice of a new program.

The ability of provinces and territories to provide a second dose varicella vaccine series will depend on their current schedule, who administers the immunization (physicians vs. public health etc.) and the feasibility of incorporating the second dose into the current immunization schedule. The target population for this second dose is already being seen by their health care professional and is therefore relatively accessible. Uptake can be expected to be similar to the second dose of MMR. If the vaccine is given as a univalent vaccine rather than the combined MMRV, there may be concerns from parents related to multiple injections.
All varicella vaccines licensed in Canada require the same cold chain protocol (+2˚C to +8˚C). Implementing the program, techniques for informing the public and marketing strategies to ensure adequate uptake will be similar to those used in the past to introduce second doses for other vaccines, such as measles.

Overall, acceptability of a second dose program is likely to mirror that of the single dose varicella program, where it may take time for this to occur. However a bigger issue may be the willingness to fund such a program.

EVALUATION

As with any new immunization program, an evaluation plan for second dose varicella should be developed by each jurisdiction during the planning stages and should be specific to the activities identified in the strategy. Immunization coverage, for the general population as well as hard to access populations, are the most basic evaluation tool. Use of an immunization registry for evaluating coverage is current best practice, although some jurisdictions may make use of surveys or other methodologies.

Different schedules with respect to the timing of the second dose of a varicella vaccine implemented by jurisdictions should also be evaluated in terms of vaccine coverage and acceptability. Examining differences in varicella epidemiology between cohorts immunized at 18 months versus at pre-school time (for the second dose) will provide a greater certainty on equivalency or preference of the one schedule over the other.

What is more difficult is evaluation of the impact of second dose varicella programs on burden of disease and incidence of herpes zoster (shingles) in children and adults. There is a need for more information on the burden of shingles, particularly in younger populations. In Canada evaluation of the burden of disease is currently dependant on the IMPACT surveillance system for identifying hospitalized cases, and on special studies. There is a patchwork of passive reporting systems in some jurisdictions which is generally unreliable. A sentinel surveillance system with more active surveillance, similar to the VASP in the U.S., would provide a more effective evaluation tool. Hospitalization data could also be looked at regularly. The existing AEFI reporting system provides a basic evaluation tool for monitoring unexpected adverse events.

RESEARCH QUESTIONS

The following is a list of priority research questions related to adding a second dose of a varicella-containing vaccine to the current immunization schedule:

- How long will protection last – will a series of doses be necessary into adult life?
- What is the most effective time to deliver a second dose (18 months, preschool or during a school age program in grade 4-6)?
- Is there a change in epidemiology of primary varicella infections: changes in age specific rates, aimed primarily at detecting an increased incidence rate in adults? Will VZ rates increase at child bearing age?
- How will a second dose impact disease prevalence and severity as well as varicella-related health service use? Also, what will be the economic impact of a second dose?
- What is the impact of varicella vaccine on herpes zoster (shingles) in children and adults?
- What is the risk of febrile seizures among those receiving MMRV? What is the proportion of children having febrile seizures following MMRV compared to those who received MMR+V? Is this a question more related to the preparation rather than whether there is a one or two dose varicella schedule?
- Are the different vaccine preparations interchangeable?
- Will an adult, immunized at one year of age, require a second dose in adulthood?

OTHER CONSIDERATIONS

EQUITY CONSIDERATIONS

If publicly funded two-dose varicella immunization programs are not introduced in every province and territory in Canada, inequities in varicella disease control may arise in jurisdictions that do not implement this program. For example, jurisdictions who chose to introduce a two-dose program may experience reduced disease incidence (both the wild and vaccine virus types), help protect children against primary and secondary vaccine failure, and reduce the incidence of zoster in later years (42).

ETHICAL CONSIDERATIONS

Immunization is not mandatory in Canada and the introduction of a two-dose varicella program would continue to be voluntary in Canada. Provinces and territories have policies in place to address their specific populations to ensure continued high immunization coverage and a change in these policies is not recommended.

There may be an ethical risk for jurisdictions that choose to implement a second dose strategy later (e.g. school-age), where children who fail to mount a sufficient response to the first dose may be unnecessarily exposed to disease before the second dose is provided. However, it is expected that virus circulation would be sufficiently reduced, resulting in a lowered risk of disease (52).

Hard to reach populations are pertinent to the acceptability of the program, but also present important ethical considerations. Provinces and territories work to achieve the optimal level of coverage to ensure protection of their communities; the hard to reach populations vary by P/Ts as do the immunization rates.

Another ethical issue is related to the possibility that improved control of childhood disease could result in increases in zoster within the adult population due to less natural boosting of immunity. This is not yet an established effect, and there is also another possible intervention – the use of vaccine against zoster (i.e. ZOSTAVAX®)

PROGRAM CONSISTENCY ACROSS CANADA

Despite the 65% to 88% reduction in hospitalizations as a result of a single dose of varicella (as demonstrated through IMPACT) (24, 56), the U.S. has chosen to implement a two-dose varicella immunization program, with the second dose occurring at kindergarten (4-6 years of age). Data from the U.S. provides rationale for their 2006 recommendations for a second dose (23), in summary:

- No further reduction in cases since 2004
- An upward shift in the median age at disease onset
- Childcare centers and schools continued to report outbreaks between 2001 and 2005
- The index cases in some outbreaks were immunized children who developed breakthrough varicella and transmitted the infection to others

- Primary vaccine failure appears to be partly responsible for breakthrough disease
- Waning immunity (secondary vaccine failure) may also account for subsequent breakthrough disease, with several outbreak studies in the U.S. reporting that time since immunization was an important risk factor

The varicella vaccine is not currently recommended in the routine childhood immunization schedule for children in the U.K. However, a two dose schedule with four to eight weeks between doses is recommended for those considered to be at risk for infection, such as children with weakened immune systems and health care workers (57).

Should jurisdictions in Canada implement a two-dose varicella program, the timing of the second dose would vary between 18 months and school-age. Harmonizing immunization schedules in Canada including this vaccine program may be helpful for parents and other health providers, but it may not be feasible from a program or cost perspective for each P/T.

While the current one-dose varicella immunization program in all provinces and territories will not achieve the elimination of varicella, some type of strategy should be considered in each jurisdiction to ensure the lowest level of varicella morbidity and mortality of Canadians.

CIC RECOMMENDATIONS

Decisions on whether, when, and how to implement a second dose program will remain at the jurisdictional level.

There are three acceptable ways in which second dose varicella-containing vaccine programs can be integrated within existing immunization programs: infant, preschool and school aged programs. Each of these approaches has advantages and disadvantages, with no clear evidence-based gold standard.

Programs at the preschool visit or in school-based programs may not affect the primary failure rate in the youngest children (school-based more than preschool programs), they may protect those with primary vaccine failure by decreasing virus circulation and enhancing the herd effect. Although there are many unknowns, school-based programs may be the most cost-effective option for implementation of the second varicella dose.

The details of programs may vary from one jurisdiction to another to provide the best match with currently existing programs and jurisdictional epidemiology.

The CIC recommends that:

- Provinces and territories implement second dose varicella programs with a goal of improved control of varicella disease and to minimize the risk of outbreaks and later breakthrough disease.
- Schedules (one or two doses of varicella) be evaluated in order to make more evidence-based decisions on the most effective ways to deliver second dose programs in the future.
- Federal, provincial and territorial governments consider strategies to enhance surveillance of varicella and zoster to better inform future decision making related to these immunization programs.
- The document be put forward to PHAC and CIHR for inclusion in future discussions about research priorities.

CIC cannot make recommendations regarding catch up programs due to a lack of cost-effectiveness data.

CONCLUSIONS

Routine varicella immunization to date has resulted in significant reductions in the burden of varicella disease as well as associated morbidity and mortality. The addition of a second dose of varicella vaccine to the routine childhood immunization schedule will result in better control of this childhood disease by further reducing varicella incidence and its complications, but not elimination. Single dose programs have been shown to be acceptable to the public. The presence of a combined MMRV vaccine facilitates implementation of such programs when compared to the past.

A second dose program is also anticipated to reduce breakthrough disease among populations immunized against varicella. However, in the long term, there is great uncertainty surrounding the effect of a one dose varicella program, and an even greater uncertainty around a two varicella dose program. This uncertainty applies to the effects of such a program on the epidemiology of both varicella and zoster. The CIC does recommend the implementation of a two-dose varicella immunization program; however the Committee is uncertain of the long-term implications of such a program.

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