Recommendations for routine two-dose varicella immunization in children

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Abstract
All Canadian provinces and territories have had routine immunization programs for one dose of varicella vaccine since 2007, a strategy that has reduced varicella disease rates dramatically. However, breakthrough cases still occur, and some cases are severe. There is increasing evidence that immunity to one dose of the vaccine can wane in a vaccinated population, and the disease may be shifting to an older age group that can experience more severe disease and more complications. This statement presents the rationale for a two-dose immunization strategy in Canada, as well as recommendations for a routine two-dose varicella vaccine schedule for all Canadian children. Children who have had one dose of varicella vaccine and have not had breakthrough infection should receive another dose of varicella vaccine. This document replaces the Canadian Paediatric Society's 2005 position statement on varicella prevention.

Key Words: Canada; Canadian Paediatric Society vaccine recommendations; Children; Vaccine schedule; Varicella vaccine

The National Advisory Committee on Immunization (NACI) first recommended universal varicella vaccination for children in 1999 [1]. By 2007 all provinces and territories in Canada had incorporated routine varicella immunization programs for infants at 12 or 15 months of age. Following the institution of routine varicella immunization there was a dramatic decrease in the incidence of varicella in both Canada and the United States. Nevertheless, breakthrough cases have persisted. Breakthrough disease led the American Academy of Pediatrics to recommend a two-dose varicella immunization schedule in 2007 [2]. This recommendation has subsequently been implemented throughout the United States.

In September 2010, NACI recommended a two-dose schedule for varicella immunization [3]. The present CPS position statement, which replaces the statement published in 2005 [4], outlines the epidemiology of varicella in Canada and the rationale for a two-dose varicella immunization strategy for all children nationwide.

Canadian objectives for varicella immunization

The Canadian varicella disease prevention goal, established by a consensus conference in 2005, was to decrease the incidence of varicella in Canada by 90% by 2015 and to reduce varicella-related hospitalizations and deaths by 80% by 2010 (compared with incidence from the pre-vaccine era [5]. Reducing illness and death from complications of varicella was to be achieved through immunization programs.

It is difficult to determine the success of Canada's current varicella vaccine programs because limitations of the passive reporting system lead to under-reporting. This is especially true for cases of varicella that do not lead to hospitalization. However, the Immunization Monitoring Program, ACTive (IMPACT), a collaborative effort with the Canadian Paediatric Society and the Public Health Agency of Canada, captures varicella-related hospitalizations at 12 tertiary care paediatric hospitals in 8 provinces. When compared to historical controls, IMPACT has reported an 84% decline in varicella-related hospitalizations in provinces that introduced
publicly-funded varicella vaccination programs between 2000 and 2002. In provinces with programs instituted between 2004 and 2006, a 65% decrease in hospitalizations was observed [8]. Kwong et al reported a population-based study in Ontario and documented that the rates of hospitalization, emergency department visits and physician visits decreased by 53%, 43% and 45% respectively after the province implemented a publicly-funded vaccination program [9]. The available data show that we are approaching but have not yet met our national goal.

Primary vaccine failure versus secondary vaccine failure

Natural disease induces immunoglobulin G (IgG) varicella antibody, measurable in commercial laboratories. However, standard varicella serology does not detect antibody to the vaccine strain. There are two assays to detect antibody to the varicella vaccine strain (gpELISA and the FAMA test) but these are only available in reference laboratories. Therefore, it is often not possible to determine if a child who received vaccine is immune.

The two reasons given for improved efficacy of a two-dose varicella vaccine schedule over a one-dose schedule involve the concepts of primary and secondary vaccine failure.

Primary vaccine failure implies that after vaccine is given, a protective immune response does not develop. Even using the assays mentioned above, immunity can be difficult to prove because a threshold defining a protective titre has not been clearly established. Using definitions for protection developed for research study purposes, more patients had seroprotective antibody levels with two doses of vaccine compared to one dose [10].

Secondary vaccine failure or waning immunity is another consideration. Most reports on this come from outbreak investigations, where some report an increased chance of breakthroughs with longer time since vaccination, while others do not. Active surveillance data collected in 1995 to 2004 with a sentinel population of 350,000 were analyzed to determine whether the incidence or severity of breakthrough varicella increased with time since immunization. Children vaccinated at least 5 years previously were 2.6 times more likely to have moderate and severe breakthrough varicella than those vaccinated less than 5 years previously. The annual rates of breakthrough varicella among children aged 12 months to 12 years increased significantly with time since vaccination, after adjusting for the effects of age at infection, age at vaccination, and year of infection [11].

The relative importance of primary versus secondary vaccine failure is unknown at this point. Theoretically, a two-dose schedule should improve varicella immune response and vaccine effectiveness.

Benefits and limitations of one- and two-dose schedules

Most of the data on one- and two-dose varicella immunization efficacy comes from the United States, where a single-dose varicella vaccination program was used between 1996 and 2007. In 1999, the Centers for Disease Control and Prevention (CDC) recommended that varicella immunization be required for children attending child care and for elementary school entry. These requirements have been implemented in almost all states. In 1995, the CDC established a Varicella Active Surveillance Project (VASP) in three US communities. By 2000, varicella vaccine coverage was 74%-84% in the VASP communities and the number of varicella cases declined by 71%-84%. Varicella hospitalizations in two VASP communities declined from about 3 per 100 000 population during 1995-1998 to 0.8 per 100 000 population in 2005. The number of varicella-related deaths dropped from 115 in 1995, to 26 in 2001 and 16 in 2003 [12].

Despite these dramatic results, the CDC has reported limitations of the single-dose recommendation [13]. While the incidence of varicella disease has declined dramatically, case numbers have plateaued despite vaccine coverage rates of 90% [14]. Also, there has been a shift in the median age of disease onset for children whether or not they have received varicella vaccine. At the VASP Antelope Valley site, the median age of varicella breakthrough disease rose from 5 to 8 years of age in children who had been vaccinated, and from 5 to 13 years in those who were never vaccinated. At the West Philadelphia VASP site the shift in median age in unvaccinated cases went from 6 to 19 years [15]. These data suggest that varicella disease may be shifting into older age children and even into adults. This shift may have clinical implications since adolescents and adults with varicella infection have more severe complications than young children.
Breakthrough disease leads to questions regarding vaccine efficacy. Investigators in US outbreaks have looked at both vaccine effectiveness and disease severity. The effectiveness of a single-dose varicella vaccine was greater than 90% for preventing severe disease. However, effectiveness for preventing disease of any severity generally ranged between 70% and 85% with some studies as low as 20% [13][14]. Breakthrough disease is usually much less severe than naturally occurring varicella, but it was still associated with complications in about 5% of cases [15]. Of note, children who have been vaccinated previously with a single dose of varicella vaccine, but who then develop neoplastic disease or have immunosuppressive conditions, are at a significantly higher risk for breakthrough disease requiring antiviral therapy [16]. Several outbreak studies have also reported that effectiveness seems to wane with time since vaccination [13][17][18].

Timing of the second dose
Optimal spacing of the two doses is unknown. Theoretically, giving the second dose of varicella vaccine at 18 months of age would reduce primary failures, while giving the second dose at 4 to 6 years of age may prevent secondary vaccine failure. The relative importance of these two factors is unknown and an optimal regimen has not been established. The expert opinion of the Canadian Paediatric Society’s Infectious Diseases and Immunization Committee is that waning immunity is likely the most important factor. This committee recommends the second dose be given between 4 and 6 years of age until all provinces and territories have universal public programs in place or more data are available. The two doses must be given a minimum 3 months apart for children less than 12 years of age, and 4 weeks apart for older children. The routine primary immunization second dose can be given 3 months from the first dose, and should be received by age 6 years.

Safety
Both pre- and post-licensure studies have confirmed that varicella vaccine is safe and generally well tolerated. The only common adverse event is pain and redness at the injection site. There are slightly more injection site complaints after the second dose in a two-dose regimen [19].

Prenatal assessment for varicella immunity
There are potentially severe consequences of varicella infection during pregnancy, including severe disease in the pregnant woman, teratogenicity, and severe disease in the neonate. In vaccinated populations where the age of primary varicella disease may be increasing, pregnant women are a particularly vulnerable population. Prenatal assessment of women for evidence of varicella immunity is recommended (see below for definitions of immunity), and upon completion or termination of pregnancy, those who are not immune should be vaccinated. Breastfeeding is not a reason to delay vaccination.

Evidence of immunity
It is becoming increasingly important that all health care workers be immune to varicella. As well, prenatal assessment of women for evidence of varicella immunity is recommended. Natural disease induces an IgG varicella antibody that is measurable in commercial laboratories. People who have received varicella vaccination generally do not demonstrate an IgG to varicella zoster virus (VZV). The two antibody tests used in vaccine studies are not commercially available, so measuring vaccine-induced immunity is not possible at present.

Although a clinical history of varicella is traditionally considered as proof of immunity, the clinical diagnosis of varicella may become less reliable when wild-type disease is less common and breakthrough disease is often atypical (ie, fewer lesions, papules and/or no vesicles). Given these caveats, other strategies to confirm varicella immunity are needed.

Any of the following should be considered to be evidence of immunity to varicella:

- IgG to VZV as measured by any method (confirms natural disease)
- documentation of receipt of two doses of varicella vaccine (do not do serology)
- laboratory confirmation of varicella or herpes zoster from a lesion
- previous diagnosis of varicella disease or herpes zoster by a health care provider.
**Recommendations**

The levels of evidence reported in these recommendations have been described using the evaluation of evidence criteria outlined by the Canadian Task Force on Preventive Health Care [20]. The Canadian Paediatric Society recommends the following:

- Healthy children aged 12 months to 12 years of age should receive two doses of varicella-containing vaccine for primary immunization (A-III). The second dose of varicella vaccine may be given three months or longer after the first varicella immunization. The second dose should be given at four to six years of age in order to minimize risk of infection resulting from waning immunity, or until all provinces and territories have universal programs in place, or until more data are available on the best scheduling option.

- The first dose of a varicella-containing vaccine should be given between 12 and 18 months of age.

- Susceptible adolescents 13 years of age and older should continue to receive two doses of varicella vaccine four weeks apart.

- Children who have received one dose of varicella vaccine should be immunized with a second dose if they have not developed breakthrough disease.

- Canadian physicians should advocate for universal funding and integration of this two-dose regimen into provincial and territorial programs to ensure equitable access for all Canadian children.

- Prenatal assessment of women for evidence of varicella immunity (criteria in text) is recommended. Women who do not have evidence of varicella immunity should be vaccinated once they are no longer pregnant.

- Further research should be done in Canada to determine:
  - Duration of vaccine-induced varicella immunity, and requirements for future boosters
  - Relative contributions of primary and secondary vaccine failure
  - Optimal spacing of the two doses
  - Varicella surveillance and vaccine coverage rates in Canada.

**References**


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