Towards universal childhood immunization against chickenpox?

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Live attenuated varicella vaccine is available in Canada. The National Advisory Committee on Immunization recommended immunization of healthy susceptible individuals after one year of age. This was endorsed by a National Varicella Consensus Conference, provided that 90% coverage could be ensured. So far only Prince Edward Island has begun universal childhood immunization. Barriers to achieving high childhood vaccine coverage include: the perception that chickenpox is mild in children but severe in both adults and immunocompromised; concern that vaccine field effectiveness will be much lower than observed in pre-licensure efficacy trials; fear that waning immunity may increase adult cases and the associated disease burden; and uncertainty regarding long term morbidity due to vaccine strain reactivation. In fact, chickenpox is usually an uncomplicated illness in otherwise healthy individuals of *all* ages. Further, with varicella zoster immunoglobulin (VZIG) prophylaxis and acyclovir treatment soon after rash onset, the course in immunocompromised individuals is also usually benign. However, on a population basis, otherwise healthy children with no identifiable risk factors account for 80% to 90% of all chickenpox-associated hospital admissions and 40% to 60% of case fatalities. A more accurate assessment of the relative merits of varicella immunization should contrast the current natural history of disease (90% to 95% infected symptomatically by age 15 years, 15% lifetime risk of a moderate to severe reactivation episode) with the demonstrated vaccine effectiveness of 70% to 86% against any chickenpox, 95% to 100% against moderate to severe illness and significant reduction of frequency and severity of reactivation illness.

Key Words: *Chickenpox; Shingles; Vaccine; Varicella zoster*

Vers un vaccin antivaricelleux universel pour les enfants?

Le vaccin vivant atténué antivaricelleux est offert au Canada. Le Comité consultatif national de l'immunisation a recommandé la vaccination des individus susceptibles et en santé de plus d'un an. Cette recommandation est avalisée par la Conférence nationale de concertation sur la varicelle, sous réserve de garantir une couverture de 90 %. Jusqu'à présent, seule l'Île-du-Prince-Édouard a entrepris l'immunisation universelle des enfants. Les obstacles à l'atteinte d'une couverture vaccinale élevée des enfants s'établissent comme suit : la perception selon laquelle la varicelle est bénigne chez les enfants, mais grave à la fois chez les adultes et les personnes immunocompromises, l'inquiétude que l'efficacité du vaccin sur le terrain soit très inférieure à celle observée pendant les essais d'efficacité effectués avant l'homologation, la crainte que la baisse de l'immunité accroisse le nombre de cas chez les adultes et le fardeau de la maladie en découlant et l'incertitude quant à la morbidité à long terme causée par la réactivation des souches vaccinales. En fait, la varicelle est généralement une maladie sans complication chez les personnes en santé de *tout âge*. De plus, grâce à la prophylaxie à l'immunoglobuline du virus varicelle-zona (IGVZ) et au traitement à l'acyclovir peu après l'apparition de l'éruption, les personnes immunocompromises sont généralement atteintes d'une maladie bénigne. Cependant, dans la population générale, les enfants autrement en santé ne présentant aucun facteur de risque identifiable représentent de 80 % à 90 % de toutes les hospitalisations secondaires à la varicelle et de 40 % à 60 % des décès imputables à cette maladie. Une évaluation plus précise des mérites relatifs de l'immunisation à la varicelle devrait tenir compte de l'évolution naturelle de la maladie (90 % à 95 % de la population a souffert d'une infection symptômatique à l'âge de 15 ans, risque à vie d'une réactivation modérée à grave de 15 %) par rapport à l'efficacité démontrée du vaccin, oscillant entre 70 % et 86 % dans tous les cas de varicelle et entre 95 % et 100 % dans ceux de varicelle modérée à grave, et par rapport à la réduction considérable de la fréquence et de la gravité des cas de réactivation.

In December 1998, a live attenuated varicella zoster virus vaccine was licensed for use in Canada. The National Advisory Committee on Immunization (NACI) recommended the vaccine for primary immunization of healthy, susceptible individuals age 12 months and older (1). In May 1999, a National Varicella Consensus Conference was held to develop guidelines for use of the vaccine in Canada (2). Participants included provincial and territorial public health officials, broad representation from Canada's health professional societies including the Canadian Paediatric Society, federal delegates from the Laboratory Centre for Disease Control, Bureau of Biologics and Medical Services Branch, a delegate from the United States Centers for Disease Control and Prevention (Atlanta, Georgia), representatives of two varicella vaccine manufacturers, and a consumer advocate. Although there was

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TABLE 1: Course of chickenpox in otherwise healthy children aged younger than 20 years according to immunization status and treatment with acyclovir

	Placebo group in acyclovir trials*		Treated group in acyclovir trials†		Prelicensure VZV vaccine studies (5,6)‡
	2 to 12 years (4)	13 to 18 years (3)	2 to 12 years (4)	13 to 18 years (3)	1 to 19 years (5)
Total number of cases	357	31	367	31	162
Median number of spots	347	>500	294	>500	32 to 40
Percentage with more than 500 spots	38.4	71	21.3	58	1.7
Oral temp >37.8°C					
Rash day 1	52%	48%	46%	48%	28%
Rash day 3	25%	37%	10%	4%	Not stated
Any complication	7 (2%)	2 (6.4%)	4 (1%)	0	0
Bacterial skin infection	6	2	4		
Concomitant urinary tract infections	3	0	2		
Cerebellar ataxia	1	0			
Intervention benefit					
Illness duration			About one day less		About one day less (6)
Clinical severity			15% to 30% reduction		80% to 90% reduction

Nothing other than symptomatic therapy; †Oral acyclovir 24 h or less after rash onset; ‡Varicella zoster virus (VZV) vaccine more than 42 days preillness onset; no acyclovir

consensus that universal varicella vaccination programs should be undertaken in Canada, a refrigerator stable product was seen as key to the feasibility of achieving 90% vaccine coverage of the target population. Priorities were set for the use of the currently licensed, freezer stable vaccine, focusing on susceptible adult health care workers and selected immunocompromised hosts. Varicella susceptible healthy children from age one to 10 years were fourth and fifth on the priority list. To date, only Prince Edward Island has plans to implement a universal vaccination program against chickenpox, and there is still a diversity of opinion as to the need and potential pitfalls of embarking on such a course.

Those who are either ambivalent or who actively oppose routine childhood immunization against chickenpox express one or more of the following viewpoints or concerns.

- Chickenpox is a benign disease of childhood and as such does not need to be prevented.
- Chickenpox is a severe disease in susceptible adults and immunocompromised hosts, and should be the focus of prevention efforts.
- Under ideal study conditions, the vaccine did not prevent all cases of chickenpox. Given the temperature instability of the vaccine, it is likely that the effectiveness under 'real life' conditions will be even worse.
- Routine childhood immunization with either poor coverage or waning immunity may result in a shift of disease to an older population, thereby increasing morbidity and mortality relative to the current status quo.
- Herpes zoster or shingles may result from the vaccine strain with the potential to cause worse problems than those seen currently.

In each of these statements lie some truth and some fallacy as will be discussed below.

CHICKENPOX IS A DISEASE OF CHILDHOOD BUT IT IS NOT SO BENIGN

The lifetime risk of chickenpox is 95%, and there are about 350,000 cases each year in Canada (1). Of these, nearly 50% occur before age five years, 85% before age 10 years and 92% before age 15 years (1). Table 1 shows the clinical features of untreated chickenpox among otherwise healthy children and contrasts them with illness modified by early treatment with acyclovir (3,4) or prior immunization (5,6). Untreated chickenpox results in an average of three to four missed days of school or daycare and may cost an additional 0.5 to three days when exclusion rules are in effect (7).

Minor complications, primarily secondary bacterial skin infections, nausea, mild dehydration and otitis media, occur in 2% to 10% of cases (3,4,8). Despite these low numbers, a consistent finding across nearly all studies of the health care impact of uncomplicated chickenpox in North America, Europe and Australia is that from 20% to 50% or more of children with chickenpox see a physician (1,7). In Canada, this translates to about 170,000 physician visits a year, of which 47% involve children younger than age five years, 80% involve children younger than age 10 years and 88% involve children younger than 15 years of age (9). The rationale for these visits is not clear, and acyclovir is seldom prescribed in outpatient settings. Nevertheless, medical costs for the outpatient management of chickenpox are estimated to be about $11 million/year in Canada or about $32/child with chickenpox/year (7).

Serious complications of chickenpox, resulting in hos-

TABLE 2: Presentation and hospital course according to prior immune status for children admitted to a Canadian Immunization Monitoring Program ACTive (IMPACT) centre between January 1, 1991 and March 31, 1996 for chickenpox or a related complication

Prior health status	Healthy	Immuno-compromised
Number	488	298
Mean age (years) (range)	4.0 (0.1 to 17.4)	6.4 (0.1 to 20)
VZIG prophylaxis	NA	38.5%
Days of rash prior to hospital admission	5	2
Percentage with varicella complication at admission	90%	20%
Hospital course		
Admitted to intensive care	5%	3%
Required mechanical ventilation	2%	1%
Treated with acyclovir in hospital	24%	98%
Median days in hospital (range)	4 (1 to 57)	6 (1 to 50)
Mortality	0.2% (1)	0.5% (1)

VZIG Varicella zoster immunoglobulin. Adapted from references 1 and 18

pitalization, occur in 0.1% to 0.6% of cases. These rates are low, but the consequences are substantial. Each year in Canada there are an estimated 1700 to 2200 hospitalizations for chickenpox or a related complication (1). Of the hospitalizations, 70% involve children younger than age five years, about 85% involve children younger than 10 years and 90% involve children younger than 15 years. About two-thirds of the cases are in otherwise healthy children. Chickenpox increases the risk of severe group A beta-hemolytic streptococcal illnesses such as necrotizing fasciitis, toxic shock-like syndrome and sepsis by a factor of 40- to 60-fold (10). It has been estimated that preventing chickenpox could prevent 15% or more of such illnesses. The estimated annual cost of hospital-based management of paediatric chickenpox in Canada is $12.8 million or about $37/child with chickenpox/year (11). Dividing the hospital cost by all cases in healthy children reflects the reality that it is impossible to predict which child will become seriously ill due to varicella or a related complication.

Finally, healthy children do die as a result of chickenpox, albeit rarely. Of the annual 70 to 100 deaths reported in the United States, nearly 50% involve children younger than age 15 years, of whom 90% have no known underlying risk factor (12).

As shown in Table 1, acyclovir therapy can reduce the severity of chickenpox, but the benefit is small and the cost is high. Although vaccine is not 100% effective in preventing chickenpox, the clinical severity of breakthrough infection is minimal relative to wild type infection in nonimmune individuals.

AMONG ADULTS, CHICKENPOX IS RELATIVELY MORE SEVERE THAN AMONG CHILDREN; HOWEVER, THE ABSOLUTE SEVERITY HAS BEEN OVERSTATED

Population-based studies show that during an episode of acute chickenpox the risk of any hospital admission among adults is 12- to 17-fold higher than among children aged younger than 15 years and 3.3-fold higher than among adolescents 15 to 19 years; the respective risks of being admitted with varicella pneumonia are 20.5-fold and 11-fold higher and with varicella zoster virus (VZV) encephalitis are 3.7- and 1.1-fold higher (13). In absolute terms, however, among all adults with acute chickenpox, 1% to 2% are admitted to hospital and 0.27% to 0.5% are admitted for pneumonia. If varicella pneumonia is based on radiographical abnormalities, roughly 15% of adults with chickenpox develop pneumonia (14). However, if the case definition requires clinical symptoms of respiratory disease, then 0.5% to 1.8% have pneumonia and not all require hospital care. Smoking is a major risk factor for varicella pneumonia (15). Among smokers with varicella, 45% have symptomatic and radiographical pulmonary abnormalities, and another 25% have impaired carbon monoxide diffusion capacity on pulmonary function testing. Most reports of severe varicella pneumonia among adults do not provide data regarding smoking. In a controlled study of early treatment with acyclovir for varicella pneumonia, 71% of the enrollees smoked, and a history was not available for the other 29% (14). Similar points can be made about the case fatality rate of chickenpox, which is 20- to 25-fold higher among adults relative to children over one year of age and fourfold higher relative to children aged younger than one year (16). However, in the absence of underlying disease, the absolute mortality for all ages is less than 0.03% of cases.

FOR IMMUNOCOMPROMISED HOSTS, CHICKENPOX IS A POTENTIALLY SEVERE AND FATAL DISEASE; HOWEVER, CURRENT STANDARDS OF MANAGEMENT HAVE SIGNIFICANTLY CHANGED DISEASE COURSE AND OUTCOME

Hospital-based surveillance for chickenpox in Canada was conducted by the Immunization Monitoring Program ACTive (IMPACT) from January 1991 through March 1996. During the surveillance period, the IMPACT network, which is funded by Health Canada and administered by the Canadian Paediatric Society, included 11 tertiary care paediatric centres, which together admitted about 100,000 children per year and accounted for 85% of available paediatric tertiary care beds in Canada (17). All children admitted to an IMPACT centre were prospectively followed during hospitalization, and data on a child's prior health status, frequency and type of complication(s), and hospital course were recorded by a nurse monitor. Table 2 (1,18) compares and contrasts host and illness features for 298 children immunocompromised as a result of immunosuppressive therapy, underlying malignancy, or congenital or acquired immunodeficiency

versus 488 previously healthy children. Clearly, routine varicella zoster immunoglobulin prophylaxis and rapid admission to hospital for acyclovir therapy have greatly reduced the morbidity and mortality of chickenpox among the immunocompromised population.

To summarize, for most adults including pregnant women (19), the course of chickenpox is usually uncomplicated unless there are risk factors such as smoking or comorbid disease. For immunocompromised hosts, chickenpox can still be deadly, but VZIG prophylaxis and/or early treatment with acyclovir assure a good outcome most of the time. Two realities shared by VZV-susceptible adults and immunocompromised hosts are the inherent difficulty of preventing infection through active immunization programs and the fact that children are the major source of VZV infection. It follows that preventing chickenpox in children, through routine immunization programs, will decrease the likelihood of exposure for both groups.

UNDER IDEAL STUDY CONDITIONS, THE VACCINE DID NOT PREVENT ALL CASES OF CHICKENPOX. GIVEN THE TEMPERATURE INSTABILITY OF THE VACCINE, IT IS LIKELY THAT THE EFFECTIVENESS UNDER 'REAL LIFE' CONDITIONS WILL BE EVEN WORSE

Depending on the specific dose and lot, vaccine efficacy for preventing chickenpox has ranged from 65% to 90% (20). However, as shown in Table 1, when infection does occur among vaccinees, the course is significantly milder than that suffered by nonimmune children, regardless of acyclovir therapy (3-6). Further, the vaccine is virtually 100% protective against severe illness.

Concern regarding the temperature instability of varicella vaccine continues to be a major issue, as noted at the Canadian National Varicella Consensus Conference. Yet, three case-control studies of chickenpox outbreaks in daycare settings have shown the current vaccine to be 86% effective despite its use under uncontrolled field conditions (20,21). These data are reassuring, although clearly it is essential to maintain vigilance regarding proper storage and handling of the vaccine.

To reiterate, 65% to 90% fewer cases of chickenpox are expected among vaccinated individuals and the cases that do occur will be 80% to 90% less intense.

ROUTINE CHILDHOOD IMMUNIZATION WITH EITHER POOR COVERAGE OR WANING IMMUNITY MAY RESULT IN A SHIFT OF DISEASE TO AN OLDER POPULATION, THEREBY INCREASING MORBIDITY AND MORTALITY RELATIVE TO THE CURRENT STATUS QUO

Routine immunization programs for measles, mumps and rubella (MMR) in Canada currently achieve coverage in excess of 90% (22). Because the varicella vaccine program would likely be linked to provision of MMR shortly after the first birthday, high coverage rates are feasible. Further, it is likely that a combined MMR-varicella vaccine will be available within the next few years.

Accumulated evidence suggests that waning immunity is not a problem in terms of preventing severe disease. In Japan, 20 years after immunization, vaccinees had comparable levels of humoral and cellular immunity as did naturally infected individuals (23). Given vaccine coverage levels of less than 30% in Japan, ongoing exposure to varicella may have boosted immunity in vaccinees. However, in a children's institutional setting, where there was no evidence of circulating varicella, immunity persisted among 16 vaccinees five years after immunization, and was comparable with that measured in seven children with a past history of natural varicella (24). American studies confirm the durability of the immune response but, to date, cover a span of only five to 10 years (21).

Clearly, long term follow-up studies regarding persistence of immunity over time are essential. It is possible that a two-dose vaccine schedule will ensure persistence of immunity better than a single dose. In the meantime, there is no question that both the incidence and severity of varicella-like illness are significantly decreased among vaccines (Table 1) (5,6). Further, among vaccinees who develop varicella-like illness, there seems to be no increase in severity of infection as the interval since immunization increases (5,6).

Thus, although the age distribution of varicella may increase after initiating universal immunization programs, the net number of cases and the attendant morbidity and mortality will be greatly diminished.

HERPES ZOSTER OR SHINGLES MAY RESULT FROM THE VACCINE STRAIN WITH THE POTENTIAL TO CAUSE WORSE PROBLEMS THAN THOSE SEEN CURRENTLY

In the absence of immunization, the lifetime risk of reactivation of herpes zoster illness presenting as shingles is 15% to 20% (20). The incidence increases sharply after the fifth decade of life as cellular immunity wanes. Herpes zoster can be an extremely debilitating illness with long lasting morbidity, especially if postherpetic neuralgia develops. This painful complication may last three months or more in up to 40% of those whose shingles occurs after age 60 years. The attenuated vaccine strain of varicella does establish latency and may reactivate to cause herpes zoster. However, the frequency and severity of reactivation illness among child, adult and immunocompromised vaccinees is significantly less than that seen following natural varicella (20).

CONCLUSIONS

The relative merit of universal immunization against chickenpox should be examined in view of the natural history of both primary and reactivation VZV infection, and the current status quo of disease among all age groups. VZV infection is an event that virtually everyone faces during his or her lifetime. In the absence of an immunization

program, children will go on bearing the overwhelming burden of illness due to chickenpox, and 15% to 20% of adults will go on to suffer at least one episode of reactivation illness with its attendant morbidity. A selective immunization program focused on susceptible adolescents, adults and immunocompromised hosts will help most immunized individuals but will do little or nothing to change the overall status quo. In contrast, universal immunization with varicella vaccine offers the potential to reduce significantly the burden of both primary and reactivation disease within the lifespan of the first group of vaccinees. Finally, in Canada we have a choice. It is time to choose.

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