

## Appendix 4: Varicella immunization: evidence review for newly arriving immigrants and refugees

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### ABSTRACT

**Background:** A large proportion of adolescents and adult immigrants from tropical countries are susceptible to varicella (>30%) due to the fact that varicella occurs at an older age in tropical countries and that most of these countries do not have a varicella vaccination program. This is important because adults are more likely to develop severe varicella, and to be hospitalized or die from varicella than children. Screening blood tests to measure varicella immunity and a highly effective vaccine are widely available. Screening for varicella immunity and vaccinating susceptible individuals is not done routinely in immigrants after arrival in Canada. We conducted an evidence review to determine the burden of varicella in the immigrant population, and to assess the effectiveness of screening and varicella vaccination programs to prevent morbidity and mortality from varicella.

**Methods:** A systematic search for evidence of the burden of varicella in the immigrant population, and the benefits and harms, applicability, clinical considerations, and implementation issues of screening and varicella vaccination programs in the general and the immigrant populations was performed. The quality of this evidence was assessed and ranked using the GRADE approach.

**Results:** The impact of the universal childhood varicella vaccination program in Canada and the United States has been dramatic with a significant decrease in the numbers of cases, hospitalizations, and deaths due to varicella in all age groups. Varicella vaccine has a low side effect profile. A large proportion of immigrant adolescents and young adults are susceptible to varicella (>30%). After arrival in temperate and cold countries, immigrant adults have been involved in several varicella outbreaks and have increased varicella-associated mortality.

**Interpretation:** Immigrants and refugees from tropical countries have an increased burden due to varicella compared to the Canadian-born population and would benefit from targeted screening and vaccination programs.

**Competing interests:** None declared.

**Contributions:** All of the authors contributed to the conception and refinements of the study design and the analysis and interpretation of the data. CG drafted the initial manuscript, and all of the other authors provided critical revisions. All of the authors approved the final manuscript submitted for publication.

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**Box 1: Recommendations on varicella vaccination from the CCIRH****Varicella (Chicken Pox)**

Ensure that immigrants and refugees of all ages are immune to varicella to decrease morbidity and mortality from varicella.

Vaccinate all children < 13 years of age with varicella vaccine without prior serotesting.

Screen all immigrants and refugees from tropical countries ≥ 13-years of age for serum varicella antibodies (IgG) and vaccinate those found to be susceptible.

**Basis of Recommendation**

- **Balance of benefits and harms:** Childhood varicella vaccination programs have substantially decreased ambulatory care visits (number needed to vaccinate NNV 794 (688 to 990) and mortality due to varicella (NNV 3,031,773) in all age groups. The side effects of vaccination are minimal and include minor pain and redness at the injection site, rashes and fevers. A large proportion (>30%) of adolescents and adult immigrants from tropical countries are susceptible to varicella due to the fact that varicella occurs at an older age in tropical countries and most of these countries do not have a varicella vaccination program. As a result immigrants from tropical countries are at increased risk of developing severe varicella after arrival in Canada as they develop varicella at an older age and there are no systematic catch up varicella vaccination programs for immigrants.
- **Quality of evidence:** Moderate
- **Values and preferences:** The Committee attributed high value to reducing morbidity and mortality from varicella which has a high burden of disease in adolescent and adult immigrant populations. For children <13 years of age, it is cost-saving to vaccinate all without prior serotesting. In adults, different varicella vaccination strategies are cost-saving depending on the expected seroprevalence. In a cost-effectiveness analysis of adults immigrants and refugees it was most cost-effective to vaccine without prior screening with a seroprevalence of <84% (children, most adolescents and some adults) and to serotest prior to vaccination when the seroprevalence is between 85% and 95% (some adolescents and most adults).

If serologic testing results in extra costs or presents a barrier to vaccination series completion, vaccination without pre-vaccination serology should be offered. The most effective strategy will be one that is tailored to the vaccination setting and balances the cost and anticipated uptake of the vaccine and the availability, compliance with and costs of serologic testing.

## The cases

Christine is a 28-year-old woman from St. Vincent (in the Caribbean) who has been living in Canada for one year. She is 12 weeks pregnant and has just been discharged from the hospital after a 10-day admission for severe varicella pneumonia that required intensive care support for four days. What preventive measures could have been taken when Christine first arrived in Canada? What are the risks to her foetus?

Sonia is Christine's 5-year-old daughter who also arrived in Canada one year ago and who began attending daycare in the previous few months. Sonia was seen in a walk-in clinic and diagnosed with chickenpox three weeks before her mother became ill. What preventive measures could have been taken when Sonia arrived in Canada? What preventive measures could have been taken when she was diagnosed with chickenpox?

## Introduction

The epidemiology of varicella is very different in tropical and temperate/cold countries. Varicella occurs at an older age in tropical countries and most of these countries do not have varicella vaccination programs, resulting in a large proportion of adolescents and adult immigrants from tropical countries being susceptible to varicella (>30%).<sup>1-13</sup> This is important because adults are more likely than children to develop severe varicella with higher rates of varicella associated pneumonia, encephalitis, hospitalization and death.<sup>14-17</sup> Varicella may also result in poor outcomes for pregnant women and their foetuses and infants.<sup>18-20</sup> Seroprevalence studies of varicella immunity in immigrants after arrival in temperate countries confirms the pattern of immunity seen in their countries of origin.<sup>21-25</sup>

Immigrants bear a disparate burden of illness from varicella. Several outbreaks of varicella have been documented in young adult immigrants from tropical countries soon after arrival in temperate or cold countries.<sup>26-31</sup> The mortality for varicella is also higher in the foreign-born as compared to the US-born population.<sup>32</sup> Despite this disparity and the widespread availability of both screening tests for varicella immunity and a safe and effective vaccine (~85%),<sup>33</sup> there are no programs in Canada to verify the immune status to varicella nor are there systematic targeted or catch-up varicella programs for the immigrant population. We conducted a review to quantify the burden of varicella in the immigrant population, to search for evidence for the effectiveness of screening and vaccination programs, and to identify barriers or challenges to implementation of such programs.

## Methods

We used the 14-step methods approach developed by the Canadian Collaboration for Immigrant and Refugee Health methods team.<sup>34</sup> The Clinician Summary Table highlights the population of interest, the epidemiology of disease within this population, population-specific considerations and potential key clinical actions (Appendix 2). We then constructed a logic model to define the clinical preventive actions (intervention), outcomes and key clinical questions.

Search strategy for systematic reviews and guidelines and population specific literature

We designed a search strategy in consultation with a medical librarian to identify relevant systematic reviews and guidelines to address the effectiveness of screening for varicella and providing varicella vaccination in the immigrant population. For this search, we reviewed five electronic databases [MEDLINE (Ovid), MEDLINE InProcess, EMBASE, CINAHL, and Cochrane Database of Systematic Reviews] from 1950- December 9, 2009. The terms immigrant or refugee AND varicella were used and restricted to guidelines and systematic reviews. We conducted a similar search for systematic reviews and guidelines for varicella with the same objectives in the general population for the same five databases, but restricted the search dates from January 1996- Dec 9, 2009. Any eligible systematic reviews were assessed for their application of a consistent and comprehensive approach, transparency (clarity about the process involved), quality of methods (appropriate methods and analysis) and relevance. An updating search, focusing on randomized controlled trials and systematic reviews during the period of Jan 1, 2009- January 19, 2011, was conducted to determine if there were any recent publications that would change the position of the recommendation. In addition, we conducted a web-based search of the following websites up until January 31, 2011 to search for other guidelines pertaining to varicella: the CMA Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guideline Clearing House (<http://www.guideline.gov/>). We also searched the websites of official organizations that produce guidelines, including: the Canadian Task Force on Preventative Health Care (CTFPHC), the Public Health Agency of Canada (PHAC), the National Advisory Committee on Immunization (NACI), the U.S. Preventative Task Force (USPTF), Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practice

(ACIP), Infectious Disease Society of America (IDSA), NICE, and the World Health Organization (WHO).

We conducted a separate search for varicella and the immigrant population to address population-specific concerns classified as: 1) baseline risk/prevalence in comparison to the Canadian-born population; 2) risk of clinically important outcomes; 3) genetic and cultural factors (e.g. preferences values, knowledge); and 4) compliance variation using the same five databases (1950 to January 19, 2011). To increase retrieval of articles documenting important outcomes resulting from implementation of varicella vaccine programs, we also performed a separate search with the terms varicella AND each of the following terms: cost, screening, hospitalization, mortality in the same five electronic databases mentioned above but restricted the search from January 1997 to December 2009 (Appendix 1).

Synthesis of evidence and values

We synthesized evidence from systematic reviews and pertinent cohort studies and clinical trials using the GRADE summary of findings tables, which describe both relative and absolute effects of interventions (relative risk and absolute event rate). We also appraised the quality of each outcome using the GRADE quality assessment tool, which assesses study limitations, directness, precision, consistency, and publication bias across all studies (Box 2). In the search and synthesis of data on clinical considerations, we identified both clinically relevant considerations and implementation issues relevant to our population. Finally, we identified gaps in the research and evidence base.

## Results

In the search for systematic reviews/guidelines in immigrants, six records were identified and screened and only one met eligibility criteria<sup>35</sup> but was excluded because it was a narrative review on medical screening immigrants and did not follow a systematic review methodology. We identified and screened 743 records from the web-based search and our search for systematic reviews/guidelines in the general population; of these, 20 met eligibility criteria (were guidelines or reviews) but only 11 were included due to relevance or recency. The most recent guidelines on varicella vaccine from Canada<sup>36-38</sup> and the United States (US) were included<sup>39</sup>. Other articles identified included, one review of varicella in pregnancy,<sup>40</sup> two reviews on the efficacy and adverse events due to varicella vaccine and the effectiveness of varicella vaccination programs,<sup>41,42</sup> one review of the predictive value of a history of varicella infection,<sup>43</sup> one

systematic review on the cost-effectiveness of varicella vaccine,<sup>44</sup> one review of barriers to adolescent vaccination,<sup>45</sup> one systematic review on interventions to improve compliance with vaccination<sup>46</sup> and a key article on the impact of childhood varicella vaccination on health care utilization.<sup>47</sup> A flow chart of these combined searches for guidelines and systematic reviews is outlined in Figure 1 (Appendix 1). The updating search for systematic reviews and guidelines from 2009-Jan 19, 2011 only identified one US guideline on measles, mumps, rubella, varicella (MMRV) vaccine that did not change the recommendations.<sup>48</sup> In addition, the search on varicella and immigrants identified 95 primary articles, of which 31 were relevant and addressed the following areas: epidemiology, cost-effectiveness of vaccination and screening, vaccine knowledge and compliance. The search for varicella associated morbidity and mortality (varicella AND cost, hospitalization, mortality) identified 3,400 articles of which 122 were relevant. These included articles on epidemiology, varicella hospitalization and mortality, screening for varicella immunity, vaccination efficacy and cost-effectiveness, and vaccine knowledge and compliance. The key article on varicella-associated mortality (used in Table 1) was identified in this search (Appendix 3).<sup>32</sup>

### **What impact has the Varicella Vaccination Program in Canada and the United States had on varicella disease burden?**

Varicella was a common childhood illness in Canada prior to the implementation of a universal childhood vaccination program. In the pre-vaccination era, an estimated 350,000 new cases occurred in Canada annually, the peak incidence of disease was among 4-5 year olds and by age 20 years >95% of individuals had varicella antibodies.<sup>49</sup> Since the widespread implementation of childhood varicella vaccine programs in Canada (2005) and the US (1995) the numbers of cases of the number of cases and varicella-associated hospitalizations and deaths in all age groups, including adults have dramatically decreased.<sup>32,47,50-52</sup> In a recent study of the impact of varicella vaccine in Ontario (5 years after private coverage and 2 years after a universal program) there was a decrease in varicella-associated hospitalization by 53% (95% CI 48-58%), emergency room visits by 43% (95% CI 41-44%) and physician visits by 45% (95% CI 44-45%) in the publicly funded vaccination period (2005-2006) compared to the pre-vaccination period (1992-1998).<sup>50</sup> More complete data on the impact of varicella vaccine on varicella epidemiology are reported from the US since they have had a universal childhood varicella vaccination program since 1995 and

have reported on outcomes for 10 years after introduction of the vaccine. From 1995 to 2005, the incidence of varicella disease declined by 70-85% in three US communities that had achieved vaccine coverage of 75-85%.<sup>52</sup> Hospitalizations decreased by 88% (2.3 to 0.3/100,000) and ambulatory visits decreased by 59% (215 to 89/100,000 population).<sup>47</sup> During this same time period, varicella-associated mortality decreased by 2.2 fold (145 to 66 deaths/years) and the death rate decreased from 0.41 to 0.14/1,000,000 population.<sup>32</sup> Although the majority of cases in the post-vaccination period still occur in young children, the age of developing varicella in unvaccinated persons increased from a mean age of 5 year to 13 years in one US community in 1995 and 19 years in another US community in 2005.<sup>52</sup> Adolescents and adults are more likely to develop complications from varicella as compared to children. This change in age trend is concerning, because as long as there is circulating wild virus, susceptible adolescents and adults will be at increased risk of severe varicella.

### **What is the burden of varicella in the immigrant population?**

Seroprevalence studies have consistently shown that the mean age of developing varicella in tropical countries occurs between age 10-15 years as compared to age 4 or 5 years in temperate or cold climates (in the pre-vaccination era). This difference in epidemiology and the fact most of these countries do not have varicella vaccination programs results in a large proportion of adolescents and adults from tropical countries being susceptible to varicella (~50% at age 15 years and ~10-15% from age 30-35 years) as compared to Canadians (~10% at age 15 years and <2% at age 30-35 years).<sup>1-13</sup> In certain tropical regions (the Caribbean, Sri Lanka, Singapore, Indonesia, and in rural areas of other countries such as Pakistan, India, etc.) the mean age of acquiring varicella may be even higher and a large proportion of adults >35 years may still be susceptible to varicella.<sup>4, 5, 8-12</sup>

The reason for the difference in epidemiology is unknown but it has been suggested that since varicella zoster virus (VZV) is a heat-sensitive virus, it may not transmit as efficiently in hot humid environments. Community crowding may be an important co-factor in tropical countries, as demonstrated in two studies that found that individuals from urban areas are more likely to be varicella immune than those from rural areas.<sup>6,7</sup> Several seroprevalence studies in immigrants from tropical countries after arrival in temperate countries



have shown the same pattern of susceptibility to varicella as reported in their countries of origin.<sup>22-25, 53, 54</sup>

The severity of varicella increases with age. In the pre-vaccination period in Canada, adults represented <5% of the cases of varicella but accounted for 25% of hospitalizations due to varicella (rate 125/10,000 varicella hospitalizations or ~1,750 hospitalizations/year), 33% of costs attributable to varicella, and 70% of varicella deaths (rate 10 deaths/10,000 varicella cases or ~50 deaths/year).<sup>14-17</sup> Pregnant women are more likely to develop varicella pneumonia, to be hospitalized and to die from varicella as compared to other adults. Congenital varicella syndrome occurs in fetuses of women who are infected during the first 20 weeks of gestation and is associated with a foetal case fatality rate of up to 50%. Survivors may have congenital anomalies including limb hypoplasia, microcephaly, and dermatomal scarring.<sup>18</sup> In addition, 20% of newborns born to women infected with varicella between 5 days prior to or 3 days following delivery will develop neonatal varicella, which carries a case-fatality rate of 30-50%.<sup>19, 20</sup>

The important burden of varicella in the immigrant population was highlighted by a recent US population based study that found varicella associated mortality rates in foreign-born populations to be higher than in the US-born population (0.35 vs. 0.19 per 1 million population) in the pre-vaccination period. Although rates decreased in both groups after the introduction of the universal childhood vaccination program, they remained higher in the foreign-born population (0.10 vs. 0.07 per 1 million population) the majority of which occurred in older adults.<sup>32</sup> Furthermore, young immigrant adults originating from tropical countries have been involved in several outbreaks of varicella (mean age of 20-25 years of age and attack rates of ~30%) within a few months after arrival in host countries with temperate or cold climates.<sup>26-31</sup> In addition to the individual burden of varicella in the immigrant population there is potential for societal burden due to costs to the health care system and the spread of varicella to vulnerable groups in the native born population. Many immigrants are health care and child care workers and if they develop varicella they will potentially expose elderly immunosuppressed individuals at risk for severe disseminated disease or young children who have not yet been vaccinated in the universal vaccination program.

The childhood vaccination program has resulted in less circulating virus with the benefit of protection of susceptible groups through herd immunity. A concern however in the absence of catch up varicella vaccination programs for the immigrant population is the potential

for outbreaks of severe varicella among the older native born individuals that did not develop immunity through the vaccination program and among the accumulating pool of susceptible adults immigrants that remain susceptible because they are not exposed to circulating virus after arrival in Canada.

### **Does screening for immunity for varicella and vaccinating those who are susceptible decrease morbidity and mortality from varicella?**

#### **Diagnostic tests to screen for varicella antibodies**

The fluorescent antibody to membrane antibody (FAMA) test is the most extensively validated assay and correlates best with susceptibility to and protection against clinical varicella (>95% sensitivity). It is not widely used however, because it is labour-intensive and difficult to implement in all laboratories. The most widely available tests to detect VZV antibodies are enzyme immunoassays (ELISA); they are less sensitive than the FAMA, but have good specificity (>95%). ELISAs are sufficiently sensitive to detect protective antibodies after natural VZV infection (60-92%) but inadequately sensitive to detect protective antibodies resulting from vaccination (<60%).<sup>55</sup> Given that the majority of adult immigrants at risk for varicella in Canada originate from countries without routine childhood vaccination programs and have naturally acquired antibodies, the ELISA test is an acceptable method of screening for immunity to varicella in this population. ELISAs will incorrectly classify some immune individuals as susceptible, which will lead to over vaccination, which has relatively low risk but adds unnecessary cost. It is preferable to under vaccinate, since the risk of severe varicella in those falsely labelled as immune can result in poor clinical outcomes.<sup>55</sup>

#### **History of reported prior varicella to determine varicella immune status**

The reliability of a positive history to predict protective antibodies to varicella is influenced primarily by the expected seroprevalence of the population tested. The majority of adults who report a history of varicella are immune to varicella (>95%) and many of those whose status is unknown or who report a negative varicella history will also be immune to varicella (75-80%).<sup>22,43,56</sup> In this situation, a positive history reliably predicts protective varicella antibodies (positive predictive value of >97%) and serologic testing and vaccination are not required. Many of these individuals with a negative or unknown history of varicella will also be immune to

varicella and serologic testing prior to vaccination would avoid unnecessary vaccination.

A positive history for varicella, however, may less reliably predict protective varicella antibodies in immigrant populations in whom the varicella seroprevalence is lower than expected for their age. In a study of refugees with a median age of 26 (range 7-83 years), the overall varicella seroprevalence was 75% and the positive predictive value of a positive history for varicella was only 85%.<sup>21</sup> Similarly, in hospital workers from tropical countries with a mean age of 32 years, the overall varicella seroprevalence was 85% and the positive predictive value of a positive varicella history was 91%.<sup>57</sup> In adult immigrant populations in whom the seroprevalence is expected to be low and there is an increased risk of severe infection (given their older age), it may be more prudent to serotest adults prior to vaccination or empirically vaccinate (if serologic testing is not available) to avoid potential poor outcomes of varicella.

#### **Efficacy and safety profile of varicella vaccination**

A single dose of varicella vaccine is 80% to 85% effective in preventing diseases of any severity and >95% effective in preventing severe varicella.<sup>41,48,58</sup> Efficacy for adults has been estimated to be approximately 80%. Due to plateauing rates of varicella between 2003 and 2006 and ongoing outbreaks despite a one-dose vaccination schedule, the US recommended a universal two-dose childhood varicella vaccination program (the first dose at 12-15 months and a second dose at 4-6 years of age) in 2006.<sup>39</sup> In Canada, all provinces recommend a single dose of vaccine for children 1-12 years of age, and a two-dose regimen for those aged 13 years.<sup>36, 37</sup> In September 2010, the National Advisory Committee on Immunization (NACI) recommended that children of all ages receive 2 doses of varicella vaccine however, this is yet to be implemented in Canada.<sup>37</sup> The vaccine has a low side effect profile.<sup>59</sup> Vaccine adverse events include pain and redness at the injection site (22-35%), rash (sometimes varicella-like) (1-5%), and fever (4-7%). Post-licensure surveillance has shown that 5% of adverse events reported to Vaccine Adverse Event Reporting System (a passive surveillance system managed by the CDC and the US Food and Drug Administration) were classified as serious (2.6/100,000 doses distributed). Secondary transmission has been documented from five vaccine recipients.<sup>60</sup> Varicella is a live attenuated vaccine that should be avoided in immunosuppressed individuals but can be given to HIV infected individuals with a mild to moderate symptoms and a CD4 count >200 x 10<sup>6</sup>/L or >15%.<sup>38</sup>

#### **Cost-effectiveness of varicella vaccination**

Cost-effectiveness analysis of routine varicella immunization of pre-school-age children demonstrated cost saving when both direct and indirect costs were considered.<sup>44,61</sup> A recent study showed that both single-dose and two-dose immunization programs were cost-saving from a societal point of view in the US compared with no program.<sup>62</sup> Most cost-effectiveness studies support serologic testing before giving varicella vaccine to adolescents and adults.<sup>44</sup> A recent cost-effectiveness analysis of strategies to prevent varicella in adult immigrants and refugees found that different varicella vaccination strategies were cost-saving compared to no intervention at the following varicella seroprevalence thresholds; vaccinating all without prior serotesting (84%, would include immigrant children <13 years of age, many adolescents and some adults), serotest all and vaccinate all those found to be susceptible (85%-92%, would include some adolescents and most adults), serotest only those with a negative or unknown history of varicella and vaccinate those found to be susceptible (93%-95%, some adults) and no intervention (>95%, some older adults).<sup>63</sup> In this study the positive predictive value of a prior history of varicella for immunity was 97%, higher than has been reported in 2 other studies done in immigrant and refugee populations.<sup>21, 57</sup> In a US study, serotesting prior to vaccination was cost-effective for adults aged 20-29, but was not if compliance with immunization was <70%.<sup>64</sup> Both of these studies used static modelling and did not take into account the change in transmission dynamics of varicella after introduction of a childhood vaccination program. Dynamic modelling would take in to account the competing processes of; protection of susceptible individuals from herd immunity with the potential for outbreaks of severe varicella from the accumulation of susceptible adolescents and adults due to low levels of circulating wild type virus.

#### **Clinical considerations**

##### **Is varicella vaccination updated in the immigration process?**

All immigrants undergo a pre-immigration medical exam but vaccinations, including varicella vaccination, are not given during this assessment. There are no programs to systematically screen for varicella immune status nor are there targeted or catch-up varicella vaccination programs outside of the childhood vaccination program for the immigrant population after arrival in Canada.<sup>65</sup> Varicella vaccine is not uniformly required for school entry.

## What are the potential implementation issues?

There are few data on barriers to uptake of varicella vaccine in children. The studies that described factors associated with low varicella vaccine uptake found that they were similar to those for other vaccines e.g. low socioeconomic status, low parental education, younger maternal age, lack of knowledge about the disease and vaccination, negative beliefs or attitudes towards immunization, fear of side-effects or vaccine risks, lack of transport, inconvenient clinic hours, and cost (being the most important barrier).<sup>66-73</sup> Provider barriers to vaccination include lack of knowledge about indications and contraindications for vaccination (especially with the recent addition of new vaccines and complex schedules), logistical barriers such as vaccine storage, capacity or lack of access to prior immunization records, and missed opportunities for immunization.<sup>71</sup>

We did not find data on the factors specifically influencing rates of varicella vaccination among newly arrived immigrants or refugees. In a recent US national study, however, there were no racial differences (Hispanic, Black and White) in the uptake of varicella vaccine among children after 1998.<sup>73</sup> The data on vaccination coverage in immigrant children after arrival in a host country for other vaccines is mixed. In Canada and the UK (where many of the migrants are South Asian), immigrant children were more likely to be vaccinated than the host population.<sup>74-78</sup> This may be due to cultural factors particular to this community that favour immunization uptake. In contrast, in Spain, Germany, Austria and Holland, immigrant children were less likely to have been vaccinated than their host populations.<sup>79-82</sup> An interesting and consistent finding across many studies and several countries is that immunization rates appear to be higher in recently-arrived immigrants, those with limited English proficiency and those who are less acculturated.<sup>75, 78, 83, 84</sup> This may be due to the fact that these communities may be shielded from anti-vaccine messaging that may be prominent in local media sources, increased trust of physicians or other unmeasured cultural factors.<sup>75, 78, 85</sup>

Adolescents and adults face additional vaccination barriers as compared to children. These include lack of awareness of the need for vaccination by parents, patients and providers, the lack of routine well adolescent or well adult visits and the lack of coordinated immunization programs for these populations.<sup>86-90</sup> We did not find any studies that specifically reported on the uptake of varicella vaccine in adults. The two most important barriers to vaccination in adult immigrants are likely to be cost and educating health care providers that

adult immigrants are at increased risk for severe varicella. Although childhood varicella vaccination has been free in all Canadian provinces since 2005, some still do not provide free vaccine for adults. In a recent study in the US, varicella vaccination coverage for children was >90% but only 42% of adults were assessed for the need for varicella vaccine.<sup>91</sup> In certain settings serologic testing may result in extra costs or may present a barrier to vaccination series completion. If this occurs vaccination without pre-vaccination serology should be offered.

We did not identify any studies that examined interventions to increase uptake of varicella or other vaccines in immigrant populations. However, interventions to improve uptake of vaccinations in the general population recently have been reviewed systematically.<sup>46,92,93</sup> The most effective interventions were instituting reminder or recall systems, educating target populations and vaccine providers, and reducing out of pocket costs.<sup>46,92</sup> The most effective interventions to improve vaccination coverage in adults are standing orders and expanding access to vaccines in non-traditional settings (schools, work place, social gathering places such as church, sports clubs, etc.)<sup>86, 89, 90, 92</sup>

## Other recommendations

The National Advisory Committee on Immunization (NACI) in Canada recently recommended that all children between the ages of 12 months to 12 years receive two doses of varicella vaccine as primary immunization.<sup>37</sup> Persons older than  $\geq 13$  years of age should receive two doses of vaccine a minimum of 6 weeks apart.<sup>36</sup> Certain groups at increased risk for varicella such as immigrants from tropical countries, women of child-bearing age, household contacts of immunocompromised people, health care workers and adults who work in other occupations with increased exposure to varicella (teachers, day care workers, etc.) should be considered for targeted varicella vaccination.<sup>36</sup> Although immigrants from tropical countries are identified as a high-risk group of adults that could benefit from vaccination the optimal or preferred prevention strategies for updating vaccination is not outlined. Since 2006, the Advisory Committee on Immunization Practice (ACIP) in the US has recommended that both children and adults receive two doses of varicella vaccine.<sup>39</sup> The ACIP suggests vaccinating similar target groups as Canada but they do not identify immigrant adults from tropical countries as a high-risk group.<sup>39</sup>



## The cases revisited

Christine originates from a country where the mean age of developing varicella is in adolescence or early adulthood. If she had been screened for varicella antibodies when she had arrived in Canada and had been vaccinated, this episode could have been avoided. Adults are at higher risk for developing severe varicella than children, and pregnant women are the highest risk adults for developing severe varicella (pneumonia, hospitalizations and death). Her fetus has a 2% risk of developing congenital varicella with a 50% case fatality rate.

Sonia arrived in Canada when she was six years old and would not have been immunized in the routine childhood varicella vaccination program. Sonia's case represents a missed opportunity of varicella vaccination and highlights the importance of giving varicella vaccine to all children at risk. Varicella is highly transmissible and when Sonia was diagnosed with varicella, it would have been important to verify the varicella status of all household members. Those found to be susceptible could have been offered "post-exposure vaccine", or varicella immune globulin (VZIG) could have been given to her susceptible pregnant mother.

## Conclusions and research needs

Newly arrived immigrants and refugees, both children and adults, are more likely to be susceptible to varicella than the Canadian-born population and at risk for severe varicella. In the post universal childhood vaccination program the age of acquiring varicella in the native population has increased and susceptible adult immigrants are less likely to be exposed to varicella and remain susceptible due to low levels of circulating virus. The accumulation of these susceptible older populations may increase the risk for varicella outbreaks and associated severe varicella cases. Dynamic modelling studies on the impact that the universal childhood vaccination program will have on the potential for large outbreaks of severe varicella in the absence of catch-up varicella vaccine programs, will be critical.

To design the most effective targeted varicella vaccination programs, data on the acceptability of varicella vaccine and varicella vaccine coverage in immigrant children and adults need to be studied. The absence of infrastructure to routinely update vaccination in adolescents and adults will be a particular challenge to implementing a catch up varicella vaccination program in the immigrant population. Finally, health care providers need to be made aware of the unique epidemiology of varicella in this population so that they can ensure that

immigrants and refugees are assessed for susceptibility and given vaccination where appropriate.<sup>94</sup>

## Key points

- A large proportion of adolescents and adults from tropical countries are susceptible to varicella (~50% at age 15 years and ~10% from age 30-35 years).
- In certain tropical regions (the Caribbean, Sri Lanka, Singapore, Indonesia, and in rural areas of other countries such as Pakistan, India, etc.) the mean age of acquiring varicella may be even older and a large proportion of adults >35 years may still be susceptible to varicella.
- Pregnant immigrant women and their babies are at highest risk for complications from varicella.
- Immigrants and refugees of all ages from tropical countries would benefit from having their varicella immune status verified and being offered varicella vaccine if found to be susceptible.

### Box 2: Grading of Recommendations Assessment, Development and Evaluation Working Group grades of evidence ([www.gradeworkinggroup.org](http://www.gradeworkinggroup.org))

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

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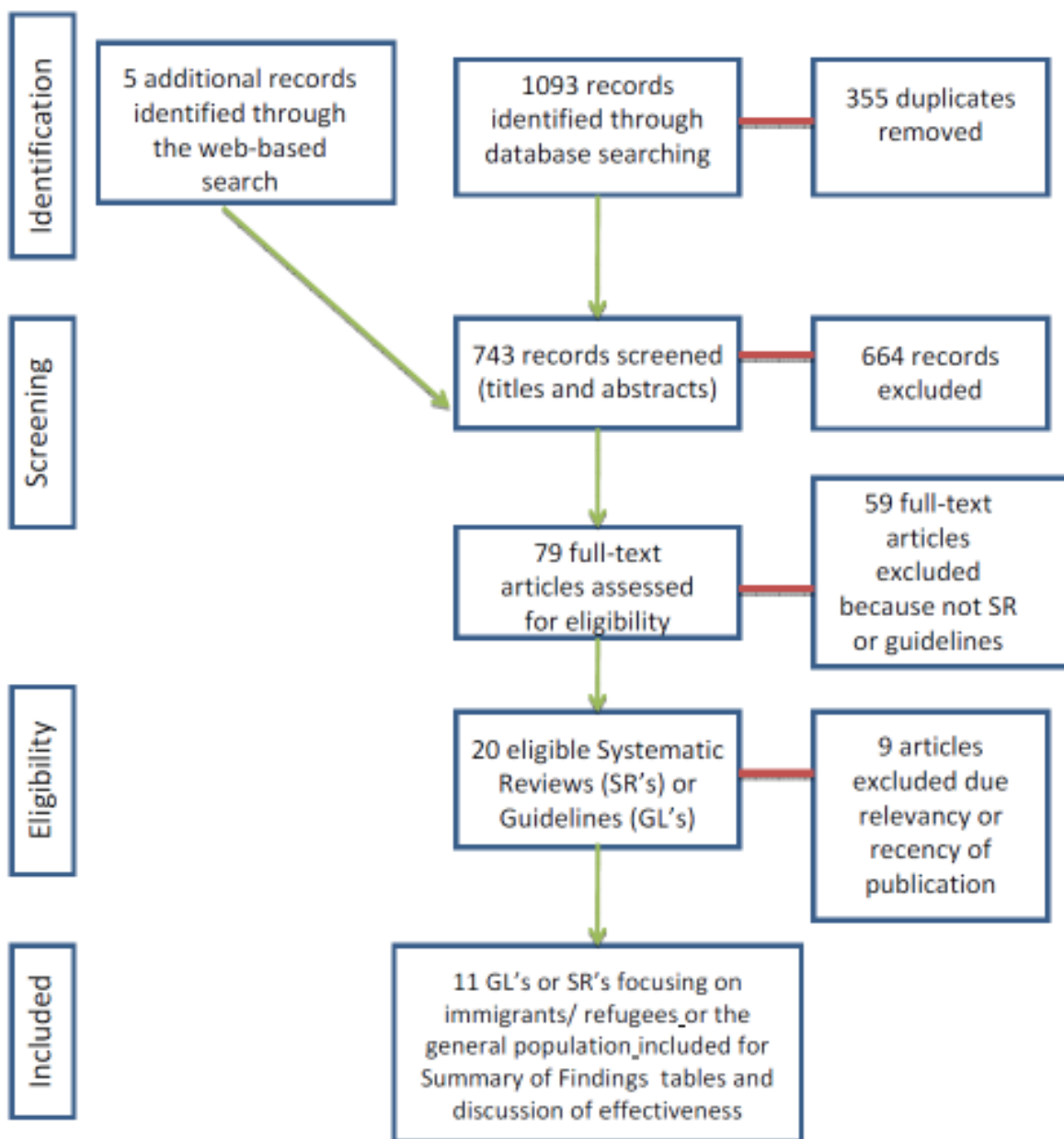
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#### Clinical preventive guidelines for newly arrived immigrants and refugees

This document provides the review details for the CMAJ CCIHR Varicella paper. The series was developed by the Canadian Collaboration for Immigrant and Refugee Health and published at [www.cmaj.ca](http://www.cmaj.ca).

Appendix 1: Figure 1

Figure 1: Varicella Search for Systematic Reviews and Guidelines in the Immigrant/Refugee Population or General Population Selection Flow Sheet





## Appendix 2: Varicella Evidence Based Clinician Summary Table

Ensure that immigrants and refugees of all ages are immune to varicella to decrease morbidity and mortality from varicella.

Vaccinate all children < 13 years of age with varicella vaccine without prior serotesting. Screen all immigrants and refugees from tropical countries  $\geq$  13-years of age for serum varicella antibodies (IgG) and vaccinate those found to be susceptible.

**Prevalence:** A large proportion of adolescents and adults from tropical are susceptible to varicella (~50% at age 15 years and ~10% from age 30-35 years) as compared to Canadians (~10% at age 15 years and <2% at age 30-35 years). In certain tropical regions (the Caribbean, Sri Lanka, Singapore, Indonesia, and in rural areas of other countries such as Pakistan, India etc) a large proportion of adults >35 years may still be susceptible to varicella.

**Burden of Illness:** Adults from tropical climates are more likely to be involved in varicella outbreaks compared to populations born in temperate or cold countries. Although cases, hospitalizations and deaths have decreased in the post-vaccination period, the foreign-born are still more likely to die from varicella as compared to the host population.

**Access to Care:** The barriers to varicella immunization in immigrant and refugee children are likely similar to those for other children. In addition to the usual barriers of adults accessing vaccination, cost and physician unawareness of the epidemiology of varicella in adult immigrants are important additional barriers to uptake of varicella vaccination. More data on the barriers to uptake of varicella vaccination and vaccination coverage in child and adult immigrants are needed.

**Key Risk Factors for Varicella:** Immigrant children are likely to be exposed to varicella in daycares or schools and may in turn expose their susceptible family members including their mothers (of child bearing age and at risk for transmission to their foetus), adolescents or other adults at increased risk for severe varicella.

**Screening Test:** Serologic tests to detect varicella natural immunity are inexpensive, and are acceptably sensitive and specific. In adult immigrant populations where the seroprevalence is expected to be low and there is an increased risk of severe infection (given their older age), it may be more prudent to serotest all prior to vaccination or empirically vaccinate (if serologic testing is not available) to avoid potential poor outcomes of varicella.

**Vaccination:** Varicella vaccination is highly effective and a universal one-dose varicella childhood vaccination program has resulted in decreased cases, hospitalizations and deaths but despite this, there is ongoing risk of varicella outbreaks. Immigrants and refugees from tropical countries are a large and growing group that is susceptible to varicella and could benefit from targeted vaccination programs. Primary care providers must be made aware of the unique epidemiology of varicella in this population and the need to verify their varicella immune status and offer vaccines to those found to be susceptible.

**Special Considerations:** Varicella is a live attenuated vaccine that should be avoided in immunosuppressed individuals but can be given to HIV infected individuals with a mild to moderate symptoms and a CD4 count >200 x 106/L or >15%.

### Appendix 3: Table 1 Summary of Findings Table: Vaccination for preventing Varicella and related morbidity and mortality

**Patient or population:** 0-49-year-olds.<sup>47</sup> National death records.<sup>32</sup>

**Setting:** MarketScan databases with enrollees from over 100 health insurance plans of approximately 40 large US employers, from 1994 to 2002.<sup>47</sup> National Center for Health Statistics Multiple Cause-of-Death Mortality Data for 1990 through 2001<sup>32</sup>

**Intervention:** Varicella vaccination

**Sources:** Zhou F et al. Impact of Varicella Vaccination on Health Care Utilization. JAMA. 2005;294:797-802. Nguyen et al. Decline in Mortality Due to Varicella after Implementation of Varicella Vaccination in the United States. N Engl J Med 2005;352:450.

Outcomes	Absolute Effect		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk for control group (pre-vaccine era)	Difference with vaccination				
Hospitalizations (varicella primary diagnosis)	<b>2.3 per 100,000</b>	<b>2.0 less per 100,000</b>	<b>RR 0.13</b> (0.04 to 0.41)	Not reported (1 study) <sup>1</sup>	□□□□ <b>high</b> <sup>2</sup>	<b>NNT 49,975</b> (45,384 to 73,443)
Ambulatory visits (varicella primary diagnosis)	<b>215 per 100,000</b>	<b>126 less per 100,000</b>	<b>RR 0.41</b> (0.32 to 0.53) <sup>3</sup>	Not reported (1 study) <sup>1</sup>	□□□ <b>moderate</b> <sup>3</sup>	<b>NNT 794</b> (688 to 990)
Death from varicella	<b>0.56 per 1,000,000<sup>4</sup></b>	<b>0.33 less per 1,000,000<sup>4</sup></b>	<b>RR 0.41</b> (0.25 to 0.66)	Not reported (1 study)	□□□ <b>moderate</b> <sup>3</sup>	<b>NNT 3,031,773</b> (2,393,719 to 5,314,626)
Death from varicella – foreign-born	<b>0.35 per 1,000,000<sup>5</sup></b>	<b>0.25 less per 1,000,000<sup>5</sup></b>	<b>RR 0.29</b> (0.14 to 0.58)	Not reported (1 study)	□□□ <b>moderate</b> <sup>3</sup>	<b>NNT 4,024,145</b> (3,322,259 to 6,802,721)
Death from varicella – US-born	<b>0.19 per 1,000,000<sup>5</sup></b>	<b>0.12 less per 1,000,000<sup>5</sup></b>	<b>RR 0.37</b> (0.15 to 0.88)	Not reported (1 study)	□□□ <b>moderate</b> <sup>3</sup>	<b>NNT 8,354,219</b> (6,191,950 to 43,859,649)

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Zhou F et al. Impact of Varicella Vaccination on Health Care Utilization. JAMA. 2005;294:797-802.

<sup>2</sup> Graded up two levels for very strong evidence of association (RR < 0.2)

<sup>3</sup> Graded up one level for strong evidence of association (RR < 0.5)

<sup>4</sup> Age-adjusted rates from Nguyen et al. Decline in Mortality Due to Varicella after Implementation of Varicella Vaccination in the United States. N Engl J Med 2005;352:450-8.

<sup>5</sup> Unadjusted rates from Nguyen et al. Decline in Mortality Due to Varicella after Implementation of Varicella Vaccination in the United States. N Engl J Med 2005;352:450-8.