Routine immunization of adults in Canada: Review of the epidemiology of vaccine-preventable diseases and current recommendations for primary prevention

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Vaccination is one of the greatest achievements in public health of the 20th century. However, the success of vaccine uptake and adherence to immunization guidelines seen in pediatric populations has not been observed among adult Canadians. As a result of the disparity in susceptibility to vaccine-preventable disease, there has been an increasing shift of vaccine-preventable childhood diseases into adult populations. Accordingly, morbidity and mortality due to vaccine-preventable illnesses now occur disproportionately in adults. All Canadians, irrespective of age, should have immunity to measles, mumps, rubella, tetanus, diphtheria, pertussis and varicella. All adult Canadians with significant medical comorbidities or those older than 65 years of age should receive the pneumococcal polysaccharide vaccine and yearly trivalent inactivate influenza vaccines. The present review summarizes the burden of illness of these vaccine-preventable diseases in the Canadian adult population and reviews the current immunization recommendations. Vaccination of all Canadians to these common agents remains a vital tool to decrease individual morbidity and mortality and reduce the overall burden of preventable disease in Canada.

Key Words: *Influenza; Measles; Pertussis; Pneumococcus; Tetanus; Varicella*

L'immunisation systématique des adultes au Canada : Une analyse de l'épidémiologie des maladies évitables par un vaccin et les recommandations à jour pour la prévention primaire

La vaccination est l'une des plus grandes réalisations de la santé publique au XX^{e} siècle. Cependant, on n'observe pas la même réussite de l'assimilation des vaccins et le même respect des lignes directrices en matière d'immunisation chez les adultes canadiens qu'au sein de la population pédiatrique. Étant donné la disparité de la susceptibilité aux maladies évitables par un vaccin, les maladies infantiles évitables par un vaccin s'observent de plus en plus au sein des populations adultes. C'est pourquoi la morbidité et la mortalité imputables à ces maladies sont présentes de manière disproportionnée chez les adultes. Tous les Canadiens, quel que soit leur âge, devraient être immunisés contre la rubéole, la rougeole et les oreillons, le tétanos, la diphtérie, la coqueluche et la varicelle. Tous les adultes canadiens ayant des comorbidités médicales importantes ou qui sont âgés de pus de 65 ans devraient recevoir le vaccin antipneumococcique ainsi que, tous les ans, le vaccin trivalent inactivé contre l'influenza. La présente analyse résume le fardeau de ces maladies évitables par un vaccin au sein de la population adulte canadienne et expose les recommandations courantes en matière d'immunisation. La vaccination de tous les Canadiens contre ces agents courants demeure un outil essentiel pour réduire la morbidité et la mortalité individuelles ainsi que le fardeau global des maladies évitables au Canada.

The advent and implementation of immunization programs for control and elimination of endemic diseases has been hailed as one of the greatest achievements of medicine (1). While only smallpox has been eradicated, endemic transmission of poliomyelitis, diphtheria, rubella and measles is now extraordinarily rare. Despite these successes, the burden of mortality due to vaccine-preventable disease remains high. It is estimated that 30,000 to 50,000 North Americans die each year from vaccine-preventable illnesses (primarily from influenza and invasive *Streptococcus pneumoniae*) (2,3). Furthermore, the burden of cost of vaccine-preventable deaths in the United States is estimated by the Centers for Disease Control and Prevention (USA) to be approximately $10 billion per year (4).

While the greatest emphasis in Canadian vaccination policy has always been on the provision of vaccinations to children, most vaccine-preventable deaths now occur in adults. As a whole, vaccine uptake in adult populations is much lower than in children (2). Factors associated with reduced vaccine uptake in adult and pediatric populations include lower levels of education, lower incomes, lack of transportation access and irregular interaction with health care professionals (5-7). Many reasons exist to explain the apparent lack of success in immunizing adult populations, and these have been well summarized (8). Ensuring optimal immunization of Canadians through adulthood is important not only to reduce the burden of morbidity, mortality and health care expenditures for vaccine-preventable diseases in this population, but also to reduce the number of susceptible hosts, thereby providing additional protection to those groups at highest risk (ie, infants, the elderly and the immunocompromised).

With high levels of immunization achieved in pediatric populations, we are increasingly observing a shift in classically pediatric illnesses such that their incidence occurs more frequently in older populations (9). This is particularly concerning for illnesses such as varicella, measles and rubella, in which clinical outcomes are potentially much more severe in adult

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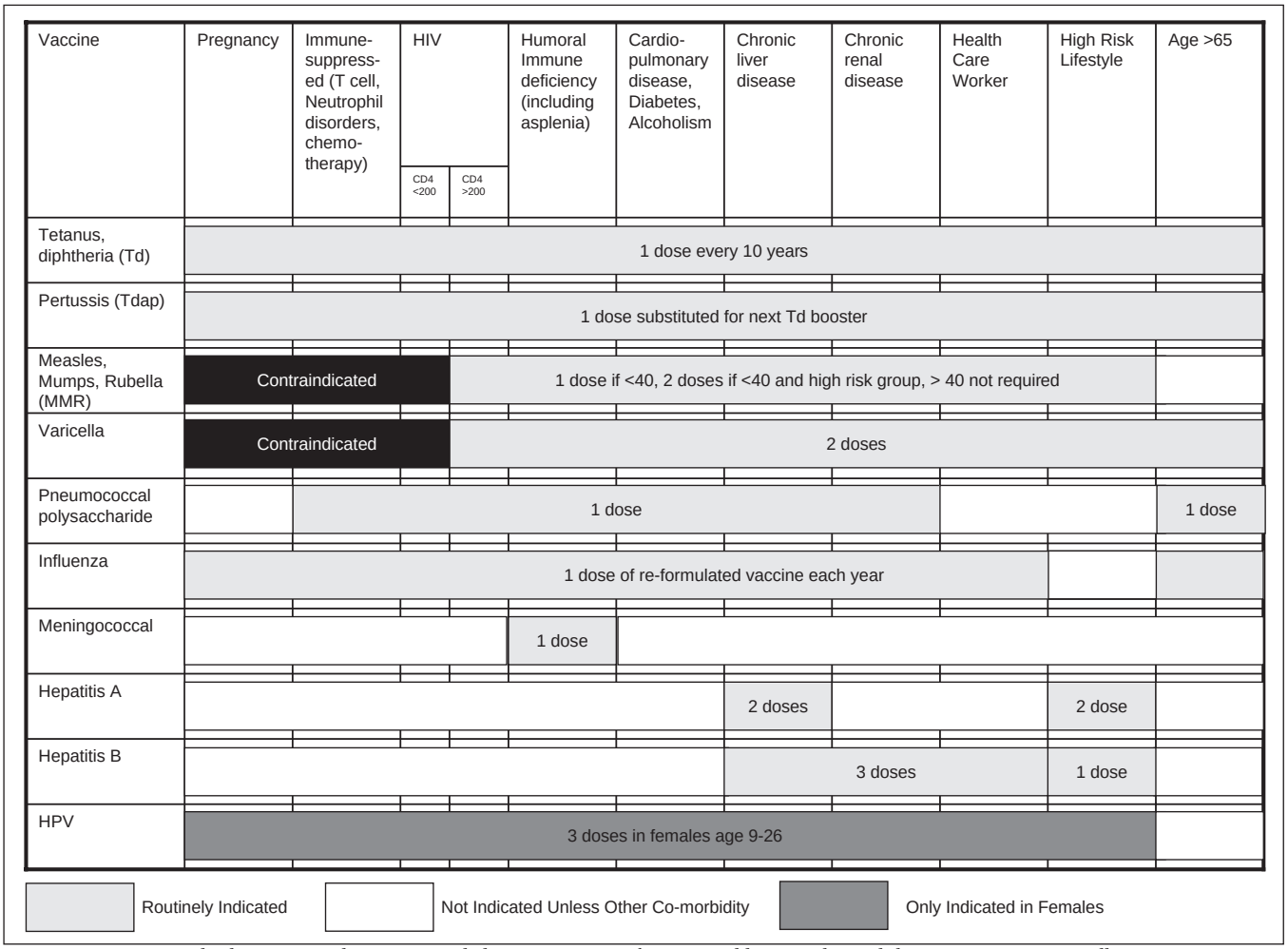

Figure 1) *Routine and other commonly recommended immunizations for susceptible Canadian adults. HPV Human papillomavirus*

populations. This observation can be explained on the basis of two key principles of vaccinology – the cohort effect and the herd-immunity effect (10). In the cohort effect, immunization results in a decrease in the incidence of disease in pediatric populations; however, it has no impact on the incidence of disease in unvaccinated or undervaccinated adult populations. Therefore, it results in an overall increase in the proportion of affected adults. The herd-immunity effect explains that as vaccine coverage increases in a population, fewer susceptible hosts exist, and as such, more time is required to pass before immunologically naïve individuals are likely to come in contact with the infectious agent, thereby increasing the average age of infection (10,11).

The present article reviews the current recommendations for routine immunizations of adults in Canada by the National Advisory Committee on Immunizations (NACI). Beyond the scope of this review are immunizations of specific adult populations such as those with significant medical comorbidities (12), advanced immunosuppressive conditions (HIV [13], stem cell [14] or solid organ transplant [15]) and newly immigrant Canadians (16). It is currently recommended that all adults be immunized against measles, mumps, rubella, tetanus, diphtheria, pertussis and varicella (17). Pneumococcal vaccination and yearly influenza vaccines are required for all adults 65 years of age and older or for those with significant medical comorbidities. Other vaccines targeted toward high-risk populations include meningococcus, and hepatitis A and B (Figure 1). Specific immunization recommendations exist for travellers to regions with diseases not endemic to Canada including typhoid, polio, yellow fever, rabies, cholera and Japanese encephalitis virus. Vaccine recommendations for selected adult populations are beyond the scope of the present review. For specific details regarding dosing schedules, administration procedures and contraindications of individual vaccines the reader is referred to the *Canadian Immunization Guide* (17).

DIPHTHERIA EPIDEMIOLOGY

Diphtheria is a potentially life-threatening respiratory tract illness caused by toxigenic strains of *Corynebacterium diphtheriae*. It is characterized by low-grade fevers, anterior cervical lymphadenopathy, and laryngitis, nasopharyngitis or tonsillitis distinguished by a grayish adherent membrane. The release of systemic toxin is associated with delayed morbidity, including cases of myocarditis and peripheral neuropathies. Diphtheria has an associated mortality rate of 5% to 23%, with the highest rates reported at extremes of age (18,19). Vaccines based on formalin-treated diphtheria toxoid have been available since 1926. Because immunity to diphtheria is mediated by antibodies

against the toxin rather than the organism per se, vaccinated individuals may still have oropharyngeal colonization. Since the introduction of diphtheria vaccines in North America, there has been a greater than 99% decline in diphtheria-related deaths (20), with the last Canadian death reported in 1983 (21). Over the past 10 years, there have been eight cases reported in Canada (range zero to two per year) (22). The last Canadian diphtheria case was reported in 2004.

However, in areas where diphtheria immunization programs have struggled, there has been a resurgence of disease. Most notably, this was observed in all 15 independent states of the former Soviet Union where major economic and social changes led to inconsistent enforcement of immunization standards which ultimately led to an outbreak between 1990 and 1993 that was responsible for approximately 150,000 cases and approximately 5000 deaths (19). Depending on the state, adults represented 38% to 82% of cases, and had the greatest case-fatality rate. Detailed information on rates of immunity to diphtheria in the general Canadian population is lacking, and must be inferred from small studies. The most recent estimates suggest that 17% to 20% of Canadians do not have protective levels of diphtheria antitoxin (23,24). This increases to 42% in those older than 60 years of age. Although endemic transmission of diphtheria does not exist in Canada, Canadians remain at risk for imported disease, both through travel exposures and exposures to new immigrants from endemic areas.

Recently, nontoxigenic strains of *C diphtheriae* are being identified as rare causes of invasive disease. Cases are observed primarily among socially marginalized populations, such as those abusing intravenous drugs or those who are homeless (25). Because diphtheria vaccines have been developed against diphtheria toxin, this confers no protection against invasive nontoxigenic strains.

TETANUS EPIDEMIOLOGY

Tetanus is a condition characterized by spasmodic paresis secondary to the neurotoxin produced by *Clostridium tetani*. The organism is ubiquitous in soil and gastrointestinal flora of animals and has the potential to cause disease with penetrating injuries. It is important to note, however, that 27% of cases reported in North America have no identifiable inciting event (17). Vaccines against tetanus are largely unchanged since their introduction in 1940, and consist of formalin-inactivated tetanus toxin combined with aluminum salts. Since the introduction of routine vaccination and appropriate postwound management algorithms in the United States, the incidence of tetanus has declined by 93% and related mortality by 99% (20). However, tetanus remains a very common disease in many developing countries throughout the world and is responsible for approximately 800,000 to 1,000,000 deaths annually (22).

The incidence of tetanus remains very low in Canada. During the period from 1980 to 2006, an average of four cases of tetanus per year (range one to 10) were reported (22,26). However, case-fatality rates remain high at 20%. Unfortunately, tetanus immunity is waning in many populations. Few data are available to accurately assess the level of tetanus immunity in the general Canadian population, and they must be inferred from small studies. Protective levels of tetanus antibody were detected in only 82% of adult Toronto blood donors (decreasing to 58% in those older than 60 years of age) (24). Furthermore, because tetanus is ubiquitous in the environment and no opportunity for herd protection exist, all nonimmunized individuals are potentially susceptible to tetanus infection.

A number of risk factors for having inadequate antibody titres to tetanus toxoid have been identified and include advancing age, female sex, non-Caucasian status, poverty and lower levels of education (6). Furthermore, certain groups are well recognized as suffering disproportionate burden of tetanus disease. Data from Australia suggest that individuals over 65 years of age account for excessive tetanus morbidity and mortality, accounting for 44% of tetanus-related hospitalizations and 83% of tetanus related deaths between 1993 and 2002 (27). More recently, increased incidence of tetanus have been reported in injection drug abusers (28).

Tetanus and diphtheria prevention

In Canada it is recommended that all children and adults should be vaccinated against tetanus and diphtheria (17). To maintain immunity, booster doses of adsorbed tetanus and diphtheria toxoids delivered as Td (adult formulation of tetanus-diphtheria vaccine) are recommended every 10 years throughout adulthood. In adult Canadians who may not have received a primary tetanus immunization series, such as immigrants and refugees, three doses are required – the first two separated by at least four weeks and a third six to 12 months later.

PERTUSSIS EPIDEMIOLOGY

Pertussis (whooping cough) is an acute respiratory illness caused by *Bordetella pertussis*. The classic manifestations of the disease are paroxysmal coughing followed by an inspiratory whoop and post-tussive vomiting. In the prevaccine era, pertussis was one of the most common illnesses of childhood. In the 1940s, the first whole cellular extracts of *B pertussis* became available and were incorporated into routine childhood vaccination schedules (17). Immunization with cellular and more recently acellular pertussis vaccines has resulted in a 92% decline in incidence and 99% decline in pertussis-related mortality (20). Between 1990 and 2006, there was a mean of 4853 cases/year of pertussis reported in Canada (range 2165 to 10,151) (17,22). However, this is likely a dramatic under-representation of the true burden of disease. While commonly perceived as a childhood illness, pertussis is the etiological agent responsible for 9% to 20% of those adults with upper respiratory tract infection and cough lasting more than seven days (29). Accordingly, adults comprise up to one-third of cases (30). Incident data extrapolated for adults 19 to 64 years of age from prospective surveillance studies consistently show pertussis annual incidence rates of 176 per 100,000 person-years to 386 per 100,000 person-years (31). However, there may be considerable variation in regional pertussis incidence rates, which can be further compounded by regional outbreaks, as illustrated by a 2006 outbreak in Toronto, Ontario, in which pertussis rates increased fivefold relative to background (32).

While pertussis infection in infants is a very serious illness and results in two to three Canadian infant deaths each year, it does not typically cause death in adults (17). Pertussis is, however, associated with considerable morbidity in adult populations. The mean duration of cough in adults is 12 weeks, and 28% of adults experienced complications such as sinusitis, pneumonia, otitis media and urinary incontinence (33).

Furthermore, pertussis results in a mean of seven days of work absenteeism. Not surprisingly, those individuals at greatest risk of pertussis are teachers (RR=4) and health care workers (RR=1.7) (33). Adults are the identified vector to infants – the most vulnerable group to pertussis-related morbidity and mortality – in 75% of cases (34).

Historically, pertussis vaccination policies did not target adolescent and adult populations because whole cell extracts of *B pertussis* that were used resulted in unacceptably frequent and severe injection site reactions. However, since 1997, an acellular vaccine based on *B pertussis* virulence factors – pertussis toxoid, filamentous hemagglutinin and pertactin – has been used. Acellular pertussis vaccines have an efficacy of approximately 85% and are now recommended in all age groups (30). The goal of pertussis control is to decrease the morbidity and mortality secondary to pertussis in all Canadians, irrespective of age.

Published data on the proportion of Canadian adults vaccinated with aceullar pertussis are lacking; however, anecdotal reports suggest this to be very low.

Strategies targeting contacts of infants (women contemplating pregnancy, their partners and grandparents), termed 'cocooning', with acellular pertussis vaccine have been suggested as a means to minimize transmission of pertussis to infants – those at greatest risk of complications (35). Modelling suggests that 'cocooning' strategies would result in significant reduction in the incidence of infant pertussis but would confer only a relatively modest reduction in pertussis incidence in all age groups (36). Targeting vaccination efforts toward health care workers has been suggested as it may result in reduced transmission and limit resource-intensive hospital investigations and infection control measures, resulting in significant cost savings (35).

Pertussis prevention

All adults who have not previously had a dose of acellular pertussis should receive a single dose (17). This can be administered with a routine Td booster in the combination form Tdap (tetanus-diphtheria and acellular pertussis), in place of Td. Vaccination with Tdap can be done in adults with specific need (ie, contacts of infants) within two years of receipt of Td, without significant risk of adverse effect (35); shorter intervals may be used. Studies to determine the durability of the immune response are currently underway, but as yet, no recommendations exist for repeated doses for adults. While inactivated vaccines are usually considered safe in pregnancy, long-term studies of Tdap's effect on the fetus are unknown. Tdap should only be used in pregnancy when benefits outweigh risks.

MEASLES EPIDEMIOLOGY

Measles is an acute illness caused by the rubeola virus characterized by fevers, cough, coryza, pathognomonic buccal mucosal lesions known as Koplik's spots and a maculopapular rash favoring the head (37,38). Complications may ensue and include pneumonia (5% to 10%), otitis media (10% to 15%), encephalitis (0.1%) and the potential for a lethal progressive neurological condition known as subacute sclerosing panencephalitis. Measles is highly infectious; 75% to 90% of household contacts of an infected individual will develop the disease. In developing countries, measles-associated mortality can be 1% to 5%; however, this is reduced in developed nations to 0.03% (39). Adults remain at increased RR for both complications and death due to measles (38). While measles was formerly endemic in North America, the advent and implementation of routine childhood measles immunization programs has led to a reduction in measles incidence and attributable mortality by greater than 99.9% in the United States (20). However, measles remains endemic in many developing nations and is responsible for an estimated 777,000 worldwide deaths per year (22,39). Physicians should be aware of atypical measles syndrome, which occurs in individuals with incomplete measles protection (as a result of vaccination with a killed measles virus vaccine, or with a live attenuated virus that was heat inactivated during disruptions of cold chain) who acquire wild type measles characterized by high fevers, headache, myalgias and rash that is reminiscent of Rocky Mountain spotted fever.

The current vaccine uses a live attenuated version of the Enders' attenuated Edmonston strain of measles to induce host immunity. This vaccine has been available as part of routine Canadian immunization protocols since 1970. Individuals born before this year are likely to have previously developed natural immunity given the very high prevalence of measles during this time. Following multiple regional outbreaks between 1989 and 1995 despite high vaccine coverage, it became evident that a single dose of measles vaccine was inadequate because 10% to 15% of individuals failed to develop a protective antibody response (17, 40). Accordingly, in 1996 a second dose of the vaccine was incorporated into provincial/territorial immunization schedules and in many regions a 'catch up' program was adopted (17).

As a result of effective vaccination policies in Canada, endemic measles transmission has virtually been eliminated, and almost all cases of measles since 1998 have been imported or have been secondary to transmission from an imported case (41). The average number of measles cases reported annually in Canada between 2001 and 2005 was 14 (range six to 34). However, between April and November 2007, two successive outbreaks occurred in southeastern Quebec (40). These spread to involve 95 individuals throughout the province. Most individuals affected (92%) were either unvaccinated or undervaccinated having received only a single dose of MMR. The index case was a child attending an alternative school who was not vaccinated because of religious beliefs. While these outbreaks were concentrated in children (mean age of 14 years), a considerable number of adult cases occurred (range 18 to 46 years of age). More recently, several cases of measles were documented in downtown Toronto resulting in considerable concern regarding the potential for secondary spread because patients had commuted via the underground PATH pedestrian tunnel system (42).

MUMPS EPIDEMIOLOGY

Mumps is a clinical syndrome caused by the mumps virus characterized by acute parotitis. Clinical presentations vary with classic bilateral parotitis occurring in only 40% of patients. Subclinical infection is commonplace. More serious sequelae are rare. While aseptic meningitis can occur in 10% to 30% of patients, long-lasting effects are infrequent. Orchitis is common, affecting 20% to 25% of males, but rarely results in sterility (43). Mortality from mumps in the postvaccine error is rare, and no deaths have occurred in recent outbreaks (20).

Before the advent and implementation of live viral mumps vaccines in 1969, mumps was a ubiquitous childhood disease (44). Nearly every child acquired mumps before 15 years of age (45,46). Immunization has proven to be very effective in preventing mumps. The use of the combined MMR vaccine (containing the live attenuated Jeryl Lynn mumps strain) in North America has resulted in a decrease in the incidence of mumps by 96% and a greater than 99% decrease in mumps-related mortality (20). However, mumps remains endemic in many developing countries. In fact, only 57% of World Health Organization member countries have a mumps vaccine program (47). In nonoutbreak conditions vaccine efficacy has been shown to be in the order of 95% (48,49). However, in outbreak settings, efficacy has been shown to be considerably less (range 62% to 91%) (50-53). Depending on the population studied, the seroprevalence of mumps antibodies ranges from 80% to 94% suggesting that vaccine uptake remains suboptimal (17,54).

Mumps immunization protocols for infants began to change in 1991 when several provinces instituted a second dose of MMR because of concerns of inadequate protection with a single dose (55,56). By 1996 to 1997, this became the national standard (47). This second dose of MMR is thought to provide a much more durable, lifelong protective response. Because mumps was a ubiquitous childhood disease before the implementation of routine immunization programs in 1970, it is assumed that Canadians born before this are naturally immune to mumps on the basis of previous disease. A large cohort of individuals between 12 and 17 years of age (province dependent) and 39 years are potential susceptible hosts for wild type mumps infection because they received only a single dose of MMR. With the current trend toward greater immunity in younger populations as a result of the two-dose MMR vaccination schedule, demographics of those suffering from mumps have been altered. The incidence in individuals older than 20 years of age has risen from 14% in 1988 to 1990 to 64% in 2003 to 2005 (17,47).

Between 2000 and 2006, the mean number of documented cases of mumps occurring in Canada was 79 cases per year (range 28 to 202 cases per year) (47). However, since a large scale outbreak of mumps in the United Kingdom in 2005 involving 70,000 individuals (57), there have been multiple smaller outbreaks in North America (58). The largest of these affecting Canadians is currently ongoing. While originating in the Maritime provinces, this has subsequently propogated from east to west across the entire country resulting in 1284 cases in 2007 (59). These cases were initially concentrated around postsecondary educational institutions; however, recently more than 200 cases in Fraser Valley, British Columbia, have been associated with religious communities that shun vaccination (60). The median age of patients is 23 years (range two to 79), and most patients have received a single dose of MMR vaccine. In this outbreak, receipt of a single dose of MMR has been associated with increased risk of disease acquisition relative to two doses (47,57,59,61). To extinguish the current outbreak, Nova Scotia has adopted a policy of extended vaccination coverage, now offering a second dose of MMR to those enrolled in postsecondary educational institutions, and those individuals deemed at high risk given their occupation (ie, health care workers and military recruits) in accordance with NACI guidelines (17,47,59).

RUBELLA EPIDEMIOLOGY

Rubella manifests itself as a nonspecific viral illness in most hosts, resulting in a transient erythematous rash, low-grade fevers, occipital and posterior-auricular lymphadenopathy and, occasionally, polyarthralgias. However, up to 50% of infections are subclinical. Complications remain rare, with the exception of infections during pregnancy. Acquisition of rubella during the first trimester (with decreasing risk with time thereafter) is associated with miscarriage, stillbirth and a 90% risk of congenital rubella syndrome (CRS; manifested as a constellation of neurocognitive delay, deafness, cataracts and cardiac defects). It is primarily for the prevention of CRS that routine vaccination against rubella has been adopted. Vaccines against rubella use the live attenuated Wistar RA 27/3 strain. Unlike measles and mumps, a single dose is thought to be protective, resulting in seroconversion in 97% of individuals with a durable long-lasting response. Since vaccination programs began in 1983, there has been a drop in incidence from 5300 cases/year (1971 to 1982) to approximately 30 cases/year (1998 to 2005) (17,26). Marked decline in CRS have similarly been reported and since 2000 seven cases have been reported (range zero to two per year) (22). Limited studies are available to gauge the degree of immunity to rubella in the general population; however, serological studies from military recruits suggests that 10% of the population remains immunologically naive (54). Outbreaks may still occur in undervaccinated populations including those opposing vaccination secondary to imported cases as illustrated by a 2005 outbreak in Ontario (62). Outbreaks in isolated communities, such as these, highlight the importance of maintaining a high level of immunity in the entire population for 'herd immunity' (10). While all adults should be immunized against rubella to minimize spread, it is national policy that all pregnant patients be screened for antirubella antibodies such that they can be administered the vaccine postpartum, to protect them during subsequent pregnancies.

MMR prevention

All Canadians should have immunity to MMR (17). Those adults born before 1970 can be presumed to have had previous natural exposure to MMR, and resultant immunity. Those adults born after 1970 without a documented history of immunity based on previous vaccination or natural infection (confirmed with serological testing) should receive a single dose of the MMR vaccine. Those adults perceived to be at increased risk who were born during this time period should receive a second dose of the MMR vaccine as a booster (ie those attending a post-secondary institution, military personal, health care workers or those travelling to endemic areas). The MMR vaccine components include live attenuated viruses. Accordingly, they should not be used in certain populations including pregnant patients, those with inherited or acquired immunodeficiencies.

VARICELLA

Primary infection with varicella-zoster virus (VZV) causes a vesicular exanthem accompanied by fever and malaise known as 'chickenpox'. It is highly infectious and has an attack rate of 61% to 100% in susceptible hosts (63). Before the introduction of VZV vaccine, it was estimated that approximately 350,000 cases occurred annually in Canada (17). Most children by 12 years of

age will have serological evidence of previous infection. While chickenpox has historically been considered a relatively benign disease of childhood, it has been well recognized that immunologically naive adults are at increased risk for morbidity and mortality from primary VZV infection. Complications including encephalitis, hepatitis, pneumonia/pneumonitis and secondary bacterial skin and soft tissue infections with resultant bacteremia are more common in adult patients (64). Furthermore, adults are more likely to be admitted to hospital (RR three to 18) or die (RR 23 to 29) relative to children (65,66). Data from the United States suggest that while adults represent only 5% of new cases of chickenpox annually, they account for 55% of the approximately 100 VZV-related deaths. In Canada, 53 deaths were attributable to chickenpox between 1987 and 1996; however, 70% of these were in those older than 15 years of age (67).

A subset at particularly high risk of VZV morbidity are women of childbearing age with no previous VZV exposure. Transplacental passage of VZV can be associated with congential varicella syndrome (CVS) characterized by neurocognitive delay, microcephaly, limb hypoplasia, cutaneous scarring and ocular disease. Risk of CVS varies according to gestational age of the infant, and peaks between the 13th and 19th week. A second entity of neonatal varicella may occur in those mothers that acquire the virus between five days prior and two days following delivery and is associated with neonatal mortality rates of 20% to 30% (67)

Herpes zoster or shingles is a disease that occurs as a result of waning of cell-mediated immunity to VZV. Anyone with a history of primary VZV is at risk of reactivation of latent VZV from the dorsal root ganglion causing cutaneous disease which is typically limited to a single dermatome. While acute herpes zoster is painful, it does not typically cause significant morbidity (68). However, postherpetic neuralgia can occur in up to 20% of individuals, which may result in chronic and debilitating pain causing marked reduction in quality of life (69). The risk of shingles has been calculated at 10% to 20% over an individual's lifetime; however, this risk increases to 50% in those 85 years of age or older. Other factors that can hasten an individuals risk of herpes zoster include immune suppression (including those recieving immune suppressive agents, HIV/AIDS), stress and trauma.

Data suggest that 10% of the adult population has not been exposed to VZV infection and are, therefore, at risk of the increased morbidity and mortality associated with adult-onset chickenpox (17,70). Risk factors for VZV susceptibility in adult populations include being of non-Caucasian ethnicity, born in a foreign country and being a single child (70). Vaccination is an effective means of preventing primary VZV disease.

Available vaccines against primary VZV are based on an attenuated version of the Oka strain. These vaccines have been shown to be very effective, with seroconversion rates in excess of 99%, which are sustained over time (71,72). Patient history of previous chickenpox is a relatively reliable indicator of immune status, and has a positive predictive value of 98% and a negative predictive value of 85% of serological status (63). Accordingly, serological testing should be considered for those individuals that report no previous history of primary VZV disease before administration of the vaccine.

Attempting to eliminate natural VZV infection through immunization is not without potential for adverse effects. Reducing the number of susceptible infants to VZV will result in an increased incidence of disease in adult populations – those more likely to suffer adverse VZV-related complications (73,74). Perhaps more important to the general Canadian population is the loss of immune boosting that occurs in VZV immune individuals on re-exposure to exogenous VZV from individuals with natural infection, which will inevitably occur as a result of mass reduction in the incidence of wild type VZV. Data support that adults are protective against herpes zoster disease through natural exposures to exogenous VZV and that in the absence of recurrent exogenous stimulation, natural VZV immunity may last only 20 years (74,75). VZV vaccination campaigns in children may inadvertently result in a marked increase in the overall incidence of herpes zoster and reduce the age in which this is expected to occur.

Varicella prevention

The NACI recommends that all susceptible adults without contraindications to VZV vaccine receive two vaccine doses administered subcutaneously separated by four to eight weeks (67). Absolute contraindications to vaccination include advanced immune suppression and pregnancy. Those individuals considered priorities for immunization include women of childbearing age, those with high risk of occupational exposure/transmission – including teachers and health care workers, immigrants from tropical climates, individuals with cystic fibrosis and regular contacts of individuals with immunosuppression (17). The vaccines approved in Canada for prevention of primary VZV disease are not approved for prevention of recurrent VZV disease such as shingles. A vaccine for use in individuals 60 years of age or older for the prevention of herpes zoster has been developed and recently approved for use in Canada (76). NACI recommendations regarding its use are expected in 2009.

PNEUMOCOCCUS

Streptococcus pneumoniae (pneumococcus) is a Gram-positive pathogen that has a characteristic diplococcus appearance by Gram stain. Despite its name, the *S pneumoniae* causes many types infection other than pneumonia, including: otitis media, meningitis, bacteremia, septic arthritis, osteomyelitis, endocarditis, pericarditis, cellulitis, sinusitis and brain abscess. Invasive pneumococcal disease (IPD) (as defined by pneumonia, blood stream infection or meningitis) is infrequently reported in Canada. A mean of 1926 cases were reported each year from 1999 to 2004 (range 1248 to 2544) (77). However, this is a dramatic underestimate of the true burden of disease. In the United States, approximately 500,000 cases of pneumonia, 50,000 episodes of bacteremia and 3,000 cases of bacterial meningitis are attributed to *S pneumoniae* each year (78). This corresponds to an estimated 40,000 annual deaths. While a frequent cause of disease in children, *S pneumoniae* also causes a disproportionate burden of disease in those adults with medical comorbidities or those 65 years of age or older (17,78).

Owing to tremendous serotype diversity in pneumococcus, vaccines that induce antibody responses against multiple capsular antigens have had to be developed. Pneumococcal capsular polysaccharide antigens induce serotype-specific antibodies that enhance opsonization, phagocytosis and killing by host immune response (79). A twofold or greater increase in serotype-specific antibody develops within three weeks in 80% or more of healthy

young adults; however, immune responses may not be consistent across all serotypes (78,80). Furthermore, antibody responses are typically lower and less robust in those whom are elderly, or have co-morbidities including cirrhosis, chronic obstructive pulmonary disease or diabetes mellitus (81,82). In those patients who are immune-compromised, antibody responses may be markedly diminished or even absent (78,83).

While serological response in adults has been relatively easy to demonstrate with pneumococcal polysaccharide vaccines, clinical response has been much more difficult to prove. Early nonrandomized trials suggested clinical efficacy of 55% to 70% (79,84,85). However, recent randomized placebo-controlled trials fail to show clinical benefit (86,87). Owing to the relative infrequency of the diagnosis of IPD none of these studies were adequately powered to detect a significant benefit. As such, the exact manner in which to determine pneumococcal vaccine responsiveness remains undetermined.

Each of the two Canadian-marketed 23-valent pneumococcal polysaccharide vaccines (Pneumovax 23; Merck Frosst Canada Ltd and Pneumo 23; Sanofi Pasteur Ltd) contains 25 µg of capsular polysaccharide from each of the following *S pneumoniae* serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F. Vaccine serotypes represent at least 85% to 90% of the serotypes that cause IPD (78,79,88) and include the six antibiotic-resistant serotypes most likely to cause IPD (6B, 9V, 14, 19A, 19F and 23F) (78,89).

Representative data on polysaccharide pneumococcal vaccine uptake on the entire Canadian population are lacking. In the largest study, a telephone-based survey of Toronto residents revealed low rates of prior vaccination, with only 14% of those adults younger than 65 year of age with medical comorbidities having received pneumococcal polysaccharide vaccine. Of those 65 years of age or older, 33% of individuals without medical comorbidites and 55% of those with one or more medical comorbidities had received vaccination (90). Encouragingly, these values increased over time with each successive year of study.

While a seven-valent conjugate vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) has replaced the polysaccharide vaccine for routine use in children because of enhanced antibody response and immune memory, this practice is not warranted routinely in adults. When assessed in small randomized controlled trials in specific populations of patients, no consistent increase in serological response has been observed relative to polysaccharide vaccine (91). Perhaps not surprisingly, it is increasingly apparent that protection of infants with conjugate vaccine results in reduced burden of disease in adults populations (92).

IPD prevention

Polysaccharide vaccine should be given to those adults who are at the highest risk of IPD: individuals with a history of chronic lung disease (including smoking), heart failure, chronic renal failure (including nephrotic syndrome), chronic liver disease (including alcohol dependence and cirrhosis), diabetes, diabetes mellitus, asplenia/sickle cell disease, congenital or acquired immune deficiency, chronic cerbrospinal fluid leak, residents of long-term care facilities and all those 65 years of age or older (17). Recently, homelessness and injection drug abuse were added as indications (93). Protective levels of antibodies fall after five to 10 years, and more markedly in some populations and as such repeated dosing is occasionally suggested in the highest risk groups (78).

INFLUENZA

Influenza is a respiratory tract illness caused by a segmented negative strand RNA viruses of the family Orthomyxoviridae. Influenza A and B are primarily responsible for human disease. Influenza A strains are identified and classified based on commonality of two particular surface antigens, hemagglutinin (H) and neuraminidase (N). Influenza B, which has lower diversity, is divided into two distinct lineages: Yamagata and Victoria (94). Antibodies directed against one influenza virus type or subtype confers little to no protection against other type or subtypes (95). Furthermore, antibodies against one antigenic subtype of influenza virus may not even provide protection against infection with a new antigenic variant of the same subtype. It is this frequent emergence of antigenic variants through antigenic drift that is the virological basis for seasonal influenza epidemics and the need for yearly redesign of influenza vaccines.

Annual epidemics of influenza occur yearly from November to May in the Northern hemisphere. Each year up to 20% of the population may be affected, however, the range of symptoms is considerable. In Canada, a mean of 5491 cases of laboratory confirmed influenza are reported yearly (range 2953 to 8132) (77). This, however, vastly underestimates the true burden of disease. Using data abstracted from the National Hospital data from Discharge Survey over the period of 1979 to 2001, Thompson et al (96) projected that yearly influenza epidemics were responsible for a mean of 226,000 hospitalizations per year in the United States (range 54,000 to 430,000). Furthermore, annual influenza attributable mortality within the United States was calculated at a mean of 36,000 deaths per year (range 17,000 to 51,000) for influenza seasons from 1979 to 2001 (97).

Vaccination is an effective way to prevent serious influenza-related complications (94,95). In Canada, influenza prevention is primarily mediated through vaccination with a trivalent inactivated vaccine (TIV). TIV are developed as per World Health Organization – Global Influenza Surveillance recommendations and these include two influenza A viruses (one strain of H1N1 and one H3N2), and a dominant influenza B strain. Chemoprophylaxis with either amantadine or the neuraminidase inhibitors are not a substitute for vaccination and should be preserved for those with contraindication to TIV (anaphylaxis to egg), during outbreaks and during seasons of vaccine-circulating strain mismatch. Furthermore, increasing resistance to amantadine and now oseltamavir are cause for great concern (95). While licensed for healthy individuals two to 49 years of age in the United States, cold-adapted, live-attenuated influenza virus is not available in Canada.

During seasons in which the TIV has a good match with dominant circulating strains, vaccination has been shown to prevent influenza illness in approximately 70% to 90% of adults 65 years of age or younger (98-100). In the PRISMA nested case-control study following 75,257 Dutch adults, vaccination with TIV resulted in 87% reduction in hospitalizations for influenza like illness and 78% reduction in mortality in high risk adults younger than 65 years of age (100). During years in which

vaccine mismatch occurs, some degree of protection is still conferred albeit lower with efficacies, estimated at 50% to 70% (101). Adults 65 years of age or older have a diminished immune response to influenza vaccination compared with young healthy adults. Vaccine efficacy has been estimated at 50% to 60% in this population, and decreases with increasing age (102,103). In the same PRISMA Dutch cohort, influenza vaccination reduced hospitalization for influenza like illness by 48% and mortality by 50% in those 65 years of age or older (100).

Influenza prevention

While provincial recommendations on influenza vaccination vary, NACI recommends routine adult immunization in four specific groups of adults (17,95) – those at increased risk of influenza-related morbidity and mortality (chronic cardiac or pulmonary disease, chronic renal failure, diabetes mellitus, anemias, those with cancer or who are immune-suppressed/immune deficient, pregnant or residents of long-term care facilities), those at increased risk of propagating influenza to high-risk individuals (health care workers, household contacts of individuals at high risk including infants younge than two years, child care workers and those working in confined environments), those providing 'essential community services', and those staff culling poultry infected with avian influenza. Compliance with these recommendations remains suboptimal. In 2003, only 38% of adults younger than 65 years of age with a chronic medial condition were vaccinated (104). However, those adults 65 years of age or older faired much better with 62% vaccinated (without comorbidities) and 75% vaccinated (with one comorbidity or more). Encouragingly, vaccine uptake has increased with each influenza season from 1996/1997.

CONCLUSIONS

The advent and implementation of universal vaccination programs has been a tremendous medical achievement which has significantly reduced the burden of morbidity and mortality to many infectious diseases (1,20). However, the provision of routine vaccinations to Canadian adult populations remains largely inadequate. Failure to provide these simple and cost savings interventions results in increased risk of individual morbidity and mortality as well as increases the risk to the population as a whole.

Primary prevention of infections with the use of safe and cost-effective vaccines is a lifelong process. While detailed evidence-based guidelines exist for the appropriate administration of these vaccines to adults, it is the implementation of these recommendations that remains suboptimal. Many barriers have been identified associated with reduced vaccine uptake including, vaccine safety and efficacy misperceptions in both health care providers and the general population, and confusion regarding recommendations (2,5,6). These barriers need to be overcome through aggressive promotion of a public health agenda. While beyond the scope of this article many novel strategies have previously been proposed which may serve to augment vaccine uptake in adult populations. Such strategies include the development of a efficient vaccine delivery infrastructure similar to that in pediatrics, minimizing physical and financial barriers to patient access, and education of patients, advocacy groups and healthcare providers alike (2). These strategies need to be studied in a prospective fashion and those that are determined to have validity should be incorporated into vaccine provision strategies.

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