Hepatitis A Post-exposure Prophylaxis

Provincial Infectious Diseases Advisory Committee (PIDAC)

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Introduction

Appendix A of the Ontario Ministry of Health and Long-Term Care (MOHLTC) 2009 Infectious Diseases Protocol provides case and contact management advice for reportable diseases in Ontario. The Hepatitis A virus (HAV) chapter within Appendix A provides post-exposure prophylaxis (PEP) recommendations under the section titled 'Management of Contacts'.[1] The PEP recommendations cite the 2006 Canadian Immunization Guide (CIG) which recommends to administer HAV vaccine to contacts, including contacts of food handlers, "as soon as possible", "preferably within one week after exposure but can be given up to 14 days after exposure"; and to administer Hepatitis A immune globulin for immuno-compromised contacts and children under 12 months of age.[2]

In addition, the chapter cites further contact management advice from the Provincial Infectious Diseases Advisory Committee (PIDAC) that should be "given consideration": the concurrent use of HAV vaccine and serum immune globulin for certain high risk contacts including sexual contacts, contacts who changed the diapers of an infected case, and for individuals who consumed food prepared by a case, especially if the contact is older than age 50 years or has chronic liver disease.[1] Additional PIDAC recommendations that are listed "for consideration" include advice pertaining to children in group settings: the administration of HAV vaccine to attendees, their close contacts, and staff if a case of HAV occurs in a childcare centre or kindergarten setting; and advice to administer HAV vaccine to all staff and childcare attendees if an attendee is a contact of an index case who does not attend the childcare setting.[1]

The HAV chapter of Appendix A includes additional contact management pertaining to food handlers. If the case is a food handler, the protocol suggests "considering" offering HAV vaccine to "other food handlers (best given within 2 weeks after exposure) at the same establishment and to patrons who ate food handled by the infected food handler, who were exposed during the period of communicability".[1] In response to several queries from public health professionals who work in Ontario's 36 Public Health Units (PHUs) in relation to the Hepatitis A chapter of the Protocol, a review of the 2006 PIDAC Subcommittee on Immunization (PSI) recommendations on HAV PEP was undertaken by PIDAC-Immunization (PIDAC-I),[3] with a view to informing the evergreening of the Infectious Diseases Protocol that is underway.

Objective

The objective of this report is to review the evidence base and experience base underlying the 2006 PSI recommendations to facilitate discussion among PIDAC-I members to reaffirm, revise and, or provide other options to the MOHLTC for HAV PEP recommendations. The scope is limited to the 2006 recommendations. HAV primary prevention was considered to be out of scope for this review. Guidance on case, contact and outbreak management beyond the 2006 PSI recommendations was also considered to be out of scope for this review (i.e. food handler recommendations).

Hepatitis A overview

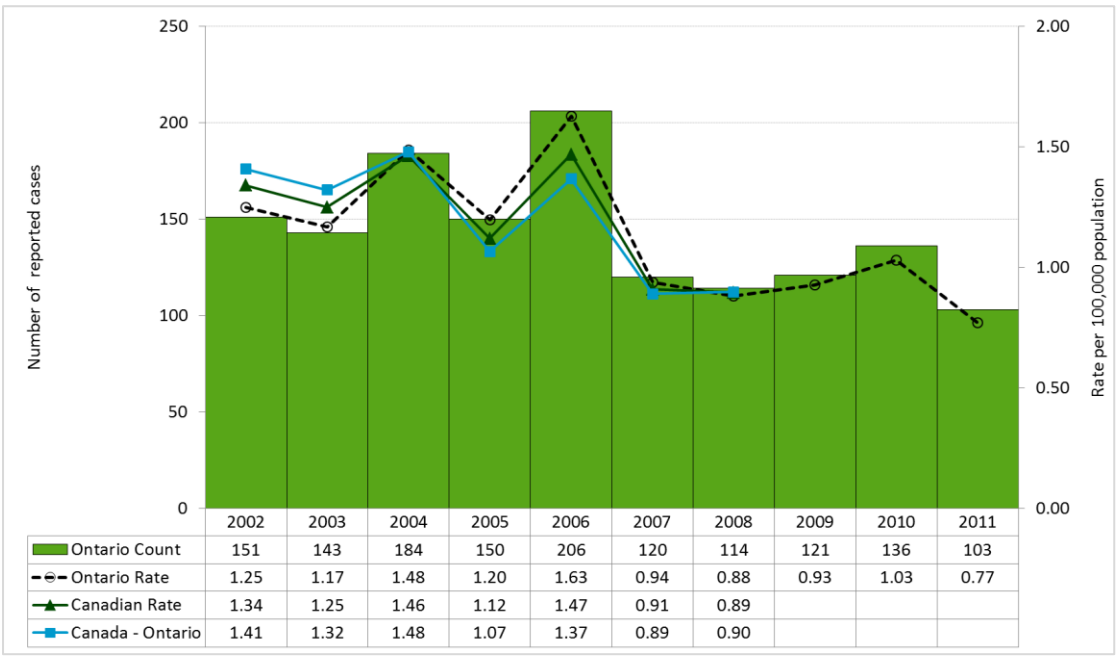
HAV is a single stranded RNA virus, and a member of the Picornaviridae family. HAV is transmitted through the fecal-oral route, including person-to-person transmission, from contact with contaminated objects, or through the ingestion of contaminated food or water. Although rare, transmission of infection through blood or blood products, obtained from donors during the incubation period, has also been reported.[4] The incubation period is relatively long, in the order of 15-50 days, with a median of 28 days.[5] The period of communicability includes the asymptomatic period of infection; cases are capable of transmitting infection 2 weeks before the onset of symptoms to 1 week after the onset of jaundice.[5]

There is evidence that young children may excrete the virus in their stool for a longer period of time.[6] The spectrum of illness of HAV is age-dependent. Approximately 70% of older children and adults will develop jaundice, in contrast to fewer than 10% of children under the age of 6 years.[7,8] Approximately 70% of children under age 6 years, will be entirely asymptomatic.[8] For most individuals, HAV infections have a self-limited course but serious sequelae do occur. Approximately 25% of adults require hospitalization and 15% of cases will have a relapsing course of infection.[9] Chronic infection does not occur. The most severe consequence of infection is progression to fulminant hepatitis and related mortality, the risk of which is significantly increased among those with pre-existing liver disease. Despite this recognized risk factor, there are case reports in the literature of healthy children requiring liver transplantation following HAV infection.[10] It is difficult to quantify the contribution of increasing age to the risk of fulminant hepatitis from HAV as studies in this area have focussed on other clinical and virological factors.[11,12] However, the case-fatality ratio (CFR) of HAV is clearly age-dependent, although not in a linear fashion. Canadian data quote a CFR of 0.1-0.3% for individuals under the age of 50 years, and 1.8% among those older than 50 years.[9] Surveillance data from the Centre for Disease Control report a CFR of 0 to 0.3% for children under the age of 14 years, 0.3% in adolescents and young adults (15-39 years of age), 0.8% among adults (40-59 years of age), rising to 2.6% in adults aged 60 years and older.[13,14]

Epidemiologic context

Canada has seen a dramatic decline in HAV incidence over the last 20 years. In 1990, the national incidence was 10.6 cases/100,000 population, which dropped to 0.9 cases/100,000 in 2008.[9] Figure 1 provides HAV incidence for Canada and Ontario over the ten year period of 2002 to 2011, where a decline in cases is also apparent. In 2011, a total of 103 confirmed cases of HAV were reported in Ontario, resulting in an incidence of 0.77 cases per 100,000 population. In 2006 there was a national investigation into a possible link between HAV and frozen berries, which partially explains the increased number of cases observed in that year.

Figure 1. Incidence of hepatitis A in Ontario and Canada: 2002-2011.

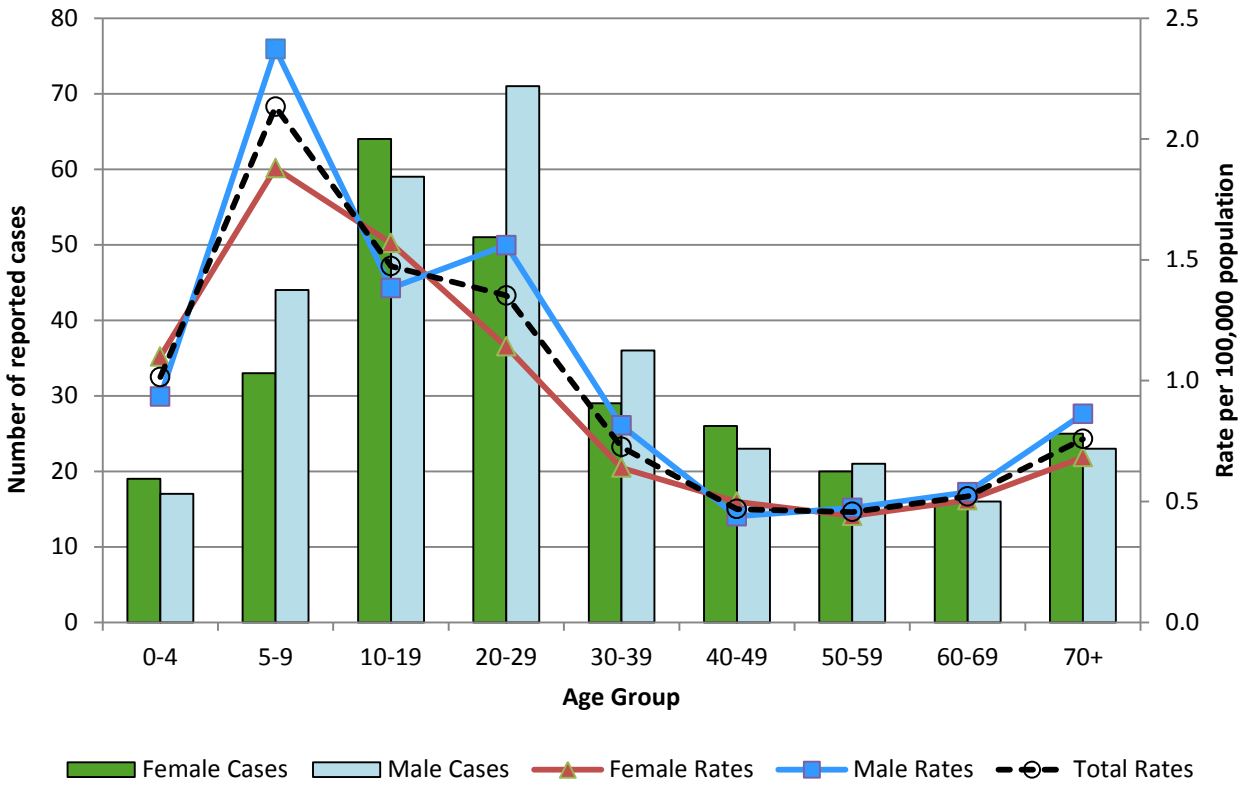


	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Ontario Count	151	143	184	150	206	120	114	121	136	103
Ontario Rate	1.25	1.17	1.48	1.20	1.63	0.94	0.88	0.93	1.03	0.77
Canadian Rate	1.34	1.25	1.46	1.12	1.47	0.91	0.89			
Canada - Ontario	1.41	1.32	1.48	1.07	1.37	0.89	0.90			

Source: *MOHLTC, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario (PHO) [2012/06/13] and Public Health Agency of Canada.*

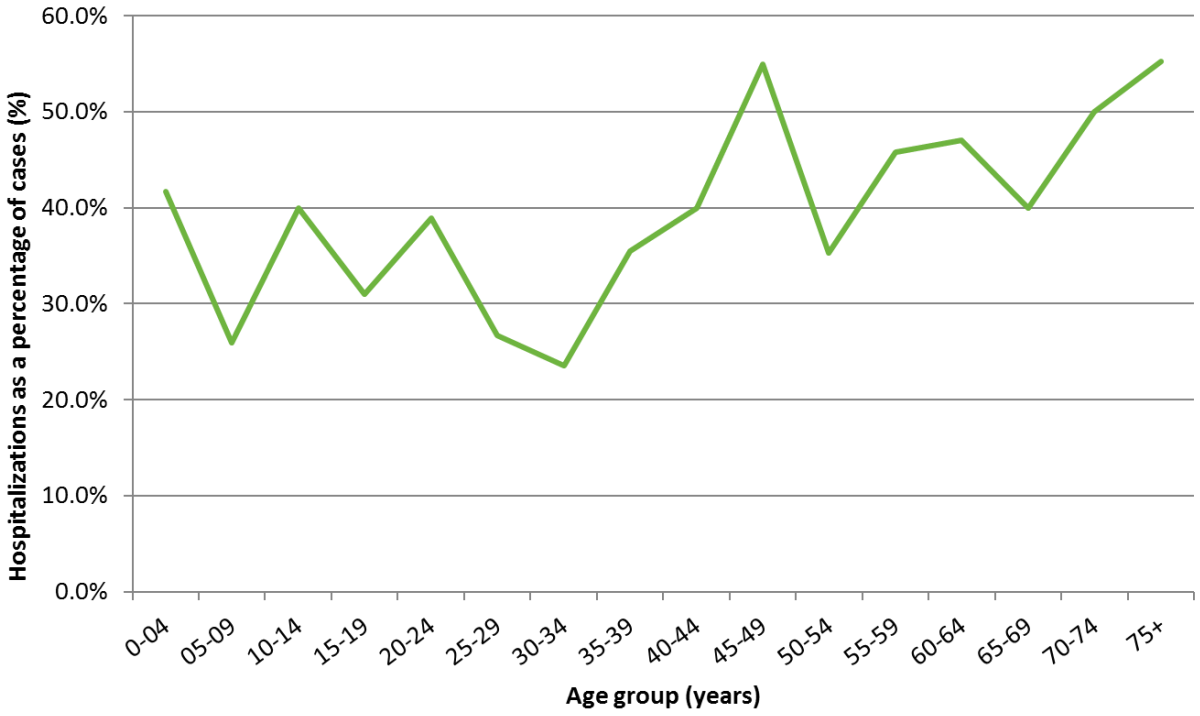
Figure 2 displays the age-specific incidence of confirmed HAV cases, by sex, in Ontario between the period of 2007 and 2011. The age specific incidence is highest among those 5-9 years of age (2.13/100,000 population), followed by youth aged 10 to 19 years of age (1.47/100,000 population). Due to the frequency of asymptomatic and mild infections among young children, the age-specific incidence rates in the youngest age groups are likely underestimated. Given secular trends in the epidemiology of HAV, and increasing HAV immunity with age, the increase in incidence between the age group of 60-69 years and greater than 70 years was an unexpected finding and could be explained by increased case finding and reporting among older adults with greater disease severity. Between 2007 and 2011, 220 of the 594 confirmed HAV cases in Ontario were hospitalized (37%) (Figure 3). This is much greater than the 25% hospitalization that is quoted in the CIG.[9] The proportion of cases requiring hospitalization increased after the age of 40 (46.8% ≥40 years versus 33.1% <40 years). Over the period of 2007-2011, there were a total of 4 confirmed cases of HAV in Ontario and reported in iPHIS where "fatal" was listed as an outcome. All fatal cases occurred among adults with the highest CFR occurring among those aged 70 years and older (2/48, 4.2%). This CFR is substantially higher than Canadian and US estimates and may be related to the smaller denominator size whereby a small number of events can have a large impact on the resulting ratio, or may be due to under-reporting of less severe cases.

Figure 2: Incidence of hepatitis A by age and sex: Ontario, 2007-2011.



Source: *MOHLTC, integrated Public Health Information System (iPHIS) database, extracted by PHO [2012/06/13].*

Figure 3: Age-specific proportion of cases requiring hospitalization, Ontario, 2007-2011.



Source: *MOHLTC, integrated Public Health Information System (iPHIS) database, extracted by PHO [2012/06/13].*

Seroprevalence of hepatitis A antibody has been assessed at a national level through the Canadian Health Measures Survey (CHMS),[15] and two research studies.[16,17] From CHMS which measured HAV seroprevalence between 2007 and 2009, seroprevalence increased with increasing age reflecting secular trends in the HAV transmission dynamics (Table 1). Among those aged 14-19 years, it was 17.3% (95% confidence interval (CI) 11.5-23.0%), rising to 64.6% (95% CI 59.6-69.5%) among those 60-79 years.[15] No regional analyses (e.g. Ontario-specific) are available because of the sampling frame used by CHMS. Duval and colleagues examined HAV seroprevalence in Canadian children aged 8-13 years residing within Canada's ten provinces and found a seroprevalence of only 2-3% in this age group, demonstrating the extent of this age group's susceptibility.[17] The difference between the seroprevalence estimates from Duval for 8-13 year-old-olds (2.7%) in 2003, as compared to 14-19 year-old-olds (17.3%) in 2007-9 via CHMS have several possible explanations including the contribution of a cohort effect, beyond simply an increase in seroprevalence with age. In addition, the inclusion of the territories in CHMS and their exclusion from the study by Duval and colleagues, might also have an impact as populations in northern Canada have been noted to have a higher burden of viral hepatitis, including HAV.[18]

Table 1. Recent Canadian HAV seroprevalence estimates

Data source	Sampling frame	Year of data collection	Age group (years)	N	%HAV positive	95% CI
Duval et al. [17]	10 Provinces	2003	8-10	474	1.9	0.9-3.5[1]
			11-13	583	3.4	2.2-5.2[1]
CHMS [15]	National	2007-2009	14-19	not provided	17.3	11.5-23.0
			20-39	not provided	28.0	21.4-34.5
			40-59	not provided	42.7	35.6-49.8
			60-79	not provided	64.6	59.6-69.5
Scheifele et al. [16]	National	2008[2]	18-29	258	17.8	13.2-22.5
			30-39	275	22.9	17.9-27.9
			40-49	339	26.3	21.6-30.9
			50-59	335	37.9	32.7-43.1
			60-69	345	53.3	48.1-58.6

Notes: 1. Calculated 95% CI (not provided in original report)
2. Year(s) of data collection not reported but preliminary analyses presented in 2008.

Options for HAV PEP

There are two interventions available for HAV PEP: active immunization with HAV vaccine or passive immunization using immunoglobulin (IG), a sterile preparation of concentrated antibodies. The immunologic principles differ between these strategies. The principle underlying the use of HAV vaccine is that a swift immune response will provide protection against infection, if administered early in the incubation period of infection. In contrast, the use of immunoglobulin results in the passive transfer of anti-HAV antibodies which provide near-immediate protection but at the trade-off of a more limited duration of protection, typically in the order of 2-6 months. The recommended dose of IG for post-exposure prophylaxis is 0.02 ml/kg of body weight.[9]

HAV vaccines are available in Canada in several formulations including monovalent products and combination products (i.e. HAV/HBV and HAV-Typhoid). It is important to note that only monovalent vaccines have been evaluated for PEP use in clinical trials. In addition, monovalent HAV vaccines contain a higher antigen content than other formulations which is anticipated to induce a more robust immune response that is required for PEP efficacy. The usual schedule for these vaccines is 2 doses, with the second dose at 6-12 months. However, only one dose is indicated for PEP efficacy and in Ontario, only one dose is publicly-funded for PEP, unless the individual is otherwise eligible for publicly-funded HAV vaccine for primary prevention. Monovalent HAV vaccines are approved for use in Canada with an age indication of ≥ 12 months with no upper age limit specified for their use. Despite the recommendation for vaccine use as a form of PEP, no monovalent vaccine in Canada has this listed as a specific indication within its product monograph (PM).

There is no HAV-specific IG product available for use in Canada; instead the IG product recommended for HAV PEP is a sterile preparation of concentrated antibodies against a number of antigens. Given the changing epidemiology of HAV in industrialized countries, many national bodies have noted a decline in the potency of IG products, with respect to anti-HAV concentrations, over time.[19,20] The World Health Organization (WHO) has recommended a specific anti-HAV titre for IG products of 98 International Units (IU)/ml. In the United Kingdom (UK), a 2008 review of IG found that the potency of anti-HAV antibodies in the UK product ranged between 60 and 87 IU/ml which led to a recommendation for a larger volume of administration to bring the concentration up to the WHO standard.[19] It is important to note that there is no routine monitoring of the anti-HAV concentration of IG carried out in Canada under specified regulatory requirements (personal communication, Health Canada). Therefore, the potency of IG available for HAV PEP use in Canada is unknown.

In Ontario, Canadian Blood Services (CBS) supplies IG, thus access to this product occurs through healthcare institutions with ready access to blood products. IG is not stocked by Ontario Government Pharmacy Medical Supply Service (OGPMSS), nor by individual PHUs.

Environmental scan: National HAV PEP recommendations

National recommendations for HAV PEP from Canada, the United States (US), the UK, and Australia were reviewed to compare and contrast with the 2006 PSI recommendations. The key features are summarized in Table 2. All guidelines indicate that PEP should ideally be administered within 14 days of exposure.

Table 2. Summary of select national recommendations on HAV PEP

Contact	Canada(9)	UK (19)	US (20)	Australia (28)
Healthy, < 2 months	IG	Vaccinate caregivers	IG	IG
Healthy, 2-12 months	IG	Vaccinate caregivers OR Unlicensed use of vaccine OR Exclude from childcare	IG	IG
Healthy, 1-40 years	Vaccine	Vaccine	Vaccine	Vaccine
Healthy, 40-50 years	Vaccine	Vaccine	IG	Vaccine
Healthy, > 50 years	Vaccine	Vaccine + IG	IG	Vaccine
Immune-compromised	Vaccine +IG	Vaccine + IG	IG	IG
Chronic liver disease	Not stated	Vaccine + IG	IG	IG

Canada

In Canada, the preferential use of vaccine over IG has been in place since the National Advisory Committee on Immunization (NACI) made this recommendation in 2000.[21] The 2000 statement indicates that "because IG is unlikely to be more effective than vaccine, and is sometimes difficult to obtain" vaccine is the preferred method of PEP. Other countries have reached different conclusions about the relative efficacy of IG over vaccine.[19,20] A randomized trial which compared vaccine versus no intervention was cited as supporting evidence by NACI,[22] graded as level 1 evidence with fair strength of evidence (B). The statement also acknowledged pragmatic advantages to the use of vaccine including the fact that the use of vaccine alone for PEP will place less demand on "potentially scarce IG needed for other medical uses".[21] An environmental scan involving a survey of Canadian provinces and territories (P/Ts) on their HAV PEP practices found that by 2003, all P/Ts had implemented HAV PEP policies that recommended the preferential use of vaccine for healthy individuals over 12 months of age.[23]

The evergreen edition of the CIG recommends that PEP be offered to household and close contacts when a case of HAV occurs in childcare centres and kindergartens (Table 3) and should be offered to co-workers and clients of infected food handlers.[9] There is limited detail about operationalizing these recommendations; for example, there is no detail about whether staff members are also considered

close contacts within childcare settings or further advice about risk assessment in relation to infected food handlers. The CIG's recommendations for the specific PEP intervention varies based on age (< or > 12 months of age) and underlying health status (immune-compromised or not), as do all national guidelines (Table 2). However, unlike other countries, there are no age-based recommendations for adults and no specific mention of individuals with chronic liver disease. In the 2006 edition of the CIG, individuals with chronic liver disease are identified as a group who should be considered to be immune-compromised.[24] However, in the most recent version of the CIG, chronic liver disease is described in the chronic disease chapter, with mention that the immune response to HAV vaccine is suboptimal in advanced liver disease.[25]

United States

Since 2007, the Advisory Committee on Immunization Practice (ACIP) has recommended the use of vaccine for healthy children ≥ 12 months and healthy adults up to age 40 years, but it preferentially recommends the use of IG even in healthy individuals over 40 years of age.[20] The rationale for this decision includes a lack of RCT evidence on vaccine efficacy for PEP in this age group and an age-dependent risk of disease severity, including CFR.[20] The ACIP guidelines differ further from those of Canada by clearly outlining individuals with chronic liver disease as a discrete risk group who should receive IG. Although there is no formal recommendation for the concurrent administration of vaccine and IG for any group, the 2007 guidance note that individuals recommended to receive IG can receive concurrent vaccine "if recommended for other reasons".[20]

HAV vaccine was recommended in 2007 for selected groups on the basis of a number of considerations including: a non-inferiority trial comparing vaccine with IG,[26] the experiences of countries such as Canada and the UK where vaccine had been used as HAV PEP for more than 5 years, HAV vaccine immunogenicity, HAV transmission in various settings, individual risk factors for HAV disease severity and the advantages and disadvantages of vaccine and IG in pragmatic terms (i.e. access, administration, and duration of protection).[20]

ACIP recommends PEP for individuals who have had close, personal contact with a HAV case. This includes household, sexual and illicit drug sharing contacts. Specific recommendations are outlined for childcare centers which are summarized in Table 3. It is important to note that ACIP has recommended universal HAV vaccination at 12 months of age, since 2006.[27]

United Kingdom

In 2009, the UK HPA released updated guidance on HAV prevention and control. Healthy individuals aged 1 to 50 years are recommended to receive vaccine for PEP.[19] In contrast, healthy individuals over the age of 50 years, and those with chronic liver disease or an immune-compromising condition are recommended to receive both vaccine and IG. The rationale for the concurrent administration of vaccine and IG is that IG provides immediate protection through the passive transfer of antibodies, as the immune system produces its active response to the vaccine, in individuals who may not mount a sufficiently rapid and/or robust immune response to offer protection following exposure. The 2009 guidance also provides specific advice about HAV control in childcare settings, summarized in Table 3.

Australia

The 2009 National guidelines from Australia recommend the use of vaccine for all contacts over the age of 1 year who are not immunosuppressed, do not have chronic liver disease, and for whom the vaccine is not contraindicated.[28] The guidelines note that US, Canadian and UK health authorities diverge with respect to recommendations on PEP in otherwise healthy individuals over the age of 40 years. However,

the guidelines do not provide a specific rationale for the decision to use vaccine in preference to IG in this age group in Australia.[28] Advice with regards to childcare settings is presented in Table 3. It is important to note that in Australia, childcare workers are listed among the occupational and other high risk groups recommended to receive HAV vaccine for primary prevention.[29]

Table 3. Summary of select national recommendations on HAV control within childcare settings

National guidance	Scenario	Advice
Canada (9)	"When HAV occurs in childcare centres and kindergartens"	PEP should be offered
United Kingdom (19)	If a case attends pre-school or childcare setting	Vaccine to close contacts (all who work in or are cared for within the same room as index case) AND Vaccine to household contacts of kids < 5 years IF: • Cannot give PEP < 14 d post-exposure OR • If > 1 case in setting
	If a case attends/works in elementary school	Risk assessment • If no obvious source of infection, consider vaccine for all children/adults in same class and close friends
	If a contact of HAV attends pre-school or childcare setting AND contact not seen until 14 days post-exposure	PEP only to contact of the index case Supervised handwashing at school
United States (20)	If $\geq$ 1 case in childcare center (staff or attendees) OR If cases in $\geq$ 2 households of attendees	PEP for all unvaccinated staff and children In centres that do NOT provide care to children in diapers, PEP for classroom contacts of index case only
	If $\geq$ 3 cases in households of attendees	Advice as above AND PEP for household contacts of attendees who wear diapers
Australia (28)	If single case in childcare setting (staff or attendees)	PEP for all susceptible staff and to classroom contacts of index case and written advice to parents and staff caring for children in other groups
	If cases in 2 or more households epidemiologically linked to centre	PEP for all susceptible staff and to classroom contacts of index case and "careful consideration should be given as to whether other contacts within facility should be offered PEP"
	If cases occur in 3 or more households epidemiologically linked to centre	Advice as above AND PEP should be considered for household contacts of attendees who wear diapers

Setting-specific risk of HAV transmission

The risk of household transmission of HAV is high with prospective transmission studies identifying secondary attack rates (SARs) in the range of 12 to 27%.[20,22,30,31] However, these studies were all conducted in areas with a much higher burden of HAV than Ontario's current epidemiology. Young children are recognized to be particularly efficient at transmitting HAV infection, most likely in relation to the toileting behaviours and suboptimal hand hygiene of this age group. A prospective transmission study conducted in Kazakhstan, which screened all household members with HAV serology after the identification of a lab confirmed case in the household, found index cases under the age of 6 years were almost five times more likely to transmit infection to members within their household (odds ratio (OR) of 4.7).[31]

Childcare settings, including daycares and nursery schools, have been associated with similar SARs, in the range of 10-28% based on the published literature.[32-36] These estimates include studies which conducted serologic screening among attendees to ensure asymptomatic cases were included in the SAR so they may over-estimate the extent of clinically apparent transmission within these settings. Table 4 summarizes representative studies.

Table 4. HAV transmission in childcare settings[32-36]

Setting	Country, year	National HAV incidence	Attack rate (AR): staff and attendees	AR: household members of attendees	Notes
Daycare (0-5 yrs)[32]	USA, 1979	10/100,000	Staff: 4/18 (22%)	26/200 (13%)	Zero cases reported among children (no serologic case finding)
Daycare (0-10 yrs)[34]	USA, 1980	10/100,000	Children: 0-3 yrs 17/76 (22%) 4-6 yrs 17/142 (12%) 7-10 yrs 4/27 (15%) Staff 6/13 (46%)	31/300 (10%)	Includes IgM positive asymptomatic children
Daycare (0-3 yrs)[35]	France, 1994	HAV not reportable at that time	Children: 11/54 (20%) Staff: 2/13 (15%)	4 parents	Includes IgM positive asymptomatic children
Nursery school (3-6 yrs)[36]	Italy, 1996	2.5/100,000	Children: 11/41 (27%)	10/114 (9%)	No mention of if/how asymptomatic children counted
Daycare (0-3 yrs)[33]	Spain, 2002-2003	1.6/100,000	Children: 8/92 (8.7%) Staff 2/16 (19%)	13 household contacts	No mention of if/how asymptomatic children counted

In the early 1980s there were several community HAV outbreaks in the US where 30-40% of cases were either directly or indirectly associated with childcare settings.[37,38] Further investigation into the HAV transmission dynamics in US childcare settings, led to the conclusion that the presence of young, diaper-wearing children between the ages of 1-2 years were the most important feature associated with the risk of HAV outbreaks occurring in these settings.[39,40] However, it is important to recall that the national incidence of HAV at the time of these outbreaks was 10/100,000, typically exceeding 20/100,000 in several US states where these extensive community outbreaks were occurring.[41] Therefore, another interpretation is that young children (i.e., diaper-wearing children) represented the introduction of susceptibles into an environment where once HAV was introduced it was rapidly transmitted among this group, in contrast to slightly older children (i.e. out of diapers) who were more likely to be immune based on prior infection.

In contrast, more recent HAV outbreaks within childcare and school settings in industrialized countries without universal HAV vaccination in childhood describe a picture of rapid transmission within highly susceptible populations that extend beyond diaper-wearing children. These outbreaks have occurred in countries with HAV incidence rates that more closely approximate Ontario's burden of disease. Commonly the infection is introduced into the childcare or school setting following travel to, or after contact with visiting friends and relatives from, HAV-endemic areas.[36,42,43] The infection is then efficiently transmitted among a highly susceptible population aided by asymptomatic cases and age-related risk behaviours.

There are few published reports of HAV outbreaks in childcare or school settings which clearly describe the impact of offering vaccine or IG as a control measure. Hauri et al. reported on an HAV outbreak in a large daycare with more than 100 attendees between the ages of 3-6 years.[44] In accordance with Germany's HAV control guidelines, all children and staff were recommended vaccination, in addition to household contacts of cases. These PEP recommendations were made 24 hours after the first notification of a case in the daycare. A total of 46/69 children were vaccinated and a further 11 received IG. Although household members of attendees were not recommended to be vaccinated, 29/184 (16%) received vaccine. These interventions were received within 14 days of symptom onset in the first notified case, although an earlier case of jaundice that did not undergo lab confirmation was identified retrospectively in the daycare. Although the outbreak was relatively short in duration at less than 3 months, seven household members of attendees developed HAV. In all 7 cases, the attendees had received vaccine for PEP. HAV developed 16-36 days after vaccination of the attendee who lived in these households, suggesting transmission had already taken place, either before or very shortly after the child was vaccinated. In 2 of the 7 households, the daycare attendee had clinically apparent HAV and in the remaining 5 households, the attendee was asymptomatic. Other case reports have also described HAV transmission within the households of classroom contacts who have received vaccine for PEP. Another report from Germany described the vaccination of a kindergarten classroom contact 7 days after symptom onset in the index case, who then went on to develop asymptomatic HAV infection which was passed on to her 3 family members 35-37 days post-vaccination.[45] The authors of this case report conclude that vaccination should also be offered to family members, and other close contacts, of persons who may be infected with HAV.[45] No other details about the outbreak, including other control measures, are described.

Finally, two school outbreak investigations from the UK provide important lessons on HAV control in these settings.[46,47] The first is an outbreak involving a nursery school, an elementary school and a special needs school.[46] Although there was no clear epi-link between the first two cases which occurred in the elementary school and nursery school, viral genotyping confirmed the two cases to be linked. In accordance with UK guidelines at that time, PEP was recommended to household contacts of cases. Staff and attendees of the special needs school were also vaccinated but there is no description of vaccination of classmates in the elementary or nursery school and no discussion of immunizing family

members of attendees. The stated rationale for the exception of the special needs school was the direct nursing care provided by teachers within this setting. Despite cases occurring within these three school environments, there was no further transmission within the special needs school or the nursery school (each had one case only associated with outbreak), despite very different PEP recommendations. The second describes the management of HAV-infected food handler who worked in a large high school.[47] Immune globulin was recommended for all students and teachers in this setting because it was not possible to ascertain which staff/students had consumed food prepared by the case and because the UK guidelines at that time suggested that vaccine was unlikely to be effective for PEP, if given more than 7 days after symptom onset in the index case. IG was administered to more than 700 students and staff on days 21 through 23, in relation to symptom onset in the index case (days 17 through 19), in relation to the onset of jaundice. Of note, the large number of contacts exhausted the supply of IG within England and immunization with IG was delayed due to the need to identify further supplies from Scotland. Only one secondary case was identified in the school, which the authors interpret as evidence of the success of the intervention. It is important to note that this scenario differs in many significant ways from those described above as this is primarily a description of IG's efficacy for PEP in relation to those who have consumed food from an infected food handler.

In summary, there is strong supporting evidence in the literature that identifies households, childcare and in some instances elementary schools, as settings where efficient transmission of HAV occurs. Unfortunately there is relatively little in the published literature that clearly assists in identifying best practices for how broadly PEP should be offered within childcare and elementary school settings. Two outbreaks in which only the childcare attendees and staff were recommended to receive PEP, found evidence of transmission to household members of attendees, even among attendees had received PEP.[44,45] In contrast, another study found no evidence of subsequent transmission to household members with more limited PEP recommendations.[46] This may represent a publication bias, whereby studies with evidence of transmission are more likely to be published than those without. No outbreak was identified in which the household members of attendees were specifically recommended to be vaccinated, in order to assess the impact of this intervention.

Efficacy of IG when used for HAV PEP

Most national guidelines on HAV PEP, quote an effectiveness of 80-90% for the use of IG against HAV infection, if administered within 14 days post-exposure.[19,20] Few studies have examined the effectiveness of IG given 14 days following exposure, and none have been controlled. Among these uncontrolled studies, there are conflicting findings regarding whether the delay in this intervention may result in an attenuation of disease severity.[48,49] Most national guidelines do not advise the use of IG, or vaccine, if more than 14 days have elapsed since exposure, except in select scenarios. Guidelines vary in their precision with language; some are clear that the 14 day period is in relation to the date of symptom onset in the index case,[19] while others refer only to the date of last exposure to the case.[9]

The 2009 UK HPA guidelines provide a very comprehensive narrative review of IG efficacy studies when used for HAV PEP, where 9 studies are summarized dating back to the 1940s.[19] A wide range of efficacy is quoted among these studies, ranging from 47% to 96%, and all compare IG with placebo or no treatment. However, a range of observational and randomized study designs are included, many studies were conducted during outbreaks where the date of onset of cases is not clearly described, and no information on the potency of the IG product used in the studies is reported. This is because most studies in this area were conducted at a time before it was technically feasible to measure the potency of IG with respect to anti-HAV antibody concentration. Although the potency of IG was not established, the concentration of anti-HAV antibodies in IG at this time is likely to have been high, based on the epidemiology of HAV when the studies were conducted. One study which attempted to explore the notion of potency, conducted a randomized, placebo controlled trial involving 2 different lots of IG to pediatric household contacts within 14 days of exposure.[50] One lot had already been identified to have a lower than anticipated concentration of anti-measles antibodies, and the second lot was derived from plasma collected following a wide scale HAV outbreak. The reported efficacies of these two lots were vastly differently: 47% efficacy for the former and 88% efficacy for the latter.[50] Although anti-HAV potency was unknown, this was an excellent demonstration of the impact changes in potency may have on IG efficacy. The lack of anti-HAV antibody measurement in these trials makes it challenging to predict the efficacy of currently available IG products in Canada, even if its potency was known.

Two systematic reviews of IG for use in both primary and secondary prevention of HAV have been published including one Cochrane Review. [51,52] The Cochrane Review identified only two RCTs that met their inclusion criteria: the placebo-controlled RCT comparing 2 lots of IG by Moseley et al.[50] described above, and an RCT comparing vaccine with IG by Victor et al.[26] described in detail below. The authors conclude that the protective effect of IG against HAV for PEP is “established but HAV vaccine may be an alternative in some circumstances”. The systematic review by Bianco et al.[52] examined only randomized trials that compared IG with placebo or no intervention and found only 2 studies that met these criteria, the trial by Moseley and colleagues and a UK study published in 1968.[50,53] Based on these two studies, the pooled RR estimate for "infectious hepatitis" after receiving IG for PEP was calculated to be 0.33 (95% CI 0.20-0.47). The authors caution that there was inadequate description of many methodological aspects of studies included in their review. Interestingly, Bianco and colleagues conclude with their view that the only indication for the use of IG for HAV PEP is in situations where there is inadequate vaccine supply, or when the ‘eight day window for vaccine has passed”.[52] In all other scenarios they recommend using vaccine on the basis of the controlled trial of vaccine efficacy for PEP where vaccine was administered within 8 days of symptoms onset of the index case,[22] the short-term duration of protection associated with IG, and the likelihood of decreasing potency of anti-HAV antibodies within IG. Of note, none of these issues were specifically addressed within the systematic review.

Vaccine efficacy when used for HAV PEP

Two randomized clinical trials (RCTs) have examined the use of vaccine for PEP when used within 14 days of exposure: a non-inferiority comparing vaccine with IG and an RCT comparing vaccine with no intervention[22,26]. No controlled studies have examined the efficacy of vaccine more than 14 days following exposure.

Vaccine as compared to no intervention

Sagliocca and colleagues conducted a randomized, un-blinded trial of vaccine versus no intervention among household contacts in Naples, Italy in 1997.[22] The authors describe Naples as HAV-endemic during the study period, which is underscored by the fact that 38% of household contacts under the age 40 who underwent baseline serology were HAV immune. Index cases were identified through hospital-based case finding using the following inclusion criteria: ALT two times the upper limit of normal, IgM positive serology, and hospitalization within one week of symptom onset. Randomization was conducted at the level of the household and only contacts under the age of 40 years were enrolled. All who agreed to participate underwent baseline serologic screening; those who were IgM positive were classified as co-primary cases. The age-based inclusion criterion for household contacts was used because previous serological surveys had found that HAV immunity over this age was extremely high in this region. Contacts either received vaccine within 8 days of symptom onset in the index case (more than half of contacts were vaccinated within 4 days) using monovalent HAV vaccine. The control arm of the study, which received no intervention, was justified by the study investigators as IG was not part of the standard of care within Naples at the time of the study. The study endpoint was the number of IgM seroconversions occurring a minimum of 2 weeks following enrollment.

A total of 380 index cases were identified, among which 146 participated (41%). Owing to the intention-to-treat analysis, they included individuals who were randomized to receive vaccine in the denominator, even if they refused to participate and those who were anti-HAV immune. In terms of estimating vaccine efficacy at the level of the unit of randomization: 2 cases occurred among 71 households (2.8%) as compared to 10 cases among 75 households in the control group (13.3%), for an efficacy estimate of 79% (95% CI of 7 to 95%). The individual level estimate was calculated to be 82% (95% CI of 20-96%). Two cases (among 197) occurred in the vaccine group (1.0%), as compared to 12 cases among 207 individuals in the control group. If the analysis is limited only to those contacts who were HAV susceptible at study enrollment, the vaccine efficacy estimate is 85% (2/110 cases in the vaccine group, 12/102 cases in the control group). This is unpublished, but calculated from data presented in the manuscript. The two cases that occurred in the vaccine group were both asymptomatic and associated with no increased AST/ALT, in contrast to the 12 secondary infections that occurred in the control arm where all cases were either symptomatic or had an increased ALT. The authors use these findings to suggest that the vaccine might also attenuate disease severity but it is unclear from the manuscript how the investigators ruled out the possibility that the IgM response was vaccine-induced, as opposed to evidence of asymptomatic HAV infection. For example, subsequent viral RNA detection in serum or stool, was not conducted but may not have been technically feasible at the time of the study.
The major critiques of this study relate to the unblinded nature of the study as well as the high baseline hepatitis A immunity in the study population which threatens the external generalizability of the study to the Canadian context.

Vaccine as compared to IG

Victor and colleagues conducted the only randomized, double-blinded, active-control, non-inferiority trial of vaccine versus IG among close contacts of HAV.[26] The study was conducted between 2002 and 2005 in Kazakhstan which was described as having intermediate HAV endemicity. Index cases were identified through routine surveillance with the following case definition: first lab-confirmed, symptomatic case in the household or daycare in the preceding 60 days. Close contacts were defined as household or daycare contacts, between the ages of 2 and 40 years of age, who had no prior HAV infection, no liver disease, no prior receipt of HAV vaccine, and no vaccine contraindications. PEP was giving within 14 days of exposure, which was counted from the date of symptom onset in the index case. Serology was conducted at baseline, and at weeks 4 and 8. A weekly symptom review was completed and additional serology and stool collected if positive symptoms were identified. The primary endpoint was lab-confirmed symptomatic HAV occurring 15-56 days post-exposure. Additional secondary endpoints looked at markers of disease severity among cases. All cases were reviewed by an independent data monitoring committee in a blinded fashion. Monovalent vaccine was used and IG produced from a US manufacturer was administered through the intramuscular route at a dose of 0.02 ml/kg. Although the potency of the IG product used in this trial was not quoted in the original manuscript, it was obtained from the principal investigator and is referenced in the UK HPA guidance document as being 18.83 IU/ml.[19]

The investigators randomized more than 4,500 contacts of 920 index cases; 31% were susceptible to HAV and 1090 cases were eligible for inclusion. The primary per protocol analysis looking at lab-confirmed symptomatic HAV as the endpoint occurred in 25 of the 568 contacts (4.4%) in the vaccine group and 17 of the 522 individuals in the IG group (3.3%), resulting in a relative risk (RR) of vaccine of 1.35 (95% CI 0.70-2.67). The non-inferiority design had pre-specified that the upper bound of a one-sided 95% CI of the RR could not exceed 3.0, in order to meet the statistical criterion of non-inferiority, which was met. The modified intention to treat (ITT) analysis estimated a RR of vaccine to be 1.32 (95% CI 0.69-2.55), based on 26/740 cases in the vaccine group and 18/674 cases in the IG group. The ITT analysis includes individuals lost to follow-up and 9 individuals (3 in the vaccine group and 6 in the IG group) who received their intervention more than 14 days post-exposure.

The critique of this study is that although the pre-specified criteria for non-inferiority were met, the rates were higher in the vaccine group as compared to the IG group for all study endpoints, suggesting that IG performed modestly better. The authors themselves note that the finding that vaccine may be "modestly less efficacious" may be clinically meaningful for those who are likely to have severe HAV, including those with chronic liver disease and older individuals.[26] Both of these groups were excluded from this trial. Furthermore, the fact that the study used a low potency IG product would make the vaccine look more efficacious relative to IG. However, if the potency of the IG product used in Canada is similarly low, it may provide a realistic assessment of the relative performance of the two interventions in the Ontario context. A further critique of this study is that, similar to the Saglioca trial,[22] nearly all index cases were hospitalized thus limiting further exposure between cases and contacts, which is not generalizable to the Canadian context where the majority of cases are managed in the outpatient setting.

Immunogenicity of HAV vaccine

A key question with respect to the use of HAV vaccine for PEP is how quickly and how robustly individuals mount an immune response to the vaccine. Thus, identifying the proportion of subjects who have evidence of rapid seroconversion can be used as indirect support for the use of vaccine in the context of HAV PEP. An antibody concentration of approximately more than 10 mIU/ml was suggestive of clinical protection in one study and has been cited as a putative immune correlate of vaccine-derived

protection for HAV with the caveat that some individuals may be protected at even lower concentrations[54,55].

Peer reviewed studies including healthy adults, have found that between 88 and 93% of subjects will have evidence of seroconversion by day 15 following vaccination in subjects ranging in age between 20 and 62 years of age.[56,57] These studies all used a titre of > 20 mIU/ml as evidence of seroconversion. The Havrix® Canadian PM quotes a seroconversion rate of 88% among subjects 18-50 years of age, and of 93% among subjects 1-18 years of age, by day 15 post-vaccination.[58] The titre used to define seroconversion in these clinical studies is not defined in the PM. The Avaxim® PM reports that using a titre of > 20 mIU/ml that greater than 90% of immunocompetent subjects were protected 14 days post-vaccination.[59] The clinical studies summarized in the PM enrolled subjects between 16 and 65 years of age. The Vaqta® PM does not quote seroconversion 2 weeks post-vaccination[60]. All monovalent HAV vaccines in Canada have been authorized for use among subjects > 12 months of age without an upper age limit for use.[58-60]

There is a more limited literature base examining seroconversion among healthy adults in an age-stratified manner. The studies summarized below all used a titre of > 20 mIU/ml as evidence of seroconversion. One study of Havrix® using 1440 ELISA units founds that 90% of healthy adults between 20 and 39 years of age (n=134) seroconverted at 15 days post-vaccination, in contrast to 77% among those 40-62 year of age (n=66).[57] A study of Epaxal®, a vaccine not licensed for use in Canada, examined seroconversion one month post-vaccination and found that 100% of adults under age 18-45 years (n=53) seroconverted, as compared to 70% in the 50-60 year age group (n=16) and only 60% in the > 60 year age group (n=14).[61] Finally, one Canadian study examined the immune response to 720 ELISA units of what is now licensed as Havrix® vaccine in Canada among healthy adults between the ages of 40 and 61 (n=64).[62] The mean age was 47.7 years. One month post-vaccination, 51/57 (89%) subjects seroconverted. What is most striking about this finding is that 720 ELISA units is the antigen content within the Havrix® vaccine that is currently licensed for use in Canada for pediatric use. This suggests that if the vaccine currently licensed for use in adults (containing 1440 ELISA units) had been used instead, the seroconversion rate may have been higher. In all three studies, 97 to 100% of subjects had evidence of seroconversion following the booster dose of vaccine, administered at 6 or 12 months following the first dose. [57,61,62] Although these studies included relatively small numbers of older subjects, two of the three studies provide evidence of a decreasing immune response with age, which is an important consideration with respect to the likely efficacy of vaccine as an intervention for PEP.

HAV vaccine immunogenicity studies in immune-compromised populations, including those with chronic liver disease have found that a smaller proportion of individuals with chronic liver disease seroconverted, as compared to healthy individuals, when assessed 30 to 60 days post vaccination.[63,64] The seroconversion rate was dependent on the extent of their underlying disease with 74-84% of those with chronic HCV or HBV responding by day 30,[63] in contrast to only 50% among those with evidence of liver failure and awaiting liver transplant, when assessed at 60 days post-vaccination.[64] Both studies used a titre of > 33 mIU/ml as evidence of seroconversion, which is a higher, and thus more conservative, titre than that used in the studies above. These studies support the CIG recommendation that those with chronic liver disease should be vaccinated against both HAV and HBV early in the disease course as the immune response to vaccine is suboptimal in advanced liver disease.[25]

Simultaneous administration of vaccine and IG

Studies which examined the simultaneous administration of vaccine and IG were reviewed to characterize the immune response following the receipt of both products. This is because simultaneous

administration is recommended within the Canadian and UK guidelines, for certain groups .[9,19]
The WHO position paper on HAV vaccines, notes that the "concurrent administration of immune serum globulin does not appear to significantly influence the formation of protective antibodies".[65] Four studies have examined this in detail, all relatively small in size ranging from 62 to 300 subjects with a duration of follow-up of 7 to 12 months after the receipt of the first dose of vaccine, or vaccine plus IG.[66-69] In all studies, subsequent doses of vaccine were administered to complete the full series: 1 study used a schedule of 0 and 6 months and 3 studies used a schedule of 0,1 and 6 months [66-69]. The studies found a similar seroconversion rate among individuals who received either vaccine alone or concurrent administration of vaccine and IG, in the range of 93-100% when assessed 1 month post-immunization, but with lower absolute values of GMTs by approximately 2 fold among the vaccine plus IG group throughout the follow-up period. Theoretically, reduced GMTs could translate into a shorter duration of protection if the maximum antibody concentration is at a lower level even before antibody decay begins. However, no study has included a follow-up duration of more than 12 months.

Ontario experience base regarding HAV PEP

The wording of the current HAV guidelines, as expressed in Appendix A of the Infectious Diseases Protocol, facilitate variation in practice and in principle, create a natural experiment to evaluate interventions. For example, Ontario's experiences could help to inform an assessment of the efficacy of vaccine when used for PEP among adults over the age of 40 or 50 years, a key question that many jurisdictions have debated. However, household contacts offered PEP are not consistently captured within iPHIS which poses challenges for any retrospective evaluation. It would also be informative to know how frequently the 2006 PSI recommendations are followed with respect to the advice to administer concurrent vaccine and IG for select groups. This type of audit is challenged by the separate processes to access vaccine versus IG and limitations in data collection for HAV contacts, outside of outbreaks. Despite a lack of Ontario-specific data on primary vaccine failures, examples of these are easily found in the literature, in relation to both primary immunization and PEP.[70,45]

Case study: HAV outbreak related to transmission in childcare settings

The 2006 PSI recommendations concerning the management of index cases and contacts who attend kindergarten and childcare settings refer to a 2004 HAV outbreak which involved a kindergarten class and two home-based childcare centres in an Ontario PHU.[3] The outbreak was associated with 15 cases of HAV: 12 lab-confirmed and 3 cases with an epidemiologic-link. The origin of HAV for this outbreak was an infant adopted from a HAV-endemic country. Although the parents were vaccinated prior to travel, none of the family's 6 other children were immunized before the infant's arrival within the home. Three of the siblings became symptomatic and were confirmed to have HAV, with the infant subsequently confirmed to also be IgM positive. Three other siblings were IgM negative and vaccinated 3 days following the identification of jaundice in the first sibling case, although an unknown duration of time following the onset of HAV in the asymptomatic infant. Despite being IgM negative at the time of vaccination, the youngest sibling transmitted HAV to a kindergarten classmate who developed jaundice. In response, vaccination was offered to the school attendees and all family members of children within the kindergarten, as well as to numerous contacts at a childcare centre attended by the new case. The contacts recommended PEP included all childcare attendees, staff and their family members and they were offered vaccine 6 days after the onset of jaundice in the case. Subsequent cases were identified in children attending the childcare centre who had been vaccinated, and among parents of attendees who had not complied with the recommendation for vaccination, with subsequent transmission to another childcare setting. At the conclusion of the outbreak, one kindergarten, two childcare centres, and multiple households were involved in the transmission dynamics of this outbreak with more than 1,200 contacts were vaccinated over a seven month time period. This outbreak highlights a number of key points: the resource intensive nature of the public health outbreak response, and evidence of PEP vaccine failures among healthy young children which resulted in further transmission. Four children who were vaccinated post-exposure later became infected with HAV and spread their infection on to others.

Summary

The summary of evidence presented in this document highlights a number of issues that are important considerations for the development of best practices for HAV contact management. These considerations include the observation that HAV clinical severity and CFR are increased among older adults and HAV transmission dynamics where young children are largely asymptomatic and efficient transmitters of infection. The evidence of PEP efficacy is challenged by RCTs of vaccine that have excluded healthy adults over the age of 40 years and where the historical literature demonstrating IG efficacy occurred at a time before HAV antibody concentration was measured. There are also practical considerations relating to the feasibility of public health action within 14 days of symptom onset of an index case given the timelines associated with health-seeking behaviour, laboratory testing, and reporting to physicians and PHUs. Finally there is the issue of alignment and consistency between Ontario and Canadian guidance on HAV PEP.

Options for consideration:

PIDAC-I suggests that the following principles be used in formulating Ontario's HAV PEP recommendations:

- The recommendation for whether PEP is to be offered should be informed by the risk of HAV transmission in the setting, for example both the nature and the duration of the contact.
- Advice on the specific PEP intervention (vaccine, IG, or vaccine plus IG) should be informed based on HAV disease severity if infected, RCT evidence of vaccine non-inferiority, and vaccine immunogenicity data. These inputs form the basis for other national guidelines, despite variability in the conclusions that have been reached.
- Information and evidence gaps should be identified and strategies to address these proposed gaps.

Contacts to be offered PEP

Household and close contacts should continue to be offered HAV PEP. Non-household close contacts include, sexual contacts, individuals who have handled diapers or who have assisted with the toileting or other personal care of cases, and individuals who have shared illicit drugs with a case. Specific scenarios involving childcare settings are discussed separately below. The issue of infected food handlers was considered to be outside of the scope of this document. The current Appendix A of the Ontario Infectious Diseases Protocol suggests that consideration be given to offering PEP to coworkers and patrons.[1] The UK guidelines have adapted a published tool to guide the risk assessment that informs whether or not to offer PEP for contacts of infected food handlers and PHUs may find this to be a helpful resource.[19,71]

Advice on PEP intervention

The following interventions are advised for the use of HAV PEP for susceptible **household and close contacts** (defined above):

- Infants < 12 months: IG
- Healthy children and adults 1-49 years of age: vaccine
- Healthy adults ≥ 50 years of age: vaccine plus IG*
- Immuno-compromised: vaccine plus IG
- Chronic liver disease: vaccine plus IG*

These recommendations are consistent with the CIG advice for contact management with the exception of the advice for the use of vaccine plus IG for healthy adults 50 years of age and older and for individuals with chronic liver disease who are not identified as a distinct risk group in the CIG recommendations (both noted with an asterisk). The rationale for recommending IG in addition to vaccine for adults $\geq$ 50 years of age is twofold: disease severity, including CFR, is increased in older adults,[9,14] and there is limited data on the immunogenicity of HAV vaccine in older age groups to support the sole use of vaccine for HAV PEP. It is challenging to define the age cut-point, above which vaccine alone may be insufficient for protection. Evidence of increased disease severity with age has been noted among individuals $\geq$ 50 years of age in Canada,[9] and greater than 60 years of age in the United States.[14] Immunogenicity data is suggestive of a less brisk immune response in older adults, although this data comes from small studies with a range of age strata. Despite the fact that individuals over the age of 40 years were excluded from the two clinical trials of PEP,[22,26] because of high levels of HAV susceptibility in older age groups, the use of vaccine for PEP can be justified in healthy adults between the ages of 40 and 49 years, because these individuals would be expected to mount a sufficient immune response to HAV vaccine on the basis of the HAV literature summarized in this document.

Those with chronic liver disease are listed as a discrete category in the recommendations contained within this document to remind those using this advice that susceptible individuals with underlying liver disease of any etiology should be regarded as being immune-compromised and should be offered vaccine plus IG. This was previously consistent with the 2006 edition of the CIG which included chronic liver disease within its chapter outlining immune-compromising conditions.[24] However, in the evergreen edition of the CIG, chronic liver disease is now referenced as a chronic condition.[25] Finally, the recommendations outlined above are consistent with those of the UK, and are similar to those of the United States given their more conservative approach to older individuals, despite the fact that the precise age cut-off differs for IG. The rationale for offering the simultaneous administration of vaccine plus IG for healthy individuals over the age of 50, as well immune-compromised individuals and those with chronic liver disease is that IG will provide immediate protection, as the immune system produces its active response to the vaccine, in individuals who may not mount a sufficiently rapid and, or robust immune response to offer protection following exposure.

Timeframe for offering PEP

Contacts of HAV should receive PEP as soon as possible, and ideally, within 14 days after exposure to a HAV case. It is important to be clear that although the CIG guidelines recommend the use of PEP "within 14 days of last exposure",[9] the RCTs in this area defined exposure in relation to the date of symptom onset in the index case, rather than the date of last exposure. For example, the UK provides very clear direction on how to assess time since exposure in order to base PEP recommendations. For continuous exposures (i.e. household contacts) the UK uses date of symptom onset in the index case. If a single exposure occurred during the case's infectious period, time since exposure would be calculated using two methods: the number of days since symptom onset in the index case and the number of days since exposure to the index case, with "whichever is the most recent" used to make decisions on contact management.[19] A similar approach to calculating time since exposure for PEP management is recommended to be undertaken in Ontario as taken in the UK for the public health management of contacts. The purpose of this approach is not to restrict who is offered PEP, but to assist in the identification and communication about true PEP failures.

Childcare settings (including nursery schools and kindergartens)

The suggested public health management involving childcare settings are outlined below and summarized in Table 5. Childcare settings include daycares (including home daycares), nursery schools and kindergartens, which is consistent with other public health advice for these settings.

In scenarios where an index case attends a childcare setting and the source of infection is obvious (e.g., recent travel of the case or of a household contact), all attendees and staff should receive PEP, ideally within 14 days of symptom onset in the index case. The purpose of providing prophylaxis to attendees and staff is to prevent secondary transmission of HAV.

However, in scenarios where more than 14 days have elapsed since symptom onset in the case, or where the source of the index case is unknown (for example, there is no recent travel history, and no contact with other HAV case(s) in the index case in the day care, or where HAV transmission is first noted in the facility via a jaundiced parent) secondary transmission may have already occurred within the facility and a broader range of contacts should be offered PEP to prevent tertiary transmission. These contacts include: all attendees, all household contacts of attendees, and all staff. It is especially important to vaccinate adult contacts (staff and household contacts of attendees) as adults are at increased risk of severe HAV infection.

In scenarios where a young child (age 5 years or younger) is a **close contact of a case of HAV** (for example, is a household contact) and attends a childcare setting, advice for the management of the contacts of the exposed child includes:

- If the contact received PEP 14 days within symptom onset in the case and asymptomatic transmission within the household is unlikely to have already occurred (eg. index case recently returned from travel), supervised hand washing and increased surveillance should occur within any childcare settings the contact attends

- If the contact did not receive PEP within 14 days of symptom onset in the index case, or where there is concern regarding asymptomatic transmission in the household, this would support a strategy to reduce the risk of further transmission: offering PEP to all close contacts of the exposed child (including fellow day care attendees and staff) should be considered.

Scenarios where there is more than one case of HAV that occur in association with a childcare setting (including staff, attendees and, or household members of attendees), should be treated as an HAV outbreak with control measures implemented based on relevant features and epidemiology of the outbreak. In these scenarios, offering PEP to all staff, attendees and household members of attendees would generally be recommended.

Finally, PIDAC-I recommends that adults 50 years of age and older, who are offered PEP in the context of suspected transmission within childcare settings receive vaccine alone. The rationale for the use of vaccine, in contrast to vaccine plus IG, is that parents and other household members are being offered PEP to limit the risk of tertiary transmission but it is not known whether they have been in contact with a case of HAV. The same logic applies to the use of vaccine only for employees of childcare centres who are over the age of 50 years, in the scenario where PEP is recommended to attendees and staff because a child exposed to HAV did not receive PEP in a timely fashion. However, if an adult over the age of 50 years is known to be a close or household contact of a case of HAV, the PEP recommendations for close and household contacts should be followed with advice for vaccine plus IG.

Table 5. Summary of Public Health Management of HAV in relation to childcare settings

Scenario	Further case details	Advice
If a case attends a childcare setting	• If PEP can be offered within 14 days of symptom onset (and no evidence of further cases in childcare setting) • Source of infection in child is known (e.g. travel by case or by case's family member)	• PEP for close contacts (all attendees and staff)
	• If > 14 days since symptom onset in index case OR • Evidence of asymptomatic transmission in setting (e.g. HAV noted in parent(s) of attendees) OR • If > 1 case epidemiologically linked to the facility	• PEP for close contacts (all attendees and staff) AND • PEP for household members of all attendees (i.e. parents , siblings and other household members of attendees). • Vaccine only is acceptable for household members ≥ 50 years (see text)
If a child exposed to HAV attends a childcare setting	• If PEP can be offered child exposed to HAV within 14 days of symptom onset in the index case AND • No concern of asymptomatic transmission within household (e.g. index case recently returned from travel)	• PEP for the exposed child • Supervised handwashing at the childcare setting • Increased surveillance within childcare setting
	• If > 14 days since symptom onset in index case OR • Unable to determine date of symptom onset in index case OR • Concern regarding asymptomatic transmission within household	• Consider offering PEP to all close contacts within childcare setting(s) (attendees and staff) attended by the child exposed to HAV • For staff ≥ 50 years, vaccine only can be used (see text)

Additional options for strengthening of Ontario's HAV control guidance include the following:

IMPROVED COMMUNICATION ABOUT EVIDENCE FOR HAV PEP IN FUTURE REVISIONS OF THE INFECTIOUS DISEASES PROTOCOL

- Specify that single antigen HAV vaccine is the recommended vaccine for HAV PEP, as compared to combined HAV-HBV or HAV-typhoid vaccines.
- Provide clear guidance that RCT evidence of PEP efficacy is based on administration of vaccine within 14 days of symptom onset in the index case.

SURVEILLANCE

- Improved data collection on contact management is needed in order to more effectively document Ontario practice, identify cases of PEP failure and monitor Ontario's contact management practices for HAV.
- This includes ensuring that immunization history is clearly recorded for all reported cases of HAV in order to prospectively monitor for primary vaccine failures and cases of PEP failure (vaccine or IG).

PRE-EXPOSURE IMMUNIZATION RECOMMENDATIONS

- Ontarians should be reminded of the importance of ensuring their immunizations are up-to-date before travel and encouraged to meet with either their healthcare provider or a travel medicine clinic to discuss vaccine recommendations (including HAV) before travelling to HAV-endemic countries, even if not covered under the Ontario Health Insurance Plan (OHIP).

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