An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Update on the Recommended use of Hepatitis A Vaccine

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

—Public Health Agency of Canada

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of the Agency's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

The following summary highlights key information for immunization providers. Please refer to the remainder of the Statement for details

1. What

Immunization with Hepatitis A (HA) vaccine is recommended for pre-exposure immunization of persons at increased risk of infection or severe HA, as well as for post-exposure prophylaxis of: susceptible household and close contacts of proven or suspected cases of HA; co-workers and clients of infected food handlers; and staff and attendees of group child care centres and kindergartens when HA has occurred in them.

2. Who

For pre-exposure immunization, immunization with HA vaccine may be provided to persons six months of age and older.

For post-exposure prophylaxis, unless contraindicated or unavailable, HA vaccine is recommended in preference to Ig for individuals six months of age and older.

Immunization with HA vaccine may be considered for all individuals receiving repeated replacement of plasma-derived clotting factors.

3. How

For post-exposure prophylaxis within 14 days of exposure of susceptible adults 60 years of age and older who are household or close contacts of a case, Ig may be provided in addition to HA vaccine.

For post-exposure prophylaxis of susceptible individuals with chronic liver disease, Ig should be provided within 14 days of exposure in addition to HA vaccine.

4. Why

The severity of HA increases with age. Children less than six years of age are commonly asymptomatic or present with mild disease without jaundice, and represent an important source of infection, particularly for household members and other close contacts. In older children and adults, HA is typically symptomatic. Older persons, and individuals with chronic liver disease and immunocompromising conditions, have an increased risk of progressing to fulminant hepatic failure resulting in death.

I. INTRODUCTION

NACI currently recommends pre-exposure immunization of persons at increased risk of infection or severe hepatitis A (HA) infection as defined in the Canadian Immunization Guide (CIG). Although not authorized for children less than 12 months of age in Canada, HA vaccine has previously been used in some First Nations communities starting at 6 months of age and in infants travelling to high risk areas.

For post-exposure prophylaxis, NACI recommends that HA vaccine should be offered to household and close contacts of proven or suspected cases of HA, as well as co-workers and clients of infected food handlers and staff and attendees of group child care centres and kindergartens when HA has occurred in them. NACI recommends the use of human immune globulin (Ig) in circumstances when protection against hepatitis A infection is required in addition to or in the absence of immunization with HA vaccine. Specific HA antibody content in Ig is not regulated by Health Canada and therefore concentrations of HA antibody may be declining due to lower levels of antibody in the general population as a result of decreased rates of natural infection.

This statement will serve as an update to previous statements and will provide the evidence used to determine the optimal timing of immunization with a HA containing vaccine by:

- Providing a review of the evidence on the immunogenicity and safety of HA vaccine when administered to infants from 6 to 12 months of age and making recommendations for the immunization of individuals in this age group
- Reviewing evidence pertaining to the administration of HA vaccine to individuals with non-malignant hematologic disorders
- Reviewing evidence pertaining to post exposure prophylaxis (PEP) in individuals with chronic liver disease and adults over 50 years of age

II. METHODS

The NACI Hepatitis Working Group (HWG) reviewed key issues concerning the currently recommended immunization schedules for HA-containing vaccines approved for use in Canada, with particular consideration given to immunogenicity and safety when a HA-containing vaccine was provided to infants between 6 and 12 months of age. Under HWG supervision, knowledge synthesis was performed by a medical advisor at the Agency. Using key words "hepatitis A" AND "vaccine“, studies evaluating safety, immunogenicity and efficacy in infants immunized between 6 and 12 months of age with an inactivated HA-containing vaccine were assessed. Following the critical appraisal of individual studies, summary tables with ratings of the quality of the evidence were prepared using NACI's methodological hierarchy (Tables 6 and 7).

NACI reviewed such considerations as: the target population; safety, immunogenicity, efficacy, effectiveness of the vaccines; vaccine schedules; and other aspects of the overall immunization principles and strategy for the use of this vaccine. NACI HWG Chair and an Agency medical advisor presented the evidence and proposed recommendations to NACI. Following the review of the evidence and consultation at the NACI meeting on February 4, 2015, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text of this update.

III. EPIDEMIOLOGY OF HEPATITIS A

The severity of HA increases with age and can range from asymptomatic or a short and mild illness, to a severely disabling disease lasting several months. Children less than six years of age are commonly asymptomatic or present with mild disease without jaundice, and represent an important source of infection, particularly for household members and other close contacts. In older children and adults, HA is typically symptomatic, with the majority of individuals developing anorexia, nausea, fatigue, fever and jaundice, usually lasting less than two months. Older persons, and individuals with chronic liver disease and immunocompromising conditions, have an increased risk of progressing to fulminant hepatic failure resulting in death.[1-5]

Although approximately 25% of adult cases in Canada are hospitalized, deaths from HA are rarely reported. Between 2006 and 2010, only eight deaths from HA were reported to Vital Statistics: five in individuals over 60 years of age, two in individuals 55 to 59 years of age and one in an individual 40 to 44 years of age. Based on the available Canadian data, case fatality rates (CFR) for individuals 40 to 59 years of age and over 60 years of age have been estimated to be 0.94% and 2.2%, respectively. This information is comparable to data from the United States of America, in which the CFRs are estimated to range from 0 to 0.3% for individuals under the age of 39 years, 0.8% for adults 40-59 years of age and 2.6% for adults 60 years of age and older.[6, 7]

HA is a reportable disease in all jurisdictions in Canada. At the national level, cases of HA are reported through the Canadian Notifiable Disease Surveillance System (CNDSS)[8] and the National Enteric Surveillance Program (NESP).[9, 10] Hospitalization data are collected through the Canadian Institute for Health Information Hospital Morbidity Database (HMD). The number of reported HA cases and mean HA incidence, hospitalization and case fatality rate by year and age group are shown in Tables 1 and 2.

Information on HA antibody seroprevalence in Canada is available through published research studies and the first cycle (2007 to 2009) of the Canadian Health Measures Survey (CHMS).[3, 11-13] Based on the available CHMS data, prevalence of protective HA antibodies has been estimated to be 17.3% (95% CI: 11.5-23.0) among individuals 14 to 19 years of age, 28.9% (95% CI: 21.2-36.7) among individuals 20 to 39 years of age, 43.4% (95% CI: 37-49.7) among individuals 40 to 59 years of age and 62.5% (95% CI: 56.6-68.3) among individuals 60 to 79 years of age. In another nation-wide seroprevalence study involving Canadian-born, unvaccinated individuals, Scheifele et al. detected HA antibodies among 2.6% (95% CI: 0.5-7.4) of individuals 18 to 29 years of age, 6.1% (95% CI: 2.8-11.2) of individuals 30 to 39 years of age, 11.4% (95% CI: 6.9-15.9) of individuals 40 to 49 years of age, 26.4% (95% CI: 19.9-32.9) of individuals 50–59 years of age and 45.9% (95% CI: 39.3-53.7) in individuals 60–69 years of age. A study by Duval et al. found a 2.7% (95% CI:1.9-3.9) HA antibody prevalence among individuals 8 to 13 years of age.[3] There is currently no information available about HA seroprevalence in children less than 12 months of age.

Table 1. Mean annual HA incidence, hospitalization and case fatality rate by age group

	Mean Annual Incidence Rate (2006-2012)[1] per 100,000 population	Mean Annual Hospitalization Rate (2006-2010)[2]	Mean Case Fatality Rate (2006-2010)[3]
<1 year	0.43	0%	0%
1-4 years	1.62	16%	0%
5-9 years	2.24	12%	0%
10-14 years	1.61	27%	0%
15-19 years	1.23	24%	0%
20-24 years	1.24	19%	0%
25-29 years	1.02	18%	0%
30-39 years	0.81	26%	0%
40-59 years	0.57	31%	0.94%
60+ years	0.65	30%	2.20%
Total	0.94	24%	0.49%

[1]Incidence rates per 100,000 population based on cases reported to CNDSS.
[2] Calculated based on number of hospitalization for Hepatitis A reported through HMD (Canadian Institute for Health Information) compared with number of Hepatitis A cases reported through CNDSS.
[3]Calculated based on number of deaths from Hepatitis A reported to Vital Statistics compared with the number of Hepatitis A cases reported through CNDSS.

Table 2. Number of HA cases reported to CNDSS from 2006 to 2012 by age group

	2006	2007	2008	2009	2010	2011	2012	Total
<1 year	2	1	3	0	1	2	2	11
1-4 years	37	15	21	12	19	35	26	165
5-9 years	72	31	38	26	33	52	30	282
10-14 years	67	34	23	22	22	29	30	227
15-19 years	31	22	26	17	29	39	28	192
20-24 years	38	20	26	25	33	35	22	199
25-29 years	29	25	23	22	23	24	18	164
30-39 years	62	28	35	46	37	30	19	257
40-59 years	94	65	56	58	47	42	37	399
60+ years	44	56	47	48	32	36	34	297
Total	476	297	298	276	276	324	246	

Hepatitis A is the most common vaccine preventable disease in travellers. The risk of HA for susceptible travellers to developing countries is estimated to range from 0.1/1000 to 1/1,000 per month. The risk may be much higher for low-budget travellers, volunteer humanitarian workers and immigrants visiting friends and relatives in their homelands, who may be eating in less hygienic conditions. Additional information about disease incidence and distribution is available in the CIG's Hepatitis A vaccine chapter.(14)

IV. VACCINES

There is no change in vaccines currently authorized and available in Canada. Additional details about the types and contents of HA-containing vaccines available for use in Canada are provided in the CIG (http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-hepa-eng.php).[14]

IV.1 Efficacy and effectiveness

No studies on the efficacy or effectiveness of HA-containing vaccines in children 6 to 12 months of age were identified through the literature search.

IV.2 Immunogenicity

A total of eight studies that included participants less than one year of age were reviewed by HWG and NACI. A full review of all studies, their methodologies and outcome measures, can be found in Table 3a. Additionally, two confidential Clinical Study Report (CSR) synopses were also provided by the vaccine manufacturer. Information from the reviewed CSR synopses was determined to be consistent with the other published data reviewed by the HWG.

In a randomized controlled trial conducted by Bell et al.[15] , immune responses of 82 infants vaccinated with HA vaccine at 6 and 12 months of age (Group 1) were compared to children who were immunized at 12 and 18 or 15 and 21 months of age (Groups 2 and 3, respectively). Seroresponse (proportion of children achieving seroprotection defined by study authors as titre ≥33 mIU/ml and GMC values) was analysed in relation to maternal HA antibody status. Following the receipt of the first vaccine dose, all children in all groups achieved and maintained seroprotection throughout the study period, except for 2 infants in Group 1 born to anti-HAV-positive mothers . While no statistically significant differences in GMC between the three groups were observed among children born to anti-HAV-negative mothers, children born to anti-HAV-positive mothers in Group 1 had significantly lower GMC than those in Groups 2 and 3 at all blood draws. A subgroup analysis showed higher GMC values following the second vaccine dose in Group 1 infants born to susceptible, compared to those born to seropositive mothers. These subgroup differences were not observed in Groups 2 and 3. When interpreting the results of the study, it is important to note the relatively small number of participants in Group 1, high seroprotective HA antibody titre threshold used by the authors, as well as high HA incidence and younger average maternal age in the geographic area where the study was conducted.

Long term immunogenicity results of the study by Bell et al. were subsequently reported by Sharapov et al,[16] who used a lower protective antibody cut-off level (titre ≥10 mIU/ml) than in the original study. Although a lower threshold for seroprotection resulted in all study participants achieving seroprotection one month after dose two, lower GMC values were noted at all time points for children in Group 1 compared to Groups 2 or 3, as well as for children born to anti-HAV-positive mothers compared to those born to anti-HAV-negative mothers. At 10 years, all but 7% of Group 1 children born to anti-HAV–negative mothers, 11% of Group 1 children born to anti-HAV–positive mothers, and 4% of Group 3 children born to anti-HAV–positive mothers maintained protective antibody levels.

Immune response of children born to anti-HAV-positive mothers was also assessed in a clinical trial by Lagos et al.[17] In the study, 91 seropositive children either received a first dose of HA vaccine at 6 months of age concomitantly with other routine infant vaccines, or two weeks

following routine infant immunization; dose 2 was provided at 12 months of age. One month after dose one, seroprotection (defined as titre ≥20 mIU/ml) was achieved by all participants and both groups achieved more than a 22 fold increase in GMT values.

In a similar study, Stojanov et al.[18] randomized 619 infants to receive HA vaccine separately (months 7 and 13) or concomitantly (months 6 and 12) with other routine vaccines. Comparison of infants according to pre-vaccination HA antibody status (protective antibody titre defined as ≥10 mIU/ml) showed a pre- and post- booster response of similar magnitude, but significantly lower GMT values in initially seropositive infants. One month after dose 2, all infants achieved protective antibody levels, independent of initial HA antibody status.

Letson et al.[19] evaluated the immune response in 123 infants who were randomized according to maternal HA antibody status to receive HA vaccine at 2, 4, and 6 months of age (infants of both anti-HAV-positive and –negative mothers) or HA vaccine at 8 and 10 months of age (12 infants born to anti-HAV-positive mothers). In the latter group, at 15 months of age, no statistical differences in seroprotective levels (antibody titre >20 mIU/mL) were observed among infants who were seronegative (n=3) and those who were seropositive (n=9) at the time of vaccination (128 mIU/mL vs 72 mIU/mL, p=0.41).

Lopez et al.[20] conducted a study of 131 infants who received either three doses of HA vaccine at 2, 4, 6 months of age or one dose at 6 months of age, and a booster dose at 15-18 months of age. Seroprotective levels (defined as titre ≥20 mIU/ml) were achieved by all 30 participants who received the initial vaccine at 6 months of age, at one month following both primary and booster immunization, independent of prior antibody status (10% were seronegative at the time of enrolment). A 34-fold increase in pre- and post- booster GMC values was also observed among these study participants.

Usonis et al.[21] measured immune responses of 60 children following the receipt of the first dose of HA vaccine at either 5 to 10 months of age or 4 to 7 years of age, with a booster provided 12 months later. Half of the 26 infants who received a booster dose were seronegative (seroprotection defined as antibody titre ≥20 mIU/ml) prior to primary immunization. All infants achieved and maintained seroprotective antibody titers for the duration of the study, independent of the presence of maternal antibodies, with no statistically significant differences in antibody levels between the groups at month 12. Although the increase in GMT values following booster immunization was approximately four-fold higher in infants without maternal antibodies than in infants with maternal antibodies at baseline, all infants achieved more than fifty-fold higher antibody levels than those considered to be protective by the study authors.

In a study of 1084 children, Nolan et al.[22] compared immune responses of 218 children allocated to receive 2 doses of HA vaccine, starting at 11 to 13 months of age to children receiving the first dose of HA vaccine at 15 to 18 or 23 to 25 months of age. All children in all age groups reached seroprotective levels (defined as titre ≥15 mIU/ml) one month after dose 2. Seroresponse based on GMC values was found by authors to be equivalent between vaccine responders in the 11 to 13 and 23 to 25 month age groups.

There are limited data regarding HA vaccine immunogenicity in adults over the age of 40 years.[23-25] In a study by Briem et al[25], immune responses were compared between 200 adults 20-39 years of age (Group 1) and 40 to 62 years of age (Group II). Although 15 days post vaccination, Group 1 achieved higher seroresponse rates than Group 2 (90% vs. 77%), at month 1 post-vaccination a seropositivity (titre ≥20 mIU/ml) rate of 97% was observed in both groups. Another study by D'Acremont et al.[23] that compared immune responses among 53

adults 18-45 years of age with 16 adults 50-60 years of age found higher seropositivity (titre ≥20 mIU/ml) in the younger age group (100% vs. 70%). In a study by Scheifele et al.[24] in which 57 adults 40-61 years of age were provided with a pediatric dose of HA vaccine (HAVRIX® pediatric), seroprotection (titre ≥20 mIU/ml) was achieved by 89% of study participants one month following initial immunization and all participants one month after the receipt of the second dose.

Three studies[26-28] assessing the immunogenicity of HA vaccine in individuals with chronic liver disease were reviewed by the HWG. In a study conducted by Keeffe et al.[26], immune response was compared between healthy adults and adults with chronic liver disease. Although the extent of liver damage in study participants did correlate to vaccine response, GMC values and seroconversion rates (titre ≥33 mIU/ml) after the first dose of HA vaccine were found to be statistically lower in adults with chronic liver disease. Similarly, in a study of 22 adult patients with liver failure and liver transplants conducted by Dumont et al[27], seroconversion rates of 0% and 50% respectively, were much lower than those historically observed in healthy individuals. In another non-randomized control study conducted by Fereirra et al.[28], statistically lower seroconversion rates ($p<0.05$) were observed in children 1 to 16 years of age with chronic liver failure (76%), compared to healthy, age matched, children (94%).

It should be noted that, although immunity to HAV, by convention, has been established as IgG anti-HAV antibody titre above 10–20 mIU/ml (depending on the immunoassay used), the absolute lower limit of protective antibody level has not been determined.[2] It is also important to note that antibody levels induced by immunization have generally been observed to be lower in comparison to those induced by natural infection. [15, 16, 19] Available studies have primarily measured immune responses in children born to mothers who acquired antibodies through natural infection with HAV. Therefore, the ability to extrapolate the findings from these studies to children born to immunized anti-HAV positive mothers is limited.

Review of all immunogenicity studies, their methodologies and outcome measures can be found in Tables 3a, 4 and 5.

IV.3 Safety

Safety data for HA vaccine in infants 6 to 12 months of age were obtained from six of the reviewed studies. A review of these studies, their methodologies and outcome measures can be found in Table 3b. Additional information that was obtained from two confidential CSR synopses provided by a vaccine manufacturer was consistent with other reviewed studies. A supplementary safety-relevant data analysis available through the Agency did not indicate any safety concerns with HA vaccine at any age. Fewer than 10 reports involving infants 6 to 12 months of age were submitted to the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) from January 2011 to June 2014, with most including a HA-containing vaccine co-administered with routine infant vaccines. However, it is important to note that the actual number of individuals who were immunized in this age group is not known and therefore the data obtained through CAEFISS must be interpreted with caution.

Similar to the safety and reactogenicity of HA vaccines in older subjects, the most frequently reported adverse event in infants 6 to 12 months of age was injection site reaction, with the majority of symptoms described as mild or moderate and resolving within 1 to 2 days after vaccination.

V. RECOMMENDATIONS

Comparable to the results reported in clinical trials of children more than 12 months of age, all reviewed studies have consistently shown that vaccination of infants 6 to 12 months of age with inactivated HA vaccines is immunogenic and safe. Following the receipt of two doses, seroprotection (as defined by study authors) was achieved, independent of age, schedule used or initial HA serological status. When the vaccine was provided to seronegative infants, immune response and long-term antibody levels were comparable to those achieved following immunization at an older age. In all infants born to seropositive mothers, despite lower antibody levels that were observed following immunization, booster vaccination elicited a robust anamnestic response, suggesting good priming and an established immune memory potential despite maternal antibody interference. However, because of very low rates of anti-HA seropositivity as a result of natural infection among women of reproductive age in Canada, potential concerns regarding maternal antibody interference are likely not to represent a significant issue. Recommendations 1 to 3 pertain to products which have been approved for use in children one year of age.

Recommendation 1: HA vaccine may be provided, beginning at six months of age, to infants who are at increased risk of infection or severe HA. (*NACI recommendation Grade B*)

Infants at increased risk of severe HA infection may include those with an underlying liver disease of idiopathic, metabolic, infectious or cholestatic etiology. Canadian-born infants travelling to HA endemic countries, including children of new Canadians returning to their country of origin to visit friends and relatives, may be at increased risk of HA infection.

Recommendation 2: HA vaccine may be provided to infants beginning at six months of age, who are living in a household with an individual who is at increased risk of infection or severe HA. (*NACI recommendation Grade B*)

Recommendation 3: For post-exposure prophylaxis, unless contraindicated or unavailable, HA vaccine is recommended in preference to Ig for healthy individuals six months of age and older. *(NACI recommendation Grade B)*

Because the HA antibody content of Ig is assumed to decrease over time as a result of lower population-level antibody levels (due to lower rates of natural infection), and because of an excellent safety profile of inactivated HA-containing vaccine, immunization is preferred over the administration of a blood-derived product.

Recommendation 4: Immunization with HA vaccine may be considered for all individuals receiving repeated replacement of plasma-derived clotting factors. *(NACI recommendation Grade I)*

The solvent-detergent (S/D) method used to prepare plasma-derived clotting factor concentrates does not reliably inactivate the HA virus. However, historically there has been no evidence of HA transmission from plasma-derived clotting factor in Canada and the risk of transfusion-related HA is extremely low because all pooled plasma is tested for HA. Due to a theoretical possibility of infection, immunization of individuals receiving large quantities of plasma-derived clotting factors may be considered. In Canada, product monographs of all S/D plasma-derived products used in the treatment of conditions requiring clotting factor substitution include recommendations for HA immunization.

Recommendation 5: For post-exposure prophylaxis within 14 days of exposure of susceptible adults 60 years of age and older who are household or close contacts of a case, Ig may be provided in addition to HA vaccine. *(NACI recommendation Grade I)*

Individuals without a history of disease or previous immunization are susceptible to HA infection. Evidence is suggestive of reduced immunogenic response to HA vaccine, as well as of higher HA infection-related hospitalization and case fatality rates with increasing age. However, due to significant uncertainty about the incremental value of passive immunization on disease outcomes, (including Ig HA antibody content), high HA antibody prevalence in older age groups and a small number of cases of HA infection-related complications in individuals over 60 years of age, the decision to include Ig for post-exposure HA prophylaxis should be made on a case-by-case basis. Given the lack of data to support benefit of Ig after 14 days, there is no recommendation for its use after this time period. Post exposure prophylaxis with vaccine alone is recommended for outbreak response.

Recommendation 6: For post-exposure prophylaxis of susceptible individuals with chronic liver disease, Ig should be provided within 14 days of exposure in addition to HA vaccine. *(NACI recommendation Grade B)*

Because of the risk of severe disease and a suboptimal immune response to HA vaccine among individuals who are immunocompromised and with chronic liver disease, Ig is recommended to provide immediate protection against HA infection until an active response to the vaccine is produced. Given the lack of data to support benefit of Ig after 14 days, there is no recommendation for its use after this time period.

VI. SURVEILLANCE AND RESEARCH PRIORITIES

- Enhanced epidemiological surveillance that can provide information about the incidence of HA infection, stratified by risk factors and age group, as well as data on post exposure management of HA cases and contacts
- Enhanced safety surveillance of immunized infants less than one year of age
- Studies on long-term protection, including antibody duration and persistence of immune memory
- Studies on post-exposure efficacy and vaccine failure or breakthrough of disease following the receipt of one vs. two vaccine doses.
- Studies to determine the importance of post-immunization titres and anti-HAV antibody waning in protection against clinical infection
- Studies on efficacy of Ig used in Canada for the prevention of HA

TABLES

Table 3a: Summary of evidence related to immunogenicity of inactivated Hepatitis A-containing vaccine in infants 6-11 months of age

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
Bell BP, Negus S, Fiore AE, Plotnik J, Dhotre KB, Williams J, Shapiro CN, McMahon BJ. *Immunogenicity of an inactivated hepatitis A vaccine in infants and young children.* Pediatr Infect Dis J. 2007 Feb;26(2):116-22.[15]	HAVRIX® Glaxo SmithKline Biologicals, 720 EL.U/ per dose Intramuscular (IM), thigh Other infant vaccines provided at 6 months of age: HB DTaP Hib IPV	Phase IV RCT Single-blind Two-center Alaska, US Seropositive defined as titer ≥33 mIU/ml Antibody status determined at the time of first vaccine dose (baseline) and at 1, 7 and 12 months thereafter. All children tested at age 13 months for responses to recommended routine vaccinations	N=248 enrolled Group 1 (n=82): vaccinated at ages 6 and 12 months Group 2 (n=83): vaccinated at ages 12 and 18 months Group 3 (n=78): vaccinated at ages 15 and 21 months (control) HA vaccine administered with other age-appropriate infant vaccines 79% of study participants	All participants in all groups seropositive following dose 2 except Group 1 infants born to immune mothers (94%; 34/36). No statistically significant differences in GMC at any point between Groups 3 and either Group 2 or Group 1 in children born to anti-HAV-negative mothers Statistically significant differences in GMC at all times between Groups 1 and Group 2 or Group 3 in children born to anti-HAV-positive mothers ($p<0.05$) No difference observed in responses to routinely administered vaccines **Infants born to anti-HA-positive mothers** Group 1; n=36 (% seropositive infants; GMC mIU/mL (95% CI)) : *Baseline*: 94%; 295(184–473) *One month after dose 1*: 94%; 173 (109–272) *One months after dose 2*: 94%; 794 (488–1293) *Six months after dose2:* 94%; 229 (143–367) Group 2; n=34 (% seropositive infants; GMC mIU/mL (95% CI)): *Baseline:* 15%; 18.7 (15.5–22.7) *One month after dose 1:* 64%; 44.7 (31.6–63.2 *One months after dose 2:* 100%; 2296 (1719–3068) *Six months after dose2:* 100%; 698 (499–976) Group 3; n=38 (% seropositive infants; GMC mIU/mL (95% CI)):	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
			were full or part Alaska Native	*Baseline:* 3%; 15.6 (8.8 –16.3) *One month after dose 1:* 68%; 70.2 (42.8–115.2) *One months after dose 2:* 100%; 2715 (2073–3557) *Six months after dose2:* 100%; 909 (633–1306) **Infants born to anti-HA-negative mothers** Group 1; n=46 (GMC in mIU/mL): *One month after dose 1*: 54%; 49.0 (33.6 –71.5) *One month after dose 2*: 100%; 2083 (1462–2967) *Six month after dose2:* 100%; 727 (527-1003) Group 2; n=49 (GMC in mIU/mL): *One month after dose 1:* 60%; 54.0 (37.5–77.9) *One month after dose 2:* 100%; 3166 (2413–4156) *Six month after dose2:* 100%; 937 (719–1221) Group 3; n=45 (GMC in mIU/mL): *One month after dose 1:* 73%; 64.6 (46.1–90.6) *One month after dose 2:* 100%; 3153 (2450–4059) *Six month after dose2:* 100%; 933 (711–1224)		
Lagos R, Munoz A , R. Dumas, S. Pichon, B. Zambrano, M. Levine, E. Vidor *Immunological priming of one dose of inactivated hepatitis A vaccine given during the first year of*	Avaxim™ pediatric, Aventis Pasteur, 80 HA antigen units per dose; IM, deltoid Other infant vaccines provided at 6 months of age: DTwcP Hib OPV Other infant	Phase II open descriptive study Multi-centre Santiago, Chile Seropositivity defined as titer ≥20 mIU/ml	N=103 enrolled Group 1: vaccinated at ages 6.5 and 12 months (2 weeks following routine vaccination at 6 months) Group 2: vaccinated at ages 6 and 12 months	88% seropositive at inclusion Group 1; n=43 (% seropositive infants; GMT mIU/mL (95% CI)) : *Baseline*: 100%(91.8-100); 353(264–470) *One month after dose 1*: 100%(91.8-100); 173 (236–362) *Before dose 2:100%* (91.8-100); 77.6 (63.8-94.4) *One months after dose 2*: *100%* (91.8-100); 1731 (1198–2501) Group 2; n=48 (% seropositive infants; GMT mIU/mL (95% CI)) : *Baseline*: 100%(92.6-100); 293(200–430) *One month after dose 1*: 100%(92.6-100); 278 (215–359) *Before dose 2:100%* (92.3-100); 76 (60.3-95.7) *One months after dose 2*: *100%* (92.3-100); 1866	Level III	Poor

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
life in presence of maternal antibodies. Vaccine, 21 (2003), pp. 3730–3733[17]	vaccines provided at 12 months of age: MMR		concomitantly with routine vaccination	(1250–2786) Pre/post booster immunization GMT ratio of over 22 observed in both groups.		
López EL, Contrini MM, Xifró MC, Cattaneo MA, Zambrano B, Dumas R, Rouyrre N, Weber F. *Hepatitis A vaccination of Argentinean infants: comparison of two vaccination schedules.* Vaccine. 2007 Jan 2;25(1):102-8. Epub 2006 Jul 28.[20]	Avaxim™ pediatric, Aventis Pasteur, 80 HA antigen units per dose; IM, thigh	Phase II RCT Monocenter, double-blind non-inferiority study (4 vs. 2-dose regimen) Buenos Aires, Argentina Seropositivity defined as titer ≥20 mIU/ml	N=131 enrolled Group 1: three doses at 2, 4, 6 months of age and booster dose at 15–18 months Group 2: one dose at 6 months of age and booster dose at 15–18 months	**Seronegative prior to immunization** Group 2; n=5 (% seropositive infants; GMC mIU/mL (95% CI)) : *Baseline*: 0; 11.9(6.46-21.7) *One month after booster dose:* 100%; 5970 (1404-25358) **Seropositive prior to immunization** Group 2; n=55 (% seropositive infants; GMC mIU/mL (95% CI)) : *Baseline*: 100%(93.9-100); 3637(2712–4878) *One month after dose 1*: 100%(93.5-100); 248 (193–321) *One month before booster dose:* 91%(79.3-96.9) *One month after booster dose:* 100% (92.5-100); 1687 (1148–2479)	Level I	Fair
Nolan T,	HAVRIX®, GSK	Open,	N=1084	Group 1; n=218 (% seropositive infants; GMC mIU/mL (95% CI)) :	Level II-1	Fair

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
Bernstein H, Blatter MM, Bromberg K, Guerra F, Kennedy W, Pichichero M, Senders SD, Trofa A, Collard A, Sullivan DC, Descamps D. *Immunogenicity and safety of an inactivated hepatitis A vaccine administered concomitantly with diphtheria-tetanus-acellular pertussis and haemophilus influenzae type B vaccines to children less than 2*	Biologicals, 720 EL.U/ per dose; IM, thigh Other infant vaccines provided according to schedule: DTaP Hib	nonrandomized, multicenter study; allocation based on age and previous vaccination history 70% of the study population from US Seropositivity defined as antibody titer >15 mIU/mL Seroresponse defined as converting from seronegative to seropositive or maintaining or increasing ab titre if initially seropositive Anti-HAV GMC between groups	enrolled Group 1 (11-13 mo): 2 doses of HAV vaccine 6 months apart Group 2 (15-18 mo): 2 doses of HAV vaccine 6 months apart Group 3 (15-18 mo): 2 doses of HAV vaccine 6 months apart and 1 dose of DTaP, and Hib at month 0 Group 4 (15-18 mo): DTaP, and Hib at month 0, and 2 doses of HAV vaccine at months 1 and 7 Group 5 (23-25 mo): 2	*Baseline*: 6.4%; 8.4 *One month after dose 1*: 88.8%; 46.1 *One month after dose 2*: 100%; 1412 Group 2; n=200 (% seropositive infants; GMC mIU/mL (95% CI)) : *Baseline:* 2%; 7.6 *One month after dose 1:* 89.2%; 58.1 *One month after dose 2:* 100%; 1635.4 Group 3; n=131 (% seropositive infants; GMC mIU/mL (95% CI)) : *Baseline:* 1.5%; 7.7 *One month after dose 1:* 84.6%; 40.5 *One month after dose 2:* 100%; 1498.3 Group 4; n=115 (% seropositive infants; GMC mIU/mL (95% CI)) : *Baseline:* 1.7%; 7.6 *One month after dose 2:* 100%; 1492.5 Group 5; n=211 (% seropositive infants; GMC mIU/mL (95% CI)) : *Baseline:* 3.8%; 7.9 *One month after dose 1:* 96.2%; 85.3 *One month after dose 2:* 100%; 1910.7 Equivalence of anti-HAV GMCs in responders after the first dose of HAV vaccine (secondary study objective) demonstrated between Group 1 and Group 5 (GMC ratio: 0.62; 95% CI: 0.51–0.75)		

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
years of age. Pediatrics. 2006 Sep;118(3): e602-9.[22]		considered equivalent if 95% CI included within protocol defined limits of [0.5; 2.0].	doses of HAV vaccine 6 months apart			
Sharapov UM, Bulkow LR, Negus SE, Spradling PR, Homan C, Drobeniuc J, Bruce M, Kamili S, Hu DJ, McMahon BJ. *Persistence of hepatitis A vaccine induced seropositivity in infants and young children by maternal antibody status: 10-year follow-up.* Hepatology. 2012	HAVRIX®, Glaxo SmithKline Biologicals; 720 EL.U/ per dose IM, thigh	Phase IV RCT Single-blind Two-center Long-term follow-up (Bell et al, 2007) Alaska, US Seropositivity defined as titer ≥10 mIU/ml Antibody status determined 1 and 6 months after dose 2, and at 3, 5, 7 and 10 years of age.	N=197 available for follow-up study; n=82 received HA vaccine at 6 months of age Group 1: infants vaccinated at ages 6 and 12 mo; Group 2: infants vaccinated at ages 12 and 18 mo; Group 3: infants (control) vaccinated at ages 15 and 21 mo. HA vaccine	In group 1, all children born to anti-HAV–negative mothers remained seropositive through 3 years. At year 5, 7, and 10 seroprotection was lost in 3%, 5%, and 7% of children. All children in Group 2 and 3 remained seropositive during 10 years of follow-up. Consistently lower GMC values between Group 1 and Group 2 or 3; statistically significant difference only in children born to anti-HAV-positive mothers Lower GMC values in children born to anti-HAV-positive mothers in all groups; significant only for the first three time periods. **Infants born to anti-HA-positive mothers** Group 1 (% seropositive infants; GMC mIU/mL (95% CI)) : *One month after dose 2*: 100%; 646 (370-1127) *Six months after dose 2*: 100%; 233 (144–376) *At 3 years of age:* 100%; 115 (63–178) *At 5 years of age:* 99%; 65 (46-91) *At 7 years of age:* 98%; 46 (32-64) *At 10 years of age*:89%; 29 (20-40) Group 2 (% seropositive infants; GMC mIU/mL (95% CI)): *One month after dose 2*: 100%; 988 (528-1849) *Six months after dose 2*: 100%; 3993(229-696) *At 3 years of age:* 100%; 422 (207-886)	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
Aug;56(2):516-22. doi: 10.1002/hep.25687. Epub 2012 Jun 11. [16]			administered with other age-appropriate infant vaccines 96% of study participants were full or part Alaska Native	*At 5 years of age:* 100%; 156 (73-331) *At 7 years of age:* 100%; 105 (52-210) *At 10 years of age:*100%; 79 (42-150) Group 3 (% seropositive infants; GMC mIU/mL (95% CI)): *One month after dose 2*: 100%; 1690(1093-2611) *Six months after dose 2*: 100%; 504 (291-873) *At 3 years of age:* 100%; 400 (220–730) *At 5 years of age:* 98%; 65 (91-271) *At 7 years of age:* 97%; 46 (60-155) *At 10 years of age:* 96%; 29 (38-138) **Infants born to anti-HA-negative mothers** Group 1 ((% seropositive infants; GMC in mIU/mL): *One month after dose 2*: 100%; 1177 (843-1642) *Six months after dose 2*: 100%; 421 (314–566) *At 3 years of age:* 100%; 214 (141-325) *At 5 years of age:* 97%; 103 (68-156) *At 7 years of age:* 95%; 63 (42-95) *At 10 years of age:*93%; 51 (35-74) Group 2 ((% seropositive infants; GMC in mIU/mL): *One month after dose 2*: 100%; 1558 (1107-2193) *Six months after dose 2*: 100%; 547 (405-739) *At 3 years of age:* 100%; 585 (428-801) *At 5 years of age:* 100%; 262 (185-372) *At 7 years of age:* 100%; 154 (107-221) *At 10 years of age:*100%; 107 (79-143) Group 3 ((% seropositive infants; GMC in mIU/mL): *One month after dose 2*: 100%; 1568 (1175-2092) *Six months after dose 2*: 100%; 599 (468-766) *At 3 years of age:* 100%; 514 (363-730) *At 5 years of age:* 100%; 190 (137-263) *At 7 years of age:* 100%; 137 (102-184) *At 10 years of age:*100%; 97 (71-133)		
Stojanov S, Liese JG,	VAQTA, Merck, 25	Open, multicenter,	N=619	**Seronegative infants**	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
Belohradsky BH, Vandermeulen C, Hoppenbrouwers K, Van der Wielen M, Van Damme P, Georges B, Dupuy M, Scemama M, Watson M, Fiquet A, Stek JE, Golm GT, Schödel FP, Kuter BJ; HEXAVAC/VAQTA Study Group. *Administration of hepatitis A vaccine at 6 and 12 months of age concomitantly with hexavalent (DTaP-IPV-PRP*	IU/dose IM Hexavalent (HV) vaccine: DTaP IPV Hib HBs	RCT Belgium and Germany Seropositivity defined as titer ≥10 mIU/ml Baseline seropositivity determined at 2 months of age	Group 1 (separate): HV vaccine at 2, 4, 6, and 12 months of age and one dose of the HA vaccine at 7 and 13 months of age. Group 2 (concomitant): HV vaccine at 2, 4, 6, and 12 months of age and one dose of the HA vaccine at 6 and 12 months of age	<u>Group 1; n=153 ((% seropositive infants; GMT in mIU/mL)</u>: *Baseline:* N/A *Prior to dose 2*: 100% (97.7-100); 187 (162-217) *One months after dose 2*: 100% (97.7-100); 3380 (2977-3838) <u>Group 2; n=145((% seropositive infants; GMT in mIU/mL)</u>: *Baseline:* N/A *One month after dose 1:* 91% (85.2-95.1); 35.7 (31.2-40.8) *Prior to dose 2:* 99.3% (96.3-100);165 (141-193) *One months after dose 2:* 100% (97.6-100); 2637 (2279-3051) **<u>Seropositive infants</u>** <u>Group 1; n=80 ((% seropositive infants; GMT in mIU/mL)</u>: *Baseline:* 100% 95.7-100); 952 (603-1505) *One month after dose 1:* 71.3% (60-80.8); 53.6 (35.1-81.9) *Prior to dose 2:* 98.6%(92.7-100); 123(98.2-155) *One months after dose 2:* 100%(95.5-100); 2137 (1591-2870) <u>Group 2; n=80 ((% seropositive infants; GMT in mIU/mL)</u>: *Baseline:* 100% (95.7-100); 433 (274-684) *One month after dose 1:* 100% (95.5-100); 86(66.7-111) *Prior to dose 2*:98.7%(93-100); 112 (86.1-145) *One months after dose 2:* 100% (95.4-100); 1361 (994–1864)		

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
approximately T-HBs) combination vaccine. Vaccine. 2007 Oct 23;25(43):7549-58. Epub 2007 Sep 4.[18]						
Usonis V, Bakasenas V, R. Valentelis, G. Katiliene, D. Vidzeniene, C. Herzog *Antibody titers after primary and booster vaccination of infants and young children with a virosomal hepatitis A vaccine (Epaxal).* Vaccine, 21 (2003), pp. 4588–4592[21]	Epaxal, Berna Biotech Ltd., ≥500 RIA (radioimmunoassay) units of HAV antigen; IM thigh (infants) or deltoid (children)	Open, uncontrolled, single-centre pilot study Lithuania Seropositivity defined as titer ≥20 mIU/ml	N=60 Group 1 (infants): One dose of HA vaccine at 5 to 10, months of age with booster 12 months later. Group 2 (children): One dose of HA vaccine at 4 to 7, years of age with booster 12 months later.	**<u>Seropositive infants</u>** <u>Group 1; n=16 (% seropositive infants; GMT mIU/mL (95% CI))</u> : *Baseline*: 130(91-186) *One month after dose 1*:100%; 204 (136-306) *Prior to dose 2:*100 (56-179) *One months after dose 2*: 100%; 1185 (747-1879) **<u>Seronegative infants</u>** <u>Group 1; n=14 (% seropositive infants; GMT in mIU/mL (95% CI))</u>: *Baseline*: 4(3-5) *One month after dose 1*:100%; 169 (109-259) *Prior to dose 2:*180 (100-324) *One months after dose 2*: 100%; 4341 (2736-6885) <u>Group 2; n=30 (% seropositive infants; GMT in mIU/mL)</u>: *Baseline:* 4(3-5) *One month after dose 1:* 100%*;* 126 (94–169) *Prior to dose 2:* 108 (73-162) *One months after dose 2:* 100%; 2542 (1834–3522)	Level III	Fair

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
Letson GW, Shapiro CN, Kuehn D, Gardea C, Welty TK, Krause DS, et al. *Effect of maternal antibody on immunogenicity of hepatitis A vaccine in infants*. J Pediatr 2004;144(3:327–32.[19]	HAVRIX®, Glaxo SmithKline Biologicals; 360 EL.U/ per dose; IM, thigh HB vaccine	Prospective, randomized, single-blinded USA American Indian infants Seropositivity defined as titer ≥20 mIU/ml	N=123 Group 1 Infants of anti-HAV–negative mothers; HA vaccine at 2, 4, and 6 months of age Group 2 Infants of anti-HAV–positive mothers; HA vaccine at 2, 4, and 6 months of age Group 3 Infants of anti-HAV–positive mothers; HB vaccine at 2, 4 and 6 months of age; HA vaccine at 8 and 10 months of age	Results for only 12 infants in Group 3 available at 15 months of age follow-up; 9 (75%) had seroprotective levels before first dose. No statistically significant difference post immunization between antibody levels among infants with and without protective antibody levels at the time of initial HA vaccine administration	Level I	Poor

Table 3b: Summary of evidence related to safety of inactivated Hepatitis A-containing vaccine in infants 6-11 months of age

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Bell BP, Negus S, Fiore AE, Plotnik J, Dhotre KB, Williams J, Shapiro CN, McMahon BJ. Immunogenicity of an inactivated hepatitis A vaccine in infants and young children. Pediatr Infect Dis J. 2007 Feb;26(2):116-22.[15]	HAVRIX® Glaxo SmithKline Biologicals, 720 EL.U/ per dose IM, thigh Other infant vaccines provided at 6 months of age: HB DTaP Hib IPV	Phase IV Two-center RCT Alaska, US Pain, redness or swelling at any injection site and fever, indications of irritability or other changes in behavior or any illness noted for 3 days after vaccination	N=248 enrolled; n=82 received HA vaccine at 6 months of age Group 1 infants vaccinated at ages 6 and 12 mo; Group 2 infants vaccinated at ages 12 and 18 mo; Group 3 infants (control) vaccinated at ages 15 and 21 mo. HA vaccine administered with other age-appropriate infant vaccines 79% of study participants were full or part Alaska Native	The most frequently reported solicited adverse events were pain at the injection site (20–32%), sleepiness (17–34%) and fussiness (18–30%); majority of symptoms resolved within 1 to 2 days after vaccination. Fever of 1 day's duration was reported by 12% of participants after either vaccine dose; fever of at least 3 days' duration was uncommon (0–6%). No differences between three groups were reported.	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
López EL, Contrini MM, Xifró MC, Cattaneo MA, Zambrano B, Dumas R, Rouyrre N, Weber F. *Hepatitis A vaccination of Argentinean infants: comparison of two vaccination schedules.* Vaccine. 2007 Jan 2;25(1):102-8. Epub 2006 Jul 28.[20]	Avaxim™ pediatric, Aventis Pasteur, 80 EL.U/ per dose IM, thigh	Phase II RCT Monocenter, double-blind Buenos Aires, Argentina Local and systemic reactions and events recorded daily during the 7 days after injections. All medical events occurring within 28 days after the vaccinations were listed, and serious adverse events were reported whenever they occurred during the entire duration of the study.	N=131 infants; n=59 primed only at 6 months of age Group 1: three doses at 2, 4, 6 months of age and booster dose at 15–18 months Group 2: one dose at 6 months of age and booster dose at 15–18 months	Pain at injection site was the most frequent local reaction in both groups, reported for 42 subjects (42 of 59 events). Rates of local reactions were similar in Groups 1 and 2 after the booster injection, 14.5% and 12.5%, respectively. Except for one case of severe pain in each group after both the first injection and the booster, all local reactions were described as mild or moderate. Fever was the most common systemic reaction in both groups, in 14.8–25.8% in Group 1 and 11.5–17.5% in Group 2 for primary doses.	Level I	Fair
Nolan T, Bernstein H, Blatter MM, Bromberg	HAVRIX®, GSK Biologicals, 720 EL.U/ per dose	Open, nonrandomized, multicenter study with	N=1084 enrolled; n=243 in group 11-13 mo of age (Group 1)	Redness most frequently occurring solicited local AE in Group 1. Rates of grade 3 injection-site AEs low and comparable in both groups. Most frequently occurring solicited general AE for all of	Level II-1	Fair

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
K, Guerra F, Kennedy W, Pichichero M, Senders SD, Trofa A, Collard A, Sullivan DC, Descamps D. *Immunogenicity and safety of an inactivated hepatitis A vaccine administered concomitantly with diphtheria-tetanus-acellular pertussis and haemophilus influenzae type B vaccines to children less than 2 years of age.* Pediatrics. 2006	IM, thigh Other infant vaccines provided according to schedule: DTaP Hib	allocation based on age and previous vaccination history 70% of the study population from US Solicited local AEs included pain, swelling, and redness at the injection site(s) during 3 days following immunization.; Solicited general (systemic) AEs included drowsiness, fever (rectal body temperature >38.0°C), irritability, and loss of appetite during 3 days following immunization.	Group 1 (11-13 mo): 2 doses of HAV vaccine 6 months apart Group 2 (15-18 mo): 2 doses of HAV vaccine 6 months apart Group 3 (15-18 mo): 2 doses of HAV vaccine 6 months apart and 1 dose of DTaP, and Hib at month 0 Group 4 (15-18 mo): DTaP, and Hib at month 0, and 2 doses of HAV vaccine at months 1 and 7 Group 5 (23-	the groups was irritability (46.5% in Group 1). Rates of grade 3 solicited general AEs were low (0.8% in Group 1).		

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Sep;118(3): e602-9.[22]		All unsolicited AEs that occurred within 1 month after each dose of vaccine were recorded irrespective of severity or causal relationship to vaccination.	25 mo): 2 doses of HAV vaccine 6 months apart			
Stojanov S, Liese JG, Belohradsky BH, Vandermeulen C, Hoppenbrouwers K, Van der Wielen M, Van Damme P, Georges B, Dupuy M, Scemama M, Watson M, Fiquet A, Stek JE, Golm GT, Schödel FP, Kuter	VAQTA, Merck & Co, 25 EL.U/ per dose IM Hexavalent (HV) vaccine provided according to schedule: DTaP IPV Hib HBs	Open, randomized, multicenter study Belgium and Germany Injection-site pain, redness, swelling and warmth were reported but not measured; other injection-site reactions were spontaneously reported through 4 days post-dose.	N=619 Group 1 (separate): HV vaccine at 2, 4, 6, and 12 months of age and one dose of the HA vaccine at 7 and 13 months of age. Group 2 (concomitant): HV vaccine at 2, 4, 6, and 12 months of age and one dose of the HA vaccine at 6	The observed incidence of injection-site reactions at the HA vaccine site was generally similar between the two groups (8.9% versus 10.0%following dose 1 and 7.1% versus 12.5% following dose 2 in Groups 1 versus 2, respectively). After the 6-month visit, systemic events were reported by 39.9% of subjects in Group 1 and 42.7% in Group 2. After the 12-month visit, systemic events were reported by 43.0% of subjects in Group 1 and 41.7% in Group 2. Overall, within 14 days after the first three vaccination visits, fever was reported in 21.8% of subjects in Group 1 and 21.3% in Group 2. After the 12-month visit, 34.2% of subjects in Group 1 and 30.2% in Group 2 reported fever. HA vaccine was administered alone only at the 7- and 13-month visits, after which 22.1% and 22.9% of subjects, respectively, reported fever.	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
BJ; HEXAVAC/ VAQTA Study Group. *Administration of hepatitis A vaccine at 6 and 12 months of age concomitantly with hexavalent (DTaP-IPV-PRP approximately T-HBs) combination vaccine.* Vaccine. 2007 Oct 23;25(43):7549-58. Epub 2007 Sep 4.[18]		Rectal temperatures were recorded through 4 days after each dose of vaccine; other unsolicited adverse events were recorded through 14 days post-dose. Any serious and/or related adverse event occurring from 15 days after all vaccinations until 30 days after the last dose, until the next vaccination, or until the last study visit, was also recorded.	and 12 months of age.			
Usonis V, Bakasenas V, R. Valentelis, G. Katiliene,	Epaxal, Berna Biotech Ltd., ≥500 RIA (radioimmunoassay) units	Open, uncontrolled, single-centre pilot study Lithuania	N=60 Group 1 (infants): One dose of HV vaccine at	In both children and infants, the most commonly reported solicited local events were pain/tenderness (up to 14.7%) and swelling/tumefaction (up to 7.4%). In one infant and one child, the body temperature increased above 38.5 ◦C after primary vaccination, none after booster vaccination	Level III	Fair

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
D. Vidzeniene, C. Herzog *Antibody titers after primary and booster vaccination of infants and young children with a virosomal hepatitis A vaccine (Epaxal).* Vaccine, 21 (2003), pp. 4588–4592[21]	of HAV antigen; IM thigh (infants) or deltoid (children)	Solicited local and systemic reactions, including pain/tenderness, swelling/tumefaction, hardness/induration, redness > 5 mm, fatigue, loss of appetite and temperature (all subjects), headache, nausea, and arthralgia (children), and persistent crying and irritability (infants) recorded throughout 4-day period. Unsolicited reported and observed adverse events documented by investigators	5 to 10, months of age with booster 12 months later. Group 2 (children): One dose of HV vaccine at 4 to 7, years of age with booster 12 months later.			

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
		at baseline and at 1, 12 and 13 months.				
Letson GW, Shapiro CN, Kuehn D, Gardea C, Welty TK, Krause DS, et al. *Effect of maternal antibody on immunogenicity of hepatitis A vaccine in infants*. J Pediatr 2004;144(3):327–32.[19]	HAVRIX®, Glaxo SmithKline Biologicals; 360 EL.U/ per dose; IM, thigh HB vaccine	Prospective, randomized, single-blinded clinical USA American Indian infants Seropositivity defined as titer ≥20 mIU/ml	Group 1 Infants of anti-HAV–negative mothers; HA vaccine at 2, 4, and 6 months of age Group 2 Infants of anti-HAV–positive mothers; HA vaccine at 2, 4, and 6 months of age Group 3 Infants of anti-HAV–positive mothers; HB vaccine at 2, 4 and 6 months of age; HA vaccine at 8 and 10 months of age	The frequency of adverse events was exceedingly rare (<1%; data not shown).There were no serious adverse events associated with any of the vaccines used during the study.	Level I	Poor

Table 4: Summary of evidence related to immunogenicity of inactivated Hepatitis A-containing vaccine in older adults

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
D'Acremont V, Herzog C, Genton B. *Immunogenicity and safety of a virosomal hepatitis A vaccine (Epaxal®) in the elderly*. J Travel Med. 2006;13(2): 78-83.[23]	Epaxal, Berna Biotech Ltd. IM, deltoid	Open, uncontrolled, single-centre study Switzerland Seropositivity defined as titer ≥20 mIU/ml Antibody status determined 1 week before and 1, 6 and 12 months after initial vaccination, and 1 month after the second dose	N=90 Groups 1: Pre-booster 59 adults 18 to 45 years of age; post-booster 53 adults 18 to 45 years of age (42 adults 18 to 30 years of age and 11 adults 31 to 45 years of age) Group 2: Pre-booster 31 adults 50 years of age and older; post-booster 30 adults 50 years of age and older (16 adults 50 to 60 years of age and 14 adults over 60 years of age)	Group 1 (% seropositive, GMT in mIU/mL (95% CI)): One month after dose 1: 100%, 110 (CI:87-140) Twelve months after dose 1: 65 (CI:37-112) One month after dose 2: 2,020 (CI:1,567-2,605) Group 2 (% seropositive, GMT in mIU/mL (95% CI)): One month after dose 1: 65%, 64 (CI:37-112) Twelve months after dose 1: 37 (CI:19-73) One month after dose 2: 1,226 (CI:665-2,259) When subdivided by age groups 31 to 45 years (n=11), 50 to 60 years (n=16) and >60 years (n=14), differences in GMT values at all time points and seroprotection at 6, 12 and 13 months were not significant between subgroups When lower threshold of 10 IU/mL was applied, all the subjects aged 50 to 60 years and 93% of subjects aged >60 years were seroprotected at 1 month	Level II-1	Poor
Briem H, Safary A. *Immunogenicity and safety in*	Inactivated hepatitis A vaccine, SmithKline Beecham	Open, uncontrolled, single-centre study	N=200 Group 1 (n=134):	Group 1 (% seropositive, GMT in mIU/mL): Two weeks after dose 1: 90%, 282 One months after dose 1: 97% , 589 Six months after dose 1: 94%, 181 One month after dose 2: 100% , 3,629	Level III	Poor

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
adults of hepatitis A virus vaccine administered as a single dose with a booster 6 months later. J Med Virol. 1994;44(4): 443-5.[25]	Biologicals; 1,440 EL.U/dose. IM , deltoid	Iceland Seropositivity defined as titer ≥20 mIU/ml Antibody status determined 1-2 weeks before and 2 weeks, 1, 6 and 7 months after initial vaccination	adults 20-39 years of age Group 2 (n=66): adults 40-62 years of age Vaccine provided at 0 and 6 months	Group 2 (% seropositive, GMT in mIU/mL): Two weeks after dose 1: 77%, 262 One months after dose 1: 97%, 357 Six months after dose 1: 88%, 206 One months after dose 2: 100%, 2,320 Seropositivity rates significantly higher in group 1 only at day 15 ($p < 0.05$)		
Scheifele DW, Bjornson GJ. *Evaluation of inactivated hepatitis A vaccine in Canadians 40 years of age or more.* CMAJ. 1993 [cited 2013 Oct 18];148(4): 551-5. [24]	Inactivated hepatitis A vaccine, SmithKline Beecham Biologicals; 720 EL.U/dose. IM , deltoid	Open, uncontrolled, single-centre study Canada Seropositivity defined as titer ≥20 mIU/ml Antibody status determined 2 weeks before and 1, 2, 6 and 7 months after initial vaccination	N=64 Healthy adults 40 to 61 years of age Vaccine provided at 0, 1 and 6 months	Seroconversion (titer ≥20 mIU/ml) occurred in 89% of study participants after dose 1. All study participants achieved protective antibody levels after dose two and remained seropositive at 6 months (before dose 3).	Level III	Fair

Table 5: Summary of evidence related to immunogenicity of inactivated Hepatitis A-containing vaccine in individuals with chronic liver disease

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
Keeffe EB, Iwarson S, McMahon BJ, Lindsay KL, Koff RS, Manns M, et al. *Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease.* Hepatology. 1998;27(3): 881-6.[26]	HAVRIX®, Glaxo SmithKline Biologicals; 1440 EL.U/ per dose; IM, deltoid HBV	Open, prospective, comparative, 8-centre study United States and Europe Antibody status determined prevaccination and at months 1, 2, 6, and 7 post immunization Seroconversion defined as titer ≥33 mIU/mL in previously seronegative individuals	N=392 Group 1 (n=185): Healthy adults Group 2 (n=43): Adults with chronic hepatitis B; Group 3 (n=99): Adults with chronic hepatitis C Group 4 (n=65): Adults with non-viral chronic liver disease HA vaccine at months 0 and 6 HB vaccine at months 0,1 and 6	Group 1 (% seropositive, GMC in mIU/mL (95%CI)): One month after dose 1: 93% , 175 (CI:150-206) Two months after dose 1: 87.1% , 100 (CI:87-115) Six months after dose 1: 73.3%, 74 (CI:63-87) One month after dose 2: 98.2% , 1315 (CI:1086-1593) Group 2 (% seropositive, GMC in mIU/mL (95%CI)): One month after dose 1: 83.7% , 93 (CI:68-127) Two months after dose 1: 71.7% , 69 (CI:49-97) Six months after dose 1: 51.1%, 43 (CI:31-60) One month after dose 2: 97.7% , 749 (CI:519-1080) Group 3 (% seropositive, GMC in mIU/mL (95%CI)): One month after dose 1: 73.7% , 77 (CI:60-98) Two months after dose 1: 56.7% , 46 (CI: 38-58) Six months after dose 1: 37.6%, 32 (CI: 26-40) One month after dose 2: 94.3% , 467 (CI:345-631) Group 4 (% seropositive, GMC in mIU/mL (95%CI)): One month after dose 1: 83.1% , 112 (CI:83-149) Two months after dose 1: 72.7% , 64 (CI:50-81) Six months after dose 1: 63.5%, 44 (CI:36-53) One month after dose 2: 95.2% , 562 (CI:403-783) Statistically higher seroconversion in healthy adults compared to individuals in Groups 3 and 4 after the first dose of HA vaccine. Statistically higher GMC values in healthy adults compared to Groups 2, 3 and 4 at all time points	Level II-1	Fair

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
Dumot JA, Barnes DS, Younossi Z, Gordon SM, Avery RK, Domen RE, et al. *Immunogenicity of hepatitis A vaccine in decompensated liver disease*. Am J Gastroenterol. 1999;94(6): 1601-4.[27]	HAVRIX®, Glaxo SmithKline Biologicals; 1440 EL.U/ per dose. IM, deltoid	Open, prospective, one-centre study United States Antibody status determined at months 2 and 4 post immunization Seropositivity defined as titer ≥33 mIU/mL	N=24; 8 liver transplant patients and 14 liver failure patients HA vaccine at months 0 and 2	The median antibody titer at 2 months was lower (p= 0.01) in liver transplant patients, 0.0 mIU/ml (range 0–4.0) compared to liver failure patients 33.5 mIU/ml (range 0 to 528.0). The rate of seroconversion was lower (*p*= 0.02) in liver transplant recipients (0/8) patients compared to the liver failure patients (7/14)	Level III	Poor
Ferreira CT, da Silveira TR, Vieira SM, Taniguchi A, Pereira-Lima J. *Immunogenicity and safety of hepatitis A vaccine in children with chronic liver disease.* Journal of	HAVRIX®, Glaxo SmithKline Biologicals; 720 EL.U/ per dose. IM, deltoid	Open, prospective, control study Brazil Antibody status determined at months 1 and 7 post initial immunization Seropositivity defined as titer ≥15 mIU/mL	N=89 Group 1 (n=34): children 1-16 years of age with chronic liver disease (cirrhosis) Group 2 (n=55): healthy children 1-16 years of age HA vaccine at	Group 1 (% seropositive, GMT in mIU/mL (95%CI)): One month after dose 1: 76% , 107.77 (CI:65.5-177) One month after dose 2: 97% , 812.4 (CI:479-1373) Group 2 (% seropositive, GMT in mIU/mL (95%CI)): One month after dose 1: 94% ,160.77 (CI:122.5-219) One month after dose 2: 100% , 2344.9(CI:1824-3002)	Level II-1	Poor

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings and Outcome Data**	**Level of Evidence**	**Quality**
pediatric gastroenterology and nutrition 2003;37(3): 258-61.[28]			months 0 and 6			

Table 6. Levels of Evidence Based on Research Design

I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 7. Quality (internal validity) Rating of Evidence

Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design specific criteria are outlined in Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20:21-35.

Table 8. NACI Recommendation for Immunization -- Grades

A	NACI concludes that there is **good** evidence to recommend immunization.
B	NACI concludes that there is **fair** evidence to recommend immunization.
C	NACI concludes that the existing evidence is **conflicting** and does not allow making a recommendation for or against immunization; however other factors may influence decision-making.
D	NACI concludes that there is **fair** evidence to recommend against immunization.
E	NACI concludes that there is **good** evidence to recommend against immunization.
I	NACI concludes that there is **insufficient** evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

LIST OF ABBREVIATIONS

Abbreviation	***Term***
CIG	Canadian Immunization Guide
CHMS	Canadian Health Measures Survey
CNDSS	Canadian Notifiable Disease Surveillance System
CSR	Clinical Study Report
HA	Hepatitis A
HB	Hepatitis B
HMD	Hospital Morbidity Database
HV	Hexavalent Vaccine
HWG	Hepatitis Working Group
Ig	Human immune globulin
IM	Intramuscular
GMC	Geometric mean antibody concentration
GMT	Geometric mean titres
mIU/ml	milli-International Units/milliliter
NESP	National Enteric Surveillance Program
NACI	National Advisory Committee for Immunization
RCT	Randomized Controlled Trial
S/D	Solvent-detergent

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