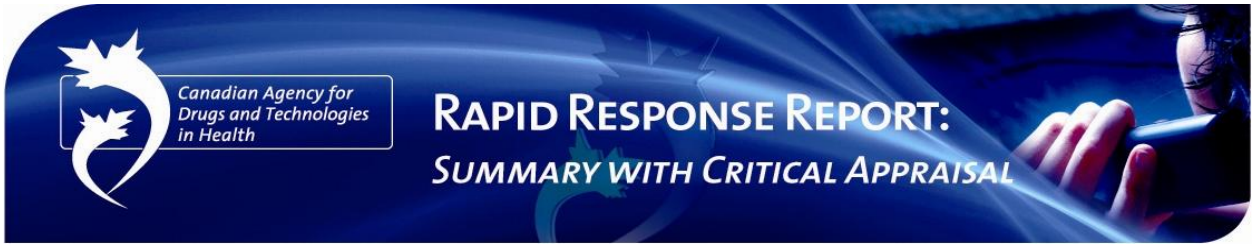


TITLE: Immune Response to Hepatitis B Vaccination: A Review of the Clinical Evidence

DATE: 28 March 2012

CONTEXT AND POLICY ISSUES

There are three vaccines against hepatitis B virus (HBV) licensed for adult use in Canada: Engerix-B, Recombivax HB, and Twinrix.[1-3] All three contain purified hepatitis B surface antigen (HBsAg) made from yeast.[1-3] In addition, the Twinrix vaccine also protects against hepatitis A virus (HAV).[3]

Protective levels of hepatitis B surface antibody (anti-HBs >10 mIU/mL) are generally achieved with three doses of HBV vaccine, however certain factors (e.g., smoking, obesity, cirrhosis, genetic factors, immune suppression, renal failure, etc.) are known to result in decreased vaccine response.[4,5] Patients with antibody levels lower than 10 mIU/mL four to twelve weeks after basic immunization are not considered to be protected against the virus.[6,7] In such cases, an additional one to three doses of HBV vaccine may be administered.[5-9] When revaccinated, 15-25% of patients tend to produce an adequate antibody response after one additional dose and 30-50% after three additional doses.[1,5] Fewer than five percent of the population will fail to mount a sufficient immune response after six doses of HBV vaccine.[5] These patients are referred to as “non-responders” or “hyporesponders”.[5]

Identifying a vaccination strategy that is most effective in preventing hepatitis B virus infection in patients who fail to respond to the standard course of HBV vaccination is important in reducing the mortality and morbidity associated with this infection. It has been hypothesized that the bivalent vaccine (Twinrix) may offer increased immunogenicity compared to the monovalent HBV vaccines (Engerix-B and Recombivax HB) due to the presence of the hepatitis A antigen.[10]

This report will review the evidence on the comparative effectiveness of combined hepatitis A and B vaccination versus hepatitis B alone for generating an immune response to hepatitis B virus as well as any evidence-based guidelines on hepatitis B vaccination of non-responders.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of combined hepatitis A and B vaccination versus hepatitis B alone for generating an immune response to hepatitis B virus?

2. What are the evidence-based guidelines for hepatitis B vaccination of non-responders?

KEY MESSAGE

Evidence from randomized controlled trials and non-randomized studies indicates that the combined hepatitis A/hepatitis B (HAV/HBV) vaccine may be more effective than the HBV vaccine for generating an immune response to hepatitis B virus, however the data are not conclusive. No evidence-based guidelines recommending the use of HAV/HBV vaccine in non-responders to HBV vaccination were identified.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. To address research question 1, methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies. To address research question 2, methodological filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and February 28, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

Table 1: Selection Criteria

Population	Any
Intervention	Combined hepatitis A / hepatitis B vaccine (e.g., Twinrix)
Comparator	Hepatitis B vaccine alone
Outcomes	Immune response Guidelines
Study Designs	Health technology assessments (HTA), systematic reviews and meta-analyses, randomized controlled trials (RCTs), non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1. Evidence-based guidelines for standard hepatitis B vaccination were excluded.

Critical Appraisal of Individual Studies

The quality of the included RCTs and non-randomized studies was assessed using the Downs and Black checklist.[11] A numeric score was not calculated, instead the strengths and limitations of each study were described. No HTAs, systematic reviews, or evidence-based guidelines were identified for critical appraisal.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search identified 294 citations for review. After examination of titles and abstracts, 266 were excluded and 28 were retrieved for full-text screening. Fifteen potentially relevant reports were identified in the grey literature. Of these, 35 did not meet the inclusion criteria. In total, eight publications were selected for inclusion. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Five RCTs[12-16] and three non-randomized studies[10,17,18] comparing the clinical effectiveness of the combined HAV/HBV vaccine product versus the monovalent HBV vaccine product in the generation of an immune response to HBV were selected for inclusion. Two of the included RCTs[13,16] and all three non-randomized studies[10,17,18] compared Twinrix versus HBV vaccine administered alone. Additionally, two RCTs comparing Twinrix versus HBV vaccine co-administered with HAV vaccine and one comparing Twinrix co-administered with HBV vaccine versus HBV vaccine alone were included. No HTAs, systematic reviews, or meta-analyses were identified for inclusion.

No evidence based guidelines on the vaccination of HBV vaccine non-responders were identified. Guidelines that did not meet the inclusion criteria, but addressed primary vaccine failure after three doses of HBV vaccine[5-9] are included in Appendix 2.

Summary of Study Characteristics

Study design

Included in the review are eight studies, comprising of five RCTs,[12-16] two prospective, non-randomized studies,[17,18] and one retrospective chart review.[10] Detailed characteristics of the included studies are summarized in Appendix 3.

Populations

The eight included studies investigated the comparative clinical effectiveness of HAV/HBV vaccination versus HBV vaccination alone in a variety of distinct patient populations. Three trials evaluated the vaccines in healthy, unvaccinated populations; adults,[12] youths,[13] and older adults (>40 years)[15]. The remaining five investigated the comparative effectiveness of HAV/HBV vaccination versus HBV vaccination in patients with pre-existing conditions: hemodialysis

patients,[14] chronic hepatitis C patients,[18] HIV-infected youths,[16] HIV-infected adults,[10] and children newly diagnosed with cancer.[17]

Interventions and comparators

HAV/HBV vaccine versus HBV vaccine alone

Two of the included RCTs[13,16] and all three non-randomized studies[10,17,18] compared Twinrix versus HBV vaccine administered alone. Flynn et al.[16] evaluated three preventative regimens: (1) Engerix-B (20µg), (2) Engerix-B (40µg), and (3) Twinrix, with all vaccines administered according to a standard schedule (0, 4, and 24 weeks). Cunningham et al.[13] compared Twinrix versus Recombivax HB, used a 2-dose schedule (0 and 24 weeks). Pettit et al.[10] retrospectively compared Twinrix versus Engerix-B (20µg) administered according to a standard schedule (0, 1, and 6 months). Kramer et al.[18] aimed to make the same comparison prospectively, although the actual intervals between administered doses were 86 days (range 29-175) between first and second dose and 109 days (range 49-217) between second and third dose in those receiving Twinrix, and 91 days (range 28-112) between first and second dose and 108 days (range 70-182) between second and third dose among those receiving Engerix-B. Finally, the study by Koksal et al.[17] evaluated Twinrix and Engerix-B, using both a rapid course (months 0, 1, 2, and 12) and an accelerated course (days 0, 7, 21, and 365).

HAV/HBV vaccine in combination with HBV vaccine vs. HBV vaccine alone

The study by Tung et al.[14] evaluated Twinrix in combination with Engerix-B, compared with Engerix-B alone. Participants in the Twinrix arm were vaccinated with both Twinrix and Engerix-B (20 µg) at 0, 1, 2, and 6 months plus Engerix-B (40 µg) at month 2. Participants in the control arm were vaccinated with Engerix-B (40 µg) at 0, 1, 2, and 6 months. Thus, both groups received a total dose of 160 µg of hepatitis B antigen.

HAV/HBV vaccine vs. HBV vaccine in combination with HAV vaccine

Two included trials used HBV vaccine in combination with HAV vaccine in comparison with Twinrix.[12,15] In the study by Chlibek et al.[15], the clinical effectiveness of Twinrix (0, 1, and 6 months) was compared with a combination of Engerix-B (0, 1, and 6 months) and Havrix (HAV vaccine) (0 and 6 months). A third study arm evaluated the combination of HBVAXPRO (0, 1, and 6 months) and Vaqta (HAV vaccine) (0 and 6 months). Connor et al.[12] compared four doses of Twinrix (0, 7, 21 to 30 days, and 12 months) with a combination of four-dose Engerix-B (0, 1, 2, and 12 months) and two-dose Havrix (0 and 12 months).

Outcomes

Main study outcomes in the RCTs were seroprotection rates[12,14,15] and antibody responses.[12,13,15-17] Length of follow-up ranged from 28 weeks[13,16] to four years.[15]

Summary of Critical Appraisal

The quality of the included RCTs and non-randomized studies was assessed using the Downs and Black checklist.[11] The domains evaluated were reporting, external validity, internal validity (bias and confounding), and power. Strengths and limitations of each study are described in Appendix 4. In general, the included studies were well-reported, although three studies[12,15,17]

failed to provide a comparison of patient characteristics between study groups. In the majority of included RCTs, there was no attempt to blind study participants or researchers – although this is not expected to affect the results in terms of vaccine effectiveness. Small sample size was a common study limitation.

Summary of Findings

Comparative clinical effectiveness of combined hepatitis A and B vaccination versus hepatitis B alone for generating an immune response to hepatitis B virus

Results from one of the two RCTs evaluating Twinrix versus HBV vaccine alone support the hypothesis that vaccination with Twinrix results in greater HBV vaccine response than vaccination with standard-dose Engerix-B.[16] The second RCT evaluating Twinrix versus HBV vaccine alone was not sufficiently powered to detect a difference between study arms.[13] Two prospective, non-randomized studies[17,18] indicate that Twinrix may be a more effective option than Engerix-B alone, however both studies are limited by small sample sizes. Finally, a single-centre retrospective chart review[10] found that, among HIV-infected adults, receipt of Twinrix was associated with more frequent seroconversion, compared to receipt of Engerix-B.

The evaluation of Twinrix + Engerix-B versus Engerix-B alone found a significant difference in seroprotection rates between the two study arms in favour of Twinrix + Engerix-B.[14]

Two larger RCTs evaluating Twinrix versus Engerix-B in combination with HAV vaccine in healthy adults both favoured Twinrix. Chlibek et al.[15] measured seroprotective/seropositivity rates and geometric antibody concentrations of anti-HBs four years post-vaccination and found that 57.1% of patients in the Twinrix arm had anti-HBs ≥10 mIU/mL, compared with 40.1% of patients administered Engerix-B and HAV. In the trial by Connor et al.[12], seroprotection rates were higher in the Twinrix arm than the Engerix-B + HAV arm at all time points, however only at day 37 (following three doses of a four-dose vaccine regimen) was the difference statistically significant.

A more detailed overview of study findings is provided in Appendix 5.

Evidence-based guidelines for hepatitis B vaccination of non-responders

No evidence-based guidelines on the vaccination of HBV vaccine non-responders were identified. Guidelines that did not meet the inclusion criteria, but addressed primary vaccine failure after three doses of HBV vaccine[5-9] are included in Appendix 2.

Limitations

The eight clinical studies included in this review provide data on a combined total of 2000 study subjects. While increasing HBV immunization levels may have made identification of eligible non-vaccinated subjects difficult for study authors, small sample size is a significant limitation in a number of the included studies.[14,17,18] Different dosing schedules and the co-administration of vaccines (i.e., Havrix in combination with Engerix-B) complicates the cross-study comparison of results.

The study participants were recruited from distinct populations, many with pre-existing conditions, potentially limiting the generalizability of study findings. One trial[14] was conducted

using Canadian study subjects. The generalizability of studies from other countries may be complicated by certain factors (i.e., HBVAQPRO, a comparator in one study, is not available for use in Canada).

We were unable to identify evidence-based guidelines for the management of HBV vaccine non-responders.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The clinical studies reviewed in this report support the use of HAV/HBV vaccination among patients requiring immunity to HBV, however the comparative clinical effectiveness of combined hepatitis A and B vaccination versus hepatitis B alone for generating an immune response to hepatitis B virus is not conclusive. The eight studies presented in this report are each based on different dosing schedules and different patient populations. No evidence-based guidelines addressing the use of HAV/HBV vaccine in non-responders to HBV vaccination were identified. More evidence is required, specifically in the population of HBV vaccine non-responders, in order to inform policy making.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Product monograph: Recombiv AX AB® [Internet]. Kirkland (QC): Merck Canada; 2011. [cited 2012 Mar 13]. Available from: http://www.merckfrosst.ca/assets/en/pdf/products/RECOMBIVAX_HB-PM_E.pdf

2. Product monograph: Engerix®-B [Internet]. Mississauga (ON): GlaxoSmithKline Inc.; 2008 Sep 23. [cited 2012 Mar 13]. Available from: http://www.gsk.ca/english/docs-pdf/Engerix%20B_PM_20080923_EN.pdf

3. Product monograph: Twinrix® [Internet]. Mississauga (ON): GlaxoSmithKline Inc.; 2011 Dec. [cited 2012 Mar 13]. Available from: http://www.gsk.ca/english/docs-pdf/product-monographs/Twinrix.pdf

4. Heathcote J, Abbas Z, Alberti A, Benhamou Y, Chen C, Elewaut A, et al. World Gastroenterology Organisation practice guideline: hepatitis B [Internet]. Milwaukee (WI): World Gastroenterology Organisation; 2008 Sep. [cited 2012 Mar 15]. Available from: http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/12_hepatitis_b_en.pdf

5. Hepatits B: epidemiology and prevention of vaccine-preventable diseases [Internet]. 12th ed. In: The pink book: course textbook. Atlanta (GA): Centers for Disease Control and Prevention; 2011 Apr [cited 2012 Mar 8]. Available from: http://www.cdc.gov/vaccines/pubs/pinkbook/hepb.html.

6. Cornberg M, Protzer U, Dollinger MM, Petersen J, Wedemeyer H, Berg T, et al. Prophylaxis, diagnosis and therapy of hepatitis B virus (HBV) infection: the German guidelines for the management of HBV infection. Z Gastroenterol. 2007 Dec;45(12):1281-328.

7. National Guideline Clearinghouse [Internet]. Rockville (MD): National Guideline Clearinghouse; c2009 -. Prevention of secondary disease: preventive medicine. Viral hepatitis; 2010 [cited 2012 Mar 8]. Available from: http://www.guideline.gov/content.aspx?id=24043

8. Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR [Internet]. 2011 Nov 25 [cited 2012 Mar 9];60(7):1-45. Available from: http://www.cdc.gov/mmwr/pdf/rr/rr6007.pdf

9. The Australian immunisation handbook [Internet]. 9th ed. Canberra (AUS): Department of Health and Ageing, Australian Government; 2008. [cited 2012 Mar 8]. Available from: http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/handbook-home

10. Pettit NN, DePestel DD, Malani PN, Riddell J. Factors associated with seroconversion after standard dose hepatitis B vaccination and high-dose revaccination among HIV-infected patients. HIV Clin Trials. 2010 Nov;11(6):332-9.

11. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2012 Mar

23];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

12. Connor BA, Blatter MM, Beran J, Zou B, Trofa AF. Rapid and sustained immune response against hepatitis A and B achieved with combined vaccine using an accelerated administration schedule. J Travel Med. 2007 Jan;14(1):9-15.

13. Cunningham CK, Rudy BJ, Xu J, Bethel J, Kapogiannis BG, Ahmad S, et al. Randomized trial to determine safety and immunogenicity of two strategies for hepatitis B vaccination in healthy urban adolescents in the United States. Pediatr Infect Dis J [Internet]. 2010 Jun [cited 2012 Mar 5];29(6):530-4. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3274492

14. Tung J, Carlisle E, Smieja M, Kim PT, Lee CH. A randomized clinical trial of immunization with combined hepatitis A and B versus hepatitis B alone for hepatitis B seroprotection in hemodialysis patients. Am J Kidney Dis. 2010 Oct;56(4):713-9.

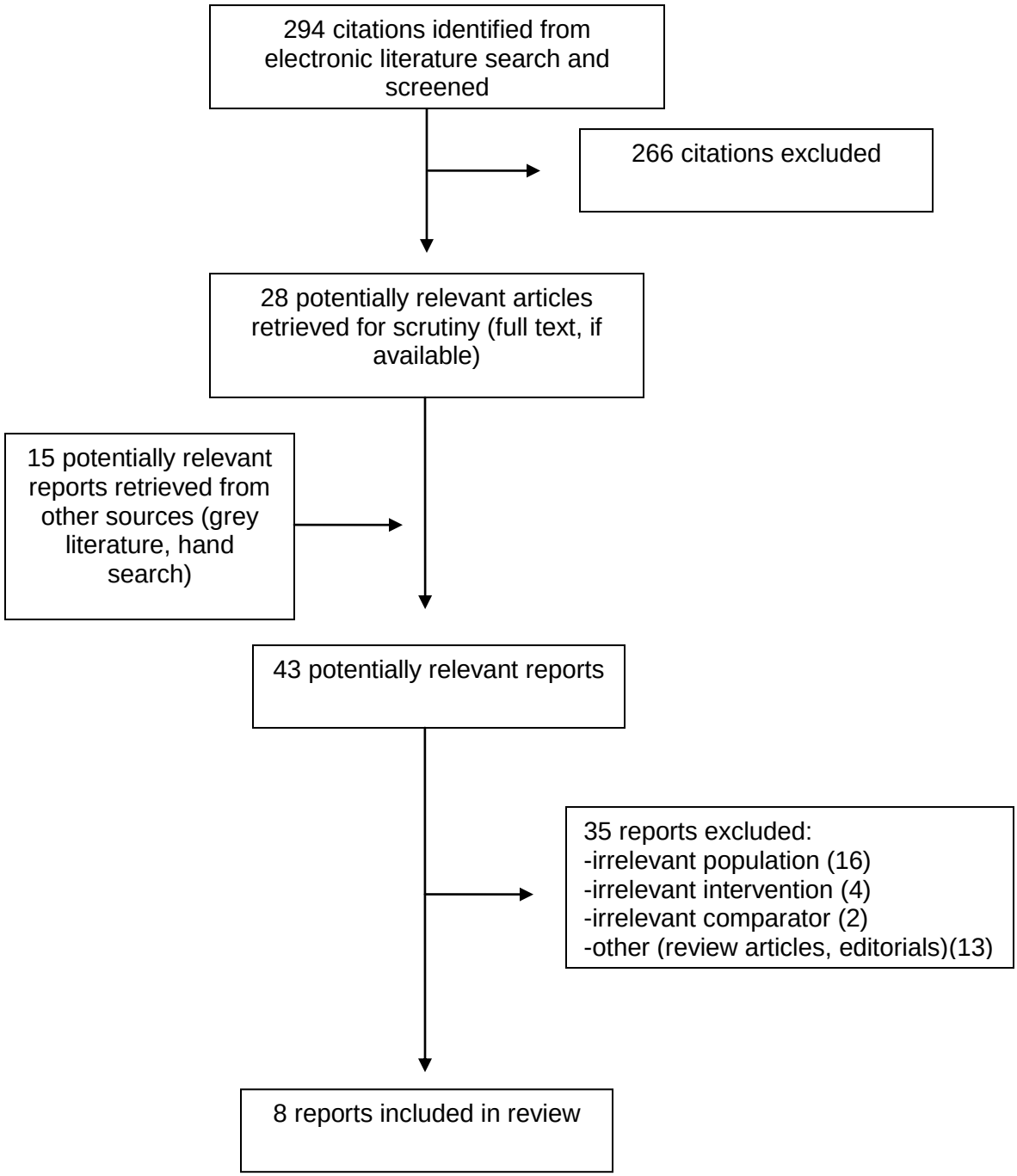
15. Chlibek R, von SF, Van DP, Smetana J, Tichy P, Gunapalaiah B, et al. Antibody persistence and immune memory 4 years post-vaccination with combined hepatitis A and B vaccine in adults aged over 40 years. J Travel Med. 2011 Mar;18(2):145-8.

16. Flynn PM, Cunningham CK, Rudy B, Wilson CM, Kapogiannis B, Worrell C, et al. Hepatitis B vaccination in HIV-infected youth: a randomized trial of three regimens. J Acquir Immune Defic Syndr. 2011 Apr;56(4):325-32.

17. Koksal Y, Varan A, Aydin GB, Sari N, Yazici N, Yalcin B, et al. Comparison of accelerated and rapid schedules for monovalent hepatitis B and combined hepatitis A/B vaccines in children with cancer. Pediatr Hematol Oncol. 2007 Dec;24(8):587-94.

18. Kramer ES, Hofmann C, Smith PG, Shiffman ML, Sterling RK. Response to hepatitis A and B vaccine alone or in combination in patients with chronic hepatitis C virus and advanced fibrosis. Dig Dis Sci. 2009 Sep;54(9):2016-25.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Guidelines recommending revaccination with HBV vaccine

Title, Group, Year of Publication	Recommendations Identified in the Guideline
Immunization of Health-Care Personnel[8], Advisory Committee on Immunization Practices (ACIP), 2011	"ACIP does not recommend more than two vaccine series in nonresponders."[8]
The Pink Book: Course Textbook - 12th Edition[5], Centers for Disease Control and Prevention (CDC), 2011	Persons who do not respond to the first series of hepatitis B vaccine should complete a second three-dose vaccine series. The second vaccine series should be given on the usual 0, 1, 6-month schedule. A 0, 1, 4-month accelerated schedule may also be used. Revaccinated healthcare personnel and others for whom postvaccination serologic testing is recommended should be retested 1 to 2 months after completion of the second vaccine series.(pp. 132 - 133)[5] Persons who fail to develop detectable anti-HBs after six doses should be tested for HBsAg. Persons who are found to be HBsAg positive should be counseled accordingly. Persons who fail to respond to two appropriately administered three-dose series, and who are HBsAg negative should be considered susceptible to HBV infection and should be counseled regarding precautions to prevent HBV infection and the need to obtain HBIG prophylaxis for any known or probable parenteral exposure to HBsAg-positive blood.(p. 133)[5]
Prevention of Secondary Disease: Preventative Medicine. Viral Hepatitis[7], New York State Department of Health, 2010	Clinicians should test for HBsAb between 4 and 12 weeks after vaccination. Nonresponders (HBsAb <10 IU/L) should be revaccinated with another three-dose hepatitis B vaccine series. If a patient's CD4 count is <200 cells/mm^3 or the patient has symptomatic HIV disease, revaccination may be deferred until several months after initiation of ARV therapy in an attempt to maximize the antibody response to the vaccine. However, revaccination should not be deferred in pregnant patients or patients who are unlikely to achieve an increased CD4 count.(p. 2)[7]
The Australian Immunization Handbook 9th Edition[9], National Health Research Council, 2008	If adequate anti-HBs levels (≥10 mIU/mL) are not reached after the third dose, the possibility of HBsAg carriage should be investigated. Those who are HBsAg negative and do not respond should be offered further doses. These can be given as either a fourth double dose or a further 3 doses at monthly intervals, with further testing at least 4 weeks after the last dose. There is limited evidence from several trials that HBsAg negative healthcare workers, who are non-responders to a primary course of vaccination and subsequent intramuscular booster schedule, as above, may respond to 5µg of Engerix-B (0.25 mL of the adult formulation) administered intradermally

Title, Group, Year of Publication	Recommendations Identified in the Guideline
	at fortnightly intervals (up to 4 doses) with anti-HBs levels measured before each dose to assess for seroconversion. Persistent non-responders should be informed that they are not protected and should minimise exposures, and about the need for HBIG within 72 hours of parenteral exposure to HBV. Individuals who are at significant occupational risk who have a documented history of a primary course of hepatitis B vaccine, but it is not known whether they ever seroconverted, and they now have an antiHBs level <10 mIU/mL, should be given a single booster dose of vaccine and have their anti-HBs level checked 4 weeks later. If the anti-HBs level is <10 mIU/mL, regard the individual as a non-responder, give 2 further doses of hepatitis B vaccine at monthly intervals, and re-test for anti-HBs levels at least 4 weeks after the last dose.(pp. 160-161)[9]
Prophylaxis, Diagnosis, and Therapy of Hepatitis B virus (HBV) Infection: The German Guidelines for the Management of HBV[6], The German Society for Digestive and Metabolic Diseases (DGVS), the German Society for Pathology (DGP), the Society for Virology (GfV), the Society for Pediatric Gastroenterology and Nutrition (GPGE, and the Competence Network for Viral Hepatitis (Hep-Net), 2007	Procedure for immunologically healthy non-responders and low-responders Healthy non-responders Question: What should be done if there is no response to hepatitis B vaccination (anti-HBs after three vaccinations < 10IU/L)? Recommendation: Persons who have anti HBs concentration of < 10IU/L (“non-responder”) 4-8 weeks after basic immunization should be vaccinated again (B).* Consensus: 100% Comment: Several studies show that 50-100% of non-responders sero-convert after up to 3 additional vaccinations in 1-3 month intervals(IIb)*. Therefore non-responders should receive up to three additional vaccinations (in 1-3 month intervals. Several investigators describe the use of intradermal vaccinations in non-responders. Although this is immunologically plausible, so far there is no proof that this immunization procedure results in a significantly better immune response (Ib)*. (p.1309)[6]

*Classification of the “evidence”: “evidence” level (1-5) and recommendation grade (A-D) according to Oxford Centre of Evidence Based Medicine (p. 1284)[6]

Evidence Classification used in Prophylaxis, Diagnosis, and Therapy of Hepatitis B virus (HBV) Infection: The German Guidelines for the Management of HBV6

Recommendation Level	Evidence Level	Description
A	Ia	systematic review of randomized controlled studies (RCT)
	Ib	appropriately planned RCT
	Ic	all or none principle
B	IIa	systematic review of well-planned cohort studies
	IIb	well-planned cohort study/ RCT of moderate quality (e.g. <80% follow-up)
	IIc	outcome-research studies
	IIIa	systematic review of well-planned case-controlled studies
	IIIb	"case-controlled studies
C	IV	case-series/cohort and case-controlled studies of moderate quality
D	V	expert opinion without explicit critical evaluation or based on physiologic models, laboratory research results or "first principles"

APPENDIX 3: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Randomized Controlled Trials - HAV/HBV vaccine vs. HBV vaccine alone					
Flynn[16], 2011, Bahamas, Brazil, South Africa, and US	Randomized trial, 28 weeks	n=371 (enrolled and randomized), 336 (completed), HIV-infected youth (aged 12-25) with no serological evidence of HBsAb, HBsAg, or HBcAb, recruited from ATN and IMPACT	n=118, Engerix-B (20 µg) at week 0, 4, and 24	n=126, Engerix-B (40 µg) at week 0, 4, and 24 n=127, Twinrix (20 µg) at week 0, 4, and 24	Vaccine response (HBsAb ≥10 IU/mL) at week 28
Cunningham[13], 2010, US	Randomized, single-blinded (patients), multicenter (9 centres) trial, 76 weeks from initial dose	n=123 (enrolled), 102 (completed), healthy urban youth (ages 12-17) at participating ATN sites, having received no more than one prior HBV immunization, with negative HBV and HIV serology	n=55, Twinrix at 0 and 24 weeks	n=47, Recombivax HB at 0 and 24 weeks	Post-second dose antibody response at week 28
Randomized Controlled Trials - HAV/HBV vaccine in combination with HBV vaccine vs. HBV vaccine alone					
Tung[14], 2010, Canada	Prospective RCT, 7 months	n=96 (ITT), 73 (PP), HBV-seronegative hemodialysis patients	n=48, Engerix-B (20 µg) and Twinrix (20 µg) at 0, 1, and 6 months and Engerix-B (40 µg) at 2	n=48, Engerix-B (40 µg) at 0, 1, 2, and 6 months	Difference in seroprotection rates (antibody titres >10 mIU/mL) at 7 months

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
			months		
Randomized Controlled Trials - HAV/HBV vaccine vs. HBV vaccine in combination with HAV vaccine					
Chlibek[15], 2011, Belgium and Germany	Prospective, multi-centre, open-label study, 4 years	n=596, adults (>40 years)	n=199, Twinrix at 0, 1, and 6 months	n=200, ENG +HAV group: Engerix-B at 0, 1, and 6 months + Havrix at 0 and 6 months n=197, HBVX + VAQ group: HBVAXPRO* at 0, 1, and 6 months + Vaqta at 0 and 6 months	Seroprotective/seropositivity rates, GMC of anti-HBs and anti-HAV antibodies and vaccine response rates
Connor[12], 2007, US and EU	Randomized, open-label, multicenter (12 centres) trial, 13 months from initial dose	n=496, healthy non-pregnant adults (aged ≥18) seronegative for anti-HAV, anti-HBs, and anti-HBc, and for HBsAg	n=250, Twinrix at 0, 7, 21 to 30 days, and 12 months	n=246, Separate injections of Havrix at 0 and 12 months and Engerix-B at 0, 1, 2, and 12 months.	Seroprotection rate against HBsAg, seroconversion rate for anti-HAV, and anti-HBs and anti-HAV GMC measured at month 13, 1 month after the last dose of the vaccine
Non-randomized Studies - HAV/HBV vaccine vs. HBV vaccine alone					
Pettit[10], 2010, US	Single-centre, retrospective chart review	n=215 (received SDV), 30 (received HDR), HIV-infected adults (mean age: 39, range: 18-70)	n=93, Twinrix at 0, 1, and 6 months	n=122, Engerix-B at 0, 1, and 6 months	Positive HBsAb after vaccination
Kramer[18], 2009, US	Prospective, non-	n=52, patients enrolled in the	n=40, Twinrix at baseline, 86	n=12, Engerix-B at baseline, 91	Serological response to vaccination in patients who

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
	randomized trial, 3 months following the completion of the last vaccination	Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial, negative for HBsAg and anti-HIV	days (range 29-175), and 109 days (range 49-217)	days (range 28-112), and 108 days (range 70-182)	tested negative for anti-HBV surface prior to vaccination.
Koksal[17], 2007, Turkey	Open, prospective, non-randomized trial, 7 months from initial dose	n=51 (enrolled), 48 (completed), children (aged 2 – 16, median age of 11) newly diagnosed with cancer	n=11, Twinrix Rapid course: months 0, 1, 2, and 12 n=10, Twinrix accelerated course: days 0, 7, 21, and 365	n=14, Engerix-B rapid course: months 0, 1, 2, and 12 n=16, Engerix-B accelerated course: days 0, 7, 21, and 365	Postvaccination serum anti-HAV IgG and anti-HBs titres were tested at months 1,3, and 7 to evaluate seropositivity rates under chemotherapy

Ag = antigen; Anti- = antibodies; ATN = Adolescent Medicine Trials Network for HIV/AIDS Interventions; EU = European Union; GMC = geometric mean antibody concentrations; HAV = hepatitis A virus; HBc = hepatitis B core; HBs = hepatitis B surface; HBV = hepatitis B virus; HDR = high-dose revaccination; HIV = human immunodeficiency virus; IMPAACT = International Maternal, Pediatric, and Adolescent AIDS Clinical Trials; ITT = intention to treat; PP = per protocol; SDV = standard dose vaccination; US = United States; vs. = versus

*NOTE: HBVAXPRO is not currently licensed for use in Canada

APPENDIX 4: Critical appraisal of included studies

First Author, Publication Year	Strengths	Limitations
Randomized Controlled Trials - HAV/HBV vaccine vs. HBV vaccine alone		
Flynn[16], 2011	• Excellent reporting of study objectives, methods of randomization, characteristics of study participants, interventions of interest, and sample size calculation. • Actual probability values were reported (rather than simply <0.05). • Sensitivity analyses for missing data and per-protocol analyses were conducted (primary analysis was modified ITT)	• No attempt to blind study subjects or those measuring the main outcome. • Characteristics of patents lost to follow-up not well described.
Cunningham[13], 2010	• Main outcomes to be measured, characteristics of study participants, and interventions of interest were clearly described. • Actual probability values were reported (rather than simply <0.05). • Patients were blinded.	• Safety data collected, but not presented. • Characteristics of patients lost to follow-up [17/123 (13.8%)] not described. • Small sample size • Characteristics of patents lost to follow-up not well described. • No attempt to blind those measuring the main outcome. • Method of randomization not described.
Randomized Controlled Trials - HAV/HBV vaccine in combination with HBV vaccine vs. HBV vaccine alone		
Tung[14], 2010	• Good reporting of study objectives, characteristics of study participants, interventions of interest, and sample size calculation. • Laboratory personnel performing tests for antibody levels and the independent statistician were blinded. • Adverse events were recorded after each dose. • Actual probability values were reported (rather than simply <0.05).	• Small sample size. • Method of randomization not described.

First Author, Publication Year	Strengths	Limitations
Randomized Controlled Trials - HAV/HBV vaccine vs. HBV vaccine in combination with HAV vaccine		
Chlibek[15], 2011	• Main outcomes to be measured and interventions of interest were clearly described. • Actual probability values were reported (rather than simply <0.05). • Appropriate statistical analysis.	• Study objectives were not clearly described. • Distribution of principal confounders in each group of subjects was not provided. • Main findings of the study were not clearly described. • No attempt to blind study subjects or those measuring the main outcome. • Characteristics of patents lost to follow-up not well described.
Connor[12], 2007	• Study objective and outcomes to be measured were well-described. • Comprehensive attempt to capture adverse events. • Actual probability values were reported (rather than simply <0.05).	• Characteristics of study participants included in the study were not clearly described. • Method of randomization not described. • Study does not report number of subjects lost to follow up. • No attempt made to demonstrate external validity. • No attempt to blind study subjects or those measuring the main outcome described. • Immunogenicity was analyzed on the ATP cohort.
Non-randomized Studies - HAV/HBV vaccine vs. HBV vaccine alone		
Pettit[10], 2010	• No loss to follow-up (retrospective analysis). • Actual probability values were reported (rather than simply <0.05).	• Adverse events not captured. • No attempt to blind study subjects or those measuring the main outcome. • Subjects were not randomized to intervention groups. • Unable to determine how allocation was determined.
Kramer[18], 2009	• Study objectives were clearly described. • Fair reporting of characteristics of study participants and interventions of interest. • Authors compared characteristics of participants	• Adverse events not captured. • Limited number of study participants; particularly in the HBV vaccine arm. • Study results may not be generalizable to other

First Author, Publication Year	Strengths	Limitations
	with non-participants.	patient groups or patients from different geographic areas. • Subjects were not randomized to intervention groups. • Variability in vaccine administration schedule.
Koksal[17], 2007	• Study objectives and interventions of interest were clearly described. • Adverse events were captured.	• Subjects were not randomized to intervention groups. • Distribution of principle confounders in each group of subjects not clearly described. • Small sample size. • Actual probability values not reported if >0.05.

ATP = according to protocol; ITT = intention to treat

APPENDIX 5: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Randomized Controlled Trials - HAV/HBV vaccine vs. HBV vaccine alone		
Flynn,[16] 2011	At week 28, % patients with Anti-HBs ≥10 IU/mL was: 60.4% in the Engerix-B (20µg) group 73.2% in the Engerix-B (40µg) group *(P = 0.04 for Engerix-B 40µg vs.20µg)* 75.4% in the Twinrix group *(P = 0.02 for Twinrix vs. Engerix-B 20µg)* Anti-HBs antibody GMCs were: 52.5 IU/mL in the Engerix-B (20µg) group 77.6 IU/mL in the Engerix-B (40µg) group *(P = 0.17 for 40µg vs. 20µg)* 97.7 IU/mL in the Twinrix group *(P = 0.03 for Twinrix vs. Engerix-B 20µg)*	In HIV-infected youth, vaccination with either high-dose Engerix-B (40µg) or Twinrix resulted in greater HBV vaccine response, compared with standard-dose Engerix-B (20µg) at week 28.
Cunningham,[13] 2010	At week 28, response rates were: 94.6% (95% CI 84.9-98.9%) for Twinrix group 87.2% (95% CI 74.3-95.2%) for Recombivax HB group *(P = 0.30 for Twinrix vs. Recombivax HB)* At week 76, response rates were: 88.0% (95% CI 75.7-95.5%) for Twinrix group 81.1% (95% CI 64.8-92.0%) for Recombivax HB group *(P = 0.38 for Twinrix vs. Recombivax HB)*	"The response rates in the Recombivax HB and Twinrix arms were not significantly different, but the study was not designed to detect a difference between arms." (p. 4)[13]
Randomized Controlled Trials - HAV/HBV vaccine in combination with HBV vaccine vs. HBV vaccine alone		
Tung,[14] 2010	At month 7, using per-protocol analysis, 68% of patients in the treatment group had experienced seroconversion vs. 49% in the control group. *(P= 0.05)* Using ITT analysis, 58% of patients in the treatment group had experienced seroconversion vs. 38% in the control group. *(P= 0.02)* At month 3, using per-protocol analysis, 25% of patients in the treatment group had experienced seroconversion vs. 27% in the control group. *(P= 0.4)* Using ITT analysis, 23% of patients in the treatment group had experienced	A statistically significant difference in seroprotection rates was observed between hemodialysis patients immunized with Engerix-B + Twinrix vs. Engerix-B alone. Vaccination with hepatitis A/B may be more effective than hepatitis B alone in this population.

<table>
<tr><td></td><td>seroconversion vs. 21% in the control group. (P= 0.4)</td><td></td></tr>
<tr><td colspan="3">Randomized Controlled Trials - HAV/HBV vaccine vs. HBV vaccine in combination with HAV vaccine</td></tr>
<tr><td>Chlibek,[15] 2011</td><td>At year 4, anti-HBs seropositivity rates were:
76.9% in the HAB group
61.9% in the ENG + HAV group
51.6% in the HBVX + VAQ

% patients with Anti-HBs ≥10 mIU/mL was:
57.1% in the HAB group
40.1% in the ENG + HAV group (P ≤ 0.005 for HAB vs. ENG + HAV)
26.6% in the HBVX + VAQ (P ≤ 0.0001 for HAB vs. HBVX + VAQ)

Anti-HBs antibody GMCs were:
42.3 mIU/mL in the HAB group
23.6 mIU/mL in the ENG + HAV group
13.7 mIU/mL in the HBVX + VAQ</td><td>The combined hepatitis A/B vaccine induced higher and more persistent antibody levels (≥10 mIU/mL) against hepatitis B than corresponding monovalent vaccines in adults >40 years.</td></tr>
<tr><td>Connor,[12] 2007</td><td>Seroprotection rates for anti-HBs were:
<table>
<tr><td></td><td>Twinrix (%)</td><td>Havrix + Engerix-B (%)</td><td>P value</td></tr>
<tr><td>Day 37</td><td>63.2</td><td>43.5</td><td><0.001</td></tr>
<tr><td>Month 3</td><td>83.2</td><td>76.7</td><td>0.110</td></tr>
<tr><td>Month 12</td><td>82.1</td><td>77.8</td><td>0.315</td></tr>
<tr><td>Month 13</td><td>96.4</td><td>93.4</td><td>0.251</td></tr>
</table></td><td>Combined hepatitis A/B vaccination on a 0, 7, and 21 to 30 day schedule, with a booster at 12 months may represent the preferred option for individuals at imminent risk for hepatitis A and hepatitis B.</td></tr>
<tr><td colspan="3">Non-randomized Studies - HAV/HBV vaccine vs. HBV vaccine alone</td></tr>
<tr><td>Pettit,[10] 2010</td><td>The use of Twinrix was associated with more frequent seroconversion compared to Engerix-B (54% vs. 45%, adjusted OR, 2.4; P = 0.003).</td><td>Twinrix may be more effective than Engerix-B, although the possibility of improved immunogenicity should be confirmed with further prospective studies.</td></tr>
<tr><td>Kramer,[18] 2009</td><td>In patients with chronic hepatitis C, 60.0% of patients who received Twinrix developed protective HBV surface antibody, compared to 41.7% of patients who received Engerix-B.</td><td>In patients with HCV and advanced fibrosis, “administration of the combination hepatitis A/B vaccine may enhance the vaccination response to HBV.”(p. 2024)[18]</td></tr>
<tr><td>Koksal,[17] 2007</td><td>Seroconversion rates for anti-HBs were:</td><td>“The combined hepatitis A/B</td></tr>
</table>

	Time (months)	Rapid schedule (months 0, 1, 2, and 12)			Accelerated schedule (days 0, 7, 21, and 365)			vaccine is more effective than the monovalent hepatitis B vaccine" in children receiving chemotherapy due to malignant disease."(p.593)[17]
		Engerix-B	Twinrix	*P*	Engerix-B	Twinrix	*P*	
	1	35.7	54.5	>0.05	25	50	>0.05	
	3	57.1	60	>0.05	18.8	70	0.03	
	7	70	60	>0.05	50	77.8	>0.05	

Anti-HBs = anti-hepatitis B surface antigen; GMC = geometric mean concentration; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; OR = odds ratio; SDV = standard dose vaccine