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Systematic Review and Meta-Analysis: Seroprevalence, Vaccination Rates, and Response for Hepatitis A in Inflammatory Bowel Disease

Anuraag Jena[1] Anupam Kumar Singh[1] Pardhu B. Neelam[1] Ritin Mohindra[2] Praveen Kumar-M[3] Shubhra Mishra[4] Amol Patil[5] Vikas Suri[2] Vishal Sharma[1]

[1] Department of Gastroenterology, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[2] Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[3] Nference Lab, India
[4] Department of Gastroenterology, Asian Institute of Gastroenterology, Chandigarh, India
[5] Department of Pharmacology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Address for correspondence Vishal Sharma, MD, DM, Department of Gastroenterology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India (e-mail: docvishalsharma@gmail.com).

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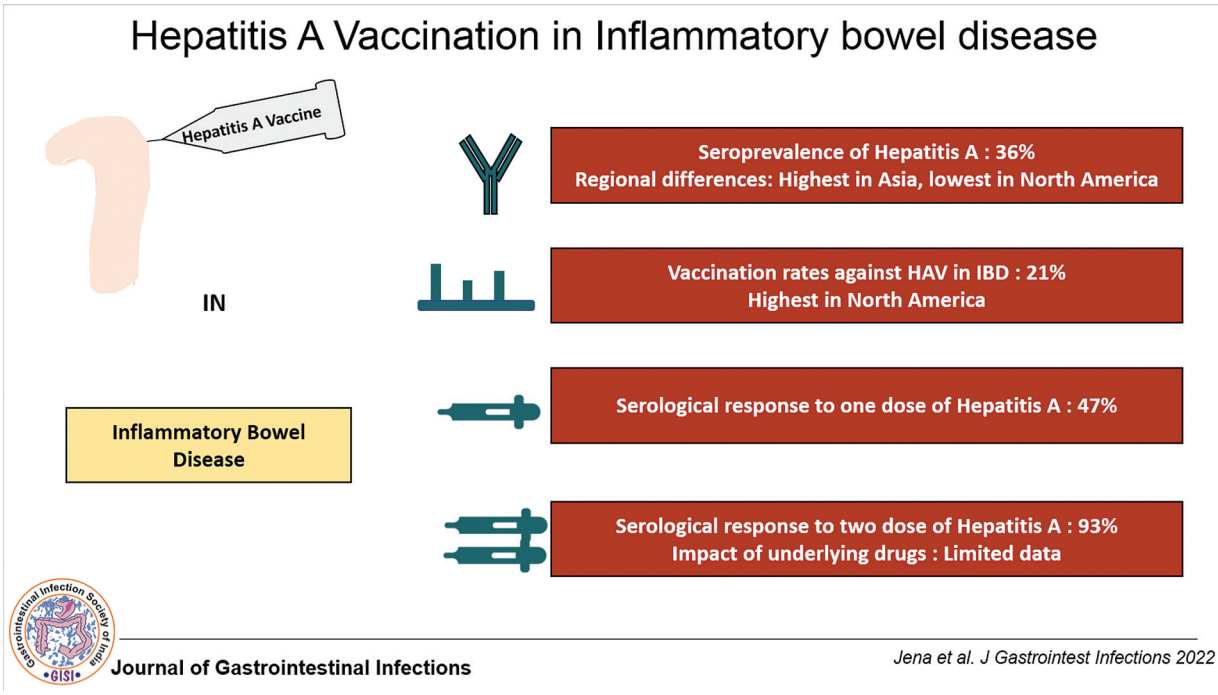

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Abstract

Introduction Guidelines recommend hepatitis A virus (HAV) vaccination in individuals with inflammatory bowel disease (IBD). We performed a systematic review to inform the clinical practice regarding this guidance.

Methods After a PubMed and Embase search, duplicates were removed and the remaining titles screened for studies reporting relevant outcomes. Pooled seroprevalence rates for HAV, pooled vaccination rates, and pooled seroconversion rates were calculated. We also calculated pooled relative risk of seroprevalence for HAV among IBD and control population. Heterogeneity was investigated using subgroup analysis.

Results The pooled seroprevalence of HAV antibodies in patients with IBD (14 studies, 2,370 patients) was 0.36 (95% confidence interval [CI]: 0.22–0.53, $I^2 = 95\%$). On comparing the seroprevalence of HAV in IBD with controls (4 studies), the pooled relative risk was not different between the two (0.94, 95% CI: 0.66–1.34, $I^2 = 76\%$). The pooled seroconversion rate after two doses of HAV vaccination (5 studies, 221 patients) was 0.93 (95% CI: 0.88–0.96, $I^2 = 0\%$). Three studies (104 patients) reported on the seroconversion after a single dose of HAV vaccination and the pooled seroconversion rate was 0.47 (95% CI: 0.35–0.59, $I^2 = 20\%$). The pooled vaccination rate for hepatitis A among patients with IBD (18 studies, 9,521 patients) was 0.21 (95% CI: 0.14–0.30, $I^2 = 99\%$).

Conclusion Hepatitis A vaccine has good immunogenicity in patients with IBD. The decision to routinely vaccinate IBD patients may be made in light of underlying seroprevalence of HAV.

Keywords

- hepatitis A
- ulcerative colitis
- Crohn's disease
- inflammatory bowel disease
- immunization
- vaccine

Introduction

The management of inflammatory bowel disease (IBD) has many complex issues which need to be tackled by the clinicians. IBD not only involves the gastrointestinal system but may have extraintestinal manifestations. Liver disease in patients with IBD may be related to the extraintestinal manifestations, adverse effects of various therapies, or as a consequence of underlying viral infections which may flare due to use of immunosuppression.[1] Around 5% of IBD patients may have underlying hepatobiliary disease while a third could have derangements in liver function tests.[1,2] Therefore, any strategy which is effective in preventing hepatic morbidity in these patients should be implemented. Vaccination is an effective strategy for prevention of hepatitis A virus (HAV) and hepatitis B virus (HBV) and has been recommended for IBD patients by various guideline panels.[3–5]

The need for vaccination with respect to HBV is unequivocal since the disease is associated with chronic liver disease and may eventually lead to hepatocellular carcinoma. However, there are several arguments for or against the strategy of routine vaccination for hepatitis A in patients with IBD. HAV typically causes a self-limiting disease and the occurrence of adverse outcomes like acute liver failure is relatively rare in childhood.[6] Further, childhood infection is common in many regions of the world and this provides an immunity against further infections during adulthood.[7] On the contrary, infection in adults may be associated with more risk of adverse outcomes and the childhood infection rates may be much lower in certain countries especially the Western world.[8] Further, patients with IBD may avoid eating out and be more likely to have safer eating habits leading to lesser likelihood of exposure to HAV infection. Therefore, the acquisition of infection in adulthood with possible underlying immunosuppression (disease or therapy related) and the presence of underlying liver disease in a subset may predispose to more adverse outcomes in patients with IBD.

Therefore, we conducted a systematic review to inform the clinical practices in relation to HAV vaccination in patients with IBD. We assessed the overall seroprevalence of HAV in patients with IBD, seroconversion after HAV vaccination in patients with IBD, and the uptake of HAV vaccination in patients with IBD.

Methods

We followed the guidance provided in the Meta-analysis Of Observational Studies in Epidemiology statement for the present systematic review.[9]

Database Search

We searched PubMed and Embase from inception till September 11, 2021. The keywords used were hepatitis A, inflammatory bowel disease or ulcerative colitis (UC) or Crohn's disease (CD), and vaccination combined with the operator AND. ►**Supplementary Table S1** (available in the online version) shows the detailed search strategy used for this systematic review. We searched for additional papers from the references of these studies. After combining the

results, the duplicates were manually removed. The remaining results underwent initial screening for titles and abstracts to identify papers eligible for the full-text screening by two reviewers (V.S., P.B.). The differences were resolved by discussion among the reviewers.

Study Selection

We included studies which provided information regarding baseline seroprevalence rates of previous HAV infections with IBD, the vaccination rates for HAV in patients with IBD, and the seroconversion rates after HAV vaccination (single and double dose) in patients with HAV vaccination. These reports were included irrespective of language, geographic, or age-related restrictions or the type of publications. For vaccination rates we included all reports irrespective of the manner in which this was estimated (records, questionnaires, or Internet-based surveys). However, physician surveys intended to evaluate the practices regarding vaccination were not included. We excluded studies where there was suspicion of duplication of data (same center with multiple reports from overlapping time periods). For any analysis we excluded a study if the total population reported was less than 10 patients. The studies were excluded if they did not provide relevant information or if the data was not extractable.

Data Extraction

The data were extracted on a preformat and included the details regarding the study duration, region, and study population (IBD, CD, and UC; adult or pediatric; any specific population, e.g., pregnancy or postpartum). The details of study (retrospective, prospective, trial) were also extracted.

Outcomes

The outcomes of interest relevant to the systematic review for which data were extracted included:

1. Seroprevalence of HAV infection in IBD population. The data were also extracted for UC and CD separately to compare the seroprevalence rates in these two groups. The data from controls/healthy population was also extracted when available.
2. The seroconversion after HAV vaccination after one and two doses of vaccine was also extracted.
3. The vaccination rates of IBD patients for HAV were also extracted and the method of estimating vaccination rates was also extracted (survey or records).

Analysis

Apart from the base package of the R statistical software version 4.0.1, meta and metafor packages were also utilized for the analysis.[10,11] We used the random effect model with inverse variance approach to calculate pooled seroconversion rates after HAV vaccination. The individual seroconversion/seroprevalence/vaccination rates were logit transformed prior to pooling. The seroprevalence rates between the IBD population and control population were compared using pooled relative risk obtained by the Mantel–Haenszel method. I^2 and p-values were used for the assessment of heterogeneity. Subgroup analysis, where feasible, were performed to address and investigate any significant heterogeneity ($I^2 > 50\%$). Baujat plot was also constructed to identify any specific studies contributing to the heterogeneity.

Methodological Quality and Risk of Bias Assessment

The publication bias was assessed by the visual assessment of the funnel plot (if studies > 10). Also, the Egger test was conducted to identify the publication bias. Two investigators (A.J. and P.B.) separately and independently assessed the methodological quality and risk of bias for each study using the Joanna Briggs Institute critical appraisal tool for prevalence studies.[12] Any disagreement was resolved by mutual consensus after discussion with V.S.

Results

Study Selection

We identified 444 records after PubMed and Embase search. After removing duplicates, 349 records were eligible for title and abstract screening. Three hundred and two titles were excluded for various reasons (►**Fig. 1**). Of the 47 titles assessed for full-text screening, 10 were excluded for various reasons (►**Supplementary Table S2**, available in the online version),[13–22] and eventually 37 papers were included in the systematic review. Fourteen studies were included in the analysis about baseline seroprevalence of hepatitis A in the setting of IBD,[23–36] 5 studies reported on the seroconversion after complete HAV vaccination,[26,37–40] while 18 studies reported about the HAV vaccination rates in IBD patients[30,41–57] (►**Tables 1**,**2**,**3**).

Seroprevalence of Hepatitis A in Inflammatory Bowel Disease

The pooled seroprevalence of HAV antibodies in patients with IBD on the basis of 14 included studies (2,370 patients) was 0.36 (95% confidence interval [CI]: 0.22–0.53, $I^2 = 95\%$) (►**Fig. 2**). To explain the high degree of heterogeneity we performed a subgroup analysis on the basis of factors which are likely to impact the underlying seroprevalence, that is, age of included population and the region of the studies. As expected, the seroprevalence was higher in adults (0.42, 95% CI: 0.27–0.59, $I^2 = 95\%$) as compared with the pediatric studies (0.18, 95% CI: 0.04–0.55, $I^2 = 94\%$), however, the heterogeneity was high (►**Supplementary Fig. S1**, available in the online version). Regional differences were apparent with studies from Asia reporting highest seroprevalence rates and those from North America reporting the lowest seroprevalence rates but the heterogeneity even among various region-based groups was high (►**Supplementary Fig. S2**, available in the online version). Baujat plot could identify two studies which contributed the maximum to the heterogeneity (►**Supplementary Fig. S3**, available in the online version). The sensitivity analysis by excluding the two studies which did not report the method to determine seroprevalence did not change the pooled seroprevalence rates (0.32, 0.19–0.49, $I^2 = 95\%$) (►**Supplementary Fig. S4**, available in the online version). On comparing the

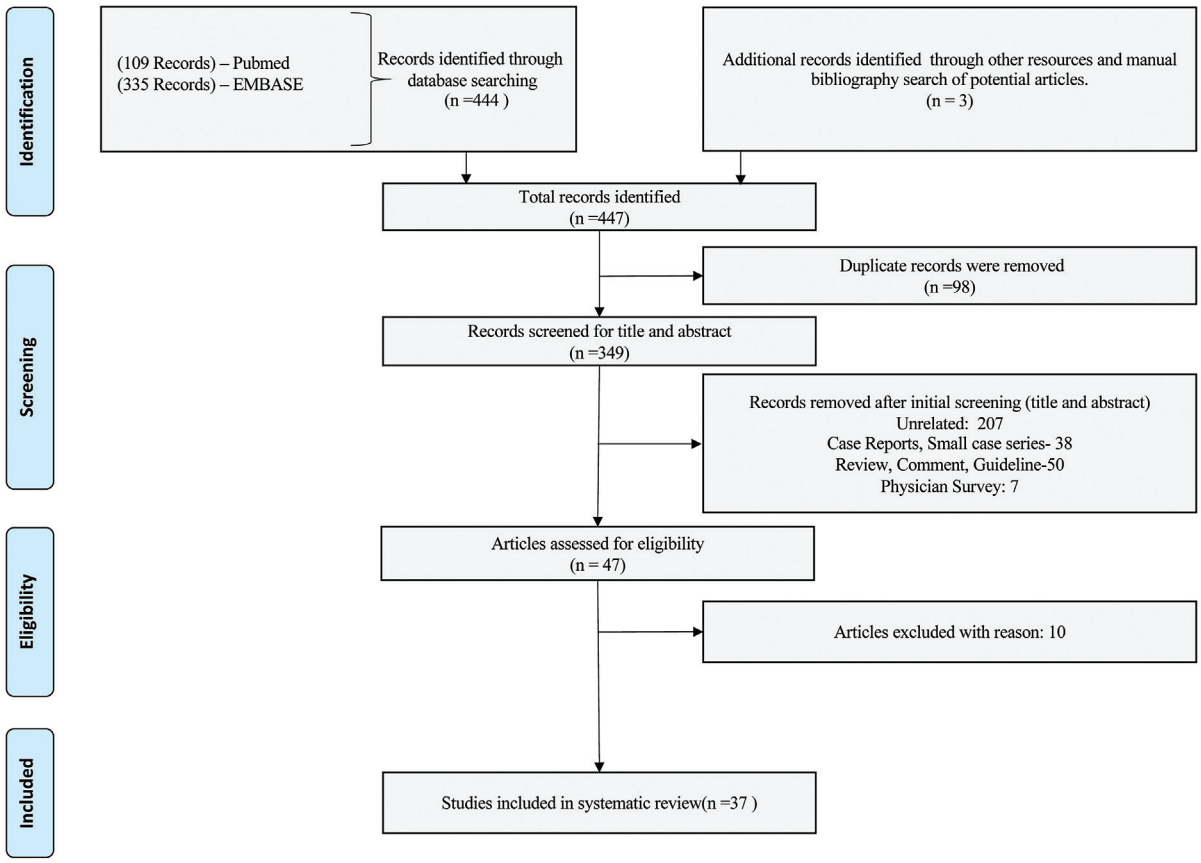

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart showing the selection of studies for the systematic review.

seroprevalence of HAV in IBD as compared with controls, the pooled relative risk (4 studies) was not different between the two groups (0.94, 95% CI: 0.66–1.34, $I^2 = 76\%$) (►**Fig. 3**).

Seroconversion after HAV Vaccination

There were five studies (221 patients, two in the pediatric age group) reporting response to two doses of hepatitis A vaccination in patients with IBD. The pooled seroconversion rate to two doses of HAV vaccination was 0.93 (95% CI: 0.88–0.96, $I^2 = 0\%$) (►**Fig. 4**). Three studies (104 patients) reported on the seroconversion after a single dose of HAV vaccination and the pooled seroconversion rate was 0.47 (95% CI: 0.35–0.59, $I^2 = 20\%$) (►**Supplementary Fig. S5**, available in the online version).

Vaccination Rates for Hepatitis A in Patients with IBD

The pooled vaccination rate for hepatitis A among patients with IBD (18 studies, 9,521 patients) was 0.21 (95% CI: 0.14–0.30, $I^2 = 99\%$) (►**Fig. 5**). To explain the heterogeneity, we performed subgroup analysis based on the region (continents) and the population (adults, pediatric, and pregnant). Interestingly, the HAV vaccination rates were highest among the pregnant population (0.56, 0.45–0.66, $I^2 = 90\%$) as compared with adults (0.18, 012–0.27, $I^2 = 98\%$) (►**Supplementary Fig. S6**, available in the online version). The vaccination rates were higher in the North American population (0.29, 0.19–0.41, $I^2 = 99\%$) as compared with the other three continents (►**Supplementary Fig. S7**, available in the online version). A subgroup analysis on the basis of study type indicated that the vaccination rates in prospective studies was 0.37 (0.15–0.66, $I^2 = 98\%$), in retrospective studies was 0.18 (0.09–0.33, $I^2 = 99\%$), and in surveys was 0.19 (0.11–0.32, $I^2 = 97\%$) (►**Supplementary Fig. S8**, available in the online version). Baujat plot identified three studies which had maximum contribution to heterogeneity (►**Supplementary Fig. S9**, available in the online version).

Risk of Bias

For seroprevalence of HAV, both the funnel plot and the Egger test suggest absence of any publication bias (►**Supplementary Fig. S10**, available in the online version). The risk of bias analysis of studies included in the analysis of seroprevalence, seroconversion rates, and vaccination rates are shown in ►**Supplementary Tables S3**–**S5** (available in the online version), respectively. For pooled HAV vaccination rates in IBD of HAV, the visual analysis of the funnel plot and the Egger test suggest that publication bias is unlikely (►**Supplementary Fig. S11**, available in the online version). However, majority of studies were of low risk. Some of the studies available as abstracts could not be completely assessed for all domains.

Discussion

Hepatitis A vaccination is recommended for patients with IBD. However, it is unclear if the vaccination should be done

Table 1 The studies reporting the seroprevalence of HAV the details regarding patients, vaccinations, and outcomes

	Reference	Region	Study period	Study type	Patient population	Adult/ Pediatric	Age	Male gender	Definition of seropositivity
1	Hong et al 2022	South Korea	January 2016 and December 2018	Cohort	263 IBD	Adult	30 years (IQR, 22 to 46)	167 [67.3%]	anti-HAV IgG $\geq$ 20 U/mL
2	Kalra et al 2021	India	August 2015 to October 2016	Case–Control	41 CD	Adult	33.5 (median)	27 [65.8%]	IgG anti- HAV antibody
3	Ruiz-Cuesta et al 2016	Spain	January and March 2012	Cohort	153 IBD, 77 UC, 76 CD	Adult	43.30 $\pm$ 14.19	69 [45.1%]	Prevaccination serological testing
4	Urganci and Kalyoncu 2013	Turkey	2000 and 2012	Case–Control	47 IBD, 25 UC, 14 CD, 8 IBDU	Pediatric	11.06 $\pm$ 3.74	25 [53.2%]	Prevaccination serological testing
5	Hafner et al 2008	Germany	July 1999 and May 2003	Case–Control	121 IBD, 73 CD, 48 UC	Adult	36.8 $\pm$ 10.5	65 [53.7%]	HAV titers greater than 10 IU/L
6	Melmed et al 2006	United States	2004–2005	Cohort	16 of 169 IBD patients with serostatus for HAV	Adult	NA	NA	Detectable anti-HAV antibody
7	Feeney et al 2002	United Kingdom		Case–Control	137 UC, 139 CD	Adult	NA	NA	Hepatitis A IgG status
8	Moon and Moon 2021	United States	2009–2010	Retrospective analysis of NHANES	55 IBD patients and 4,443 non-IBD	Adult	NA	NA	Hepatitis A seropositivity
9	Shao et al 2015	Australia	March–May 2015	Retrospective audit and prospective survey	150 IBD patients screened for HAV	Adult	NA	NA	NA
10	Moreira Goncalves et al 2015	Portugal	NA	Prospective study	139 patients, 68 UC, 71 CD	Adult	NA	53 [38.1%]	?serologic status
11	Morace et al 2013	Italy	NA	Questionnaire and serology	192 IBD	Adult	51 years	94 [48.9%]	Serology
12	Riestra et al 2013	Spain	September 2011 to October 2012	Prospective study	787 IBD, 467 CD, 293 UC, 27 unclassified	Adult	44.3 years	357 [45.4%]	Serological status
13	De Bruyn et al 2012	Canada	September 2011–August 2012	Cross-sectional	156 IBD, 93 CD, 37 UC, 16 unclassified	Pediatric	NA	NA	Positive detection of HAV IgG
14	Alkhouri et al 2010	United States	NA	Cohort	100 IBD, 91 CD, 9 UC	Pediatric	NA	60 [60%]	Serology HAV IgG

Abbreviations: CD, Crohn's disease; HAV, hepatitis A virus; IBD, inflammatory bowel disease; IBDU, inflammatory bowel disease unclassified; IgG, immunoglobulin G; IQR, interquartile range; NA, not available; NHANES, National Health and Nutrition Examination Survey; UC, ulcerative colitis.

Table 2 Studies reporting seroconversion after HAV vaccination

	Reference	Region	Study period	Study type	Patient population	Adult/ Pediatric	Age	Male gender	Dosage	Response
1	Urganci and Kalyoncu 2013	Turkey	2000–2012	Prospective	47 IBD, 25 UC, 14 CD, 8 indeterminate 23 received vaccine	Pediatric	11.06 ± 3.74	25 [53.2]	720 milliELISA units of inactivated hepatitis A virus vaccine (HAV) (0 and 6 months)	anti-HAV IgG
2	Moses et al 2011	United States	NA	Prospective	12 IBD patients on infliximab	Pediatric	18.3 years	8 [66.6%]	710 milliELISA units at 0 and 6 months or double (if age > 19 years)	anti-HAV IgG
3	Radzikowski et al 2011	Poland	October 2006 and August 2009	Prospective	66 adolescents and children with IBD	Pediatric	13.61 ± 0.4	33 [50%]	Two doses of HAV in a 6- to 12-month interval	Seroconversion at 12 weeks after 2nd dose (> 20 IU/mL)
4	Dimas et al 2019	Greece	NA	Prospective	356 IBD patients 90 got two doses 21 got single dose	Adult	50.0 [33.5–63.1]	NA	1 mL, two doses, one at baseline and the second 6–12 months after the first dose	Positive anti-HAV IgG > 3 months after 2nd dose
5	Karmiris et al 2014	Greece	NA	Prospective	167 IBD patients, only 43 were eligible for vaccination	Adult	45.4 [30.3–60.3]	103 [61.7%]	Havrix, 1 mL, two doses, 0 and 6–12 months	anti-HAV IgG > 20 mIU/mL

Abbreviations: CD, Crohn's disease; HAV, hepatitis A virus; IBD, inflammatory bowel disease; IgG, immunoglobulin G; NA, not available; UC, ulcerative colitis.

Table 3 Studies reporting the vaccination rates for HAV in patients with inflammatory bowel disease

1	Pittet et al 2021	Switzerland		Cross-sectional study	306 IBD	Adults	Median 42.7		Using questionnaire, immunization records review
2	Chiarella-Redfern et al 2022	Canada	September 2012–December 2018	Retrospective cohort study	303 pregnant IBD	Pregnancy	31.24	0	Vaccine records
3	García-Serrano et al 2020	Spain	Records until December 2016	Cross-sectional, retrospective study	1,722 IBD	Adults	NA	866 [50.3%]	Online records
4	Mao et al 2019	USA	2007 onwards	Prospective national registry	628 IBD pregnant	Adults			Questionnaire
5	Pham et al 2018	USA	2010 and 2013	Retrospective cohort study	1,401 IBD on anti-TNF therapy	Adults	40.6 ± 16.8	668 [48.4%]	Electronic database
6	Malhi et al 2015	Canada	September 1, 2013 and January 31, 2014	Patient survey	300 IBD	Adults	35.4 ± 13.2	146 [48.7%]	Patient Survey
7	Yun et al 2013	South Korea	November 2011 to February 2012	Questionnaire survey	192 IBD	Adults	39.7	121 [63.0%]	Patient survey
8	Moon and Moon 2021	USA	2009–2010	Retrospective analysis of NHANES	48 IBD	Adults	NA	NA	NHANES data
9	Hussain et al 2020	USA	March 1, 2019 to December 31, 2019	Retrospective study	356 IBD	Adults	NA	172 [48.3]	Two IBD clinics electronic checklist
10	Strasse et al 2019	Brasil	July 2015 to June 2016	Questionnaire survey	239 IBD	Adults	46.4 ± 12.7	87 [36.4]	Patient survey
11	Kowalska-Duplaga et al 2019	Poland	September 2015 and September 2016	Prospective study	214 children IBD	Children	14.5 (11.5–16.0)	117 [54.7%]	Review of immunization cards
12	Kakati et al 2018	USA	2016	Retrospective charts	210 IBD	Adults	NA	NA	Review of charts
13	Waszczuk et al 2018	Poland	NA	Self-completed patient survey	195 IBD	Adults	37 ± 15	98 [50.2%]	Patient survey
14	Vellanki et al 2018	USA	January 1, 2007 to December 31, 2016	Retrospective data review	1396 IBD	Adults	NA	NA	Database review
15	Ryu et al 2010	South Korea	November 2013 and February 2015	Questionnaire survey	287 IBD	Adults	29 years (range, 16–69)	188 [67.6%]	Questionnaire
16	Love et al 2012	USA	44-month period	Retrospective	24 IBD on anti-TNF	Adults	NA	NA	Electronic records
17	Xu et al 2019	USA	2015–2016	National Health Interview Survey	951 IBD	Adults	NA	360 [37.9]	Patient survey
18	Wasan et al 2012	USA	NA	Prospective Internet patient survey	958 IBD	Adults	45 (IQR 31–57)	260 [27.2%]	Internet-based survey

Abbreviations: HAV, hepatitis A virus; IBD, inflammatory bowel disease; IQR, interquartile range; NA, not available; NHANES, National Health and Nutrition Examination Survey, TNF, tumor necrosis factor.

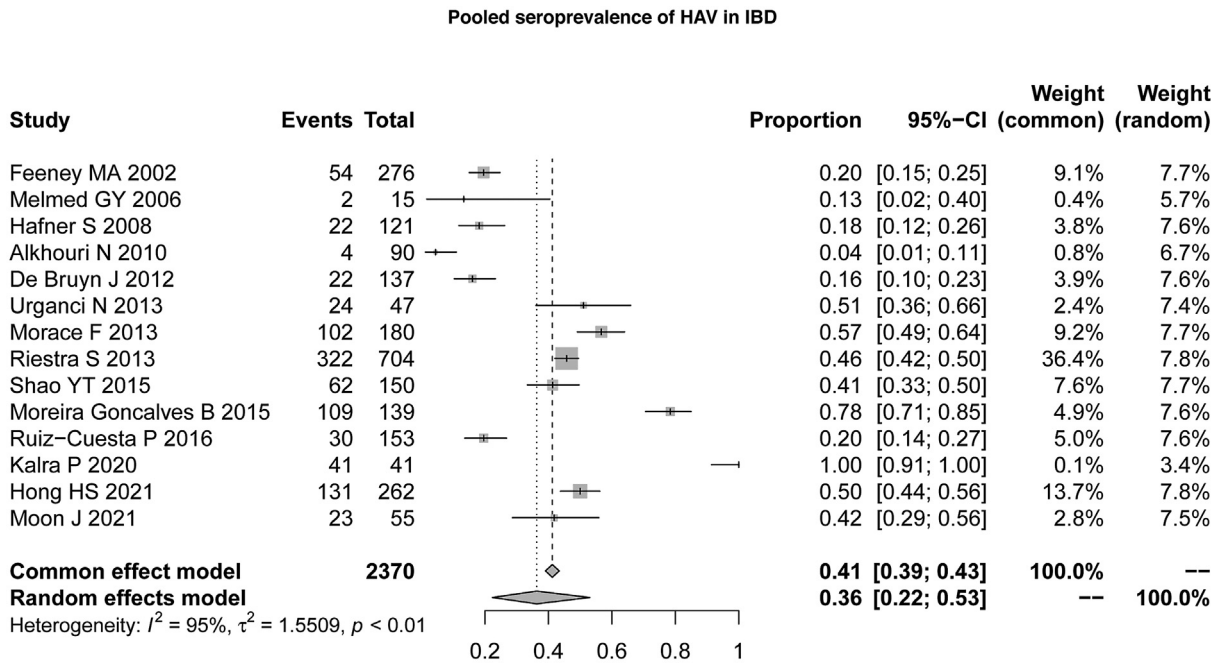

Fig. 2 Forest plot depicting the pooled seroprevalence rates for hepatitis A virus (HAV) in patients with inflammatory bowel disease.

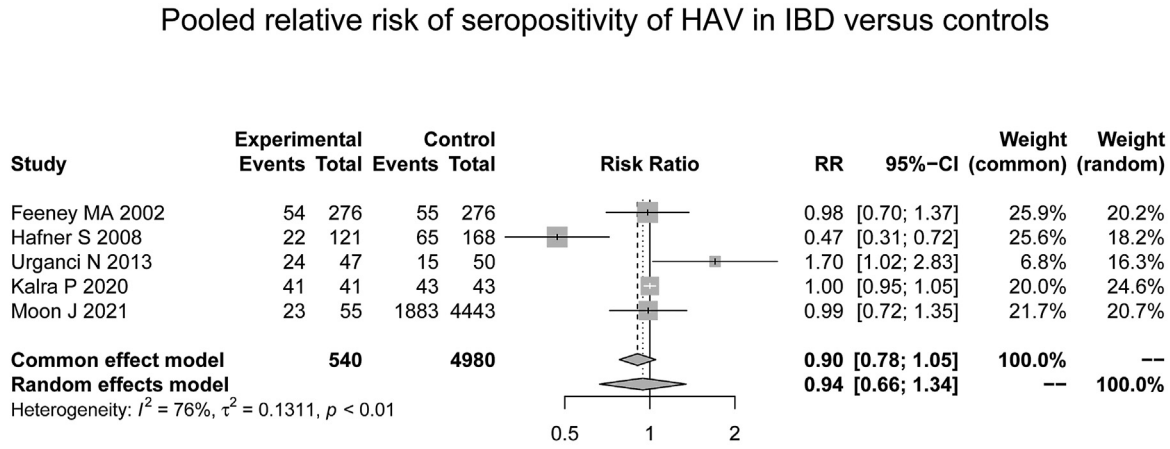

Fig. 3 Pooled relative risk of seropositivity of hepatitis A virus (HAV) in patients with inflammatory bowel disease (IBD) as compared top controls.

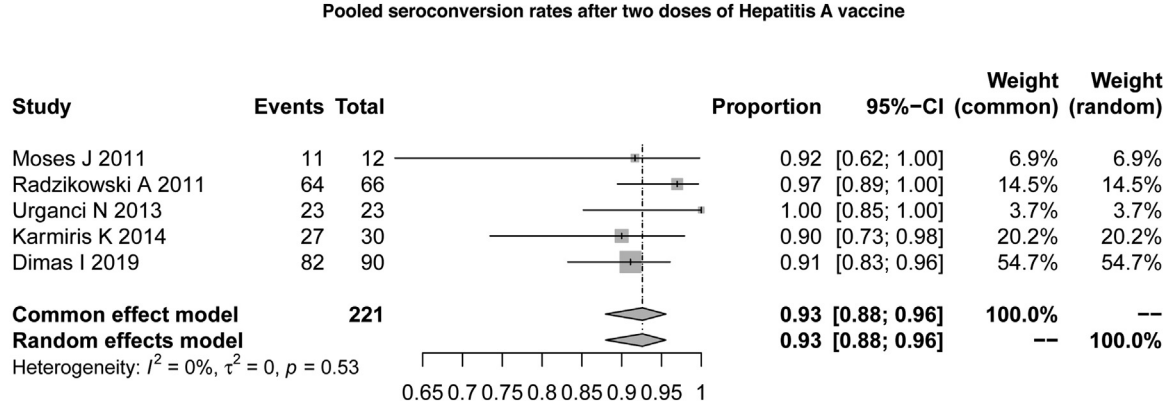

Fig. 4 Pooled seroconversion rates after two doses of hepatitis A virus (HAV) vaccination in patients with inflammatory bowel disease (IBD).

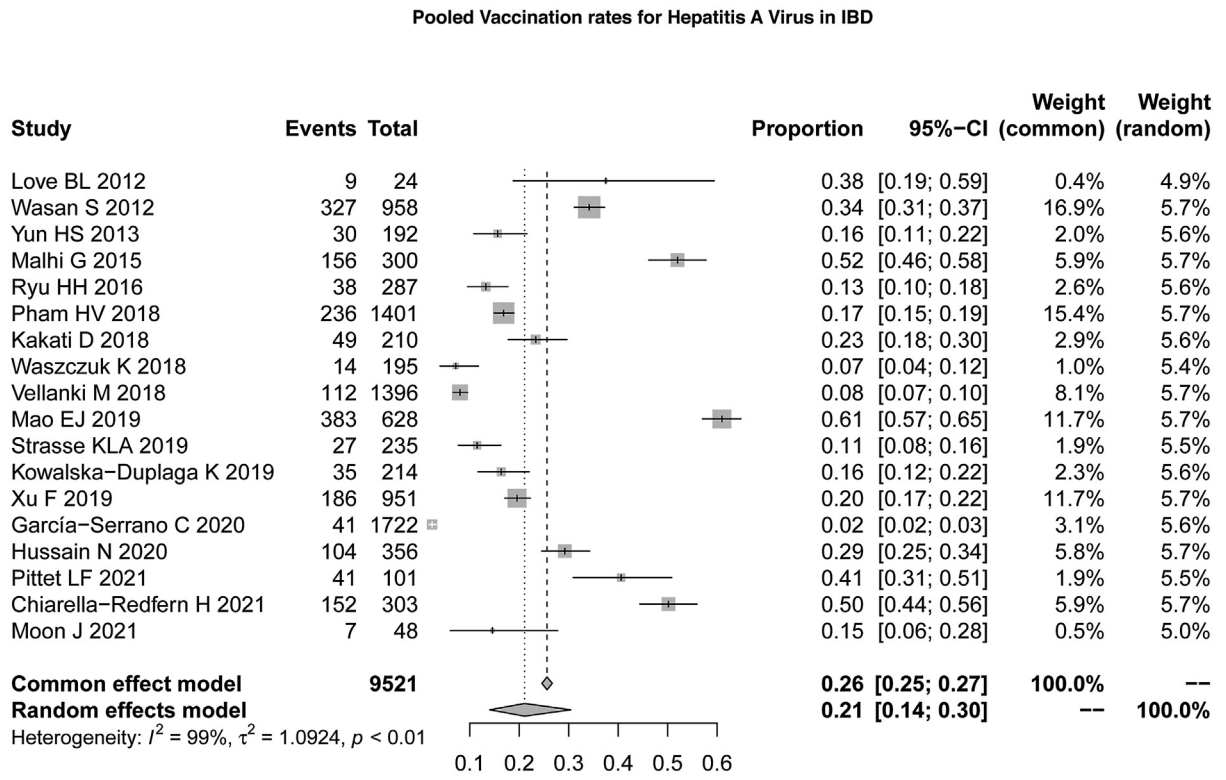

Fig. 5 Pooled rates of vaccination for hepatitis A virus (HAV) in patients with inflammatory bowel disease (IBD).

routinely or after checking the presence of previous exposure. Also, in regions with high baseline seroprevalence, the utility of vaccination at the time of diagnosis is uncertain as many individuals may have been exposed to HAV in the past. The present systematic review provides evidence that the seroprevalence of hepatitis A infection is variable across the globe and the highest rates are found in Asia while North America may have the lowest rates. Importantly, the seroprevalence rates in the IBD population are similar to the controls, suggesting that the population level data can be used as a proxy indicator of seroprevalence in IBD patients and guide the testing/vaccination strategy. Further, the results suggest that the vaccination rates against hepatitis A are low across the globe. This is even true in North America where the baseline seroprevalence is low and the vaccination rates are higher as compared with other regions of the globe.

Usually, there is a concern about response to vaccination (like HBV and coronavirus disease 2019) in patients who are on certain drug therapies like immunomodulators and biologicals.[58,59] Our analysis demonstrates that this may not be a significant concern with complete HAV vaccination although the data are limited. Four of the five included studies provided information about the underlying drugs used. While seroconversion was good with most drugs, one report suggested that seroresponse may be attenuated in those on anti-tumor necrosis factor.[39] Another study, however, suggested good response in the patients who were on infliximab.[37] This suggests that post-vaccination testing of seroconversion may not be required even in patients with underlying exposure to immunomodulators. The response to a single dose of vaccination is also fair and therefore, vaccination can be administered at the time of starting any immunosuppressive therapy.

Hepatitis A is an important cause of acute viral hepatitis in the world. It is a positive single-stranded ribonucleic acid virus belonging to the Picornaviridae family and primarily undergoes replication in hepatocytes. The risk factors of HAV infection include intravenous drug abuse, chronic liver disease, travel to endemic areas, occupational exposure, prisoners, older persons, and immunocompromised. The transmission is usually by fecooral route while the virus is excreted in human bile and stool. With prolonged immunosuppression in patients of IBD, hepatitis A infection is a concern. Infection with hepatitis A can lead to acute viral hepatitis and acute liver failure.[6] Rarely hepatitis A infection can cause relapsing hepatitis and prolonged cholestasis. With vaccination available, hepatitis A-related liver disease is preventable in patients with IBD. Although this is the first systematic review on hepatitis A vaccination in IBD, there are certain limitations. We could not separately assess the effect of underlying disease (UC or CD), activity, and drug classes because of the limited number of studies. Further, the studies for a particular region regarding seroprevalence were limited and may not be directly applicable to the entire region.

In regions with low seroprevalence, a strategy to vaccinate without testing of prior exposure may be appropriate. However, in regions with high seroprevalence (100% in one study from India), the need for routine vaccination of all IBD patients is questionable.[24] However, with improvements in sanitation there may be decline in childhood exposure to HAV and changes in such policies may be needed with changing seroprevalence data. In this regard, the seroprevalence rates in the general population can guide the strategy

because these are proxy indicators of seroprevalence of HAV in the IBD population. Further, increasing immigration rates bring their own challenges in making blanket policies for a particular region. The systematic review suggests that a single global policy for HAV vaccination may not be appropriate and the policy should be based on regional seroprevalence rates, cost of testing, and the cost of vaccination.

Ethical Statement

Not applicable as there was no direct research on human or animals as the study is a systematic review of previously published literature.

Author Contributions

A.J.: Search, screening, RoB, draft, initial draft and approval. A.K.S.: RoB, approval. P.B.N., R.M., S.M.: Screening, approval. V.Suri, A.P., P.K.M.: Important intellectual content and approval. V.Sharma.: Conception, search, analysis, draft and revision.

Data Availability Statement

There is no data associated with this work and the data used are available in public domain.

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Conflict of Interest

None declared.

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