HBV Catch-up Vaccination in Children and Adults with Incomplete or Unknown Vaccination to Reduce Hepatitis B-related Morbidity: A Systematic Review

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ABSTRACT

Background. Hepatitis B virus causes life-threatening chronic liver infection and increases the risk of death from cirrhosis and liver cancer. A three-dose series of universal HBV vaccination initiated from birth is effective against the disease. It is unclear if catch-up vaccination is also effective in those with incomplete or no HBV vaccination.

Objective. To review the evidence on the effect of HBV catch-up vaccination on children and adults to decrease HBV-related morbidity.

Methods. We searched MEDLINE, Cochrane CENTRAL, ChinaXiv, MedRXIV, BioRXIV, Google Scholar, and ongoing and completed trials on USA: https://clinicaltrials.gov/; China: http://www.chictr.org.cn/searchprojen.aspx, and WHO: https://www.who.int/clinical-trials-registry-platform. The last search date was 30 June 2023. We considered experimental or observational studies, meta-analysis/systematic reviews, completed trials and preprints that investigated the efficacy of catch-up HBV immunization in decreasing morbidity from hepatitis B infection including acute and chronic hepatitis B infection, liver cirrhosis, and hepatocellular carcinoma. There was no age and language restriction. Two reviewers independently rated the quality of included studies using Newcastle – Ottawa Quality Assessment Scale for cohort and cross-sectional studies. GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach was used to determine the certainty of evidence. Data was presented as number (%) for categorical values. Differences between the unvaccinated and vaccinated group was described as relative risk or odds ratio for categorical variables. Data was pooled using Review Manager 5.4.

Results. A total of four observational studies were included, one of which had data in children and adults [two (one with data in adults) studies in children; 3 in adults]. The cross-sectional study was assessed as good quality; and the three cohorts as fair to good. In children, a high certainty evidence study showed that catch up vaccination in 9 to 18 years old decreased risk of HBsAg positivity [RR: 0.09 (0.004, 0.21)], reduced HBV DNA detection [RR: 0.084 (0.026, 0.273)], and increased anti-HBs seroconversion [RR: 2.08 (1.84, 2.33)]. The quality of evidence was deemed high based on a large treatment effect. Another low certainty evidence study in Italy showed that HBV mass immunization in 0-10 years old decreased the prevalence of HBsAg anti-HBc and increased anti-HBs seroconversion after vaccination.

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In adults, three low certainty evidence studies were included. Two studies showed decreased incidence of acute hepatitis B [OR: 0.08 (0.05, 0.12), I2 = 33%]. Another study demonstrated a decreased prevalence of hepatocellular carcinoma with HBV vaccination with the incidence ratio of vaccinated with chronically infected at 0.04 (0.02, 0.07) showing a large magnitude of benefit for vaccination against HCC when chronic HBV infection is prevented. The studies were deemed to have low quality due to issue of directness and study design.

Conclusion. HBV catch-up vaccination in adults is effective in decreasing the prevalence of acute hepatitis B and hepatocellular carcinoma. It likewise decreased the prevalence of HBsAg and anti-HBc, and provided anti-HBs protection in 0 to 18 years.

Keywords: HBV vaccination, cirrhosis, acute hepatitis

INTRODUCTION

Hepatitis B virus causes life-threatening chronic liver infection and increases the risk of death from cirrhosis and liver cancer. HBV universal vaccination has been shown to be effective in decreasing the incidence of HBV-related morbidities and mortality including acute[1,2] and chronic hepatitis B infection[3-7], fulminant hepatic failure in infancy[8] and hepatocellular carcinoma[1, 9-11]. In those who did not receive the three-dose series from birth, catch-up vaccination refers to the action of vaccinating an individual who, for whatever reason, has not received or has incomplete vaccination. A cost-effective analysis in China demonstrated that the catch-up immunization program is cost saving in terms of reduction of future cost of progression of disease and its treatment, and number of lives saved.[12] The effect of catch-up vaccination however and the risk of developing hepatitis B infection and sequelae is unclear.[13] This review gathered evidence on the effect of HBV catch-up vaccination in children and adults in reducing hepatitis B-related outcomes.

METHODS

Criteria for Considering Studies for this Review

We considered experimental or observational studies, meta-analysis/systematic reviews, completed trials, and preprints that investigated the efficacy of catch-up HBV immunization in decreasing morbidity and mortality from hepatitis B infection including acute and chronic hepatitis B infection, liver cirrhosis, and hepatocellular carcinoma. The search was performed in duplicate by two researchers. There was no language restriction applied in the search. Both pediatric and adult patients were included. Outcome measure after HBV catch-up vaccination included prevalence of: (a) HBsAg, anti-HBs, anti-HBc; (b) acute hepatitis B infection, cirrhosis, hepatocellular carcinoma, and liver failure.

Search Methods for Identification of Studies

We searched MEDLINE, Cochrane CENTRAL, ChinaXiv, MedRXIV, BioRXIV, Google Scholar, and ongoing and completed trials on USA: https://clinicaltrials.gov/; China: http://www.chictr.org.cn/searchprojen.aspx; and WHO: https://www.who.int/clinical-trials-registry-platform. The last search date was 30 June 2023 (Appendices 1 and 2).

The following search strategy was done:

"hepatitis b"[MeSH Terms] AND "vaccines"[MeSH Terms] AND ((("catch"[All Fields] OR "catches"[All Fields] OR "catching"[All Fields]) AND "up"[All Fields]) AND "vaccines"[MeSH Terms])) OR (("boostered"[All Fields] OR "boostering"[All Fields] OR "immunization, secondary"[MeSH Terms] OR ("immunization"[All Fields] AND "secondary"[All Fields]) OR "secondary immunization"[All Fields] OR "booster"[All Fields] OR "boosters"[All Fields]) AND "vaccines"[MeSH Terms]) "carcinoma, hepatocellular"[MeSH Terms] OR ("carcinoma"[All Fields] AND "hepatocellular"[All Fields]) OR "hepatocellular carcinoma"[All Fields] OR ("hepatocellular"[All Fields] AND "carcinoma"[All Fields]) OR "chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields] OR "virally"[All Fields] OR "virals"[All Fields] OR "virology"[MeSH Terms] OR "virology"[All Fields] OR "viral"[All Fields]

Data Collection, Selection of the Studies, and Analysis

Two review authors screened the title and abstract of all studies identified using the above search strategies. We reevaluated the full text of any potentially eligible reports and excluded those studies that did not meet all of the inclusion criteria. We discussed any disagreements until we achieved consensus.

Quality of Included Studies

Two reviewers assessed independently the quality of the included studies using Newcastle Ottawa Scale for cohort and cross-sectional studies (Appendix 3).

Assessment of Overall Certainty of Evidence and Data Management

GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach was used to determine the certainty of evidence.[14] Data was presented as number (%) for categorical values. Differences between the unvaccinated and vaccinated group were described as relative risk or odds ratio for categorical variables. Review Manager 5.4 was used to pool the data for acute hepatitis B infection.

RESULTS

Characteristic of Included Study (Appendix 4)

After a thorough search, there were no RCTs that looked into catch-up vaccination among healthy children and adults in reducing hepatitis B-related outcomes.

There were four observational studies (three cohorts, one cross-sectional) that were included. There were two studies in pediatrics[2,6] and three studies in adult.[1,2,11] One study reported both pediatric and adult patients.[2] The cross-sectional study[6] was assessed to have good quality; the cohort studies were judged as fair[6] and good[1,11] quality.

Pediatrics

A cross-sectional study in Nunavut, Canada included participants who had blood taken for unrelated medical tests.[6] Convenience sampling was done from 19 communities within the region and 4774 were tested for anti-HBS, anti-HBc, HBsAg and HBV DNA. The participants were grouped based on the year of birth. Group 1: Non vaccinated (born before 1980); Group 2: Catch-up vaccination (born between 1980-1994); and Group 3: Universal vaccination (born after 1995). The quality of evidence of the pediatric study in Nunavat, Canada was deemed high based on a good quality observational study with a large treatment effect on the outcomes of decreased risk of HBsAg positivity, reduced HBV DNA detection and increased anti-HBs seroconversion (Appendix 5).

Another cohort study in Afragola, Italy from 1983 to 1989 included 7,000 children up to 10 years and compared the infection rate of HBsAg, anti-HBc and anti-HBs in 1978 before HBV vaccination in the country and in 1989 after the mass vaccination.[2] This study also included 1500 subjects aged 11 to 60 years.

Adults

There were three observational studies in adults. The quality of evidence of these studies was deemed low due to issues of directness and study design (Appendix 6).

A cohort study done in Korea recruited 370,285 males aged ≥30 seen in a health examination program for government employees.[11] These patients were followed up with an average of 3 years and 10 months and divided into four cohorts namely: (1) Chronically infected (n=18,914); (2) Unvaccinated but have developed natural immunity from past exposure (n=78,094); (3) Vaccinated (n=35,934); and (4) Susceptible (unvaccinated and uninfected) (n=237,343). Incidence rates of HCC by record linkage were then compared between groups to ascertain vaccination status and risk for HCC.

Two other cohort studies compared the incidence of acute symptomatic hepatitis B infection before and after completion of immunization.[1,2] In Anchorage, Alaska, 65,000 Alaskan Natives were screened and 44,100 were identified to be susceptible individuals who underwent catch-up vaccination.[1] And in Afragola, Italy, 1500 subjects 11 to 60 years of age were included in the HBV pilot project for mass vaccination between 1983 to 1989.[2]

Chronic Hepatitis B Carriers and Anti-HBs Seroconversion

Pediatrics

The study in Canada showed a decrease in HBsAg prevalence after catch-up vaccination of students from Grade 4 up to high school (usually between 9-18 years) compared to the period before universal vaccination.[6] Universal vaccination in Nunavut, Canada started in 1995, and the HBsAg prevalence in those born 15 years before this was 2.5% (50/2004). After catch up vaccination of the students, HBsAg prevalence was 0.21% (4/1869). (RR: 0.09 [95% CI 0.0004, 0.2100]). The same study showed a reduction in the HBV DNA detection from 1.9% (38/2001) before universal vaccination to 0.161% (3/1868) after catch-up vaccination (RR: 0.084 95% CI 0.026, 0.273). There was also an increase in anti-HBs seroconversion from 16.4% (329/2007) before universal vaccination to 34% (635/1871) after catch up vaccination (RR: 2.08 [95% CI: 1.84, 2.33]).

The HBV mass immunization study in Italy in children 0-10 years revealed that after vaccination, HBsAg prevalence decreased from 9.2% to 1%, anti-HBc from 49.7% to 3%, and anti-HBs was noted in 63% of subject.[2]

Adults

Incidence of acute hepatitis B infection

The study in Alaska demonstrated that after screening and identification of 44,100 susceptible individuals, catch-up vaccination decreased the incidence of acute hepatitis B infection from 215/100,000 in 1982 to 14/100,000 in 1986.[1] Similarly, the study in Italy of 0 to 60 years of age showed a decrease in the incidence from 91/100,000 to 10/100,000 after a mass immunization program.[2] Pooled incidence rates showed that catch-up vaccination decreased acute hepatitis B infection [OR: 0.08 (0.05, 0.12), I^2 = 33%] (Figure 1).

Prevalence of hepatocellular carcinoma

A total of 302 cases of HCC in Korea identified between 1983 to 1989 and the overall incidence rate of HCC during this period was 21.7 per 100,000 person-years with different incident rates according to the serological status of the person.[11] (Table 1) The incidence ratio of the vaccinated and susceptible individuals was 0.58 (95%, 0.24-1.39) while the ratio of the vaccinated and those with natural immunity was comparable at 1.84 (95%, 0.82-4.10). The incidence ratio of vaccinated with chronically infected was 0.04 (95%, 0.02-0.07), showing a large magnitude of benefit for vaccination against HCC when chronic HBV infection is prevented.

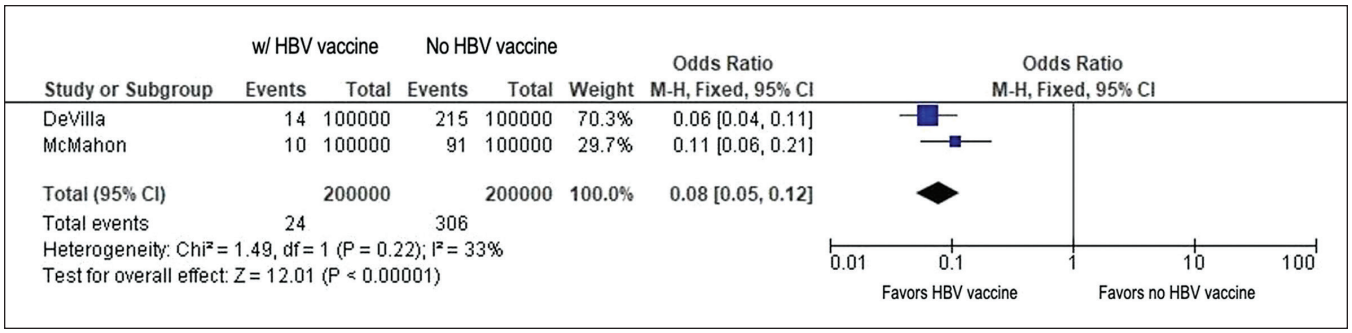

Figure 1. Pooled incidence rate of acute hepatitis B infection before and after HBV catch-up vaccination.

Table 1. Incidence Rate of Hepatocellular Carcinoma in Korea in 370,285 Males Categorized according to the Serological Test for Hepatitis B[11]

	Incidence Rate of Hepatocellular Carcinoma (person-years)
Chronically infected	215.9/100,000
Unvaccinated with natural immunity	4.4/100,000
Vaccinated	8/100,000
Susceptible	13.7/100,000

DISCUSSION

Our present review showed that catch-up vaccination whether in children or adults is effective in decreasing the prevalence of acute hepatitis B and hepatocellular carcinoma in adults and in decreasing the prevalence of HBsAg and anti-HBc, and providing anti-HBs protection if given in individuals less than 18 years. HBsAg is used as a marker of acute or chronic infection, anti-HBc for past HBV exposure, and anti-HBs as an indicator if the person has developed life-long immunity to the disease.

Hepatitis B virus (HBV) infection can cause an acute or chronic infection. In 2019, there were around ≈300 million chronic infections worldwide resulting in 820,000 deaths from cirrhosis and liver cancer annually.[15] Recognizing the large global disease burden, the United Nations Sustainable Development Goals for 2030 included combating hepatitis B and one of the means of doing this is by HBV immunization. Universal HBV vaccination has been implemented in most countries of the world. In the Philippines, a law was enacted in 2011 for the mandatory vaccination of all newborns with HBV within 24 hours of birth.[16] However, for those born before 2011, some may still have an incomplete or no HBV vaccination. The recent NDHS in 2022 also showed that for children one to two years old, only 86% received the first dose of the HBV vaccine and only 77% completed the three-dose series.[17] These subjects are the target for catch-up immunization. As demonstrated in the study in Nunavut, Canada[6] and in Afragola, Italy[2], the prevalence of the HBsAg and anti-HBc decreased during the catch-up vaccination.

HBV vaccination provides benefit if administered at any age in unvaccinated individuals as it will prevent the infection of the individual and for the virus to be transmitted to another person.[1] In neonates born to HBeAg positive mothers, the risk of perinatal infection is 90%.[18] This decreases to 30 to 50% if infection is acquired horizontally before 6 years of age. In older children and adults, the risk of chronicity is between 5-10%. Once infected, the HBV carriers become a reservoir in transmitting the virus.

The protective effect of HBV vaccination was demonstrated in the observational studies conducted in Alaska[1] and Italy[2] which showed a decrease in the prevalence of acute symptomatic hepatitis B. Acute hepatitis B infection is usually self-limiting but studies have shown that in those who develop the disease, 5-10% will develop chronicity.[19] Acute hepatitis B infection is also the cause of acute liver failure in 126/2614 (5%) of adults[19] and in 65% of Taiwanese children[20].

It can also be inferred from our findings that HBV vaccination decreased the incidence of hepatocelullar carcinoma in adult as shown in South Korea based on an over one million person years of follow up.[11] Fifty to seventy percent of HCC cases were secondary to HBV in several Asian countries including China, Hong Kong, Republic of Korea, Vietnam, Malaysia, and Thailand.[21] Similarly, in Taiwan, which was previously considered a country with high endemicity for the virus, 70% of Taiwanese children with HCC were positive for HBV.[22]

HBV vaccine is also affordable, with a three-dose series amounting to US$30 at US$10 per vial. In China, a cost-effectiveness analysis was done to assess the hepatitis B catch-up program. Using a Markov model, the HBV catch-up immunization program of children 1-19 years old was reported to have a 97% chance of being cost-saving and a 98% chance of having an incremental cost-effectiveness ratio of less than $2,500 per QALY gained.[12] Similarly, in Shandong China, HBV Catch-up program was dominant in preventing symptomatic acute hepatitis B, HBsAg carriers, disease progression to cirrhosis and hepatocellular carcinoma, and deaths due to HBV infection compared with no vaccination.[23] In the Philippines, the approximate unit cost of one vial of pediatric or adult HBV vaccine is PhP

250 to 300 which translates to approximately 1000 pesos for the entire vaccination series. HBV treatment with oral anti-nucleoside for at least one year ranges from P18,250 to PhP 91,250 at PhP 50-250 per tablet and if the patient decompensates and require liver transplant, the cost is about PhP 5,000,000. Catch-up vaccination in pediatrics and adults is also recommended by different organizations including the Advisory Committee on Immunization Practices (ACIP) of the Center for Disease Control[24], American Association of Study of Liver Disease[25], American Academy of Pediatrics[26], and local organizations including Philippine Society of Microbiology and Infectious Disease[27] and Philippine Foundation for Vaccine[28].

The review was limited by the available information on HBV catch-up vaccination as most of the studies were on the effect of the primary HBV series and not on those with incomplete or unknown vaccination status. All included studies were observational which were more prone to bias and confounding. In the study on effect of HBV vaccine on hepatocellular carcinoma, selection bias was present as the population was limited to male participants while in the incidence of acute hepatitis B infection, the data involved both children and adults. Sampling bias may also exist for the evidence on HBV catch-up vaccination in children as HBV vaccination status was only assumed based on the age of the patient with no medical records or vaccination card to verify it. Nonetheless, the report provides important information on HBV catch-up vaccination as its implementation will provide optimal protection against the sequelae of the disease especially in an endemic country like the Philippines.

In conclusion, HBV catch-up vaccination in adults is effective in decreasing the prevalence of acute hepatitis B and hepatocellular carcinoma. It likewise decreased the prevalence of HBsAg and anti-HBc, and provided anti-HBs protection in 0 to 18 years.

Recommendations on HBV Catch-up Vaccination from Other Groups

Centers for Disease Control[24]

The CDC recommends the following for HBV catch-up immunization:

1. Unvaccinated persons should complete a 3-dose series at 0, 1–2, 6 months.
2. Adolescent age 11–15 years may use an alternative 2-dose of adult recombinant formulation schedule with at least 4 months between doses.
3. Adolescent age 18 years or older may receive a 2-dose series of adjuvanted Hepatitis B vaccine at least 4 weeks apart.
4. Adolescent age 18 years or older may receive the combined HepA and HepB vaccine as a 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).

American Academy of Pediatrics 2021[25]

1. Administer the 3-dose series to those not previously vaccinated at 1 month interval for the first two doses and the third dose after eight weeks or at least 16 weeks from the first dose.
2. A 2-dose series 4 weeks apart of adult formulation is licensed for children aged 11 through 15 years.

American Association for the Study of Liver Disease[26]

1. Follow-up testing is recommended for those who remain at risk of infection, such as HCWs, infants of HBsAg-positive mothers, sexual partners of persons with CHB, chronic hemodialysis patients, and immunocompromised persons, including those with HIV.
2. Annual testing of hemodialysis patients is recommended given that immunity wanes rapidly in these individuals who are at a high risk of continued exposure to HBV.
3. Booster doses are not indicated in immunocompetent individuals if the primary vaccination series is completed, as long-term follow-up studies indicated that immune memory persists despite declining anti-HBs levels.
4. For individuals undergoing postvaccination serological testing, especially immunocompromised patients (such as persons on dialysis or with chronic inflammatory conditions, including HIV), a booster injection is advised when the anti-HBs titer falls below 10 mIU/mL.

Philippine Society of Microbiology and Infectious Diseases (PSMID)[27]

1. Among high-risk groups, the standard hepatitis B vaccination schedule of 0,1 and 6 months should be used to confer long term protection among high-risk groups who do not need immediate protection and rapid seroconversion.

Pediatric Infectious Disease Society of the Philippines[28]

1. For 1-18 years old, administer three doses at 0, 1 and 6 months for those not previously vaccinated.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

Both authors declared no conflicts of interest.

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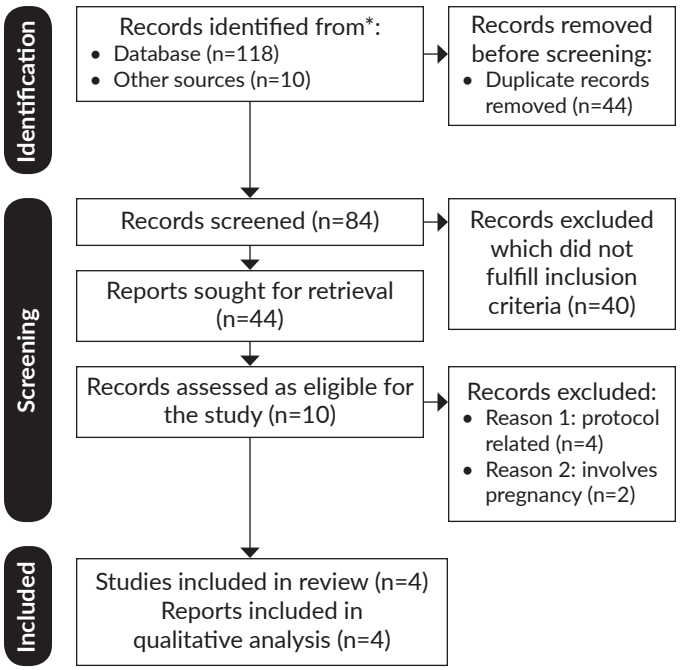
APPENDICES

Appendix 1. Electronic search strategy for the effect of catch-up vaccination on children and adult to reduce HBV-related morbidity

#	Query	Results
1	(Hepatitis B) OR (Hepatitis B [MeSH Terms}) OR (Hepadnaviridae) OR (HBV)	109,808
2	(Catch-up immunization) OR (catch up immunization [MeSH Terms]) OR (catch up vaccination [MeSH Terms]) OR (catch up vaccination) or (immunization [MeSH Terms]) OR (vaccination [MeSH Terms])	193,371
3	#1 AND #2	8,820
4	(vaccine) AND (vaccine[MeSH Terms])	252,656
5	#3 AND #4	6,283
6	"carcinoma, hepatocellular"[MeSH Terms] OR ("carcinoma"[All Fields] AND "hepatocellular"[All Fields]) OR "hepatocellular carcinoma"[All Fields] OR "hepatoma"[All Fields] OR "hepatomas"[All Fields]	148,480
7	"liver cirrhosis"[MeSH Terms] OR ("liver"[All Fields] AND "cirrhosis"[All Fields]) OR "liver cirrhosis"[All Fields] OR "cirrhosis"[All Fields] OR "fibrosis"[MeSH Terms] OR "fibrosis"[All Fields] OR "liver failure"[All Fields] OR "chronic liver disease"[All Fields]	419,101
8	#5 AND #6 AND #7	110



Appendix 2. PRISMA flow diagram on electronic search strategy for the effect of catch-up vaccination on children and adult to reduce HBV-related morbidity.

Appendix 3. Assessment of quality of study for cross-sectional and cohort study

Newcastle Ottawa Scale for Cross-sectional Study	Hunyh (2017)[6]
SELECTION	
1. Representativeness of the sample a. Truly representative of the average in the target population b. Somewhat representative of the average in the target population (non-random sampling) c. Selected group of users/convenience sample d. No description of the derivation of the included subjects	*
2. Sample size a. Justified and satisfactory (including sample size calculation) b. Not justified c. No information provided	*
3. Non-respondents a. Proportion of target samples attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded b. Unsatisfactory recruitment rate, no summary data on non-respondents c. No information provided	*
4. Ascertainment of the exposure (risk factor) a. Vaccine records/vaccine registry/clinic registers/hospital records only b. Parental or personal recall and vaccine/hospital records only c. Parental/personal recall	Based only on surrogate marker (anti-HbS)
COMPARABILITY (MAX OF 2 STARS)	
1. Comparability of subjects in different outcome groups on the basis of design or analysis Confounding factors controlled a. Data/results adjusted for relevant predictors/risk factors/confounders e.g., age, sex, time since vaccination, etc. b. Data/results not adjusted for all relevant confounders/risk factors/information not provided	**

Appendix 3. Assessment of quality of study for cross-sectional and cohort study *(continued)*

Newcastle Ottawa Scale for Cross-sectional Study	Hunyh (2017)[6]
OUTCOME	
1. Assessment of outcome:	**
a. Independent blind assessment using objective validated laboratory method	
b. Unblinded assessment using objective validated laboratory methods	
c. Used non-standard or non-validated laboratory methods with gold standard	
d. No description/non-standard laboratory method	
2. Statistical test:	
a. Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and probability levels (p value)	*
b. Statistical test not described or inappropriate	
Overall ASSESSMENT	GOOD

Very good studies: 9-10 stars; Good studies: 7-8; Satisfactory studies: 5-6; Unsatisfactory studies: 0-4

Newcastle Ottawa Scale for Cohort Study	McMahon[1] (1987)	DaVilla[2] (1993)	Lee[11] (1997)
SELECTION			
1. Representative of exposed cohort	*	*	*
2. Selection of non-exposed cohort	*	*	*
3. Ascertainment of exposure	*		
4. Demonstration that outcome of interest was not present at the start	*		*
COMPARABILITY			
1. Comparability of cases and controls			
a. Study controls for age, sex, marital status; study controls for other factors	* (HBV status)	* (age)	* (Disease)
b. Study controls for other factors		* (region)	
c. Cohort is not comparable on the basis of the design or analysis controlled for confounders			
OUTCOME			
1. Assessment of outcome (independent blind assessment, record linkage, self-report, no description)	*	*	*
2. Was follow up long enough for outcomes to occur? (Yes or No).	Yes*	Yes*	Yes*
3. Adequacy of follow up of cohorts			
a. Complete follow up of all subjects accounted for	*		*
b. Subjects lost to follow up unlikely to introduce bias – numbers lost <20% of those lost and those followed up			
c. Follow up rate <80% and no description of lost to follow up			
Overall ASSESSMENT	GOOD	FAIR	GOOD
SELECTION	****	**	***
COMPARABILITY	*	**	*
OUTCOME	***	**	***

Good quality: 3 or 4 stars in selection; 1 or 2 stars in comparability; 2 or 3 stars in outcome
Fair quality: 2 stars in selection; 1 or 2 stars in comparability; 2 or 3 stars in outcome
Poor quality: 0 or 1 star in selection; 0 star in comparability; 0 or 1 star in outcome

Appendix 4. Table of Included Study

Country/ Study Setting	Study Design	Population	Intervention	Comparator	Outcome
Hunyh C[6] (2017) Nunavut, Canada	Cross-sectional	Three groups of participants 1. Unvaccinated: born before 1980 2. Catch-up group: born between 1980-1994 (9-18 years) 3. Universal vaccination: born after 1995	Catch-up vaccination in those born between 1980 to 1994	Unvaccinated group	Prevalence of HBV DNA, HBsAg, anti-HBs, anti-HBc in the different groups
Lee[11] (1998) South Korea	Retrospective cohort	Adult males	Vaccinated	1. Non vaccinated 2. Chronic infection 3. Natural immunity	Incidence of hepatocellular carcinoma
McMahon[1] (1981) Anchorage, Alaska	Prospective cohort	Infants, children, and adult Alaskan natives	Vaccination of all susceptible individuals		Incidence of acute hepatitis B before and after immunization
Da Villa[2] (1993) Afragola, Italy	Prospective cohort	Children (0-10 years old) and adults	Mass immunization	Incidence of HBsAg, anti-HBc, HBsAg and anti-HBc and anti-HBs	Incidence of acute hepatitis B before and after immunization Incidence of HBsAg, anti-HBc, HBsAg and anti-HBc and anti-HBs

Appendix 5. GRADE evidence profile on effect of catch-up vaccination on HBsAg, HBV DNA and anti-HBs detection

		Certainty assessment					No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Catch-up vaccination	No vaccination	Relative (95% CI)	Absolute (95% CI)	Certainty
Catch-up vaccination to decrease HBsAg prevalence											
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would reduce the demonstrated effect	4/1869 (0.2%)	50/2004 (2.5%)	RR 0.0836 (0.0310 to 0.2370)	23 fewer per 1,000 (from 24 fewer to 19 fewer)	⨁⨁⨁⨁ HIGH
Catch-up vaccination to decrease HBV DNA detection											
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would reduce the demonstrated effect	3/1868 (0.2%)	38/2001 (1.9%)	RR 0.08 (0.03 to 0.27)	17 fewer per 1,000 (from 18 fewer to 14 fewer)	⨁⨁⨁⨁ HIGH
Catch-up vaccination and anti HBs detection											
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would reduce the demonstrated effect	635/1871 (33.9%)	329/2007 (16.4%)	RR 2.07 (1.84 to 2.33)	175 more per 1,000 (from 138 more to 218 more)	⨁⨁⨁⨁ HIGH

CI – Confidence interval, RR – Risk ratio

Appendix 6. GRADE evidence profile on effect of catch-up vaccination on hepatocellular carcinoma and acute hepatitis B

		Certainty assessment					No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Catch-up vaccination	No vaccination	Relative (95% CI)	Absolute (95% CI)	Certainty
HCC incidence (follow up: mean 3 years; assessed with: Record Linkage)											
1	observational studies	serious[a]	not serious	serious[b]	not serious	none	8/100000 (0.0%)	216/100000 (0.2%)	RR 0.04 (0.02 to 0.07)	2 fewer per 1,000 (from 2 fewer to 2 fewer)	⨁⨁◯◯ LOW
Acute Hepatitis B (follow up: range 3 years to 6 years; assessed with: Incidence Rate)											
2	observational studies	serious[a]	not serious	serious[c]	not serious	none	24/100000 (0.0%)	306/100000 (0.3%)	RR 0.08 (0.05 to 0.11)	3 fewer per 1,000 (from 3 fewer to 3 fewer)	⨁⨁◯◯ LOW

CI – Confidence interval, RR – Risk ratio

Explanations:
[a] Pre- and at-intervention confounding expected due to study design as assessed using ROBINS-I Tool
[b] Population was exclusively male
[c] Studies included all susceptible individuals (children and adults)